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Everyday cognitive failure in patients suffering from neurosarcoidosis

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Abstract. *Background:* Cognitive failure is associated with memory and concentration problems. Previously, a prevalence of one third was found in a general sarcoidosis population. The aim of this study was to assess if neurosarcoidosis patients are at higher risk for developing everyday cognitive failure using the Cognitive Failure Questionnaire (CFQ) and to determine what factors were associated with cognitive failure. *Methods:* A cross-sectional web-based survey was conducted from April to May 2017 in a national sample of neurosarcoidosis patients. The survey asked about complaints and included 3 questionnaires (Fatigue Assessment Scale [FAS], Small Fiber Neuropathy Screening List [SFNSL] and CFQ. Data were compared to a general sarcoidosis population. *Results:* Of the 152 patients who completed the survey, 131 had neurosarcoidosis. The mean CFQ score was significantly higher in the neurosarcoidosis (45.6±20.7) compared to the general sarcoidosis population (36.2±15.9; p< 0.0001). High CFQ scores (≥43) were found in 55.7% and 33.9%, respectively (p<0.0001). The FAS score (OR 21.4) and SFNSL score (OR 4.3) were the strongest positive predictors of a high CFQ score. *Conclusion:* Cognitive failure is a significant problem in neurosarcoidosis. More than half of the patients reported cognitive deficits, compared to one third of a general sarcoidosis population. Fatigue and small fiber neuropathy play a role in cognitive failure. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 2-10)*

Key words: neurosarcoidosis, cognitive failure, small fiber neuropathy (SFN), fatigue, sarcoidosis

Introduction

Cognitive failure is a cognitive error occurring during the performance of a task that a person would normally execute successfully in everyday life (1, 2). Cognitive failure is characterized by concentration problems, memory loss and decreased perception. It is associated with various disease entities, such as chronic obstructive pulmonary disease, obstructive sleep apnoea, chronic heart failure, rheumatoid arthritis, primary Sjögren syndrome, multiple sclerosis and sarcoidosis. Factors associated with a higher prevalence of cognitive failure in these different disease entities include fatigue, depression, pain due to small fiber neuropathy (SFN), microangiopathy, inflammatory molecules such as TNF-alpha, cerebrovascular disease and chronic hypoxia (1, 3-7).

Sarcoidosis is a multisystem inflammatory disorder of unknown etiology in genetically predisposed

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individuals, affecting 1-40 per 100 000 persons (8, 9). The natural history and prognosis of sarcoidosis are highly variable and its course is often unpredictable. Clinical manifestations vary, depending on the organs involved (10, 11). Involvement of the nervous system, neurosarcoidosis, is present in approximately 5% of the cases and has a heterogeneous clinical presentation, from chronic meningitis to myelopathy (12, 13).

Apart from organ-related symptoms, patients may suffer from a variety of nonspecific disabling symptoms that cannot be explained by granulomatous inflammation of an organ, such as fatigue and small fiber neuropathy (SFN) (14). Both have a high prevalence. Fatigue occurs in 50-85% of sarcoidosis patients (11, 15) and SFN in 40-60% (16, 17). In addition, Elfferich et al. found everyday cognitive failure in 35% of the cases they studied in a general sarcoidosis population (1). Cognitive failure has a great impact on the lives of sarcoidosis patients, since they are mostly young.

Broadbent et al. developed the Cognitive Failure Questionnaire (CFQ), a self-report questionnaire assessing failures in everyday errors of attention, perception, memory and motor function (2). In general, the CFQ appears to be a reliable and brief measure useful in clinical practice.

We hypothesized that everyday cognitive functioning may be even more impaired in patients with neurosarcoidosis. The aim of this study was therefore to examine the prevalence of everyday cognitive failure using the CFQ in patients suffering from neurosarcoidosis compared to a general sarcoidosis population. We also studied what factors were associated with cognitive failure.

Methods

Study design

A cross-sectional web-based anonymous survey was conducted from April to May 2017 among a national sample of neurosarcoidosis patients (Group I). The recruitment procedure aimed to compose a representative sample of neurosarcoidosis patients in the Netherlands. Data from the study by Elfferich et al., performed in a general sarcoidosis population (n=343) served as a control group for comparisons of the scores on the CFQ, the small fiber neuropathy screening list [SFNSL], and the fatigue assessment scale [FAS] (1). This latter population was subdivided in those without neurosarcoidosis (Group II, n=330) and those with neurosarcoidosis (Group III, n=13).

This study was performed in accordance with the Declaration of Helsinki and its amendments. The Medical Ethics Committee of the St. Antonius Hospital Nieuwegein, The Netherlands, decided that, under the Dutch act on medical research involving human subjects, approval of this study by a Medical Ethics Committee was not necessary.

Study sample and procedure

The overall study sample (group I) comprised patients from our online Dutch Neurosarcoidosis Registry and neurosarcoidosis patients from the Dutch Sarcoidosis Society. The diagnosis of neurosarcoidosis was confirmed for each of the patients by a neurologist, using the Zajicek or Marangoni (modified Zajicek) criteria, labelling patients as possible, probable or definite neurosarcoidosis (18, 19). SFN was classified as 'paraneurosarcoidosis', since the hallmark of sarcoidosis (granuloma formation) is not found in the small fibers (20-23). Patients suffering solely from SFN were therefore excluded from this study.

All patients included in the Dutch Neurosarcoidosis Registry have agreed to participate in online research studies. Patients from the Dutch Sarcoidosis Society (Sarcoidose.nl) were recruited without incentives, since the survey was anonymous. There was no overlap in registrations between the two sources. All patients had sufficient command of Dutch and had access to the internet.

A survey was developed using the online questionnaire tool *Surveymonkey* (www.surveymonkey.com). The survey included self-reported complaints, sarcoidosis manifestations, demographics (gender, age, duration of sarcoidosis), use of medication, daily impairments and a set of questionnaires validated for sarcoidosis, the CFQ (2), the SFNSL (24) and the FAS (25). An invitation to complete the electronic survey was sent by email to all the patients in our online Dutch Neurosarcoidosis Registry. Additional patients were recruited by means of an advertisement on the website of the Dutch Sarcoidosis Society, Sarcoidose.nl, providing a link to the electronic sur-

vey. Of the 153 patients who started the survey, 152 (99%) completed it.

Questionnaires

In the sarcoidosis population, so far no questionnaires regarding evaluation of cognitive failure are validated. Broadbent et al. developed the CFQ to evaluate cognitive failure, which appears to be a brief and reliable questionnaire that is useful in clinical practice. Since this questionnaire was previously used to evaluate cognitive failure in the general sarcoidosis population, we decided to also use the CFQ in the neurosarcoidosis population (1). The CFQ is a self-report questionnaire consisting of 25 items assessing deficits regarding attention, perception, memory and motor functioning in everyday life. The total CFQ score is calculated by summation of all answers and scores range from 0-100. A higher total score indicates more subjective cognitive failure. A high CFQ score is defined as a score ≥43 (mean of the controls plus one standard deviation) (2).

The FAS is a 10-item self-report fatigue questionnaire. In addition to the total fatigue score, the FAS yields a mental fatigue score and a physical fatigue score. The response scale is a five-point scale (1 never to 5 always); scores on the FAS can range from 10 to 50. A score >22 indicates fatigue and a score >34 indicates extreme fatigue. The reliability and validity of the FAS have been shown to be good in sarcoidosis patients (25).

The SFNSL is a 21-item self-administered questionnaire to screen for symptoms related to small fiber neuropathy (SFN). The response scale is a five-point scale (0 never to 4 always); scores on the SFNSL can range from 0 to 84. The cut-off score of the SFNSL is 11: a score below 11 indicates no or few symptoms related to SFN, while a score of 11-48 indicates probable or highly probable SFN and a score above 48 is indicative of SFN (24).

Statistical analysis

All statistical analyses were performed using SPSS version 24 for Mac. Standard descriptive statistics were computed. The chi-square test and Student t-test were used to test for statistically significant differences between two groups of neurosarcoidosis patients (i.e. those with CFQ <43 and those with CFQ ≥43). Chi-square tests were also performed to assess the prevalence (%) of cognitive failure (CFQ) in patients with neurosarcoidosis compared to a general sarcoidosis population. ANOVA was used for comparison between the general sarcoidosis population and the neurosarcoidosis population. Pearson correlations were calculated to evaluate the association between the CFQ scores and fatigue (FAS scores) as well as symptoms suggestive of SFN (SFNSL scores). Multivariate logistic regression analyses were used to assess the influence of the FAS scores and SFNSL scores on the CFQ scores, after adjustment for age, sex, treatment, depressive symptoms and sleeping disturbances. Because of the large number of correlations examined, a probability value of less than 0.01 was considered to be statistically significant.

Results

A total of 152 patients (99%) completed the survey. Neurosarcoidosis had been established in 131 patients (86.2%), 12 patients did not have neurosarcoidosis, and in 9 cases the diagnosis remained unclear. Finally, therefore, 131 patients suffering from neurosarcoidosis were included in this study. The studied population is approximately 25% of the estimated total neurosarcoidosis population in the Netherlands. The various neurosarcoidosis manifestations in the studied population were cranial nerve palsy (45.1%), spinal cord involvement (29.4%), chronic meningitis (26.5%), cerebral involvement (20.6%), peripheral neuropathy (15.7%), myelitis (9.8%), neuro-endocrine involvement (9.8%), hydrocephalus (6.9%), brainstem involvement (4.9%), and cerebral vascular involvement (3.9%). Almost half of the population had multiple manifestations (45%). Demographic and clinical data are summarized in table 1.

The mean CFQ score in the neurosarcoidosis population we studied was 45.6±20.7. There were no significant differences between the subgroup with a high CFQ score and the subgroup with a normal CFQ score as regards sex, age, time since diagnosis, or medication use. Pain, pulmonary symptoms (cough and dyspnea), self-reported depressive symptoms and self-reported sleeping disturbances were

Table 1. Summary of the characteristics of the studied neurosarcoidosis population subdivided into those with normal Cognitive Failure Questionnaire (CFQ) scores and those with high CFQ scores

	Total	CFQ < 43	CFQ ≥43	p-values#
Patients, n (%)	131	58 (44.3)	73 (55.7)	-
Sex (male:female), n (%)	67(51.1): 64 (48.9)	27(46.6): 31 (53.4)	40 (54.8): 33 (45.2)	0.349
Age, years (range)	51.9±10.4 (21-75)	52.8±11 (21-75)	51.4±10.0 (28-74)	0.444
Time since diagnosis, years (range)	8.7±7.2 (0-35)	8.0±6.7 (0-35)	9.3±7.6(1-35)	0.292
Symptoms				
- Pain, n (%)	92 (70.2)	32 (55.2)	60 (82.2)	0.001
- Cough and dyspnea, n (%)	30 (22.9)	5 (8.6)	25 (34.2)	0.001
- Ocular, n (%)	57 (43.5)	21 (36.2)	36 (49.3)	0.133
- Cardiac, n (%)	9 (6.9)	4 (6.9)	5 (6.8)	0.992
- Skin, n (%)	48 (33.6)	15 (25.9)	31 (42.5)	0.048
- Joint, n (%)	89 (67.9)	33 (56.9)	56 (76.7)	0.016
- Hypercalcemia, n (%)	9 (6.9)	2 (3.4)	7 (9.6)	0.168
- Kidney stones, n (%)	3 (2.3)	0 (0)	3 (4.1)	0.118
Medication use				
- never, n (%)	26 (24.4)	12 (20.7)	14 (19.2)	0.829
- first line treatment, n (%) (prednisone or dexamethasone)	99 (75.6)	43 (74.1)	56 (76.7)	0.733
- second line treatment, n (%) (methotrexate azathioprine, mycolfenolate mofetyl)	50 (38.2)	20 (34.5)	30 (41.1)	0.439
- third line treatment, n (%) (anti-TNF-alpha: adalimumab, infliximab)	22 (16.8)	10 (17.2)	12 (16.4)	0.903
Psychological variables				
Self-reported				
Depressive symptoms	33 (25.2)	8 (13.8)	25 (34.2)	0.007
Sleeping disturbances	70 (53.4)	18 (31)	52 (71.2)	<0.0001
Questionnaires				
CFQ score	45.6±20.7	27.0±10.9	60.3±13.4	<0.0001
FAS total score	34.8±8.0	30.2±7.8	38.5±6.3	<0.0001*
- FAS-score <22, n (%)	10 (7.6)	9 (15.5)	1 (1.4)	
- FAS-score 22-34, n (%)	51 (38.9)	33 (56.9)	18 (24.7)	
- FAS-score >34, n (%)	70 (53.4)	16 (27.6)	54 (74)	
FAS mental score	15.8±4.4	13.5±4.0	17.6±3.9	<0.0001
FAS physical score	19.0±4.1	16.7±4.1	20.8±2.9	<0.0001
SFNSL score	39.7±21.3	29.0±18.9	48.3±19.3	<0.0001*
- SFNSL score <11, n (%)	11 (8.4)	10 (17.2)	1 (1.4)	
- SFNSL score 11-48, n (%)	69 (52.7)	38 (65.5)	31 (42.5)	
- SFNSL score >48, n (%)	51 (38.9)	10 (17.2)	41 (56.2)	

Data are expressed as means ± SD, n=absolute number or percentages. # p-value CFQ <43 vs CFQ ≥43, *p-value for total and subscores. CFQ=Cognitive Failure Questionnaire, FAS=Fatigue Assessment Scale, SFNSL=Small Fiber Neuropathy Screening List

more prevalent in the group with a high CFQ score (see table 1).

The prevalence of a high CFQ score in the neurosarcoidosis sample (55.7%) was significantly higher than in the general sarcoidosis population studied by Elfferich (n=330, 33.9%, p<0.0001; see table 2) and comparable with the results in a subgroup of neurosarcoidosis patients (n=13) in the study by Elfferich et al. (55.7% versus 53.8%) (1).

Almost all neurosarcoidosis patients in our study reported fatigue (n=121; 92.4%), 53.4% of whom experienced extreme fatigue (see table 1). Fatigue was more prevalent in neurosarcoidosis patients with a high CFQ score (98.6% vs 84.5%, respectively; p=<0.0001). The average FAS scores were also higher in neurosarcoidosis with a high CFQ score (38.5 vs 30.2, respectively; p=<0.0001) The overall FAS scores, as well as the FAS scores in the

high CFQ score subgroup, were significantly higher in the neurosarcoidosis population compared to the general sarcoidosis population (see table 2). Symptoms suggestive of SFN (SFNSL score >11) were significantly more prevalent in the neurosarcoidosis patients with a high CFQ score (98.6% vs 82.8%, respectively; p=<0.0001). Comparison with the data of the general sarcoidosis population showed that the SFNSL scores in our study sample were comparable to those in the general sarcoidosis population and the high CFQ score subgroup (see table 2).

No statistically significant differences were found between the neurosarcoidosis sample we studied (Group I) and the subgroup of neurosarcoidosis patients included in the study by Elfferich et al. (Group III) (1) as regards overall FAS, SFNSL and CFQ scores (data not shown). The average disease duration in our sample showed no statistically significant difference compared to the population of Elfferich. Disease duration did not influence everyday cognitive failure in sarcoidosis in this latter population and the population of the present study.

Correlation of FAS, SFNSL and CFQ

In our neurosarcoidosis population, both fatigue and SFNSL scores correlated significantly with the CFQ. The FAS scores showed the strongest correlation with the CFQ (R=0.65; see table 3). Patients with extreme fatigue (>34) appeared to be more at risk of developing cognitive failure than patients with a fatigue score >22 (R=0.46 vs R=0.27 respectively; p=<0.0001). Patients suffering from SFN related symptoms reported high CFQ scores (R=0.40, p=<0.0001).

Fatigue (OR 13.2) and symptoms suggestive of SFN (OR 5.5) were the strongest predictors of a high CFQ score. The OR of the SFNSL decreased after correction for sex, age, treatment, depressive symptoms and sleeping disturbances (OR 4.3, p<0.0001,

Table 2. Scores on the Cognitive Failure Questionnaire (CFQ), Fatigue Assessment Scale (FAS), Small Fiber Neuropathy Screening List (SFNSL), gender and age of the neurosarcoidosis sample studied (Group I) and a general sarcoidosis patient population without neurosarcoidosis (Group II) (1)

	Group I	Group II	p value
Patients n	131	330	
Gender : female %	48.9	44.8	NS
Age, years (range)	52.0±10.4 (21-75)	48.6±0.9 (25-79)	NS
FAS score total group	34.8 ± 8.0	29.2 ± 8.4	0.01
FAS total score in CFQ ≥43	38.5 ± 6.3	30.4 ± 12.1	0.001
SFNSL score total group	39.7 ± 21.3	42.4 ± 16.8	NS
SFNSL score in CFQ ≥43	48.3 ± 19.3	48.2 ± 16.8	NS
CFQ score	45.6 ± 20.7	36.2 ± 15.9	<0.0001
CFQ score ≥ 43, n (%)	73 (55.7)	112 (33.9)	<0.0001

Data are expressed as means ± SD, absolute number (n) or percentages (%). NS=not significant.

Table 3. Correlation of the scores on the Fatigue Assessment Scale (FAS) and Small Fiber Neuropathy (SFN) Screening List (SFNSL) with the Cognitive Failure Questionnaire (CFQ)

CFQ scores	FAS scores: total	FAS scores: mental	FAS scores: physical	SFNSL scores
Correlation (R=)	0.65	0.60	0.64	0.53
Significance (p-value)	<0.0001	<0.0001	<0.0001	<0.0001
CFQ scores		FAS scores >22: fatigue	FAS scores >34: extreme fatigue	SFNSL scores > 48: highly likely SFN
Correlation (R=)		0.27	0.46	0.40
Significance (p-value)		0.002	<0.0001	<0.0001

Table 4 Multivariate logistic regression Fatigue Assessment Scale (FAS) and Small Fiber Neuropathy Screening List (SFNSL) scores on the Cognitive Failure Questionnaire (CFQ) scores

	OR	95% CI	p-value
SFNSL	4.3	2-11.3	<0.0001
- Sleeping disturbances	3.9	1.7-8.6	0.001
FAS	21.4	2-225.2	0.011
- Age	0.34	0.1-0.8	0.016
- Gender	0.4	0.2-1	0.048
- Sleeping disturbances	5.3	2.4-12	<0.0001

OR = odds ratio, 95% CI = 95% confidence interval

CI 2.7-11.3), while the OR of the FAS increased (OR 21.4, p=0.011, CI 2.0-225.2) (see table 4).

Discussion

To the best of our knowledge, this was the first study to examine everyday cognitive functioning in patients suffering from neurosarcoidosis and to compare this with a general sarcoidosis population using the CFQ. We found that everyday cognitive failure was a significant problem in the neurosarcoidosis sample. More than half of the patients in our sample reported cognitive deficits, compared to one-third of a general sarcoidosis population studied by Elfferich et al. (1). Fatigue and symptoms of SFN were the most important predictors of cognitive failure.

Previously, it was demonstrated by Elfferich et al. that everyday cognitive failure is a substantial problem in sarcoidosis patients (1). In this latter study, no relation was found between the CFQ scores and inflammatory parameters, lung function test results, chest X-ray stages, sleeping problems nor dyspnea. Moreover, no differences regarding these mentioned clinical data were shown between those patients with a high or normal CFQ score. In line with the latter study, the strongest predictor of cognitive failure in neurosarcoidosis was fatigue. Fatigue has been reported in 50-85% of chronic sarcoidosis patients (11, 15) and is also associated with poorer cognitive performance (1). Almost all our neurosarcoidosis patients experienced fatigue (FAS ≥22), a higher proportion than in the general sarcoidosis population (80.6%) studied by Elfferich et al. (1). Among the patients with cognitive failure, the neurosarcoidosis patients experienced more fatigue than sarcoidosis patients presenting with other manifestations. Fatigue in neurosarcoidosis patients has previously been described to affect cognitive control (26). In a study comparing non-fatigued and fatigued participants, the fatigued participants had compromised executive control (27). Studies in colorectal and breast cancer also found fatigue to be associated with perceived cognitive failure (28, 29). Moreover, fatigue negatively affects cognitive performance, in particular response inhibition. It may induce overactivation of the visual cortex, which is related to impaired cognitive performance (30). We did not find a difference between mental or physical fatigue: both were equally associated with cognitive failure in neurosarcoidosis patients.

SFN was also a predictor of cognitive failure, although to a lesser extent. The reported prevalence of SFN varies from 40 to 60% (16, 17), and has been associated with poorer cognitive performance in a general sarcoidosis population (1). SFN was even more prevalent in the neurosarcoidosis patient population we studied (91.6%). One of the main symptoms of SFN is neuropathic pain. Previous studies have reported an association between chronic pain and cognitive deficits, including attention, working memory and executive function (31, 32). A study of primary Sjögren's patients with SFN found a correlation between the intensity of pain and the performance of executive functions (6). Hendriks et al. found that everyday cognitive failure, and symptoms suggestive of SFN, appeared to be significant predictors of fatigue (33). Moreover, they also found that cognitive failure and depression are the most important predictors of high levels of fatigue (33). The study of Bosse-Henck et al. also determined depression, anxiety, muscle pain and severity of dyspnea were predictors of the development of severe fatigue (34). In line with this, we found a higher prevalence of depressive symptoms but also sleeping disturbances in neurosarcoidosis patients with cognitive failure correlating with the higher prevalence of fatigue. Moreover, sleeping disturbances are also associated with fatigue, depressive symptoms, anxiety, and dyspnea (35, 36).

Cognition seems to be - at least partly - a consequence of fatigue and SFN in (neuro)sarcoidosis or due to a common underlying mechanism explaining the strong correlation between cognition, fatigue

and SFN. In a pilot study by our group, standard neuropsychological tests were used to assess the cognitive domains of memory sensorimotor speed, information processing speed and cognitive flexibility. Only a small number of sarcoidosis patients (n=27; 63% female; age 47.2±10.8 years) were tested and compared with healthy controls. They found that cognitive failure did not imply cognitive impairment (33). Thus, subjective cognitive failure was not associated with cognitive impairment. The latter study exemplifies the difficulties of the diagnostic classification of cognitive deficits in patients suffering from sarcoidosis without major morphological lesions, and emphasizes the necessity for further research in this field. Insight into cognitive functioning is of great importance to optimise the self-management skills of patients with sarcoidosis. Indeed, cognitive deficits may lead to difficulties in managing their disease and negatively affect their treatment. Although cognitive dysfunction is a core feature of (neuro)sarcoidosis, most currently available treatments do not address cognition (1). Although treatment should first focus on treating sarcoidosis and its activity (1), alternatives could be considered if this is not effective.

The hallmark of sarcoidosis is granulomatous inflammation, which is predominantly a T-helper 1 immune response mediated by lymphocytes, macrophages and cytokines such as tumor necrosis factor alpha (TNF-alpha) and interleukins (IL) (37). It has been suggested that alterations in these immunological parameters can affect psychomotor functions. Research in mice has shown that TNF-alpha is essential for the normal functioning of memory and learning and that overexpression of TNF-alpha leads to cognitive failure, so TNF-alpha seems to have both neuroprotective and neurodegenerative effects (38, 39). Previous research has demonstrated that TNF-alpha inhibition in a sarcoidosis population was the only treatment achieving improvement of CFQ scores (1). Thus, overexpression of TNF-alpha in the pathogenesis of fatigue and cognitive failure could explain the favourable effect of anti-TNF treatment in sarcoidosis patients on cognition and fatigue (1).

The management of sarcoidosis patients with fatigue and low energy levels should focus on the increased burden of concomitant symptoms. Since fatigue usually has a multifactorial cause, risk factors should also be examined and treated in combination (14, 34). Future research involving more comprehensive neuropsychological batteries is warranted to investigate psychological functioning and fatigue in sarcoidosis. In addition, further research should give more attention to possible mediating or confounding pathways and associations between everyday cognitive functioning, fatigue and SFN-related symptoms.

Limitations of this study

Our study was a cross-sectional study, in which the neuropsychological assessment of cognitive dysfunctions was restricted to a rather general and subjective screening instrument, the CFQ. It provides an impression of the prevalence and related factors. Labelling oneself as absent-minded or forgetful depends upon the perceived discrepancy between the subject's everyday memory functioning and her or his everyday memory demands. Self-reported cognitive changes or decline do not necessarily reflect actual cognitive decline, since subjective failure was not associated with cognitive impairment (33). Beliefs about cognitive changes are strongly influenced by self-efficacy beliefs, personality, vitality, the experience of daily functioning and coping styles. Nevertheless, it seems unlikely that the favourable effect on cognitive functioning reported by patients treated with anti-TNF-α drugs is attributable to the use of a subjective screening instrument (1). Despite being subjective, therefore, this is the first sign that everyday cognitive failure is a major problem in neurosarcoidosis patients.

Response bias cannot be excluded due to the recruitment procedure, e.g. voluntary participation. Nevertheless, the response rate was high (99%). The sample we studied is approximately 25% of the estimated total neurosarcoidosis population in the Netherlands, and therefore a rather representative reflection of this population.

Since neurosarcoidosis is a rare disorder with a great diversity of manifestations (with overlapping manifestations in 45% of cases), phenotyping aiming to perform statistical analysis would not have been valid or feasible due to the rather small sample sizes for each of the manifestations, unfortunately. However, it might be interesting to consider whether central neurological manifestations for instance expose more cognitive failure than peripheral ones.

Conclusion

Sarcoidosis patients, especially neurosarcoidosis patients, are at increased risk for developing everyday cognitive failure. More than half of the patients reported cognitive deficits, compared to one-third of a general sarcoidosis population. Cognitive problems in a relatively young patient population have a great impact on daily functioning and can lead to problems at work and in social life, leading to decreased quality of life. Fatigue and symptoms suggestive of small fiber neuropathy were the most important predictors of cognitive failure. Our study points towards the necessity to integrate the growing body of knowledge about neuropsychological deficits in sarcoidosis in the management of this disease, especially for those patients suffering from neurosarcoidosis. Further studies, including imaging and biomarkers, in furthering our understanding of cognitive failure in sarcoidosis are needed to determine the relationship between cognition, fatigue, sleepiness and small fiber neuropathy in sarcoidosis, and whether they might have a common pathogenesis.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 11-17

Diagnostic approach for cardiac involvement in sarcoidosis

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Abstract. *Aims:* Cardiac sarcoidosis (CS) is a potentially life-threatening condition. Early detection of CS is therefore important. The aim of this study was to eludicate the usefulness of different investigations in a subgroup of patients with sarcoidosis regarded as having an increased risk for cardiac involvement. *Methods:* 42 sarcoidosis patients, who had an abnormal resting electrocardiogram (ECG) and/or symptoms indicating possible cardiac involvement (i.e. palpitations, pre-syncope or syncope), were included in the study. They were identified in a consecutive manner among patients followed-up at outpatient clinics for respiratory disorders. Holter monitoring, exercise test, transthoracic echocardiogram (TTE), cardiovascular magnetic resonance (CMR) and analysis of N-terminal pro B-type natriuretic peptide (NT-pro-BNP) in serum were performed. Note, that the role of FDG-PET was not investigated in this study. *Results:* In the group with a pathologic ECG 11/25 (44%) were ultimately diagnosed with CS (all with pathologic CMR). However, in the group with only symptoms but a normal ECG just 1/17 got the diagnosis CS ($p<0.05$). This patient had a pathologic Holter monitoring. The risk for CS was increased if serum NT-pro-BNP was elevated (i.e. NT-pro-BNP>125 ng/L), sensitivity 78% ($p<0.05$), specificity 67%. By adding a pathologic ECG to an elevated NT-pro-BNP increased specificity to 93% and sensitivity remained at 78%. *Conclusion:* Our findings indicate that CMR should be performed at an early stage in sarcoidosis patients with an abnormal resting ECG. Holter monitoring and elevated levels of NT-pro-BNP may enhance the diagnostic accuracy whereas exercise testing and TTE in this study had less impact on the identification of CS. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 11-17)*

Key words: sarcoidosis, extra-pulmonary involvement, cardiovascular magnetic resonance, sarcoidosis

Introduction

Sarcoidosis is an inflammatory disease with unknown origin that in at least 90% of cases affects the lungs and/or intrathoracic lymph nodes. It is characterized by the formation of non-necrotizing granulomas and almost any organ can be affected leading to a high variability in the clinical presentation (1, 2). Engagement of the heart, cardiac sarcoidosis (CS), may manifest itself as benign arrhythmias or give rise to severe conduction blocks and in worst case life threatening arrhythmias and/or heart failure secondary to infiltration of the cardiac conduction system or the myocardium (3). Early detection of cardiac involvement and evaluation of the need of glucocorticoids and/or antiarrhythmic drugs, pacemaker and/or implantable cardioverter defibrillator (ICD) is therefore of great importance

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(4). Some studies reported that approximately 5% of the patients with sarcoidosis will have symptomatic cardiac involvement and another 20-25% may have asymptomatic disease. There seems to be a variation pending on ethnic origin (5, 6) and the access to new techniques to detect cardiac disease has contributed to an enhanced detection of CS (7). There are today scarce data to compare the specificity and sensitivity of screening tests for cardiac involvement in patients with extra-cardiac sarcoidosis (6). Since there is a possibility to prevent severe events of CS, the need for good screening methods for early detection is urgent. The today commonly used methods are resting ECG, 24-hrs Holter monitoring, transthoracic echocardiogram TTE, cardiovascular magnetic resonance (CMR) and positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro- D-glucose integrated with computed tomography (FDG PET/CT) (4).

The overall objective of this study was to compare the accuracy of and usefulness of various techniques to diagnose cardiac involvement in a co-hort of well-characterized Swedish sarcoidosis patients with abnormal resting ECG pattern and/or symptoms generally regarded as compatible with CS (i.e. palpitations, pre-syncope or syncope). Note, that the role of FDG-PET was not investigated in this study. The reason was that it at the time for the study not was a routine investigation but rather used as a complement when there were contraindications to perform CMR.

Materials and Methods

Study subjects

The study included 42 sarcoidosis patients of Caucasian origin (Table 1) residing in Stockholm, Sweden and attending two different University Centers for respiratory disorders. The patients were included (from 2008 - 2014) in a consecutive order from the out-patient clinics if they had an abnormal resting ECG (n=22), were investigated because of a newly detected arrhythmia (n=3) or complained of palpitations, pre-syncope or syncope (n=17). In the majority, the investigations were conducted within a time frame of 2 months. The patients were followed until 2017 with a median time of follow-up of 6 years (min 3 years, – max 9 years). The patients were diagnosed with sarcoidosis by typical clinical and chest radiographic manifestations, findings at bronchoscopy with bronchoalveolar lavage (BAL) including an elevated CD4+/CD8+ cell ratio (>3.5), and/or granulomatous biopsies, using the criteria outlined by WASOG/ATS and ERS (8). Patients were diagnosed with CS according to HRS the diagnostic methodology established "clinical diagnosis of probable cardiac sarcoidosis" except in cases that underwent direct myocardial biopsy where a "histological diagnosis was also established", i.e. when there were no positive cardiac biopsy but CMR showed pattern compatible with sarcoidosis, the patient were judged in consensus as having CS (none of the patients had LVEF<40%, sustained ventricular tachycardia or atrioventricular block (AV-block) II, Mobitz II or AV-block III without findings on CMR compatible with CS) (4). In line with expert consensus statements from the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) all patients with CS had "probable CS" (9). Löfgren´s syndrome (LS) was found in 4/42 patients and was defined as bilateral hilar lymphadenopathy with or without parenchymal infiltration, erythema nodosum and/or ankle arthritis, and an elevated CD4+/CD8+ ratio in BAL fluid. Patients were defined as ever smokers if they had previously smoked or were current smokers. Chest radiographs were evaluated, and findings staged by one of the authors (chest radiologist K.C.) according to the following system: Stage 0 – normal; Stage I – bilateral hilar lymphad-

Table 1. Clinical characteristics of patients and medication

	All patients	Patients with CS
Subjects	42	12
Gender M/F	20/22	5/7
Age, years^	50 (28-78)	51 (42-78)
Years with sarcoidosis	7 (0-45)	1 (0-29)
Smoker (never/ever)	22/20	8/4
Radiographic stage 0/I/II/III/IV	3/10/18/2/9	2/2/5/1/2
Löfgren/non-Löfgren	4/38	0/12
Oral glucocorticoids	14	1
Cardiovasular treatment	16	7
No treatment	16	5

CS = cardiac sarcoidosis. ^Age, years at time CMR was performed: values are medians (min – max). Cardiovascular treatment, all patients: angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers [(n=9), 5 with CS], beta-blockers [(n=13), 6 with CS], diuretics [(n=6), 3 with CS], calcium channel blockers (n=1).

enopathy; Stage II – bilateral lymphadenopathy with parenchymal infiltrates; Stage III – parenchymal infiltrates alone; Stage IV – fibrotic bands and volume reduction (10). Ongoing medications at the time of inclusion are described in Table 1. An evaluation of patients was performed in December 2017. Data was missing for those who were no longer residents in Sweden (n=2). All patients with suspected CS were evaluated by two of the authors (AG and PS, both cardiologists and certified CMR specialists). Written informed consent was obtained from all subjects, and the study was approved by the Regional Ethical Review Board in the Stockholm county.

The investigation methods reflecting possible cardiac involvement and used in this study in addition to routinely performed 12-leads resting ECG were: 1 – 24-hrs Holter monitoring, 2 – exercise test, 3 – (TTE), 4 – CMR, and N-terminal pro B-type natriuretic peptide (NT-pro-BNP) in serum. Patients were only included if there were no contraindications according to current guidelines regarding investigation with CMR.

Methods used for detecting CS

Standard methods were used for evaluation with 12- leads ECG, 24-hours Holter monitoring, exercise test and TTE (11-15). For definition of pathologic findings, see Table 2. We chose VES >100/24 hour as a cut-off level, which is a widely accepted risk marker for malignant arrhythmias (16). NT-pro-BNP >125 ng/L was considered as pathologic as outlined by European Society for Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure (17). CMR was performed using a 1.5 T Philips Intera CV (Best, The Netherlands) and Siemens Aera, (Erlangen, Germany) with a phased-array five to eigtheen-channel body maitrix coil. All patients were examined in the supine position. All CMR examinations were evaluated by an experienced cardiologist after a standardized protocol which evaluates specifically right and left ventricles, edema and structural changes in the myocardium (18). Late gadolinium enhancement (LGE) images were initiated 8-12 min after the administration of 0.2 mmol/kg extracellular gadolinium-based contrast agent (gadoteric acid, Gd-DOTA; Guerbet, Gothia Medical AB, Billdal, Sweden). Patients were typically considered to have cardiac sarcoidosis if there were an increased signal intensity in water sensitive images (edema) in short- or long-axis images or a typical non-ischemic LGE pattern (infiltration with or without fibrosis) not corresponding to an ischemic lesion (an example figure is shown in online supplement) (19).

Table 2. Definitions of pathologic findings

ECG	Any degree of AV-block Bundle branch block Left axis deviation Pathologic Q waves ST-T changes Supra- and ventricular arrhythmias VES
Holter monitoring	VES >100 / 24 hour Supra- and ventricular arrhythmias
Exercise test	Supra- and ventricular arrhythmias Occurrence of VES in bigamy Development of pathologic ST-changes Poor pulse rise Pathologic blood pressure reaction
NT-pro-BNP	NT-pro-BNP>125 ng/L
TTE	Regional wall motion abnormalities Wall thickening LV systolic dysfunction (LVEF <50%)
CMR	Edema/inflammation Typical non-ischemic LGE pattern

AV-block=atrioventricular block, CMR=cardiovascular magnetic resonance, ECG=electrocardiogram, NT-pro-BNP=N-terminal pro B-type natriuretic peptide, LGE=Late gadolinium enhancement, LV=left ventricular, LVEF=left ventricular ejection fraction, VES=ventricular extrasystole and TTE=transthoracic echocardiogram

Statistical analysis

Data were analyzed by Chi-square test or in the case of small numbers by Fisher's Exact Test. Sensitivity, specificity, positive predictive value and negative predictive values were also calculated. Statistical analyses and graphs were performed with Graph Pad Prism 6 (GraphPad Software Inc., San Diego, CA, USA). P-value <0.05 was regarded as significant.

Result

All patients (n=42) in the study underwent examination with 12-leads ECG and CMR. However, not all patients were investigated with all of the other

techniques. Thus, Holter monitoring was done in 37 patients, exercise test in 29, serum analyses of NT-pro-BNP in 24 and TTE in 41 (see online supplement for detailed information). Sixteen patients out of seventeen with symptoms but a normal 12-leads ECG underwent Holter monitoring. Sensitivity, specificity, positive predictive value and negative predictive value for ECG, Holter monitoring, exercise test, TTE and NT-pro-BNP are presented in Table 3.

Among patients with a pathologic ECG (n=25), 44% were diagnosed with CS compared to one out of 17 patients with a normal ECG but with symptoms indicative of CS, p<0.05, Figure 1. The patient with a normal ECG and CS had a history of palpitations and a pathologic Holter monitoring with a high number of ventricular extra-systoles (VES). Pathologic findings on Holter monitoring were seen in 82% with CS and 50% without CS investigated with this test. Exercise test had a sensitivity of 67%, p<0.01. In common for all the patients with increase of VES from single to bigamy, was that it occurred at end of work and at rest after work. Among patients diagnosed with CS, TTE indicating cardiac involvement showed a high specificity (93%) but a low sensitivity (58%) p<0.01. Elevated NT-pro-BNP were a risk marker for cardiac involvement and was seen in 7/9 patients with CS resulting in a sensitivity of 78%, but was also seen in 5/15 without CS where NT-pro-BNP was measured so therefore the specificity was 67%. When combined with a pathologic ECG the specificity increased to 93% since only one of the patients without CS (a patient with arterial flutter) had the combination of pathologic tests (p<0.001). None of the three patients with a normal ECG, normal Holter monitoring and normal NT-pro-BNP was diagnosed as having CS.

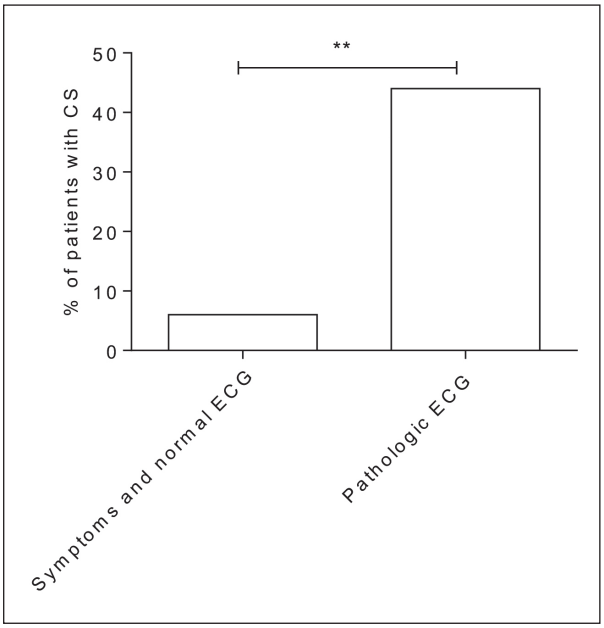

Fig. 1. Frequency of cardiac sarcoidosis (CS) in patients divided into patients with symptoms but a normal electrocardiogram (ECG) (n=one out of 17) and patients with a pathologic ECG (n=11 out of 25). Symptoms are palpitations, pre-syncope and syncope. ** <0.05

An evaluation of deceased patients was possible since patient records do simultaneously operate with the tax authority system registrating all Swedish citizens. Four patients died during the median time of follow-up of 6 years from time of inclusion in the study (min 3 years, – max 9 years). Three of the patients had advanced pulmonary fibrosis and the fourth had CS. Two patients with cardiac sarcoidosis underwent heart transplantation. Among the five patients with increased serum NT-pro-BNP levels without findings of CS, one patient had artrial flutter and pulmonary fibrosis and two presented later with artrial flutter. The two others had pulmonary fibrosis.

Table 3. Usability of diagnostic tests for cardiac sarcoidosis

	Sensitivity%	Specificity%	PPV%	NPV%	p-value
ECG	92	53	44	94	<0.05
Exercise test	67	90	75	86	<0.01
Holter monitoring	82	50	41	87	0.14
NT-pro-BNP	78	67	58	83	<0.05
TTE	58	93	78	84	<0.01
CMR	100	100	100	100	<0.0001
NT-pro-BNP and ECG (both pathologic)	78	93	87	87	<0.001

ECG=electrocardiogram, CMR=cardiovascular magnetic resonance, TTE=transthoracic echocardiogram,
NT-pro-BNP=N-terminal pro B-type natriuretic peptide, PPV=positive predictive value, NPV=negative predictive value.

Discussion

The overall objective of this study in a well-characterized co-hort of Scandinavian sarcoidosis patients was to evaluate a standardized approach of diagnostic testing for early detection of CS. We found that the risk for CS was significantly higher in sarcoidosis patients presenting with a pathologic ECG compared to patients with a normal ECG but with symptoms indicating possible cardiac involvement. This is in line what we previously have shown in a retrospective study where we found that patients who later were diagnosed with CS in most cases had an abnormal ECG at disease onset (20). In the current study, we also measured NT-pro-BNP and found that an elevated level was common in patients with CS. Measurement of NT-pro-BNP has not yet been added to diagnostic routines or guidelines for diagnosis of cardiac sarcoidosis.

The increased risk for CS in patients with a pathologic ECG, which in our study most commonly showed atrioventricular block and/or bundle branch block, matches well the findings in autopsy cases of sarcoidosis patients, where the septum most frequently was engaged thereby causing damage to the conduction system (21). In our study, CS was diagnosed in about half of the patients with a pathologic ECG. An increased incidence of CS was also seen in a study by Metha et al. where they investigated patients with symptoms indicative of CS or an abnormal ECG more carefully (22). A complement to ECG is Holter monitoring, where a high frequency of VES was reported by Suzuki et al. to be more common in patients with CS than in those without (23). We found that Holter monitoring is a good complement in symptomatic patients with a normal ECG. Further, the additive value of exercise test for the diagnosis of sarcoidosis seems less convincing. TTE is a commonly used investigation method for detection of CS. However, several of the patients in our study with findings of CS on CMR had a normal TTE. This is consistent with findings reported by Metha et al. and Kouranos et al., where TTE had low sensitivity as a single screening method for CS (22, 24). NT-pro-BNP, which is increased in patients with cardiac failure, has previously been shown by Handa et al. and Martusewicz-Boros et al. to commonly be elevated in patients with cardiac sarcoidosisis (25, 26). In our study we found that NT-pro-BNP has a higher sensitivity but lower specificity in comparison to TTE. However, if NT-pro-BNP was combined with ECG (both pathologic) the sensitivity was higher than for TTE but with the same specificity. CMR is a well-established diagnostic tool for CS and has emerged as gold standard (27). Fluorodeoxyglucose (FDG) positron emission tomographic (PET) – computed tomography (CT) is an alternative to CMR that visualizes pathologic changes due to CS. In a previous study where FDG PET-CT was compared with CMR in sarcoidosis patients, both investigation methods provided high sensitivity (28) and may complement one another (29-31). FDG PET-CT, however, uses ionizing radiation which makes it less attractive for follow-up investigations. It is also a more expensive examination method than CMR and therefore not cost-beneficial. We chose in this study not to include FDG PET-CT since we do not use it as it as the time for the study not was a routine investigation but rather used as a complement when there are were contraindications to perform CMR.

There were only a few patients with Löfgren's syndrome who met the inclusion criteria which are in line with that extra-pulmonary manifestations (erythema nodosum and ankle arthritis excluded) are rarely seen in this subgroup (32). On the other hand, three patients with more advanced disease with pulmonary fibrosis had increased NT-pro-BNP serum level without signs of CS. This may indicate that an increased NT-pro-BNP is hazardous to interpret in patients with radiologic stadium IV as it may be secondary to pulmonary hypertension.

Limitations with the study are the relatively few numbers of patients included and that not all patients had all the investigations done, e.g. NT-pro-BNP was only measured in about half of the patients. However, cardiac sarcoidosis is a relatively rare condition among Scandinavian sarcoidosis patients and during the time the patients were included NT-pro-BNP were not an established test for this patient group. Further, many of the patients were on medication, which may lead to lower levels of NT-pro-BNP and less inflammation on CMR. However, we believe that our findings clearly show the importance of following-up patients with sarcoidosis and a pathologic ECG by doing a CMR. The value of measuring NT-pro-BNP need to be investigated in larger studies, but the observation of increased values merits further investigations. Furthermore, a poten-

tial weakness is that patients were not examined with FDG PET-CT and the role of FDG PET-CT as an alternative investigation method to CMR was therefore not analyzed.

In conclusion, our results show that the risk for CS is significantly higher in sarcoidosis patients presenting with a pathologic ECG in comparison to patients with symptoms indicative of CS but with a normal ECG. The risk seems to be even higher if NT-pro-BNP in serum is elevated. In line with our findings we recommend that all sarcoidosis patients who have a pathologic ECG and/or elevated NT-pro-BNP should be further investigated with CMR. If a patient has no symptoms indicative of CS and both ECG and NT-pro-BNP are normal, the risk for clinically significant CS seems to be low.

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Authors contribution

PD designed and coordinated the study, wrote the application to the Ethics Committee, characterized patients, summarized data and drafted the manuscript. AG co-designed the study and characterized patients, evaluated CMRs, interpreted data and helped writing the manuscript. KC classified radiographs. SK and JG characterized patients, interpreted data and helped writing the manuscript. AE co-designed the study and characterized patients, interpreted data and helped writing the manuscript. PS co-designed the study and characterized patients, evaluated CMRs, interpreted data and helped writing the manuscript. All authors read and approved the final manuscript.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 18-24

Sensitivity and specificity of chest imaging for screening for sarcoidosis in patients with cardiac presentations

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Abstract. *Background:* Patients with sarcoidosis can present with cardiac symptoms as the first manifestation of disease in any organ. In these patients, the use of chest imaging modalities may serve as an initial screening tool towards the diagnosis of sarcoidosis through identification of pulmonary/mediastinal involvement; however, their use for this purpose has not been well studied. We assessed the utility of different chest imaging modalities for initial screening for cardiac sarcoidosis (CS). *Methods and Results:* All patients were investigated with chest x-ray, chest computed tomography (CT) and/or cardiac/thorax magnetic resonance imaging (MRI). We then used the final diagnosis (CS versus no CS) and adjudicated imaging reports (normal versus abnormal) to calculate the sensitivity and specificity of individual and combinations of chest imaging modalities. We identified 44 patients (mean age 54 (±8) years, 35.4% female) and a diagnosis of CS was made in 18/44 patients (41%). The sensitivity and specificity for screening for sarcoidosis were 35% and 85% for chest x-ray, respectively (AUC 0.60; 95%CI 0.42-0.78; p value=0.27); 94% and 86% for chest CT (AUC 0.90; 95%CI 0.80-1.00; p value <0.001); 100% and 50% for cardiac/thorax MRI (AUC 0.75; 95%CI 0.56-0.94; p value=0.04). *Conclusions:* During the initial diagnostic workup of patients with suspected CS, chest x-ray was suboptimal as a screening test. In contrast CT chest and cardiac/thorax MRI had excellent sensitivity. Chest CT has the highest specificity among imaging modalities. Either test could be used as an initial screening test, depending on local availability. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 18-24)*

Key words: cardiac sarcoidosis, sarcoidosis, screening, imaging, cardiomyopathy

Introduction

Sarcoidosis is a multisystem, granulomatous disease of unknown etiology. The lungs are affected in more than 90% of patients and the disease can also involve the heart, liver, spleen, skin, eyes, parotid

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gland, or other organs and tissues. Clinically manifest cardiac involvement occurs in perhaps 5% of patients with sarcoidosis (1). There is a growing realization that cardiac-related symptoms may be the first manifestation of sarcoidosis in any organ. Between 16 and 35% of patients presenting with complete atrioventricular (AV) block (aged <60) (2, 3) or ventricular tachycardia (VT) of unknown aetiology (4, 5) have previously undiagnosed cardiac sarcoidosis (CS) as the underlying etiology. Also CS as the underlying cause of heart failure is often missed (6).

The diagnosis of CS is often delayed or missed altogether as the symptoms and clinical manifestations are common to many cardiovascular diseases. Perhaps the most sensitive and specific test for active inflammation is positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG), but this technology is not readily available in many hospitals. We hypothesized that chest imaging modalities may serve as more accessible and practical screening tools to help identify patients who should undergo more comprehensive workup. In the current study, we assessed and compared the utility of different chest imaging modalities for initial screening for CS.

Methods

For the current study we included all consecutive consenting patients presenting to the University of Ottawa Heart Institute who met all of the following criteria:

1. Acute presentation with 1 or more of the following:
   (i) age < 60 years old with unexplained, new onset, significant conduction system disease
   (ii) idiopathic sustained ventricular arrhythmia (VA), defined as VA not fulfilling any of: outflow tract VA, fascicular VA or VA secondary to other structural heart disease (e.g. coronary artery disease or any cardiomyopathy other than idiopathic).
   (iii) non-ischemic cardiomyopathy
2. No previous history of sarcoidosis in any organ

All patients had a comprehensive work up including chest x-ray, FDG-PET imaging, chest CT and/or cardiac focused MRI with thoracic imaging. Patients with positive imaging suggestive of sarcoidosis underwent biopsies to confirm the diagnosis when possible. All studies were reported clinically. All readers were aware of the possibility of sarcoidosis in the differential diagnosis but were not informed of final diagnosis. The reports of all chest x-rays, chest CT and or cardiac/thorax MRI were adjudicated by 2 separate investigators (DHB and JJR). Imaging studies were defined as 'abnormal with features possibly consistent with sarcoidosis' or 'abnormal due to other findings not suggestive of sarcoidois' or 'normal'.

The protocol was approved by the local institutional ethics committees and all patients signed informed consent.

Patients were classified as having active CS (or not) based on consensus criteria (7, 8). The final patient classification and the adjudicated imaging reports (normal versus abnormal) were used to calculate the sensitivity and specificity of individual, and combinations of, imaging modalities. Categorical variables are presented using percentages or frequencies, and continuous variables using means (± standard deviation) or medians (25th, 75th percentiles), when appropriate. We compared categorical variables using the chi-square test (or Fisher's exact test when appropriate), and continuous variables using one-way analysis of variance or Kruskal-Wallis test for normally and non-normally distributed variables, respectively. Statistical analyses were conducted using SPSS, version 23 (IBM Corp, Armonk, New York). Two-sided p values <0.05 were considered statistically significant.

Results

Of 44 patients undergoing workup for suspected CS included in the current analysis, 18/44 (41%) were ultimately diagnosed with active CS. All 18 patients had abnormal FDG on cardiac PET imaging. Baseline patient and index event characteristics stratified by final diagnosis (CS versus no CS) are provided in Table 1. Table 2 summarizes the frequency of use and results of chest imaging modalities during the initial workup for CS. Chest x-ray, CT thorax, and cardiac and thorax MRI were performed in 100%, 89%, and 57% of patients, respectively.

Table 3 details the diagnsotic criteria and chest imaging findings of the 18 patients that were ulti-

Table 1. Baseline patient characteristics

Characteristic	No sarcoid (n=26)	Sarcoid (n=18)	p value
Age (years)*	54 (±9)	53 (±7)	0.63
Female– no. (%)	9 (35)	10 (56)	0.22
BMI (kg/m^2)*	28 (±5)	31 (±11)	0.15
Hypertension– no. (%)	8 (31)	5 (28)	>0.99
Diabetes– no. (%)	7 (27)	1 (5.6)	0.12
Presenting feature– no. (%)			0.16
AV block	13 (50)	10 (56)	
Ventricular arrhythmia or cardiac arrest	13 (50)	6 (33)	
Cardiomyopathy	0 (0)	2 (11)	
AV block– no. (%)			
1st degree	1 (3.8)	4 (22)	0.14
2nd degree	3 (12)	2 (11)	>0.99
3rd deagree	11 (42)	6 (33)	0.75

*mean (±standard deviation).
Abbreviations: AV, atrioventricular; BMI, body mass index; CHF, congestive heart failure; MI, myocardial infarction; TIA, transient ischemic attack.

Table 2. Summary of diagnostic imaging performed

Characteristic	No sarcoid (n=26)	Sarcoid (n=18)	p value
Chest x-ray – performed no. (%)	26/26 (100)	18/18 (100)	0.41
Abnormal	4/26 (15)	6/18 (33)	
Chest CT - performed no. (%)	22/26 (85)	17/18 (94)	0.63
Abnormal	3/26 (14)	16/18 (94)	
Cardiac/thorax MRI - performed – no. (%)	14/26 (54)	11/18 (61)	0.76
Abnormal	7/14 (50)	11/11 (100)	

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

mately diagnosed with CS. Figure 1 shows initial chest imaging in a 47 year-old male (subject 17) ultimately diagnosed with CS. During initial chest imaging, chest x-ray was normal while the CT of the chest identified mediastinal lymphadenopathy. Figure 2 shows initial chest imaging for a 45-year old patient (subject 14) who was also subsequently diagnosed with CS. For this patient, initial chest x-ray showed hilar lymphadenopathy while CT of the chest identified hilar and mediastinal lymphadenopathy.

Table 4 lists the sensitivities, specificities, and area under the curve (AUC) of individual chest imaging modalities for the screening of CS. We include information for permutations of the combination of cardiac/thorax MRI and CT chest. The p-value for the area under the curve was statistically significant for chest CT (AUC 0.90; 95% CI 0.80-1.00; p<0.001), cardiac/thorax MRI (AUC 0.75; 95% CI 0.56-0.94; p=0.04), and the combination of abnormal cardiac/thorax MRI and CT scan (AUC 0.91; 95% CI 0.76-1.00; p=0.002).

Discussion

In the current study, we assessed the utility of different chest imaging modalities for initial screening for CS in patients with clinically suspicious cardiac presentations. The key findings of this study are that chest x-ray was suboptimal as a screening test due to low sensitivity. In contrast chest CT and cardiac/thorax MRI had excellent sensitivity. Chest CT has the highest specificity among imaging modalities.

Studies suggest that CS seems to be becoming more prevalent. However, this is likely due to improvements in imaging and/or more thorough inves-

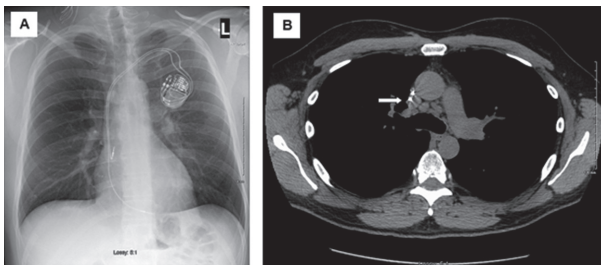

Fig. 1. Initial chest imaging in 47-year old male (subject 17) subsequently diagnosed with cardiac sarcoidosis. A. Chest x-ray showing no significant abnormalities. B. Computed tomography of the chest showing mediastinal lymphadenopathy (white arrow)

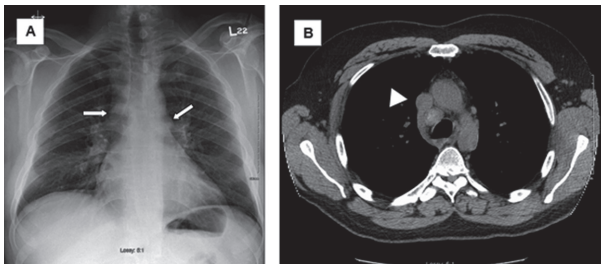

Fig. 2. Initial chest imaging in 45-year old male (subject 14) subsequently diagnosed with cardiac sarcoidosis. A. Chest x-ray showing hilar lymphadenopathy (white arrows). B. Computed tomography of the chest showing documenting hilar and mediastinal lymphadenopathy (white arrow head).

tigation rather than a true increase in prevalence. In Finland the rate of diagnosis of CS increased more than 20-fold between 1988 and 2012 (9). In the US, in patients undergoing cardiac transplantation, CS as the etiology of cardiomyopathy increased from 0.1% (1994-1997) to 0.5% (2010-2014) (10). It is still common for the diagnosis of CS to be delayed or missed altogether; for example core LV biopsies at the time of left ventricular assist device implantation found previously undiagnosed CS in 6 of 177 patients (3.4%) (6). CS can also present with features similar to arrhythmogenic right ventricular cardiomyopathy (11).

Recent data showed that cardiac presentations can be the first manifestation of sarcoidosis in any organ. In a Finnish study of 72 patients aged <55 with new onset, unexplained, significant conduction system disease, biopsy-verified CS was found in 14/72 (19%); "probable" CS was found in 4/72 (6%); and giant cell myocarditis was found in 4/72 (6%). The prognosis for CS patients was poorer versus those who had idiopathic complete AV block (2). In a similar study from a tertiary Canadian centre, CS was diagnosed in 11/32 (34%) patients aged <60 with advanced heart block (3). In a prospective study that screened consecutive patients with VT of unknown etiology for sarcoidosis, 4 of 14 patients (29%) were diagnosed with CS (4). In a study by Tung of 103 patients (85% Caucasian, 7% African American and 8% Asian) with VT and non-ischemic cardiomyopathy, 17/103 (16.5%) had undiagnosed CS (5). In these patients, the diagnosis of CS is often delayed or missed altogether because of limited pulmonary and/or other organ involvement (3, 4, 12, 13).

In this sample of patients routinely undergoing screening tests who met pre-specified criteria for suspicion of CS, we found that the initial chest x-ray had features possibly consistent with sarcoidosis in only 6/18 patients. There are likely 2 reasons for this: 1) in this group, most patients did not have pulmonary sarcoid and 2) the absence of lymph node enlargement can be explained by the pattern of lymphatic drainage from the heart. Although it is not completely understood, the principal lymphatics likely drain from the ventricular muscle to the upper mediastinum (14). The lungs primarily drain to the more central hilar lymph nodes resulting in the classic bilateral hilar lymphadenopathy of pulmonary sarcoidosis.

Our observations are consistent with a small study from Japan. Otsuka et al investigated 8 patients diagnosed with idiopathic cardiomyopathy who underwent left ventriculoplasty and were later proven to have CS by histological evaluation of the resected myocardium (15). All chest x-rays of the CS patients were normal. However, chest CT demonstrated significant mediastinal lymphadenopathy in 7 (88%) of them (15). Our findings are also similar to observations in patients presenting with possible ocular sarcoidosis. Chung et al studied 44 patients with uveitis who subsequently were diagnosed with biopsy-proven sarcoidosis (16). Chest x-ray was abnormal in 22 (50%) and chest CT in 42 (95%) (16).

Our study has some limitations; first, our population was exclusively Caucasian and it is well recognized that sarcoidosis phenotypes have important racial differences and thus our findings need to be replicated in other groups. However, our observations are similar to the small Japanese study referenced above (15).Our sample size is small and our findings should be replicated in a larger cohort. Furthermore not all patients had all scans. Also although

Table 3. Diagnostic Criteria and Findings of initial screening chest imaging modalities in patients subsequently diagnosed with cardiac sarcoidosis

Subject	HRS criteria (7)	JMHW Citieria (8)	Chest x-ray	Chest CT	Cardiac MRI	MRI Thorax
1	+	+	Normal	Axillary and mediastinal LN enlargement	Nodular mid-myocardial LV and RV LGE	Enlarged mediastinal LN
2	+	+	Increased interstitial markings*	Enlarged hilar LN; peribronchovascular nodularity	Sub- and mid-myocardial LV LGE	Enlarged mediastinal LN
3	+	+	Normal	Enlarged mediastinal and hilar LN	Not performed	Not performed
4	+	+	RUL nodule*	RUL pulmonary nodules	Not performed	Not performed
5	+	+	Normal	Enlarged hilar LN; peribronchovascular nodularity	Sub- and mid-myocardial LV LGE	Hyperintense nodular lesions in mediastinum and hilum
6	+		Bronchovascular "crowding" in hilar regions*	Enlarged hilar LN	Transmural LV LGE	Enlarged mediastinal LN
7	+	+	Pulmonary micro-nodules*	Enlarged mediastinal LN	Submyocardial and epicardial LGE	Normal
8	+	+	Normal	Left upper lobe nodule	Not performed	Not performed
9	+ except for no biopsy		Small bilateral pleural effusions	Enlarged mediastinal and hilar LN; thickened interlobular septa	Mid-myocardial LV LGE	Enlarged mediastinal LN
10	+	+	Normal	Enlarged mediastinal LN; subpleural perilymphatic nodules	Not performed	Not performed
11	+ except for no biopsy	+	Interstitial pulmonary edema	Enlarged mediastinal LN; RUL pulmonary nodules	Not performed	Not performed
12	+	+	Normal	Normal	Subepicardial LV and RV LGE	Normal
13	+ except for no biopsy	+	Diffuse interstitial changes*	Enlarged mediastinal LN; Interlobular thickening and nodularity	Not performed	Not performed
14	+ except for no biopsy	+	Enlarged hilar LN*	Enlarged mediastinal and hilar LN; perivascular pulmonary nodules	Normal	Enlarged hilar LN
15	+ except for no biopsy	+	Normal	Enlarged mediastinal and hilar LN; small bilateral pulmonary nodules	LV thinning with concomitant LGE	Enlarged mediastinal LN

(continued)

Table 3 ***(continued)*****.** Diagnostic Criteria and Findings of initial screening chest imaging modalities in patients subsequently diagnosed with cardiac sarcoidosis

Subject	HRS criteria (7)	JMHW Citieria (8)	Chest x-ray	Chest CT	Cardiac MRI	MRI Thorax
16	+ except for no biopsy	+	Normal	Enlarged mediastinal LN; peri-fissural nodules	Mid-myocardial LV and RV LGE	Normal
17	+ except for no biopsy	+	Normal	Enlarged mediastinal LN; peri-fissural nodules	Not performed	Not performed
18	+	+	Normal	Not performed	Mid-myocardial LV and RV LGE	Enlarged mediastinal and hilar LN; peribronchovascular opacities

Abbreviations: CT, computed tomography; HRS, Heart Rhythm Society; LGE, late gadolinium enhancement; LN, lymph node; LV, left ventricle; MRI, magnetic resonance imaging; JMHW, Japanese Ministry of Health and Welfare RV, right ventricle; RUL, right upper lobe.
* CXR findings were classified as 'abnormal with features possibly consistent with sarcoidosis'

we aimed to enroll patients consecutively, there is still a possibility of selection bias. Other types of bias are also possible; however our study methodology rated as low risk on all 4 domains of the quality assessment of diagnostic accuracy studies checklist (17). The cardiac MRI did not use other techniques like T2 weighted imaging which may have improved diagnostic accuracy (18). Finally it should be noted that these are 'real world data' with multiple readers of clinically performed scans. However, this study design was purposeful as we felt that over reading of all tests by physicians aware of the purpose of research may have lead to over-reporting of tests as having findings consistent with sarcoidosis.

Conclusions and clinical implications

During the initial diagnostic workup of patients with suspected CS chest x-ray was suboptimal as a screening test. In contrast chest CT and cardiac/thorax MRI had excellent sensitivity. Chest CT has the highest specificity among imaging modalities. This has important clinical implications as recent data suggests that sarcoidosis can often present with important cardiac manifestations and diagnosis can be delayed. Chest CT is widely available and could be used as initial screening test. A suggested clinical screening algorithm is shown in figure 3.

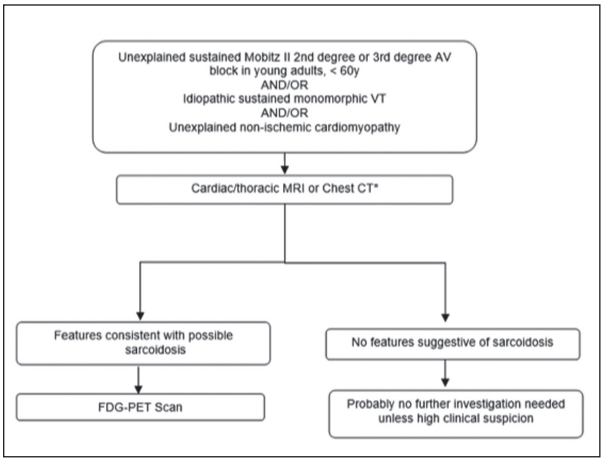

Fig. 3. Suggested algorithm for the screening of sarcoidosis in certain cardiac presentations.
*choice dependent on local availability. If both available then cardiac/thoracic MRI suggested as first.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 25-32

Neurosarcoidosis in a public safety net hospital: a study of 82 cases

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Abstract. *Objective:* To characterize clinical presentation, laboratory and imaging data, and treatment outcomes for neurosarcoidosis in an urban safety net hospital. *Methods:* The research database of Cook County Health and Hospitals system was queried for all cases of sarcoidosis from 2006 to 2013. These cases plus those identified through a survey of neurology faculty were reviewed and flagged if suspected to be neurosarcoidosis. Data were extracted in a standardized fashion, upon review by two experienced neurologists; patients were classified as definite, probable or possible neurosarcoidosis. Disagreements on classification were resolved by consensus conference. *Results:* 1706 cases of sarcoidosis were identified, with 82 (4.8%) classified as neurosarcoidosis. The cohort was predominantly African American (89%). Six were classified as definite, 34 as probable, and 42 as possible neurosarcoidosis. Neurosarcoidosis was the presenting symptom of sarcoidosis in 74% of cases. The most common presenting phenotype was myelopathy (21.7%), followed by optic nerve/chiasm involvement (16.0%) and epilepsy (11.3%). The facial nerve was involved in only 2% of cases. Chest x-ray showed abnormalities of sarcoidosis in 43.3% of cases, while chest CT did so in 78.6%. Corticosteroids were the initial treatment in 91% of cases, and outcomes were good in 53% of cases. *Conclusion:* Neurosarcoidosis remains a challenging diagnosis with the majority of patients without a previous diagnosis of systemic sarcoidosis. Chest imaging was supportive of the diagnosis in a majority of patients. Our cohort differs from others in the literature due to a low prevalence of facial nerve involvement. Prospective registry studies are needed. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 25-32)*

Key words: neurosarcoidosis, sarcoidosis, inflammatory diseases

Introduction

Sarcoidosis is an inflammatory multisystem disease of unknown etiology, histologically characterized by noncaseating granulomas. Sir Jonathan Hutchinson first described sarcoidosis in 1877, while Heerfordt's description of uveoparotid fever in 1917 is thought of as the first description of neurosarcoidosis (1). While the lungs and thorax are involved in 90% of cases of sarcoidosis, nervous system involvement in sarcoidosis is rare, occurring in 5-15% of clinical cases, and up to 25% of cases at autopsy (2-5). Despite 140 years of advances in medicine, the cause and optimal treatment of this disorder remain elusive.

The worldwide prevalence of sarcoidosis is 60 per 100,000, with age of onset typically between

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20-40 years (1). The incidence has been noted to vary among different ethnic groups, with European Americans having an incidence of 3-10 per 100,000 and an African American incidence of 35-80 per 100,000 (6). Racial and ethnic differences have been noted for age of onset of disease, clinical presentation, and putative susceptibility genes (6, 7).

Neurosarcoidosis remains a challenging diagnosis, and is another "great imitator" in modern medicine. It can involve any area of the neuraxis and can have a monophasic, relapsing, or chronic progressive course. Data on neurosarcoidosis have largely been limited to small case series, with varying frequencies of common clinical presentations having been described in various centers. African Americans have a higher incidence of sarcoidosis than other populations, and are more likely to have extrathoracic involvement (8-11). Case series of neurosarcoidosis to date have often failed to enumerate demographic data in their patients. We aimed to contribute to the existing literature by examining the clinical presentation, laboratory and imaging data, and treatment outcomes of neurosarcoidosis patients in an urban, public safety-net hospital system.

Methods

The research database of Cook County Health and Hospitals System (CCHHS) was queried for all cases of sarcoidosis from 2006 to 2013, identified by ICD 9 codes. We supplemented the potential cases with patients identified as having neurosarcoidosis through a survey of neurology faculty. Local IRB approval was obtained for this protocol, and individual patient data were de-identified after initial data extraction. Data were extracted in a standardized fashion, with initial training and audits of results during the data extraction process. Upon review by two experienced neurologists; (LW and JD) patients were classified as definite, probable or possible neurosarcoidosis according to a modified version of the criteria proposed by Zajicek, et al (4).

All diagnostic categories required a clinical syndrome compatible with neurosarcoidosis and exclusion of other potential diagnoses (Table 1). Definite neurosarcoidosis required a tissue biopsy of nervous system tissue demonstrating non-caseating granulomas. Probable neurosarcoidosis was defined as a compatible syndrome combined with a biopsy showing non-caseating granulomas in non-nervous system tissue. This category differed from the Zajicek (4) criteria in that indirect indicators such as chest imaging combined with evidence of CNS inflammation via MRI or CSF were not allowed. Possible neurosarcoidosis patients either did not have a tissue biopsy performed, or had non-diagnostic biopsies. Disagreements on classification were resolved by consensus conference (LW and JD).

Table 1. Diagnostic criteria for neurosarcoidosis

Definite	Compatible clinical syndrome, exclusion of other etiologies, nervous system tissue biopsy showing non-caseating granulomas
Probable	Compatible clinical syndrome, exclusion of other etiologies, non-nervous system tissue biopsy showing non-caseating granulomas
Possible	Compatible clinical syndrome, exclusion of other etiologies, no tissue biopsy or non-diagnostic biopsy

Statistical comparisons were made for gender, and in the comparison of neurosarcoidosis and non-neurosarcoidosis patients. Chi squared and Fisher's exact tests were used for categorical variables, while the t-test was used for continuous variables.

Results

The initial search yielded 1706 cases of sarcoidosis, of which 82 were classified as definite, probable or possible neurosarcoidosis. There were 6 definite cases (7.3% of the cohort), 34 probable cases (41.5%) and 42 possible cases (51.2%) of neurosarcoidosis identified.

Demographic data (Table 2) were available in 1702 of the sarcoidosis cases and all of the neuro-

Table 2. Demographics

	All Sarcoidosis (N=1702)	Neurosarcoidosis (N=82)
Gender	59.4% Female	47.6% Female
Race	N (%)	N (%)
Black	1467 (86.2)	73 (89.0)
Hispanic	89 (5.2)	4 (4.9)
White	65 (3.8)	3 (3.7)
Other	81 (4.8)	2 (2.4)

sarcoidosis cases. The sarcoidosis patient population was 60% female, while that of the neurosarcoidosis cohort was 48% female (p=.03). Both groups showed an African American predominance. During the time of the study, CCHHS overall patient population was 53% African American. Neurosarcoidosis was the presenting symptom of sarcoidosis in 74% of cases. The median age at time of first diagnosis was 45±11.4 years (range 21-76 years) in the neurosarcoidosis group, and 49±10.8 years (range 16-82 years) in the sarcoidosis group. For neurosarcoidosis patients, men tended to be diagnosed at a younger mean age than women, 40 vs. 52 years (P<0.0001).

Neurosarcoidosis was the presenting phenotype in 74% of cases. The most common clinical syndrome encountered was myelopathy (22%), followed by optic nerve/chiasm involvement (16%), epilepsy(12%) and both meningeal (11%) and parenchymal brain lesion (11%) (Table 3). Multiple different clinical syndromes would often affect an individual patient. Peripheral nervous system manifestations of sarcoidosis were rare, occurring in 4.8% of patients. Hypothalamic and/or pituitary lesions were counted in a category distinct from parenchymal brain lesions due to the unique implications of neuroendocrine dysfunction.

Chest X-ray data was available in 82% of the neurosarcoidosis cohort, of which 43% had abnormalities consistent with a diagnosis of sarcoidosis. Chest CT data was available in 69% of the patients, of which 79% had abnormalities consistent with sarcoidosis. Gallium scan was abnormal in 6 of 9 cases. No patients underwent whole body FDG-PET, as this imaging modality was not routinely available in our health system during the time of the study. Systemic imaging results are summarized in Table 4.

Table 3. Clinical syndromes

Syndrome (N=106)	n (%)
Myelopathy	23 (21.7)
Optic Nerve/Chiasm	17 (16.0)
Parenchymal brain lesion	11 (10.4)
Epilepsy	12 (11.3)
Meninges	11 (10.4)
Pituitary/Hypothalamic	9 (8.5)
CN lesion other than 2 or 7	7 (6.6)
Hydrocephalus	6 (5.7)
Brainstem/Cerebellar	2 (1.9)
CN 7 lesion	2 (1.9)
Headache	2 (1.9)
Peripheral Neuropathy	2 (1.9)
Myopathy	1 (0.9)
Radiculopathy	1 (0.9)

Table 4. Systemic imaging

	N (%)
CXR (N=63)	
Normal	34 (54)
Abnormal - hilar LAD	20 (32)
Abnormal - other sarcoidosis	7 (11)
Abnormal - non-sarcoidosis	2 (3)
Chest CT (N=56)	
Normal	12 (21)
Abnormal - hilar LAD	38 (68)
Abnormal - other sarcoidosis	6 (11)
Gallium scan (N=9)	
Abnormal	6 (67)
Normal	3 (33)

Brain MRI was performed in 52 patients. The most common areas of abnormality were optic nerve/chiasm (23%), followed by meninges (21%), and combined involvement of both parenchyma and meninges (17%). Spine MRI was performed in 19 patients, with abnormalities most often found involving both spinal cord parenchyma and meninges (68%) followed by isolated meningeal involvement (21%). The region of spinal cord involvement was cervical in 8 cases (42%), thoracic in 6 cases (32%) and both cervical and thoracic in 5 cases (26%). Neuroimaging is summarized in Table 5. Representative examples of MRI findings are in Figure 1.

Laboratory data are shown in Table 6. Serum ACE level was abnormal in 30% of cases. CSF leukocytosis was noted in 51% of cases, while CSF protein was elevated in 64% of cases. CSF glucose was abnormal in 2.6% of cases. Oligoclonal bands were noted 2 of 13 (15%) of tested samples. CSF ACE level was not tested. CSF was normal in 23% of patients.

Biopsies were performed 56 times in 54 patients. Results are shown in Table 7. Lung was the most common organ biopsied (most often via transbronchial lung biopsy), comprising 50% of the biopsies performed. Non-caseating granulomas were found in 79% of lung biopsies, while the remainder were non-diagnostic. Brain biopsy was performed in 6 patients, 11% of the biopsy cohort, and had abnormalities consistent with sarcoidosis in 5 patients, while

Table 5. Neuroimaging

	N (%)
CT Head (N=52)	
Normal	16 (31)
Atrophy	8 (15)
Hydrocephalus	7 (13)
Parenchymal lesion	5 (10)
Ischemic white matter	3 (6)
Meninges	3 (6)
Cavernous Sinus	2 (4)
Infarct	2 (4)
Parenchyma and Meninges	2 (4)
Pituitary lesion	2 (4)
Encephalomalacia	1 (2)
Meningioma mimic	1 (2)
MRI Brain (N=52)	
Optic Nerve/Chiasm	12 (23)
Meninges	11 (21)
Parenchyma and Meninges	9 (17)
Hydrocephalus	5 (10)
High T2 signal	4 (8)
Cavernous Sinus	3 (6)
Pituitary	3 (6)
Meningioma mimic	3 (6)
Encephalomalacia	1 (2)
Normal	1 (2)
Parenchyma only	2 (4)
Spine MRI Regions (N=19)	
Cervical	8 (42)
Thoracic	6 (32)
Cervical and Thoracic	5 (26)
Spine MRI abnormalities (N=19)	
Cord parenchyma and meninges	13 (68)
Cord parenchyma only	4 (21)
Cord atrophy	1 (5)
Meninges only	1 (5)

* Two patients had Brain MRI abnormalities fitting in more than one of the chosen categories

one brain biopsy was nondiagnostic. Skin and lymph node were the next most common biopsy sites (9% and 7% of the cases, respectively), and were abnormal in all cases. Two spinal cord biopsies were performed, both of which yielded a tissue diagnosis of neurosarcoidosis. Isolated dural biopsies were performed in 3 cases, 1 of which showed noncaseating granulomas, while the other two were nondiagnostic. Other biopsy sites included nose, parotid gland, kidney, liver, conjunctiva, and testicle.

Corticosteroids were used as initial treatment in 91% of cases. Long-term steroid use was observed in 51% of all patients, and in 83% of patients in which any chronic immunotherapy was used. Some form of chronic immunosuppression, including corticosteroids and other immunosuppressants, was used in 59% of the cases.

Steroid sparing agents consisted of methotrexate, azathioprine, infliximab, hydroxychloroquine and mycophenolate mofetil. Methotrexate was the most commonly used steroid sparing agent, but no single agent was predominant.

Data on outcomes were available in 59 patients, 72% of the cohort. Patient functional status was assessed via chart review on the last available visit. The classification was as follows:

Good: Asymptomatic, minor complaints, minor functional disability but still able to do ADLs (activities of daily living)

Fair: Moderate functional disability, unable to work, still able to do ADLs

Poor: Severe functional disability, impaired ambulation, unable to do ADLs, or dead

Based on this schema, 53% of patients had a good outcome, 20% had a fair outcome, and 27% had poor outcomes. There were two deaths in the cohort, one from gastric cancer and one due to neurosarcoidosis. The neurosarcoidosis death was in a patient who had acute decompensation of a chronic hydrocephalus, and who had refused ventriculoperitoneal shunting on multiple occasions.

Discussion

This case series of neurosarcoidosis patients is one of the largest case series published to date. Many of our findings approximate those of previously reported case series. For example, neurosarcoidosis affected 5% of the sarcoidosis cohort., and was the presenting symptom in 74% of the cases. Both of these observations fall within the range of previously reported data (3, 4, 12). The demographics of this cohort are predominantly African-American. Prior studies often omit demographics, or have lower percentages of African-American patients. African-Americans with sarcoidosis have been noted to have a higher incidence of systemic involvement, and a more aggressive course (8, 9). The age range of patients in this study was slightly higher than previously reported peak incidence of 20-40 years, but largely overlapped with prior published data. This may relate to our patient population who are largely uninsured or underinsured, presenting later in the course of disease.

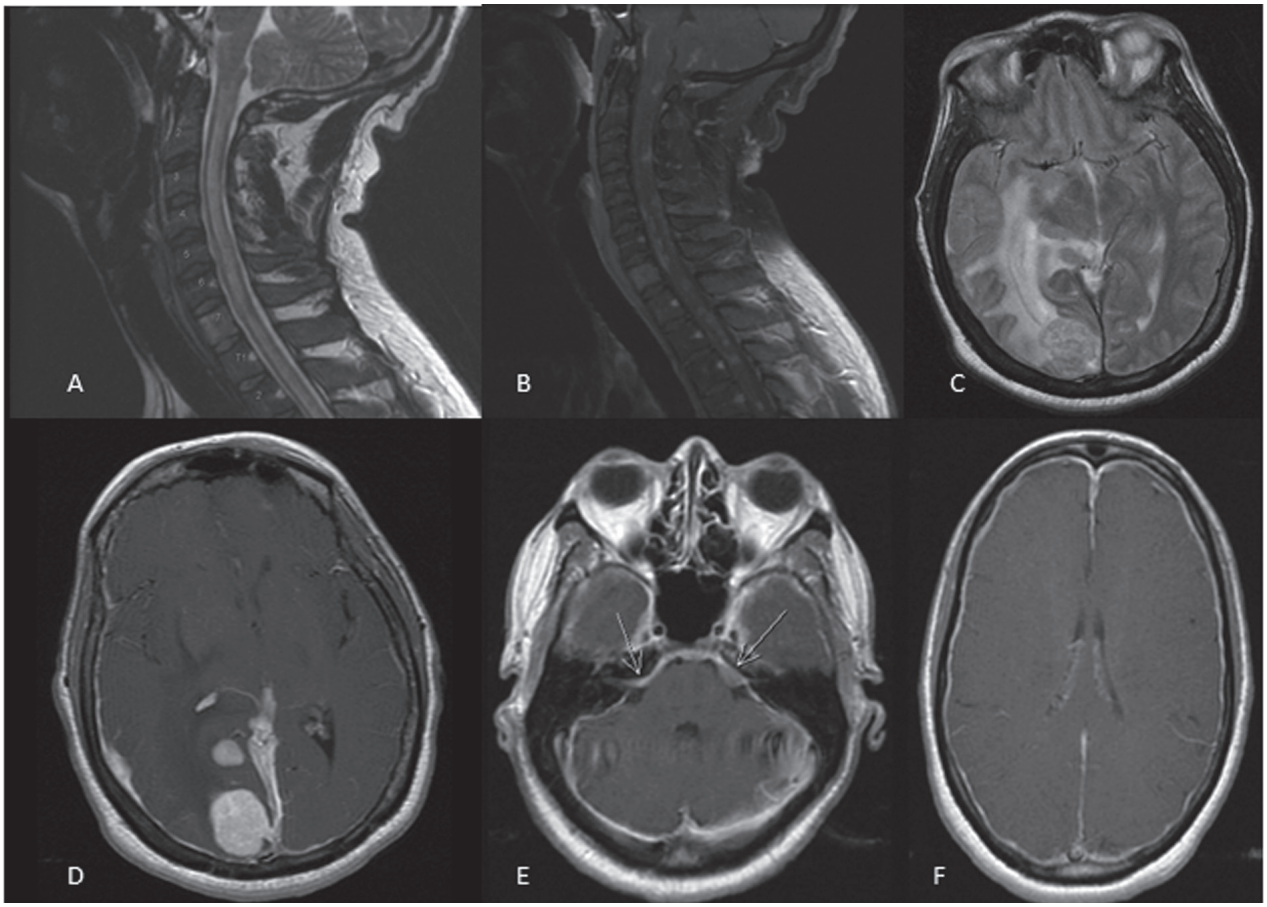

Fig. 1. MRI Images from 3 patients with neurosarcoidosis. Patient 1 had a spinal cord MRI showing T2 parenchymal hyperintensity (A) and post contrast T1 images (B) showing nodular contrast enhancement. Patient 2 had images initially concerning for a neoplastic mass lesion in (C), showing a T2 lesion with surrounding edema and (D) avid T1 homogenous enhancement of the lesion and nearby meninges. Patient 3 (E,F) had T1 enhancement of cranial nerve structures and smooth enhancement of the pachymeninges. All images are from patients with either definite or probable neurosarcoidosis

Table 6. CSF data and Serum ACE levels

	Mean	Median	St. Dev	Range	%abnormal
Serum ACE (u/L) (N=58)	45.4	33	36.7	2-193	30.1
CSF WBC (cells/uL) (N=39)	21	6	26	0-80	51.3
CSF protein (mg/dL) (N=39)	193	92	424	11-2659	64.1
CSF glucose (mg/dL) (N=39)	64.7	60	29.3	16-121	2.6

The clinical presentation of neurosarcoidosis most commonly involves the facial nerve in most case series, followed by optic neuropathy and other cranial neuropathies. Our series differed from the literature due to a low prevalence of facial nerve involvement (13, 14). This may be due to under-reporting of mild cases, but screening of all sarcoidosis cases was meant to avoid this problem. In addition, aseptic meningitis was rare in this cohort, with only 4 patients (5%) of the cohort, and typically did not occur in isolation. Peripheral nervous system sarcoidosis was also rare in this cohort, occurring in 4.8% of patients. Case series with a Caucasian predominance have reported peripheral neuropathy in 2-40% of cases, with

Table 7. Biopsy results

Total biopsies (N=56)	n (%)
Lung - abnormal	22 (39.3)
Lung - nondiagnostic	6 (10.7)
Brain - abnormal	5 (8.9)
Lymph node - abnormal	5 (8.9)
Skin - abnormal	4 (7.1)
Dura - nondiagnostic	2 (3.6)
Lung - normal	2 (3.6)
Spinal cord - abnormal	2 (3.6)
Brain - nondiagnostic	1 (1.8)
Conjuctiva - normal	1 (1.8)
Dura - abnormal	1 (1.8)
Kidney - abnormal	1 (1.8)
Liver - abnormal	1 (1.8)
Nose - abnormal	1 (1.8)
Parotid - normal	1 (1.8)
Testicle - abnormal	1 (1.8)

*56 biopsies performed in 54 patients

some authors reporting a lower frequency in African Americans (15), which may explain this finding. In addition, patients with confounding factors and peripheral neuropathy, such as diabetes mellitus, were excluded from the cohort, which could have resulted in false negative exclusions. Myelopathy was a frequent phenotype, in similar frequency to other cohorts.

Some of these findings may be due to the aforementioned tendency towards more aggressive disease in the African American population. In addition, case series differ in classification schema and reporting. For example, in this series we elected to separate out pituitary/hypothalamic lesions from parenchymal lesions due to the unique manifestations and management implications of endocrine dysfunction. As an additional example, several patients with communicating hydrocephalus in this series certainly must have had meningeal disease at some point, but could not be classified as such based on available data.

The diagnosis of neurosarcoidosis remains challenging. Neurosarcoidosis can affect both central and peripheral nervous system structures and thus present in myriad different phenotypes. Often there is a wide differential diagnosis including demyelinating diseases, infectious granulomatous diseases, neoplasms, fungal infections, vasculitis or neurosyphilis. However, there is no universally agreed upon diagnostic protocol for patients with neurosarcoidosis. A general diagnostic approach is to perform a serologic and microbiologic evaluation to exclude infectious and vasculitic processes. This is followed by imaging of the chest via CT or x-ray and imaging affected nervous system structures with MRI in order to delineate a biopsy site as well as to rule out other diseases. In lieu of a superficial biopsy site such as skin or lymph node, biopsy of a non-CNS organ such as lung or mediastinal lymph nodes may be performed to avoid the potential morbidity of biopsy of brain or spinal cord. If standard imaging techniques fail to find such a site, Gallium scintigraphy or PET-CT may be useful adjuncts.

This case series confirms that imaging studies remain an essential part of the diagnostic evaluation of neurosarcoidosis. Chest X-ray was a useful but insensitive diagnostic tool, as abnormalities in our cohort were slightly lower than other reported studies. Chest CT remained as the non-CNS imaging modality of choice, with diagnostic yield similar to other reported series (3, 4, 12, 13). Gallium scintigraphy was an infrequently used modality in our cohort. FDG-PET CT has shown promise as a diagnostic modality in the evaluation of suspected neurosarcoidosis patients for whom an amenable biopsy site is not readily apparent. This imaging modality, however, was not readily available at our institution during the time of the study and no patients in the cohort had FDG-PET CT performed.

Brain imaging included a high incidence of normal brain CT (31%), with a low incidence of normal brain MRI (2%). A reasonable approach in diagnosis would be the preferred use of MRI in non-emergent settings, with continued use of brain CT as the initial imaging modality in urgent or emergent settings, where stroke, hydrocephalus or mass lesions leading to increased intracranial pressure are suspected. Our series is notably different than others in that the percent of white matter lesions is much lower; ours was 7.7%, while other case series have reported 43% (4) and 30% (3). This may be due to referral bias, as several such studies have originated from multiple sclerosis centers. In addition, this series captures the frequent occurrence of concomitant parenchymal and meningeal disease on MRI (17%), a finding that is well known but often not captured in studies. Isolated brain parenchymal lesions lacking concomitant meningeal involvement were relatively rare in this series. Another radiologic finding of interest were 3 patients (6% of the cohort), in whom the initial radiologic impression was that of meningioma, demon-

strating yet another disorder which can be mimicked by neurosarcoidosis.

Spinal MRI was abnormal in all patients in whom it was performed. No particular predilection was noted for cervical or thoracic regions for myelopathic patients. As in the brain studies, concomitant parenchymal and meningeal disease was a common finding.

No lumbar spine MRI scans were obtained, likely due to the low incidence of radiculopathy in this case series. This differs from the case series of Sohn et al (14), wherein the lumbosacral level was involved in 37% of the patients.

Laboratory parameters in our cohort were similar to those reported in the literature. Serum ACE level was unhelpful in diagnosing sarcoidosis. CSF findings are nonspecific, but helpful in confirming CNS inflammation. CSF oligoclonal bands are helpful when present, but were noted in a minority of patients. Normal CSF was encountered in a significant (23%) proportion of cases, and thus should not be used to rule out neurosarcoidosis. CSF hypoglycorachia was rare in our study. However, this finding is at odds with other series (12, 16) and thus is not a reliable exclusionary tool. The most common phenotypes with abnormal CSF were meningitic syndromes, with or without hydrocephalus, and myelopathy. However, no clear relationship was noted between clinical syndrome and abnormal CSF. Interestingly, several cases of pachymeningitis were noted to have normal spinal fluid findings. These observations may reflect the lack of a standardized diagnostic workup in this retrospective study.

Tissue biopsy is essential for a diagnosis of sarcoidosis, with lung being the most common site as expected. The high rate of positive brain biopsy in our series likely speaks to the procedure being reserved for those patients with a high pre-test probability. Conjuctival biopsy, which has had conflicting data on utility in the literature, was only performed once in our cohort, and was normal. Some of the variance in our biopsy data compared to other series likely results from differing local practice patterns and areas of surgical expertise.

Inferring the optimal treatment course remains difficult. Two-thirds of neurosarcoidosis cases are monophasic, typically those with facial palsy or aseptic meningitis. Corticosteroids are the mainstay of treatment, but choice of second line treatment for refractory, steroid unresponsive or steroid intolerant cases remains unclear. Recent literature has generated enthusiasm for TNF alpha-blockers such as infliximab (12, 19) or adalimumab (12, 17, 18) for refractory disease, but the rarity of the disease has made study of efficacy challenging. Sarcoidosis has an inflammatory/granulomatous aspect to its pathophysiology that could reasonably be expected to respond to anti-inflammatory or immunomodulatory treatments. However, a subset of neurosarcoidosis patients remain medically refractory despite treatment with multiple immunomodulatory agents. Future research into medication efficacy will require careful patient selection and novel clinical trial designs.

Symptomatic treatment is of paramount importance to patients and their families, but receives little attention in the neurosarcoidosis literature. As in other neurologic illness, treatment of spasticity, mood disorder, epilepsy, cognitive deficits, fatigue and pain must not be neglected. The importance of a caring, knowledgeable physician maintaining a compassionate, therapeutic physician patient relationship cannot be overstated.

Our patient population was homogenous, with a predominant African American race, and tended to be patients of low socioeconomic status; two categories which tend to be underrepresented in the medical literature (20). Thus the information presented in this series represents a valuable addition to the limited available literature about neurosarcoidosis, as many published case series have failed to specify demographic information, or have a documented Caucasian predominance (3,4,21).

We acknowledge the methodological limitations of case series. The retrospective nature of our case series places limits on case ascertainment, particularly in the possible neurosarcoidosis category. Diagnostic evaluations were variable, and at the discretion of the treating physician. Similarly, treatment was also not per any prespecified protocol, thus introducing confounding factors and bias into treatment choices. Outcome assessment similarly was approximate and one must factor this in to any conclusions on prognosis.

Given the rarity of neurosarcoidosis, prospective controlled trials remain unlikely. Prospectively collected registry data is a promising next step. Examples of current registries include a sarcoidosis registry

at www.stopsarcoidosis.org. and a different registry specific to neurosarcoidosis at www.neurosarcoidosis.org . Such data should include detailed collection of demographic data, well-defined consensus phenotype classification, and a standardized minimum diagnostic evaluation, including serology, spinal fluid analysis, systemic imaging, and neuroimaging. Analysis of treatment and outcomes would need outcome assessment appropriate to phenotype (e.g. visual acuity for optic neuropathy, or functional outcome assessment for those with weakness). Treatment assessment will need to focus on steroid unresponsive patients, and stratification of patients according to phenotype, race, ethnicity or other factors may reveal the next best path forward. Neurosarcoidosis remains a challenging entity which demands further attention, particularly in defining optimal evaluation and treatment.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 33-38

Diagnostic management of occult nodal lymphangioleiomyomatosis detected during pelvic cancer staging. Localized finding or systemic disease?

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Abstract. *Background:* Lymphangioleiomyomatosis (LAM) is a neoplastic disease that generally arises in the lung (pLAM) and may be associated with "Tuberous sclerosis complex" (TSC). Occasionally, LAM can arise at the extrapulmonary sites (eLAM), such as the mediastinum, the retroperitoneum or the lymph nodes. 25-30% of the patients affected by pLAM develop eLAM. In asymptomatic patients, the presence of mediastinal and retroperitoneal eLAM preceded that of pLAM by usually 1-2 years. Nevertheless, some authors reported that the nodal eLAM, detected during pelvic cancer staging, arise in patents without pLAM and/or TSC. In this paper we review the Literature of this rare condition suggesting its diagnostic management. *Results:* To date, it has been reported 30 cases. The mean age at diagnosis is 55 years and around 30% of patients are postmenopausal. In only 2 cases was diagnosed a following p-LAM. One patient with endometrioid carcinoma and pelvic nodal eLAM reported *TSC2* germiline mutation. None case was associated with both p-LAM and TSC. *Conclusions:* The retrospective probability to have p-LAM in patients with staging pelvic nodal e-LAM is 6,6% (4/30) lower than the probability to have e-LAM in patients affected by p-LAM (25-30%). In both this association is more probable sporadically than associated with TSC. The association between cancer staging pelvic nodal e-LAM and TSC is low (3%; 1/30). The p-LAM developed are asymptomatic with a behavior, regardless of hormonal status, similar to lesions diagnosed in postmenopausal although further studies are mandatory to confirm it. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 33-38)*

Key words: pulmonary lymphangioleiomyomatosis, extrapulmonary lymphangioleiomyomatosis, tuberous sclerosis complex, pelvic cancer

Introduction

Lymphangioleiomyomatosis (LAM) is considered by WHO a low-grade destructive metastasizing neoplastic disease that generally arises in the lung (pLAM) and predominantly affect females (1). pLAM may be accompanied by symptoms such as a persistent cough, hemoptysis and chyloptysis and can be associated with the inherited syndrome "Tuberous sclerosis complex" (TSC) (2). Pulmonary lesional cells are characterized by biallelic mutations in the same gene of TSC called *TSC2* (1). Occasionally, LAM can arise at the extrapulmonary sites (eLAM), such as the mediastinum, the retroperitoneum or the lymph nodes (3). Controversy exists in the literature regarding the relationship between eLAM, pLAM

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and TSC (4). Several studies have reported eLAM in patients affected by pLAM, some of whom also had TSC. On the other hand, primary mediastinal or retroperitoneal eLAM have been identified as indicator for following pLAM (5). In this background some Authors (6) supposed that a specific eLAM consisting of occult lymph node LAM detected during surgical staging of pelvic cancer is not commonly associated with pLAM or TSC even if these patients should still be formally evaluated for both diseases (6). In this paper we review the Literature (with an additional case) about this rare condition suggesting its potential diagnostic management.

Additional case

A 44-years old Caucasian premenopausal woman diagnosed with cervical mucinous adenocarcinoma underwent surgery for radical hysterectomy PIVER3 with bilateral oophorectomy and pelvic lymphadenectomy (23 nodes isolated). The carcinoma was poorly differentiated (G3) with a maximum diameter of 3,7 cm and deepest stromal infiltration of 1,3 cm, nodal metastasis were not observed; stage IB1 according to FIGO. Histological examination revealed that four lymph node showed a neoplastic proliferation of spindle cells arranged in short fascicles "leiomyoma-like" occasionally swirling. Nuclear atypia, necrosis or mitotic activity were absent. Immunoistochemical revealed that spindle proliferating cells showed intense expression for smooth muscle actin (AML), focally for HMB45 and absent for MelanA. These characteristics were diagnostic for an incidental nodal eLAM (Fig. 1) (7,8). In adjuvant setting was performed external fields radiotherapy with VMAT technique, total 45 Gy in 25 fractions. After ten months follow-up, CT scan showed radiological features of well-defined, uniformly thin-walled cyst (maximum diameter 15 mm) that were diffusely distributed throughout both lungs (Fig. 2). According the European Respiratory Society guidelines (9) a lung biopsy was not necessary and pulmonary "definite LAM" diagnosis was produced. Lung functional tests were within the normal range and the patient was asymptomatic (Fig. 2). A TSC based on clinical criteria was excluded according the international TSC consensus group (10). A surveillance program "wait and see" was proposed and the follow up available consists of 21 months comprehensive of oncological and gynecological follow up.

Literature review

Medical Literature databases (Pubmed and Google Scholar) were searched. Inclusion criteria were: case reports and case series published before july 1st, 2017, concerning patients with "pelvic carcinoma" and/or "extrapulmonary lymphangioleyomyomatosis and/or tuberous sclerosis". Moreover, reference lists of all articles were also searched to identify additional studies.

Discussion

Pulmonary lymphangioleiomyomatosis (pLAM) is a disorder occurring almost exclusively in women, although rare cases have been reported in men with TSC. It was originally believed that lymphangioleiomyomatosis occurred primarily in women of reproductive age, but lymphangioleiomyomatosis is now increasingly recognized in postmenopausal women in whom there appear to be slower rate of disease progression. pLAM can occur sporadically or in women with TSC. Most women with sporadic LAM have renal angiomyolipoma, many have retroperitoneal and abdominal lymphadenopathy, and some have chylous pleural effusion (1). Most of extrapulmonary LAM (eLAM) occurred in lymph nodes along the lymphatic vessels of the mediastinum and the retroperitoneum with 3 major locations (decreasing frequency order): i) the posterior mediastinum, ii) the upper retroperitoneal areas close to the abdominal aorta and iii) the pelvic cavity (3).

It is thought that 25% to 30% of patients with pLAM will develop lymphatic abnormalities (lymphadenopathy or chilus ascites) visible on the abdominal CT (4). The incidence may be even higher if we consider asymptomatic clinically occult eLAM as suggested by a study performing exhaustive histopathologic examination (including autopsy) of gynecologic organs (11). So far, Chu et al. (12) reported a cohort of 35 pLAM with retroperitoneal (77%) and pelvic lymphoadenopathy (11%) whereas Urban et al. (13) found a lower incidence (24%) of abdominal lymphadenopathy in their patients. In a serie of 554

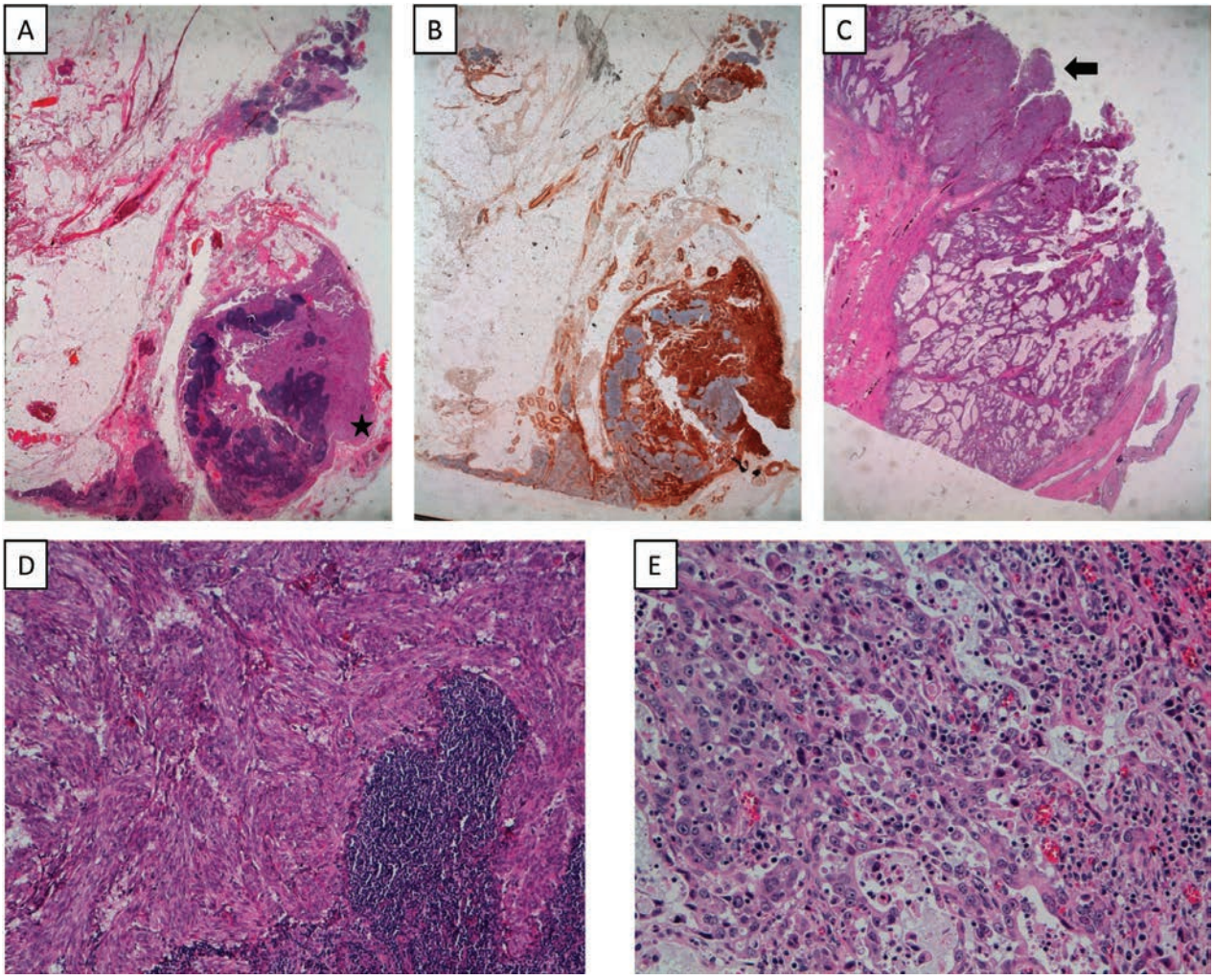

Fig. 1. Nodal and extranodal *(star)* incidental lymphangioleiomyomatosis detected during pelvic cancer staging **(A)** (10X; H&E). The lesional cells showed intense expression for smooth muscle actin **(B)** (10X; AML). Histological examination revelead spindle cells arranged in short fascicles lacking of atypia, mitosis or necrosis **(D)** (100X, H&E). Endocervical adenocarcinoma well differentiated showing a solid poorly differentiated *(arrow)* area **(C)** (10X, H&E). The carcinoma consisted of neoplastic cells whith evident atypia and mitotic activity (E) (200X; H&E).

pLAM, 189 (34%) patients were affected by eLAM stratified in 177 out of 460 (38%) sporadically and only 12 out 94 (12,8%) associated with TSC (4). This difference was statistical significant (p<0,01) and showed as the eLAM is more probable in patients without TSC (94% of all cases; 177/189) (4).

On the other hand, it's unclear whether all patients affected by primary eLAM have undiagnosed pLAM or are at risk for developing it (6). In patients entirely without signs or symptoms of pLAM, some investigators have proposed that the presence of mediastinal and retroperitoneal nodal LAM may be a high risk indicator for the development of pLAM (3). In 11 out of 16 (69%) patients reported the diagnosis of clinically significant eLAM preceded that of pLAM, established usually within 2 years (5). This was attributable to the fact that the clinical manifestations of pLAM were absent or minimal in their patients and that the corresponding radiographic changes (early cystic lesions) are evident on high-resolution CT but not on routine roentgenograms of the chest (3). Only three cases were associated with TS (19%) (5).

Recently, Rabban et al. (6) reported a specific serie of pelvic lymph node eLAM, detected incidentally during cancer staging, in which the patients

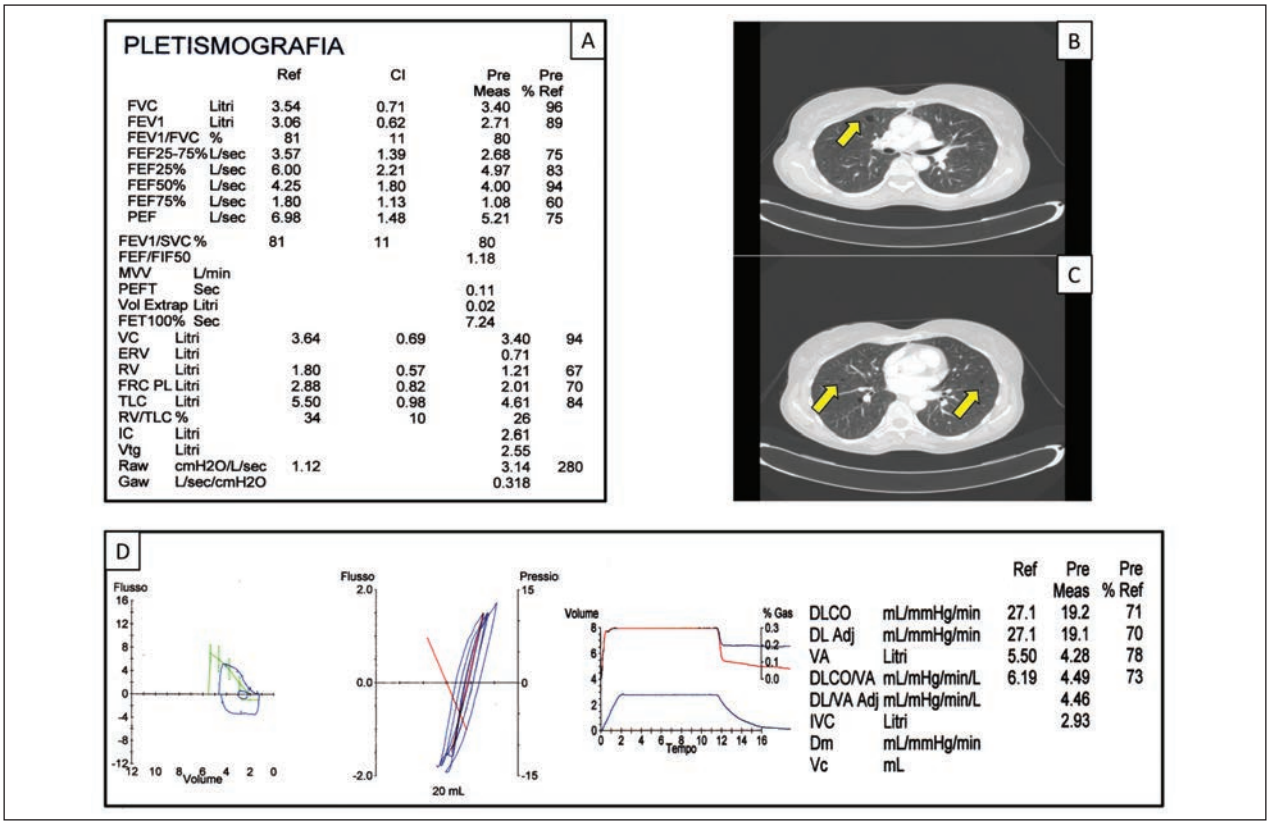

Fig. 2. Lung functional tests, within the normal range, reflect the absence of clinical syntoms **(A,D).** CT scan showed well defined, thin walled cyst *(arrow)* diffusely distribuited throughout both lungs. A lung biopsy was not necessary and pulmonary "definite LAM" was diagnosed **(B,C)**.

don't have or develop pLAM. In this scenario, the patient age can be used as a surrogate to predict the likelihood of pLAM. Because the natural history of pLAM is to progress to respiratory failure within 10 years of diagnosis, and because the most of pLAM are diagnosed around the age of 35 years, it is unlikely that neoplastic patients in their fifth decade or older without respiratory failure have pLAM or will develop it (6). To date, in Literature it has been reported (with current case) 30 pelvic nodal eLAM detected incidentally during cancer staging (Tab. 1) (2,6,14-16). The specific-organ cancer were uterine (19), ovarian (4) and bladder carcinoma (1). Six cases were squamous cervical cancer and only the current case an adenocarcinoma. (Fig. 1). The mean age at diagnosis was 55 years and around 30% of patients were postmenopausal. The probability to have or develop pLAM is 6,6% with only 2 cases diagnosed after e-LAM. These patients were asymptomatic and the presence of pLAM was not correlated with a specific hormonal status. In all cases a thoracic TC was performed within the first year after the diagnosis of nodal e-LAM and in the positive cases a lung biopsy was not necessary to diagnose the "definite LAM" (14). None case was associated with both pLAM and TSC. The report of a patient died for respiratory failure caused by late-onset symptomatic pLAM (83y) in which was diagnosed autoptically concomitant cervical carcinoma and nodal eLAM (11), suggests the necessity of a long surveillance.

About the question whether TSC patients have an increased risk of developing malignant tumors, a systematic analysis of malignancies in TSC patients is still lacking. Between the TSC, the rate of patients that have developed cancer in their lives is 6,25% against the prevalence percent of cancer in italian population of 4,4% (17). TSC patients do not seem to have an increased risk of developing malignant tumors besides renal cancer but when malignancies develop, age at cancer is younger than in the

Table 1. Cases of pelvic carcinoma associated with eLAM and/or TSC reported in Literature.
In the table are reported the clinical features of patients affected by pelvic carcinoma in association with eLAM and/or TSC.

Authors (year)	Cancer type	eLAM	pLAM	TSC (Germinal test)	Hormonal status (Age)
Iwasa et al. (16) (2011)	2 uterine corpus carcinoma 1 cervical squamous carcinoma	3\3	0\3	0\3	pre (47); post (70); post (59)
Ruiz-Molina et al. (14) (2013)	1 uterine corpus carcinoma	1\1	1\1 (A)	0\1	post (72)
Song et al. (2) (2014)	1 cervical squamous carcinoma	1\1	0\1	0\1	NA (46)
Suzuki et al. (15) (2016)	1 uterine corpus carcinoma	1\1	0\1	0\1	pre (47)
Remo et al. (2017)	1 cervical adenocarcinoma	1\1	1\1 (A)	0\1	pre (44)
Gyure et al. (20) (1995)	1 ovarian carcinoma and uterine corpus carcinoma	0\1	0\1	1\1 (B)	pre (29)
Wataga-kaneda et al. (19) (2013)	1 uterine cancer	0\1	NA	1\1 (B)	NA
Rabban et al. (6) (2015)	15 uterine corpus carcinoma 4 ovarian carcinoma 3 cervical squamous carcinoma 1 bladder carcinoma	23\23	0\23	1\23 (B) *(TSC2)*	pre - post (56)(31-79)
Jaffe et al. (18) (2015)	1 uterine corpus carcinoma	0\1	0\1	1\1 (B)	pre (39)
Peron et al. (17) (2017)	2 cervical squamous carcinoma	0\2	0\2	2\2 (A) *(TSC1; NM)*	pre (44); pre (36)

eLAM= extrapulmonary lymphangioleiomyomatosis; pLAM= pulmonary lymphangioleiomyomatosis; TSC Tuberous sclerosis complex; B= before cancer diagnosis; A=after cancer diagnosis; pre= premenopausal; post= postmenopausal; NA= not available

general population and malignant tumors are more frequently diagnosed in patients with mutations in TSC1 when compared to TSC2 and NM1 (17). In literature are reported six cases of pelvic carcinoma associated with TSC (Tab. 1) (6, 17-20). Three cases underwent to germinal test. One patient with endometrioid carcinoma and pelvic nodal incidental eLAM reported *TSC2* germiline mutation (6). The other two patients with TSC pelvic cancer, lacking of nodal eLAM, showed *TSC1* mutation and *NM*. In four patients with mental retardation the diagnosis of TSC was before the cancer whereas in two patient the TSC was diagnosed 4 and 5 years after (17).

Because eLAM may precede both TSC and pLAM, and because only a minority of patients with eLAM seek evaluation for TSC or pLAM by clinical medical genetics service, in a pratical perspective, the pathologist should document the possibility, albeit low, of pLAM or TSC when staging pelvic lymph node LAM is diagnosed (6) as introduced in other inherited pathology (Universal Screening for Lynch syndrome) (21). In this scenario the role of pathologist consist in the identification of lesions potentially caused by inherited genetic syndrome in order to enrol patient and relatives in specific screening program (22).

In conclusion, the retrospective probability to have pLAM in patients with pelvic nodal LAM detected during cancer staging is 6,6% (4/30) lower than the probability to have eLAM in patients affected by pLAM (25-30%). In both this association is more probable sporadically than associated with TSC. The association between cancer staging pelvic nodal eLAM and TSC is low (3%; 1/30) and reported associated with *TSC2* germinal mutation. The pLAM developed are asymptomatic with a behavior, regardless of hormonal status, similar to lesions diagnosed in postmenopausal althought further studies are mandatory to confirm it. The pathologist in all this cases should be suggest the possibility (low) of pLAM or TSC. The clinician should propose, within two years, a pulmonary TC to detect eventually pLAM and a close follow up (4-6 years) for excluding clinically TSC criteria. The management should be included a bland long surveillance to evaluate potential late-onset symptomatic pLAM. The routinely use of TSC germinal test is to avoid in this subset of eLAM.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 39 (1); 39-46

Newly defined acute exacerbation of idiopathic pulmonary fibrosis with surgically-proven usual interstitial pneumonia: risk factors and outcome

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Abstract. *Background:* In 2016, the diagnostic criteria for the acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) were revised. However, there have been published few clinical reports on AE–IPF published using the new criteria. The aim of this study was to investigate the incidence of, risk factors for, and mortality due to newly defined AE. Moreover, differences between triggered AE and idiopathic AE were investigated. *Methods:* The retrospective study was conducted including all IPF patients diagnosed with surgically-proven usual interstitial pneumonia through multi-disciplinary discussion between January 2006 and December 2015. Data were retrieved from a clinical chart review. *Results:* A total of 107 patients with newly diagnosed 107 IPF patients were included. The cumulative incidence of initial AE were 9.6% at 1 year, 16.8% at 2 years, 23.9% at 3 years, and 37.3% at 4 years after diagnosis. Three risk factors for AE–IPF development were identified: 1) the minimum peripheral ozygen saturation level of ≤88% during the 6-minute walk test at the time of diagnosis; 2) forced vital capacity (FVC) decreasing by ≥10% in 1 year; and 3) diffusion capacity of the lungs for carbon monoxide (DLco) decreasing by ≥15% in 1 year. There were no significant differences in background (excluding C-reactive protein), survival and treatment between patients with triggered AE and those with idiopathic AE. *Conclusions:* The 6-minute walk test and an annual decline in FVC and DLco were predictive factors for AE incidence. The causes of AE–IPF did not affect the prognosis or treatment options in clinical practice. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 39-46)*

Key words: acute exacerbation, idiopathic pulmonary fibrosis, risk factors, surgical lung biopsy, usual interstitial pneumonia

Abbreviations

AE acute exacerbation
IPF idiopathic pulmonary fibrosis
FVC forced vital capacity
DLco diffusion capacity of the lungs for carbon monoxide
PaO_2 the partial pressure of oxygen in the arterial blood
KL-6 Krebs von den Lungen-6
UIP usual interstitial pneumonia
MDD multi-disciplinary discussion
ATS American Thoracic Society
ERS European Respiratory Society
SpO_2 saturation of peripheral oxygen
SP-D surfactant protein D
CRP C-reactive protein
FiO_2 fraction of inspired oxygen
P/F PaO_2/FiO_2.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease with a poor prognosis. Although IPF progression is typically gradual, new shadows sometimes appear in bilateral lungs during the chronic stage, and an acute exacerbation (AE) can occur, leading to acute respiratory failure. In 2016, the diagnostic criteria for AE–IPF were changed so that acute respiratory failure induced by identified causes (e.g., infections, surgery, and medication) were also included in addition to acute respiratory failure of unknown causes (1). AE due to identified causes was described as triggered AE, AE due to unidentified causes was described as idiopathic AE.

There are few clinical reports on the incidence, prognosis, and treatment of the newly defined AE. In the previous criteria for AE, forced vital capacity (FVC), diffusion capacity of the lung for carbon monoxide (DLco), the partial pressure of oxygen in the arterial blood (PaO_2), Krebs von den Lungen-6 (KL-6) level at IPF diagnosis, and FVC decline greater than 10% within 6 months were reported as risk factors for the onset of AE (2-5). Risk factors for the incidence of AE using the new criteria are not well understood. Moreover, the incidence and prognosis of AE remain unknown since the diagnostic criteria have changed. It is not well understood whether there is a difference in patient characteristics, treatment, and prognosis between triggered AE and idiopathic AE in the clinical setting. Therefore, the aim of this study was to investigate the incidence of, risk factors for, and mortality due to newly defined AE. In addition, the treatment and prognosis were compared between triggered AE and idiopathic AE groups.

Methods

Subjects

A retrospective cohort study was conducted including patients with IPF who underwent surgical lung biopsy, who showed a surgically-proven usual interstitial pneumonia (UIP) pattern, and who were diagnosed through multi-disciplinary discussion (MDD) at the Kanagawa Cardiovascular and Respiratory Center between January 2006 and December 2015. IPF diagnoses were based on the 2011 American Thoracic Society (ATS)/European Respiratory Society (ERS) IPF statement (6). Three specialists were involved in MDD: 1) a pulmonologist who specialized in interstitial lung diseases; 2) a chest radiology specialist; and 3) a chest pathology specialist. Patients with cancer, including lung cancer, and those who did not receive regular check-ups at our center after undergoing a surgical lung biopsy were excluded from the study. In addition, the patients for whom the diagnosis was changed to interstitial pneumonia of known causes after the initial diagnoses of IPF (e.g., interstitial pneumonia associated with connective tissue diseases and hypersensitivity pneumonitis) were excluded from the study. The 2016 International Working Group Report on diagnostic criteria for AE-IPF was used to diagnose AE–IPF (1). The protocol for this study was approved by the ethical review board of our center (Research Ethics Committee, Kanagawa Cardiovascular and Respiratory Center, Kanagawa Prefectural Hospital Organization).

Incidence of and risk factors for AE–IPF

Risk factors for the occurence of AE–IPF were examined using data from the time of IPF diagnosis to until one year following diagnosis. The minimum saturation of peripheral oxygen (SpO_2) during the 6-minute walk test was set at 88% (7), and the threshold for the difference (ΔSpO_2) from the baseline SpO_2 to the minimum SpO_2 was set at 4% (8). In addition, using previous studies (5) (8), the thresholds for the amount of change on the lung function tests one year following diagnosis were set at a 10% decline for FVC and a 15% decline for DLco.

Prognosis of AE-IPF

The clinical characteristics at AE onset, treatment, and 90-day survival from the onset of AE–IPF were investigated. In cases with multiple incidences of AE–IPF, data from the most recent AE were used in order to compare the history of AE in patients with triggered AE and idiopathic AE.

Statistical analysis

Kaplan-Meier curves and the log-rank test were used to analyze survival. A Cox proportional hazards

regression analysis was used to analyze the risk factors for the incidence of AE–IPF. First, a univariate analysis was conducted to elicit significant factors, which were then inserted into covariates. Next, a multivariate analysis was conducted using stepwise regression. Comparison between the two groups was done using the Mann-Whitney' U test. Fisher's exact test was used in the test of the crosstab. A p-value of <0.05 was considered statistically significant. Excel Statistics (Social Survey Research Information Co., Ltd.) was used for the analyses.

Results

Subject characteristics

Overall, 145 patients were diagnosed with UIP by surgical lung biopsy between January 2006 and December 2015. A total of 38 patients were excluded: 7 patients with cancer; 11 patients who were referred to another facility after surgical lung biopsy and thus not available for follow-up; 13 patients who were determined to be non-IPF through MDD; and 7 patients whose diagnosis was changed from IPF to interstitial pneumonia of known causes (6 patients with connective tissue disease-associated interstitial pneumonia and 1 patient with hypersensitivity pneumonitis) during the observation period. Finally, 107 patients were included in the retrospective cohort analysis (Figure 1). The mean observation period was 3.9 years, and the baseline characteristics at the time of IPF diagnosis are shown in Table 1. Of the included patients, 77% were male, the mean age was 66.9 years, 25 were non-smokers (23%), and 16 patients had a family history (15%). Average KL-6 and surfactant protein D (SP-D) levels were rather elevated (1147 U/mL [152–400 U/mL] and 219 ng/mL [0–109.9 ng/mL]) respectively. The mean FVC % predicted and DLco % predicted were 85.3% and 82.1%, respectively. The 6-minute walk test was conducted under room air conditions for all patients, and the mean distance was 458 meters. The mean minimum SpO_2 was 91% during the 6-minute walk test, and the mean SpO_2 decline from baseline was 5.3%.

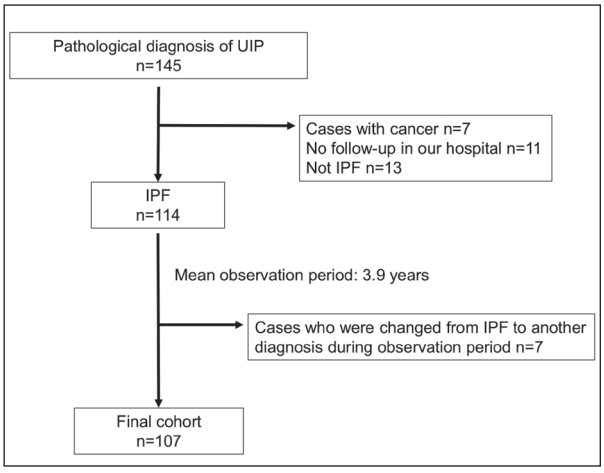

Fig. 1. Flow of this study. UIP: usual interstitial pneumonia, IPF: idiopathic pulmonary fibrosis

Table 1. Baseline characteristics at the time of IPF diagnosis

Characteristics	
Subjects	107
Male	82
Age (yrs)	66.9±7.1
Smoking history	
Never smoke	25
Current smoker	3
Ex-smoker	69
Pack-year	40.2±25.5
Surgical lung biopsy (Yes)	107
Familial interstitial lung diseases (Yes)	16
Blood tests (n=107)	
KL-6 (U/mL)	1147±826
SP-D (ng/mL)	219±139
LDH (U/L)	225±43
CRP (mg/dL)	0.40±1.81
PaO_2 (Torr)	84.9±8.3
Pulmonary function (n=107)	
FVC (L)	2.82±0.79
FVC %pred (%)	85.3±17.0
FEV_1/FVC (%)	79.0±6.5
DLco %pred (%)	82.1±19.3
DLco (mL/min/mm Hg)	14.8±3.9
6-minute walk test (n=95)	
Distance (meter)	458±82
Minimum SpO_2 (%)	91±4
Bronchoalveolar lavage fluid findings (n=81)	
Total cell count (×10^5)	2.07±1.55
Macrophages (%)	78.2±18.0
Lymphocytes (%)	16.9±16.8
Neutrophils (%)	3.4±5.0
Eosinophils (%)	1.6±1.9

Data are presented as n or mean±standard deviation. Definition of abbreviations: IPF: idiopathic pulmonary fibrosis, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein-D, LDH: lactate dehydrogenase, CRP: C-reactive protein, PaO_2: partial pressure of oxygen in arterial blood, FVC: forced vital capacity, %pred: % predicted, FEV_1: forced expiratory volume in 1 second, DLco: diffusion capacity of the lung for carbon monoxide, SpO_2: arterial oxygen saturation measured by pulse oximetry.

While the patients exhibited normal lung function, they experienced diminished exercise tolerance.

Prognosis and causes of death

The 50% survival rate from the time of IPF diagnosis was 5.6 years. The main causes of death were AE (41%), chronic respiratory failure (41%), sudden death (9%), and lung cancer (2%).

AE incidence

The cumulative incidence rates of the initial AE were 9.6% for 1 year following diagnosis, 16.8% for 2 years, 23.9% for 3 years, and 37.3% for 4 years. For the first four years, the incidence of AE–IPF occurred at a consistent rate of 7.1%-13.4% per year (Figure 2). There were 39 patients in whom an AE–IPF occured during the observation period, and there was a significant difference in the prognosis between the group with AE–IPF (median survival time, 3.65 years) and that without (median survival time, not calculable) (Log-rank test, P<0.001) (Figure 3).

Risk factors for AE

Analysis of the risk factors for the incidence of AE using a univariate Cox proportional hazards model revealed the following factors: 1) the 6-minute walk distance was short; 2) the minimum SpO_2 during 6-minte walk test was 88% or less; 3) KL-6, SP-D, and C-reactive protein (CRP) were high; 4) PaO_2 was low; 5) FVC was low; 6) there was 10% or more FVC decline in 1 year; and 7) 15% or more DLco decline in 1 year. Furthermore, the multivariate analysis found the following risk factors for the incidence of AE–IPF: 1) the minimum SpO_2 during the 6-minute walk test at the time of the diagnosis was 88% or less; 2) 10% or more FVC decline in 1 year; and 3) 15% or more DLco decline in 1 year (Table 2).

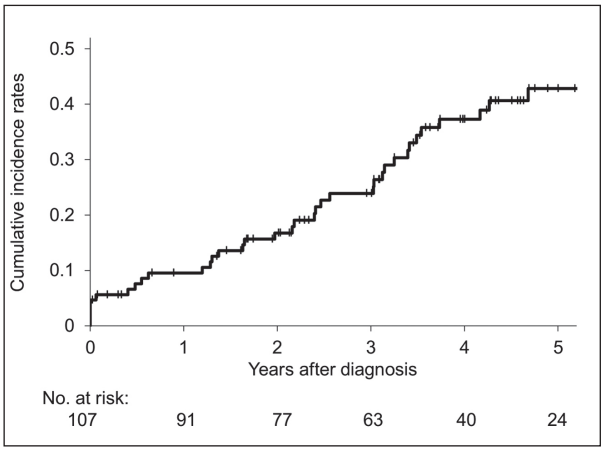

Fig. 2. Kaplan-Meier curve for cumulative incidence rates of acute exacerbation of idiopathic pulmonary fibrosis.

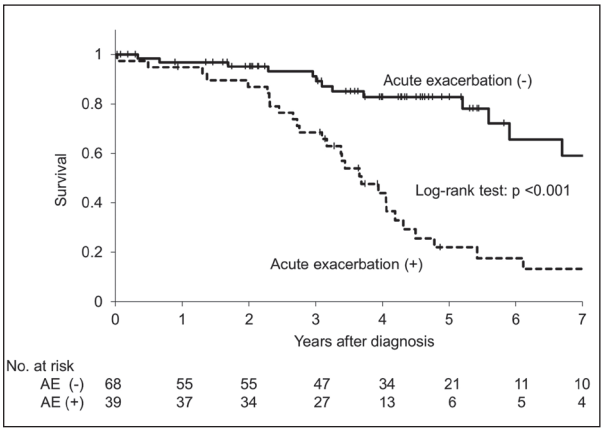

Fig. 3. Kaplan-Meier survival curves for cases with acute exacerbation of IPF and those without acute exacerbation of IPF. Median survival time of cases with acute exacerbation was 3.65 years and median survival time of cases without acute exacerbation was unreached

Second AE–IPF

Among the 39 patients with AE–IPF, eight patients (21%) experienced a second occurence of AE–IPF. Of these eight, two patients experienced a third incidence of AE–IPF.

Prognosis of AE–IPF

Among the 39 patients with AE-IPF, the mean duration from the time of IPF diagnosis until the onset of AE–IPF was 2.1 years, and 14 patients (36%) received no previous treatment before AE onset. At the time of the AE onset, the mean CRP was 9.66 mg/dL, KL-6 was 1625 U/mL, and the PaO_2/fraction of inspired oxygen (FiO_2) (P/F) ratio was 234. The 90-day survival rate from the onset of AE–IPF was 50.4% (Figure 4).

Comparison between triggered and idiopathic AE

Among the 39 patients with AE, 10 had the following types of triggered AE: infections (6 patients),

Table 2. Risk factors for the occurence of acute exacerbation

Parameters	Hazard ratio (95% CI)		p value
Univariate Cox analysis			
Males, sex	0.98	(0.43-2.24)	NS
Age (yrs)	1.02	(0.97-1.07)	NS
BMI (kg/m^2)	1.03	(0.94-1.12)	NS
Smoking history	1.01	(0.46-2.20)	NS
Family history	1.86	(0.85-4.08)	NS
BAL			
Total cell count (×10^5)	1.13	(0.89-1.43)	NS
Macrophages (%)	1.01	(0.98-1.03)	NS
Lymphocytes (%)	0.99	(0.97-1.02)	NS
Neutrophils (%)	1.03	(0.97-1.10)	NS
Eosinophils (%)	1.02	(0.84-1.24)	NS
6-minute walk test (6MWT)			
Distance (meter)	0.99	(0.988-0.99)	0.02
Minimum SpO_2, 88% or less	0.86	(0.80-0.93)	<0.001
ΔSpO_2, 4% or more	1.63	(0.74-3.55)	NS
KL-6 (U/mL)	1.001	(1.001-1.005)	0.002
SP-D (ng/mL)	1.003	(1.001-1.005)	0.003
LDH (U/L)	1.01	(0.998-1.01)	NS
CRP (mg/dL)	1.20	(1.06-1.35)	0.003
PaO_2 (Torr)	0.94	(0.90-0.98)	0.005
FVC %pred	0.97	(0.95-0.99)	0.007
DLco %pred	0.99	(0.99-1.01)	NS
10% or more FVC decline in 1 year	7.45	(3.12-17.77)	<0.001
15% or more DLco decline in 1 year	2.74	(1.06-7.10)	0.038
KL-6 increase in 1 year (U/mL)	1.21	(0.54-2.70)	NS
SP-D increase in 1 year (ng/mL)	1.67	(0.70-3.98)	NS
Multivariate Cox analysis			
Minimum SpO_2 in 6 MWT, 88% or less	5.28	(1.44-19.32)	0.012
10% or more FVC decline in 1 year	4.14	(1.26-13.65)	0.020
15% or more DLco decline in 1 year	4.66	(1.19-18.17)	0.027

Cox proportional hazards regression model was used. Definition of abbreviations: BMI: body mass index, BAL: Bronchoalveolar lavage, SpO_2: arterial oxygen saturation measured by pulse oximetry, ΔSpO_2: difference from the resting SpO_2 to the minimum SpO_2, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein-D, LDH: lactate dehydrogenase, CRP: C-reactive protein, PaO_2: partial pressure of oxygen in arterial blood, FVC: forced vital capacity, %pred: % predicted, DLco diffusion capacity of the lungs for carbon monoxide, NS: not significant.

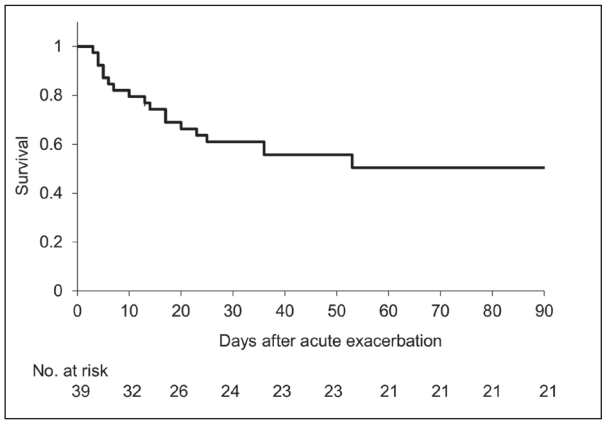

Fig. 4. 90-day survival curve from the acute exacerbation onset. 90-day survival rate was 50.4%

surgical lung biopsy (2 patients), video-assisted thoracoscopic surgery for lung cancer found during the observation period (1 patient), and alveolar hemorrhage (1 patient). The CRP level at the onset of AE was significantly higher in the triggered AE group compared to the idopathic AE group (Table 3). The median CRP level of triggered AE due to infection was 25.0 mg/dL, while that of triggered AE due to causes other than infection was 8.2 mg/dL. The 90-day survival rates for triggered and idiopathic AEs were 60% and 45%, respectively, with no significant difference in survival between the two groups (Figure 5). In addition, there was no difference in the treatment between the patients with triggered AE and those with idiopathic AE (Table 4).

Table 3. Characteristics at the onset of acute exacerbation

Characteristics	Triggered AE	Idiopathic AE	*p* value
Subjects	10	29	NS
Male, sex	9	23	NS
Age (yrs)	70.8±5.7	69.2±7.7	NS
Period from IPF diagnosis (yrs)	3.3±3.5	1.7±1.4	NS
PSL before AE	1	11	NS
Immunosuppressants before AE	0	7	NS
Anti-fibrotic agents before AE	6	16	NS
No previous treatment before AE	4	10	NS
History of AE	1	7	NS
Blood tests			
KL-6 (U/mL)	1175±778	1763±828	NS
SP-D (ng/mL)	251±212	253±123	NS
LDH (U/L)	343±164	361±125	NS
Albumin (g/mL)	3.1±0.6	3.3±0.5	NS
CRP (mg/dL)	17.7±10.2	6.8±7.2	0.007
P/F ratio	242±196	230±89	NS

Data are presented as n or mean±standard deviation. Date from the most recent acute exacerbation were used. Mann-Whitney U test was used. Definition of abbreviations: IPF: idiopathic pulmonary fibrosis, PSL: prednisolone, AE: acute exacerbation, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein-D, LDH: lactate dehydrogenase, CRP: C-reactive protein, P/F ratio: PaO_2/FiO_2 ratio, NS: not significant.

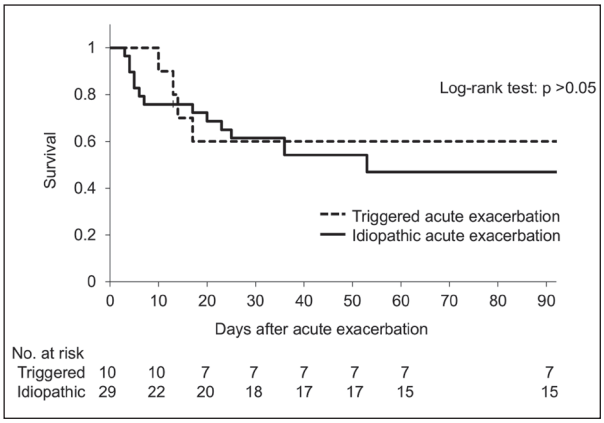

Fig. 5. Comparison of survival curves from the acute exacerbation onset between triggered and idiopathic acute exacerbation

Table 4. Treatment of triggered acute exacerbation and idiopathic acute exacerbation

Parameters	Triggered AE	Idiopathic AE	p value
Cases	10	29	
Steroid pulse	8 (80)	26 (90)	NS
IVCY	4 (40)	6 (21)	NS
Oral immunosuppressants	2 (20)	9 (31)	NS
PMX-DHP	3 (30)	6 (21)	NS
Antibacterial drugs	9 (90)	20 (69)	NS

Data are presented as n (%). Fisher's exact test was used.
Definition of abbreviations: AE: acute exacerbation, IVCY: intravenous cyclophosphamide, PMX-DHP: polymyxin B-immobilized fiber column direct hemoperfusion, NS: not significant.

Discussion

This retrospective cohort study was conducted including newly diagnosed IPF patients with UIP, as identified by surgical lung biopsy. This study investigated the incidence rates, risk factors and mortality of patients with newly defined AE. The results indicated that AE–IPF occurred at a consistent rate for the first 4 years following diagnosis. Furthermore, the analysis revealed that risk factors for the incidence of AE included minimum SpO_2 during the 6-minute walk test at the time of the diagnosis and annual declines of FVC and DLco. There were no differences in the prognosis or treatment between the triggered AE and idiopathic AE in the clinical setting.

The 2011 ATS/ERS/Japanese Respiratory Society/Latin American Thoracic Association IPF statement allowed for the diagnosis of IPF if CT images revealed UIP pattern without a surgical lung biopsy, which was previously necessary for the diagnosis of IPF (6). In the 2017 Fleischner Society White Paper, IPF diagnosis by CT images alone became more common (9). However, diagnosing IPF using CT images is difficult and there is often disagreement even among chest radiology specialists (10). We were concerned that cases other than IPF might be diagnosed as IPF in the clinical setting. Additionally, even when CT images show a typical UIP, histopathological analysis occasionally reveals that it is UIP a known cause (e.g., vasculitis and rheumatoid arthritis). Moreover, it is common for the diagnosis of UIP to be made histopathologically when there is

no typical UIP pattern on CT images (11). Although the present study has a strong bias, with only surgical lung biopsy cases, we believe that patients with IPF who have a UIP pattern on surgical lung biopsy and are diagnosed through MDD likely have an accurate diagnosis that would be minimally influenced by future changes in IPF diagnostic criteria. As IPF diagnosis by CT images alone became more common, it is expect that the frequency of surgical lung biopsy will decrease in the clinical setting. Therefore, we included IPF patients with surgically-proven UIP as the subjects in this study, even though it is important to consider AE in IPF cases without surgical lung biopsy.

During the first 4 years after the diagnosis of IPF, the cumulative rate of initial AE–IPF was consistently 7.1%-13.4%. For the fifth year, the annual incidence rate was 5.5%, which was slightly lower than that of the first 4 years. This may have occurred because the mean observation period was only 3.9 years. Previous studies have reported that the incidence rate of AE–IPF for 1 year was 4%-9% (12-14). The incidence of AE using the new AE-IPF diagnostic criteria tended to be relatively high. The reason of the increase in AE incident was that the acute respiratory failure induced by identified and unknown causes could be diagnosed as AE.

Previous reports indicated that risk factors for the AE–IPF consisted of respiratory symptoms (modified Medical Research Council breathlessness scores and St. George's Respiratory Questionnaire scores), PaO_2, FVC, DLco, and 6-minute walk distance (2-5). In addition, Kondoh et al. reported that an FVC decline greater than 10% within 6 months was a risk factor for the occurrence of AE–IPF (5) (15). In this study, FVC decline of 10% or greater and DLco decline of 15% or greater within 1 year were risk factors for AE–IPF. Even 4 years after the diagnosis, AE–IPF occurred approximately at the same frequency as 1 year after the diagnosis. Therefore, data from the time of the IPF diagnosis alone is not sufficient for predicting the incidence of AE–IPF over the long-term. The results of this study demonstrated that the amount of change in FVC and DLco in 1 year was a risk factor for the occurrence of AE, suggesting the importance of follow-up after the diagnosis. Furthermore, one study reported that FVC does not accurately reflect the prediction of disease progression in patients who also developed emphysema (16). Therefore, it might be important to check not only FVC but also DLco regularly.

In this study, the AE incidence over 4 years was higher in patients whose the minimum SpO_2 was 88% or less during the 6-minute walk test. The 6-minute walk test has been reported to correlate with maximum oxygen uptake (17), quality of life (18), and to have no correlation with spirometry in patient with chronic pulmonary disease (19). Evaluation of total exercise tolerability, such as the 6-minute walk test might be important for the prediction of AE–IPF.

The 90-day survival rate from the onset of an AE was 50.4% in this study, which is better than that described in previous reports from Japan (20, 21). A possible reason is that, unlike the Japanese AE–IPF diagnostic criteria, the 2016 AE–IPF diagnostic criteria do not include "more than 10 Torr decline in PaO_2 from baseline" which enables mild acute respiratory failure to be diagnosed as AE–IPF.

There were no differences in the prognosis or treatment (steroid pulse, intravenous cyclophosphamide, oral immunosuppressants, polymyxin B, and antimicrobial drugs) at the time of the AE–IPF between the triggered AE and idiopathic AE groups. The causes of AE–IPF did not impact the prognosis or treatment options in clinical practice; therefore, the new AE–IPF diagnostic criteria appear to be useful in clinical setting. CRP level at the onset of AE was significantly higher in triggered AE group, especially AE due to infection. CRP level might be useful for differentiating between AE caused by infection and other AEs.

This study had several limitations. This study was a retrospective investigation conducted at a single facility with a limited number of AE–IPF patients. The investigation included patients who had undergone a surgical lung biopsy; therefore, mild cases and patients who had positive attitudes toward medical care tended to be selected as the subject group. In addition, because all the patients were Japanese, it was not possible to determine whether there were any inter-racial differences in the incidence and mortality rates of AE–IPF. Despite these limitation, we believe that we could show the incidence, risk factors, and prognosis of newly defined AE in IPF patients.

In conclusion, the newly defined AE–IPF occurred at a consistent rate each year following diagnosis. Predictive factors for the incidence of AE included the minimum SpO_2 during the 6-mintue

walk test, and an annual decline in FVC and DLco. The causes of AE–IPF did not impact the prognosis or treatment options in clinical practice.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 47-52

Diffuse alveolar hemorrhage: how relevant is etiology?

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Abstract. *Background:* Diffuse Alveolar Hemorrhage (DAH) is a rare and potentially life-threatening clinical syndrome whose early recognition is essential. *Objectives:* Characterization of patients with DAH and comparison of presentation and evolution of the disease according to etiology. *Methods:* We retrospectively reviewed the clinical records of patients admitted to our hospital over a 7-year period with DAH. Criteria for DAH (1+2): 1 - hemoptysis and/or pulmonary infiltrates and/or anemia (DAH triad); 2 - hemorrhagic bronchoalveolar lavage (BAL) or siderophagic alveolitis. DAH was grouped in immune and nonimmune and the course of disease was compared. *Results:* We included 24 patients admitted with DAH, of which 11 had an immune cause: p-ANCA vasculitis (n=7), Systemic Lupus Erythematosus (n=2), c-ANCA vasculitis (n=1), Rheumatoid Arthritis (n=1) and 13 had a nonimmune cause: heart disease (n=6), amiodarone toxicity (n=2), clotting disorder (n=2), cannabis toxicity (n=1), *S. aureus* infection (n=1) and idiopathic (n=1). Patients with nonimmune DAH were significantly older than those with immune DAH (67.9±18.1 *vs* 56.6±18.8 years, p=0.042). DAH triad was observed in 54% of all patients, hemoptysis in 67%, anemia in 79%, and pulmonary infiltrates in all cases. Patients with immune DAH had more frequently pulmonary-renal syndrome (p<0.001), kidney failure (p=0.048), shock (p=0.049) and needed more frequently admition in ICU (p=0.039) and blood transfusion (p=0.043). Hospital length of stay was superior in immune group (29.5±20.0 *vs* 19.5±14.3 days, p=0.047). In-hospital mortality was exclusive to immune DAH (12.5%). *Conclusions:* Patients with DAH due to immune causes were significantly younger, had more severe presentations of the disease and worst outcomes. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 47-52)*

Key words: diffuse, alveolar, hemorrhage

Introduction

Diffuse Alveolar Hemorrhage (DAH) is a rare syndrome resulting from diffuse bleeding into the acinar portions of the lung (1). It is characterized by the association of hemoptysis, new pulmonary infiltrates on chest radiograph and anemia, although its presentation may vary, with about one-third of patients presenting without hemoptysis (2). Other symptoms are usually nonspecific and include cough, dyspnea and fever.

DAH is a potentially life-threatening syndrome and it has an overall poor prognosis, with in-hospital mortality ranging from 20 over 50% (3). Rapid identification of the underlying cause of DAH is essential in order to initiate appropriate treatment and prevent acute respiratory failure and death.

Classic treatment regimens include corticosteroids and immunosuppressive agents (4), but these can be potentially harmful when DAH is due to infection.

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The results of this research were presented at ERS International Congress, Milan, 2017, as a thematic poster.

N. de Prost et al (5) reviewed the etiology and prognosis of a series of 112 patients with DAH, but there is still a lack of studies focused on the causes of DAH and most of the series address primarily on immune causes, with the nonimmune causes being probably underestimated. The prognosis of DAH according to the specific etiology is not well documented either.

In order to help to answer these questions, we reviewed the cases of DAH in a single center over 7 years, we characterized these patients and compared the presentation, evolution and prognosis of the disease according to the specific etiology.

Methods

We performed a retrospective cohort study analysing the medical records of patients admitted between January 2010 and December 2016 for suspected DAH in our center. For patients with several admissions for DAH of the same etiology, only the first admission was considered for analysis, the following being referred to as a relapse.

The definition of DAH was based on two basic criteria. First, the clinical picture and radiological data were compatible, including hemoptysis and/or new pulmonary infiltrates on chest radiograph and/or anemia (DAH triad). Second, the bronchoalveolar lavage (BAL) fluid had to be compatible, being either macroscopically hemorrhagic (and not clearing after several aliquots) or presenting siderophagic alveolitis on the cytological analysis (≥20% of haemosiderin-laden macrophages). Patients with hemorrhage of bronchial origin were excluded.

Variables analysed included demographics, past medical history, clinical and laboratory features, hospital length of stay, need for admission in intensive care unit (ICU), need for invasive or noninvasive mechanical ventilation, hemodialysis, blood transfusion and either in-hospital death and death during a follow-up period of 1 year after discharge.

DAH causes were classified into two groups: immune and nonimmune.

For the immune causes, which included systemic vasculitides and connective tissue diseases, the diagnosis was based on compatible clinical features plus either a serological marker or histological confirmation of immune disease.

For the nonimmune causes, DAH related to heart disease was diagnosed based on compatible clinical and echocardiographic features; infection was based on compatible clinical features and microbiological tests; amiodarone toxicity was established based on compatible exposure and suggestive BAL findings; cannabis toxicity was diagnosed based on compatible exposure and urine analysis; clotting disorders were diagnosed in patients taking anticoagulant drugs and evidence of altered coagulation tests; idiopathic DAH was defined when the search for the possible causes remained negative.

Statistical analysis was performed using IBM SPSS Statistics® v.22. Continuous variables were reported as mean±standard deviation and compared with the T-test when normally distributed or the Mann-Whitney test if not normally distributed. Categorical variables were reported as percentages and compared using the chi-square or the Fisher exact test. P values less than 0.05 were considered significant.

Results

Between January 2010 and December 2016, 24 patients were admitted to our center with the first episode of DAH.

We identified 14 different causes of DAH. An immune cause was diagnosed in 11 patients (small vessel vasculitis in 8 patients, connective tissue disease in 3 patients). A nonimmune cause was diagnosed in 13 patients (heart disease in 6 patients, amiodarone toxicity in 2 patients, clotting disorder secondary to anticoagulant treatment in 2 patients, cannabis toxicity in 1 patient, *S. aureus* infection in 1 patient and idiopathic in 1 patient). The different causes of DAH are specified in table 1.

Patients with nonimmune DAH were significantly older than those with immune DAH (67.9±18.1 *vs* 56.6±18.8 years, p=0.042).

DAH triad was observed in 54% (n=13) of patients. 67% (n=16) presented with hemoptysis, 79% (n=19) with anemia and all patients had new pulmonary infiltrates on chest radiograph at admission. All of these features showed no significant difference between the two groups.

These and other demographic, clinical and laboratory data are specified in table 2.

Table 1. Etiology of DAH

Immune	**n=11**
Small vessel vasculitis	**8**
Microscopic polyangiitis	7
Granulomatosis with polyangiitis	1
Connective tissue disease	**3**
Systemic Lupus Erythematosus	2
Rheumatoid Arthritis	1
Nonimmune	**n=13**
Heart disease	**6**
Mitral stenosis	3
Left ventricle dysfunction	2
Atrial myxoma	1
Toxic-induced	**3**
Amiodarone toxicity	2
Cannabis toxicity	1
Clotting disorder	**2**
***S. aureus* infection**	**1**
Idiopathic	**1**

All patients were submitted to bronchoscopy with BAL. In 83% (n=20) of cases, the BAL fluid was macroscopically bloody and did not clear after several aliquots. In 63% (n=15) of cases, the BAL fluid cytology showed the presence of ≥20% haemosiderin-laden macrophages (siderophages). Patients in the immune group had a significantly larger percentage of neutrophils (36,1±39,0 *vs* 9,0±12,5%, p=0,027). The other variables showed no difference between the two groups and are specified in table 3.

Anti-neutrophil cytoplasmatic antibody (ANCA) tests were positive in 73% (n=8) of patients in the immune group – 7 patients had a p-ANCA pattern with MPO specificity and 1 patient had a c-ANCA pattern with PR3 specificity. ANA tests were positive in 18% (n=2) of patients in the immune group.

Kidney biopsy was performed in 36% (n=4) of patients with immune DAH and histological exami-

Table 2. Demographics, clinical and laboratory data

	All patients (n=24)	Immune DAH (n=11)	Nonimmune DAH (n=13)	P
Age, years	62,7±18,9	56,6±18,8	67,9±18,1	**0,042**
Male gender	15 (62,5)	7 (63,6)	8 (61,5)	1,000
Smoking history	6 (25,0)	4 (36,4)	2 (15,4)	0,357
Alcohol abuse	1 (4,2)	1 (9,1)	0 (0)	0,458
Known cardiac disease	16 (66,7)	6 (54,5)	10 (76,9)	0,390
Known respiratory disease	8 (33,3)	5 (45,5)	3 (23,1)	0,390
DAH triad	9 (37,5)	4 (36,4)	5 (38,5)	1,000
Hemoptysis	16 (66,7)	6 (54,5)	10 (76,9)	0,390
Pulmonary infilitrates	24 (100)	11 (100)	13 (100)	-
Anemia	19 (79,2)	10 (90,9)	9 (69,2)	0,294
Hematuria	8 (33,3)	7 (63,6)	1 (7,7)	**0,008**
Proteinuria	8 (33,3)	8 (72,7)	0 (0)	**<0,001**
Kidney failure	10 (41,7)	7 (63,6)	3 (23,1)	**0,048**
Pulmonary-renal syndrome	7 (29,2)	7 (63,6)	0 (0)	**<0,001**
Thrombocytopenia	4 (16,7)	3 (27,3)	1 (7,7)	0,300

Table 3. Bronchoalveolar lavage analysis

	All patients (n=24)	Immune DAH (n=11)	Nonimmune DAH (n=13)	P
Hemorrhagic	20 (83,3)	10 (90,9)	10 (76,9)	0,596
Total cell count, 10^3 / mL	4,0±3,0	4,7±3,7	3,4±2,2	0,288
Macrophages, %	65,7±31,6	55,3±37,3	74,5±24,0	0,142
Neutrophils, %	21,4±30,6	36,1±39,0	9,0±12,5	**0,027**
Lymphocytes, %	11,3±15,6	6,8±5,2	15,1±20,2	0,177
Eosinophils, %	1,1±1,4	1,3±1,7	0,9±1,1	0,557
Presence of ≥20% siderophages	15 (62,5)	7 (63,6)	8 (61,5)	1,000
% of siderophages (when present)	40,0±32,2	37,7±32,5	42,2±34,9	0,822

Table 4. Hospital course and outcome during follow-up period

	All patients (n=24)	Immune DAH (n=11)	Nonimmune DAH (n=13)	P
Hospital length of stay, days	24,1±17,5	29,5±20,0	19,5±14,3	**0,047**
ICU admission	6 (25,0)	5 (45,5)	1 (7,7)	**0,043**
Shock	3 (12,5)	3 (27,3)	0 (0)	**0,049**
Invasive machanical ventilation	2 (8,3)	2 (18,2)	0 (0)	0,199
Noninvasive mechanical ventilation	2 (8,3)	2 (18,2)	0 (0)	0,199
Hemodialysis	3 (12,5)	2 (18,2)	1 (7,7)	0,576
Blood transfusion	6 (25,0)	5 (45,5)	1 (7,7)	**0,043**
In-hospital mortality	3 (12,5)	3 (27,3)	0 (0)	**0,049**
Relapse of DAH	1 (4,2)	1 (9,1)	0 (0)	0,381
Mortality during follow-up	2 (8,3)	1 (9,1)	1 (7,7)	1,000

nation showed a necrotizing crescentic glomerulonephritis in 3 cases. One biopsy was not representative of kidney tissue, but the diagnosis was still assumed without histological confirmation.

We observed a significantly higher need for admission in ICU for patients in the immune group (45%, n=5 *vs* 8%, n=1; p=0,043), with also a higher incidence of shock (27%, n=3 *vs* 0%; p=0,049) and need for blood transfusion (45%, n=5 *vs* 8%, n=1; p=0,043).

Hospital length of stay was also significantly superior in the immune group (29,5±20,0 *vs* 19,5±14,3 days, p=0,047), as well as in-hospital mortality (27%, n=3 *vs* 0%; p=0,049).

During follow-up, 1 patient in the immune group, which had been diagnosed with Systemic Lupus Erythematosus (SLE), had relapse of DAH requiring a new admission to the hospital 8 months after the initial discharge.

All-cause mortality during follow-up was 21%, including both in-hospital mortality and mortality in discharged patients. 2 patients died during the follow-up period after hospital discharge, 1 of each group. The death in the immune group refers to the patient with SLE in whom DAH relapsed. In this case, DAH was directly responsible for mortality. The patient in the nonimmune group died of congestive heart failure 5 months after the initial discharge. In this case, there was no relapse of DAH.

Data on hospital course and outcome are specified in table 4.

Discussion

The first step in the diagnostic approach of a patient with suspected DAH, especially when presenting with hemoptysis, is to distinguish this syndrome from other causes of bleeding. Several infections, bronchiectasis and neoplasms may result in focal aspiration of blood and this may simulate alveolar bleeding in some cases. This distinction has important implications in terms of diagnostic approach, as well as treatment options and prognosis.

Some series report that about one-third of patients do not present with hemoptysis (6). Our series is consistent with this finding since exactly one-third of all patients did not experience hemoptysis initially. This supports the idea that the absence of this sign should not exclude the diagnosis, which is important since hemoptysis is often considered the classic sign of DAH.

Patients with DAH commonly exhibit anemia, leukocytosis and elevation of inflammatory markers, but these are nonspecific findings. Pulmonary-renal syndromes are frequently associated with specific disease markers, including anti-glomerular basement membrane (anti-GBM) antibody in Goodpasture syndrome and ANCA in granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). When clinical suspicion exists, elevation of some of these markers may help to make an early diagnosis of the cause of DAH.

Chest radiograph classically shows diffuse bilateral alveolar opacities with basal predominance, but recurrent episodes of hemorrhage may lead to fibrosis, producing a reticular interstitial pattern. Despite this, imaging of the lung can be normal in 20 to 50% of cases in the acute setting (7), so this should not discourage the physician to suspect the diagnosis. In our series, all the patients had new pulmonary infiltrates on chest radiograph at admission, which were bilateral in all cases.

Bronchoscopy with BAL is an essential tool to make a confident diagnosis of DAH but it does not diagnose the underlying etiology of hemorrhage in most cases (8), although it can be helpful in the diagnosis of infectious causes and neoplasms. A hemorrhagic BAL fluid that does not clear after sequential aliquots is consistent with DAH. Alternatively, the Golde score is often used to quantify the macrophagic hemosiderin content, which is usually observed only after the first 48 hours of bleeding. However, it is a slow process and there are some studies that have shown a good correlation between a siderophageal cell percentage ≥20% and a Golde score suggestive of DAH (9). In our series, patients with immune DAH had a significantly larger percentage of neutrophils, a finding that, to our knowledge, is not reported elsewhere in literature. The percentage of macroscopically hemorrhagic BAL fluid and the percentage of siderophages did not appear to be significantly different between immune and nonimmune groups.

Systemic vasculitides have been classically associated with DAH. Quadrelli et al (10) characterized 39 patients with DAH of proven immunological etiology, the most frequent being ANCA-related vasculitides (74%), mainly granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). In their series, these two diseases accounted for a similar number of cases (14 GPA *vs* 13 MPA). In our series, ANCA-related vasculitides were also the predominant etiology of immune-related DAH (73%), but with a higher number of MPA cases against GPA (7 *vs* 1). Connective tissue diseases accounted for the remaining cases, including one case of Rheumatoid Arthritis, which is considered a rare cause of DAH.

There are multiple nonimmune-mediated causes of DAH that are frequently ignored in studies. Heart disease and toxic causes are etiologies that are frequently overlooked. Infectious diseases can cause DAH even in immunocompetent patients, the most frequent being influenza A, dengue, leptospirosis, malaria and *Staphylococcus aureus* (11). In immunocompromised patients, the main infectious diseases that cause DAH are cytomegalovirus (12), adenovirus (13), invasive aspergillosis (14), mycoplasma (15), legionella (16) and strongyloides (17) infections. Our series included a single immunocompetent patient with DAH secondary to *Staphylococcus aureus* infection, which was isolated in the BAL fluid microbiological culture, hence strengthening the role of BAL in these patients. Heart disease accounted for 46% of the nonimmune DAH, and echocardiography has proven to be an essential tool in the evaluation of the main cardiac anomaly. N. de Prost (5) found 85% of cases of DAH secondary to heart failure not related to valvular disease. In fact, mitral stenosis has been considered the classic feature of DAH of cardiac origin (18), but several series include other cardiac anomalies. In our case, mitral stenosis accounted for half the cases of DAH due to heart disease (n=3). The other cases were due to left ventricular dysfunction (n=2) and 1 case of a large left atrial myxoma, which was later surgically removed and led to resolution of the symptoms. Our series included 3 cases of toxic-induced DAH. 2 patients had amiodarone-related pulmonary toxicity. In both cases, they were taking this medication for over 10 years and the BAL fluid cytology showed foamy macrophages. One patient had DAH secondary to cannabis smoking. This is a rare cause of DAH, with only anecdotal cases reported, and should, therefore, be sought in all patients with suspected DAH. In the 3 toxic-related cases, all the other common causes of DAH were excluded. We report only one case of idiopathic DAH. This seems to be a rare condition, but its incidence is difficult to calculate because some of the cases reported in literature could be categorised differently in the present with newer diagnostic tools (19).

N. de Prost et al (6) evaluated factors associated with in-hospital and long-term mortality. In their series, in-hospital mortality was 25%. Shock, elevated plasmatic lactate dehydrogenase level and glomerular filtration rate <60 mL/min were independently associated with in-hospital mortality. In their study, the mortality rate of discharged patients was 16% during the follow-up period. Age >60 years, previous cardiovascular disease and persistent renal failure requiring chronic hemodialysis were associated with long-term mortality. Our series reports an all-cause mortality during follow-up of 21%, including both in-hospital mortality and mortality in discharged patients, which is lower than previously reported. In-hospital mortality was significantly superior in the immune group, which is consistent with the significantly higher need for admission in ICU, blood transfusion and incidence of shock in this group of patients, suggesting a more aggressive disease. Hospital length of stay was also significantly superior in the immune group. This can be explained by the more aggressive

disease and possibly by a slower response to therapy than, for example, patients in which is possible to rapidly remove a causal factor.

In conclusion, although this is a single-center retrospective analysis, DAH appears to be a heterogeneous syndrome in which etiology may confer distinct disease course. In our series, patients with immune DAH had a significantly larger percentage of neutrophils on BAL fluid analysis, a finding that, to our knowledge, is not reported elsewhere in literature. We also report one case of cannabis-induced DAH, which is rarely reported in literature. Patients with immune DAH were significantly younger, had more severe presentations of the disease and worst outcomes. Prospective multi-center studies are needed to clearly understand the best diagnostic and therapeutic approach to each group of patients.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 59-60

The impact of skin involvement on the psychological well-being of patients with sarcoidosis

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Abstract. *Background:* Physicians frequently face challenges when screening and managing mental health impairment caused by different diseases, particularly those involving the skin. *Objective:* We aim to identify the major aspects of mental health impairment related to secondary skin involvement occurring in sarcoidosis patients. *Methods*: A total of 718 patients with a biopsy-confirmed diagnosis of sarcoidosis were included from the A Case Control Etiologic Study of Sarcoidosis (ACCESS) study. Sample was divided into two groups depending on presence or absence of skin involvement. Each recruited patient underwent mental health assessment using two measures: depression and mood scales. Demographic data of participants was obtained. *Results:* A total of 143 sarcoidosis patients had secondary skin involvement, and 575 had no skin involvement. Sarcoidosis patients with skin involvement had lost their appetite more frequently, experienced low mood more frequently, and had frequently encountered a significant loss of acceptance compared to patients without skin involvement. *Conclusion:* A multidisciplinary approach including a focused psychological assessment for patients with sarcoidosis; particularly those with skin involvement, is encouraged. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 59-60)*

Key words: sarcoidosis, chronic disease, depression, psychology, skin

Acronyms and abbreviations:
ACCESS, A Case Control Etiologic Study of Sarcoidosis
CESD, The Center for Epidemiologic Studies Depression Scale

Introduction

Skin lesions are commonly encountered in patients with different chronic systemic diseases. Such involvement can be associated with mental health impairment that is distinct from the psychological stress caused merely by the chronic illness per se. Patients with chronic skin lesions are frequently distressed by symptoms of physical disfigurement, itching, scratching and impaired daily activities (1).

Psychological factors play an important role in at least 30% of skin disorders (2). Several studies have reported high rates of mental health co-morbidities among patients with chronic skin conditions (2, 3). Furthermore, it was reported that patients with chronic skin conditions are more likely to report mental health symptoms and suicidal ideation when compared to those without chronic skin conditions (4). Previous literature has shed light on mental health disorders and symptomatology alongside primary skin conditions (e.g. acne vulgaris, psoriasis, ... etc.). However, no significant data has reported the impact of secondary skin involvement as a part of multi-systemic diseases. The present study addresses

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the psychological impact associated with secondary skin involvement in sarcoidosis.

Sarcoidosis is a multi-systemic disease characterized by the formation of non-caseating granulomas in various tissues. It is estimated that 25-30% of patients with sarcoidosis suffer from skin manifestations related to their illness (4, 5). Skin involvement can occur at any stage of the disease, but most frequently they occur at the onset; so that a dermatologist or a primary healthcare physician may be the first to encounter those patients (4, 6). In contrast, both primary healthcare physicians and dermatologists face challenges in screening as well as diagnosing mental health co-morbidities associated with other long-standing illnesses (7).

The aim of this study is to emphasize the role of dermatologists and primary healthcare physicians in addressing mental health disabilities caused by skin involvement in patients with sarcoidosis. We also aim to focus on the importance of early diagnosis and management of accompanying psychological impairment or any form of mental health disorders related to such skin manifestations occurring in patients with sarcoidosis. We retrospectively assessed a sample of patients with sarcoidosis form the A Case Control Etiologic Study of Sarcoidosis (ACCESS) study sample data for presence of any mental health impairment that can be related to their skin manifestations.

Methods

Our study was approved and informed consent was waived by Jordan University's International Review Board (IRB) committee with an agreement by the National Institute of Health (NIH).

Patient inclusion

This study included participants from A Case Control Etiologic Study of Sarcoidosis (ACCESS). ACCESS is a case-control multicenter study designed to determine the etiology of sarcoidosis, and was conducted in 10 clinical centers in the United States. ACCESS study enrolled 736 patients with recent tissue confirmation of granuloma (within 6 months) and a compatible clinical course. Tissue samples are considered positive for sarcoidosis if they demonstrate non-caseating granuloma and are read as being compatible with a diagnosis of sarcoidosis, without other possible causes such as tuberculosis or histoplasmosis. Only patients 18 years of age or older were included in the study. All patients having active tuberculosis or taking anti-tuberculosis therapy were excluded. Organ involvement was determined in each patient, using an assessment system based on findings from history, physical examination, and laboratory testing. Skin involvement was confirmed clinically as well as pathologically by the finding of non-caseating granulomas in biopsies obtained from these lesions. Further details on the study can be found in previous studies (8, 9).

In the present study, 718 participants from the ACCESS population were included. Those were participants who have a biopsy-confirmed diagnosis of sarcoidosis according to the criteria of ACCESS study. We divided our sample population into two groups: the first included 143 patients who have biopsy-confirmed skin involvement, and the second group included 575 sarcoidosis patients without skin involvement as controls. Demographic data including patient's age, gender, and marital status of each participant were obtained. The responses of recruited patients to both the depression questionnaire and mood questionnaire (Check appendix 1 and 2) were also obtained. These questionnaires are designated by the ACCESS study to determine the psychosocial- and health-related quality of life features associated with sarcoidosis. The mood questionnaire is the same as Life Orientation Test (LOT), which assesses patient's mood via a 12-item questionnaire, where each patient can choose a score from one to five based on the intensity of the mood change under question (Appendix 1) (10).

The depression questionnaire covered patients' complaints over the past week. It is a short form of the original CESD questionnaire and included 11 items derived from the 'Center for Epidemiologic Studies Depression Scale' (CESD) (11). The Center for Epidemiologic Studies Depression Scale (CESD) was created in 1977 by Laurie Radloff, and revised in 2004 by William Eaton and other (11). The CESD is a screening test for depression and depressive disorder. It measures symptoms defined by the American Psychiatric Association' Diagnostic and Statistical Manual (DSM-V) for a major depressive episode questions. Respondents are asked to choose a score

from zero to four based on the duration of the complaint during the previous week (Appendix 2).

Statistical analysis

In our statistical analysis, we used IBM SPSS for Windows release 21.0 (SPSS Inc., Chicago, IL); and implemented descriptive statistics to define our sample population. We used Independent Sample T-test to study sarcoidosis patients with skin lesions versus those without; according to variables being: age, depression scores, and mood scores. Furthermore, we used Pearson correlation to study the relation between age and depression and mood scores. We considered P value of less than 0.05 as statistically significant.

Results

A total of 718 patients diagnosed with sarcoidosis were included in this study, there were 261 (36.4%) males and 457 (63.4%) females with an age range from 18 to above 60 years of age. Our sarcoidosis patients comprised of: 143 (20%) with skin involvement (42 males, 101 females), and 575 (80%) without skin involvement (219 males, 356 females).

Upon analysis of depression questionnaire, statistically-significant correlation with skin involvement was only found with questions number two, five and eleven (appendix 2), with a seemingly direct trend. Sarcoidosis patients with skin involvement had lost their appetite (p=0.001), and had experienced the feeling of low mood (p=0.03) more frequently as opposed to those without skin involvement. Patients with skin involvement also showed a more statistically significant loss of acceptance (p=0.012). We didn't find a significant difference in the total depression score with skin involvement. Detailed percentages and p values for each question are shown in (Table 1).

Regarding the mood questionnaire (appendix 1), none of the included questions, nor the total score, showed any statistically significant correlation with skin involvement (p value >0.5). Detailed percentages and p values for each question are shown in (Table 2).

On studying the relevance between demographic data (age, gender and marital status as individual factors) and skin involvement; we found out that none of them had any statistically significant correlation with skin involvement per se. However, gender discrepancy significantly affected the type of skin lesions (p=0.01), where erythema nodosum was found to affect 44 female patients compared to 12 male patients; with a male to female ratio of approximately 1:4. Moreover, gender discrepancy was also significantly associated with several depression questions of patients in both groups; including question number two (p<0.001); which assesses loss of appetite; and question number five (p<0.001), which assesses frequency of experiencing low mood. Both questions showed a statistically significant higher frequency in females.

Discussion

Previous literature did not shed enough light on psychological aspects in patients with chronic systemic diseases such as sarcoidosis, yet several studies have managed to point out the effectiveness of addressing psychological management in such group of patients (12). It is worth noting that an estimated 25% of patients with dermatological manifestations have significant psychological morbidity (13). Literature addressing psychological aspects affecting patients with skin manifestations in chronic systemic diseases, particularly sarcoidosis, is quite scarce. In our study, we aimed to fulfill this gap, and address such a vital, yet overlooked subject.

Our study, showed that sarcoidosis patients with skin involvement had a statistically significant greater frequency of decreased appetite when compared to those without skin manifestations. This complaint was noticeably more frequent among female patients. Such a significant finding was not documented in previous literature. On the contrary, in a similar study that was conducted on children; the aforementioned relationship was not of note (7). Other studies examining stand-alone skin lesions and manifestations, have not shown any relationship to appetite (14).

It was also reported that once decreased appetite leads to weight loss in patients with chronic diseases; the general health, wellbeing and functionality are dramatically affected (15). Thus, decreased appetite is a serious co-morbidity that should not be overlooked by clinicians, and primary healthcare physicians in particular, as they are the first line of contact in most

Table 1. The following table shows the percentages of each response to the depression questionnaire (appendix 1) for sarcoidosis patients with skin involvement (Yes) and without skin involvement (No). The results of statistically comparing both groups are presented and the significant *p* values are shown in bold

Question	Skin involveed	Rarely (Less than 1 day)	Some of the time (1-2 days)	Moderate amount of the time (3-4 days)	Most of the time (almost every day)	Total % (#)	*p*-Value
1- I was bothered by things that don't usually bother me	Yes	49.7%	30.1%	11.9%	8.4%	100% (143)	0.28
	No	60.3%	24.2%	9.7%	5.7%	100% (575)	
2- I did not feel like eating, my appetite was poor	Yes	62.2%	19.6%	8.4%	9.8%	100% (143)	**0.001**
	No	68.9%	18.3%	9%	3.8%	100% (575)	
3- I had trouble keeping my mind on what I was doing	Yes	42%	33.6%	14.7%	9.8%	100% (143)	0.79
	No	53.2%	27.8%	10.6%	8.3%	100% (575)	
4- I felt everything I did was an effort	Yes	32.9%	32.2%	15.4%	19.6%	100% (143)	0.28
	No	45.9%	26.1%	14.4%	13.6%	100% (575)	
5- I felt low mood	Yes	45.5%	31.5%	7.7%	15.4%	100% (143)	**0.03**
	No	55.3%	28.5%	10.3%	5.9%	100% (575)	
6- I felt hopeful about the future	Yes	12.6%	21.7%	24.5%	41.3%	100% (143)	0.55
	No	15%	20.2%	24.9%	40%	100% (575)	
7- I felt fearful	Yes	61.5%	25.2%	7%	6.3%	100% (143)	0.21
	No	65.9%	23%	6.4%	4.7%	100% (575)	
8- My sleep was restless	Yes	28.7%	23.8%	23.8%	23.8%	100% (143)	0.20
	No	29.7%	30.6%	19.5%	20.2%	100% (575)	
9- I was happy	Yes	11.9%	19.6%	25.9%	42.7%	100% (143)	0.13
	No	6.8%	22.3%	29.2%	41.7%	100% (575)	
10- I felt lonely	Yes	60.1%	22.4%	11.2%	6.3%	100% (143)	0.11
	No	64.3%	22.6%	8%	5%	100% (575)	
11- I could not get going	Yes	41.3%	28%	14.7%	16.1%	100% (143)	**0.01**
	No	43.5%	34.4%	12.9%	9.2%	100% (575)	

cases. Nonetheless, when patients with sarcoidosis were asked to give some feedback on the Sarcoidosis Health Questionnaire SHQ, the general consensus showed dissatisfaction; and the main reason was that the questionnaire did not address the subject of appetite (16), which is consistent with our finding.

Our study showed that the frequency of experiencing low mood is higher amongst sarcoidosis patients with skin involvement. A similar finding was documented in a previous study in 2006, that was conducted on skin manifestations of chronic skin conditions in children (7). An earlier study also showed that both low mood and psychological distress are two major factors that reflect the general wellbeing, and can be used as parameters to assess psychological comorbidities related to skin conditions (1). Furthermore, lack of acceptance, i.e. refusal to accept and adapt with current circumstances, is another major finding in our study. It was evidently and significantly experienced in sarcoidosis patients with skin involvement. Other studies of similar nature showed similar findings; where psoriasis patients were found to experience lack of acceptance which was influenced by age, gender and disease duration; thus having a more complex relationship (17). Disease acceptance and adaptation to living circumstances was found to improve patients' distress (18). It was also noted to have a beneficial effect on both general and mental health status of patients diagnosed with chronic systemic diseases such as rheumatoid arthritis and multiple sclerosis (18). Accordingly, we suggest that delivering news of diagnosis or

Table 2. The following table shows the percentages of each response to the mood questionnaire (appendix 2) for sarcoidosis patients with skin involvement (Yes) and without skin involvement (No). The results of statistically comparing both groups are presented and the significant *p* values are shown in bold

	Skin involved	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Total % (#)	p-Value
1- In certain times, I usually expect the best	Yes	22.1%	33.7%	25.6%	18.6%	0%	100% (86)	0.966
	No	20.4%	35.6%	26.6%	17.4%	0%	100% (632)	
2- It is easy for me to relax	Yes	7%	38.4%	18.6%	32.6%	3.5%	100% (86)	0.158
	No	11.9%	31%	26.4%	25.5%	5.2%	100% (632)	
3- If something can go wrong for me, it will	Yes	7%	19.8%	31.4%	33.7%	8.1%	100% (86)	0.541
	No	6.8%	17.1%	25.2%	38.4%	12.5%	100% (632)	
4- I always look on the bright side of things	Yes	17.4%	43%	25.6%	14%	0%	100% (86)	0.545
	No	24.2%	37.5%	24.4%	13.9%	0%	100% (632)	
5- I am always optimistic about my future	Yes	18.6%	34.9%	31.4%	15.1%	0%	100% (86)	0.188
	No	24.1%	40.2%	21.5%	14.2%	0%	100% (632)	
6- I enjoy my friends a lot	Yes	31.4%	50%	14%	4.7%	0%	100% (86)	0.470
	No	37.5%	41.9%	16.9%	3.6%	0%	100% (632)	
7- It's important for me to keep busy	Yes	30.2%	37.2%	18.6%	14%	0%	100% (86)	0.167
	No	38.3%	39.1%	14.4%	8.2%	0%	100% (632)	
8- I hardly ever expect things to go my way	Yes	3.5%	24.4%	15.1%	40.7%	16.3%	100% (86)	0.07
	No	4.9%	12.2%	19.8%	44%	19.1%	100% (632)	
9- Things never work out the way I want them to	Yes	2.3%	7%	26.7%	48.8%	15.1%	100% (86)	0.09
	No	3.6%	10.1%	17.1%	44.6%	24.5%	100% (632)	
10- I don't get upset too easily	Yes	10.5%	36%	19.8%	22.1%	11.6%	100% (86)	0.571
	No	12.8%	38.3%	21.8%	20.1%	7%	100% (632)	
11- I am a believer in the idea that "every cloud has a silver lining"	Yes	17.4%	39.5%	30.2%	12.8%	0%	100% (86)	0.566
	No	22.6%	41.3%	24.7%	11.4%	0%	100% (632)	
12- I rarely count on good things happening to me	Yes	5.8%	10.5%	22.1%	40.7%	20.9%	100% (86)	0.415
	No	4.3%	12.7%	15.6%	43.3%	24.2%	100% (632)	

complications related to sarcoidosis, as a chronic systemic disease, to patients should be dealt with more sensitively and cautiously. As the lack of acceptance and denial of diagnosis amongst patients, could have ripples that might be of major contribution in lowering adherence rates in medical or drug therapies. Eventually, causing delays in clinical improvement of the disease as a whole.

Gender difference should also be considered. At present, our study showed that females were more frequently experiencing a decrease in their appetite and low mood. On contrary, other studies reported that age and gender are not significantly related to psychological status of patients with chronic skin diseases such as atopic dermatitis and psoriasis (1).

We suggest that healthcare professionals revisit the general assessment tools in patients with sarcoidosis. We thus advice, our fellow colleagues and physicians to pay extra attention to mental health and psychological well-being of their patients and to keep in mind the relevant risk factors discussed earlier, for "without mental health there can be no true physical health" as Dr Brock Chisholm, the first Director-General of the World Health Organization (WHO) stated many years ago.

Worth mentioning, our study had limitations that need to be taken into account. First, our study might have a mild form of selection bias as it only included patients with sarcoidosis. Whether our findings can be generalized to other chronic systemic

diseases with skin involvement is still uncertain. Second, the cofounding effect of other variables, such as employment, socioeconomic status, and existence of other psychological comorbidities, could not be ruled out as their effects were not included in the questionnaires. Third, we could not definitely rule out if some of our control group had a clinically-silent skin involvement that was not proven by biopsy at time of diagnosis, which might under-estimate our findings. Forth, we could not classify the skin involvement in our patients into acute or chronic, so we were not able to study the difference in disease impact on mental health and well-being between acute and chronic skin involvement. Finally, depression and mood questionnaires used do not ask specifically about skin, and as Sarcoidosis is a multi-system disease, the involvement of other system may have a confounding effect on our results. We encourage future research to be carried out in the same area to study a broader sample of patients with different chronic multi-systemic diseases with skin manifestations and to assess their general mental health and well-being.

In summary, skin involvement in sarcoidosis is a major player in the affected patients' psychological wellbeing. Sarcoidosis patients with skin manifestations have lost their appetite more frequently, were more prone to grief and more frequently experienced loss of acceptance compared to those without skin involvement. Our study results encourage dermatologists and primary health care physicians to carefully address skin manifestations, especially when they are part of a bigger picture of chronic multi-systemic diseases; being sarcoidosis in our study.

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N.A and S.A.A obtained the data. S.A.A. and L.M analyzed the data. S.A.A, L.M and H.A wrote the manuscript and N.A reviewed the manuscript for further details. All authors approved the final version.

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Supplementary material

Appendix 1

Mood assessment questionnaire

The following questions ask about your mood and attitudes:

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
1- In certain times, I usually expect the best.					
2- It is easy for me to relax.					
3- If something can go wrong for me, it will.					
4- I always look on the bright side of things.					
5- I am always optimistic about my future.					
6- I enjoy my friends a lot.					
7- It's important for me to keep busy.					
8- I hardly ever expect things to go my way.					
9- Things never work out the way I want them to.					
10- I don't get upset too easily.					
11- I am a believer in the idea that "every cloud has a silver lining".					
12- I rarely count on good things happening to me.					

Appendix 2

Depression assessment questionnaire

The following questions ask about your feelings during the past week. For each of the statements, please indicate if you felt that way rarely or never, some of the time, a moderate amount of time, or most of the time.

	Rarely (Less than 1 day)	Some of the time (1-2 days)	Moderate amount of the time (3-4 days)	Most of the time (almost every day)
1- I was bothered by things that don't usually bother me.				
2- I did not feel like eating, my appetite was poor.				
3- I had trouble keeping my mind on what I was doing.				
4- I felt everything I did was an effort				
5- I felt low mood.				
6- I felt hopeful about the future.				
7- I felt fearful.				
8- My sleep was restless.				
9- I was happy.				
10- I felt lonely.				
11- I could not get going.				

SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 60-73

Musculoskeletal and pulmonary outcomes of sarcoidosis after initial presentation of osseous involvement

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Abstract. *Objective:* We aimed to investigate the musculoskeletal and pulmonary outcomes of patients with osseous sarcoidosis. *Methods:* We identified 24 patients with osseous sarcoidosis and at least one year of follow-up after diagnosis (baseline). We collected outcome data at 1-year follow-up and last follow-up. We defined a composite outcome measure; worsening considered as worsening in any of the following 4 components compared to baseline: 1) osseous sarcoidosis symptoms, 2) musculoskeletal imaging of affected bone, 3) chest imaging, or 4) pulmonary function testing (PFT). *Results:* A minority of patients had a worsening composite outcome at 1-year (9/24, 38%) and last follow-up (5/24, 21%). When only considering musculoskeletal symptoms and imaging, only 25% (6/24) and 13% (3/24) of patients worsened compared to baseline at 1-year and last follow-up, respectively. Patients with a worsening composite overall outcome tended to be older at baseline than those without the outcome for both 1-year (54.3 years vs. 47.5 years, p=0.11) and last follow-up (55.0 years vs. 48.7 years; p=0.23), although these differences were non-significant. Treatment was not associated with worsening composite overall outcome at 1-year follow-up (p=0.40), but was significantly associated with decreased risk for worsening at last follow-up (p=0.05). *Conclusions:* In this retrospective cohort study of osseous sarcoidosis, most patients had a favorable outcome according to symptoms, musculoskeletal/chest imaging, and PFTs, even though only a minority were treated with glucocorticoids or DMARDs. These results suggest that the natural history of osseous sarcoidosis is often benign, although some patients experience clinical progression. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 60-73)*

Key words: sarcoidosis, health outcomes, pulmonary disease, autoimmune disease, bone tissue, pulmonary function test

Introduction

Sarcoidosis is a systemic inflammatory disease characterized by accumulation of non-caseating granulomas in affected organs (1). Sarcoidosis primarily affects the lungs and lymph nodes resulting in varying degrees of severity ranging from asymptomatic involvement to life-threatening manifestations such as pulmonary fibrosis (2–4). A less common manifestation of sarcoidosis is involvement of the skeletal system. Osseous sarcoidosis was first described in the late 1800s (5). Since then, multiple case reports and case series have detailed the features of osseous sarcoidosis (6-17), highlighting the challenge of diagnosis and treatment of the disease. Despite an extensive literature regarding the natu-

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ral history of pulmonary sarcoidosis, little is known about the epidemiology of osseous sarcoidosis and even less about the natural course of this manifestation of sarcoidosis (3, 5, 18). Recent case series have provided detailed information on the underlying characteristics and extent of osseous sarcoidosis at diagnosis, demonstrating that the disease commonly involves multiple bones, including the spine, and is often asymptomatic, with diagnosis made incidentally with imaging (5, 18, 19). However, no previous study has systematically investigated the long-term clinical outcomes of sarcoidosis from imaging, musculoskeletal, and pulmonary perspectives.

Our objective was to investigate osseous sarcoidosis over time using a retrospective cohort of patients with incident osseous sarcoidosis. Given review of previous studies, mostly focused on the presentation of osseous sarcoidosis (5, 6, 12, 20, 21), we expected that most patients would have a relatively stable clinical disease course in terms of stable or improved symptoms, pulmonary function testing (PFT), and musculoskeletal and chest imaging. We also sought to investigate whether the distribution of osseous lesions and other clinical variables at baseline might predict later clinical outcomes.

Methods

Design

We performed a retrospective cohort study investigating the musculoskeletal and pulmonary outcomes of patients following incident diagnosis of osseous sarcoidosis. The Partners HealthCare Institutional Review Board approved all aspects of the study.

Case ascertainment and study sample

Cases were ascertained from a single center (Brigham and Women's Hospital, Boston, MA) using electronic medical record searches and directed inquiry to rheumatologists in the Division of Rheumatology, Immunology, and Allergy and pulmonologists in the Division of Pulmonary and Critical Care Medicine, as previously described (19). All patients were verified to have osseous sarcoidosis based on either bone biopsy showing non-caseating granulomas or known sarcoidosis who had bone lesions on imaging that were determined to be due to sarcoidosis by the treating clinician and radiologist as well as two medical record reviewers (ERM and JAS). Inclusion criteria for the study sample were: at least one follow-up clinical visit with a pulmonologist or rheumatologist at least one year from the date of osseous sarcoidosis diagnosis (baseline). In addition, we required patients to have PFTs, musculoskeletal/chest imaging, or laboratory measures (at least one of the following: serum angiotensin converting enzyme [ACE] level, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] level, serum calcium level, or 25-hydroxy vitamin D level), associated with at least one of the follow-up visits. All follow-up visits (inpatient, outpatient, or emergency department) were reviewed retrospectively from date of first sarcoidosis diagnosis (osseous or systemic) to the end of the study on July 1, 2016.

Data acquisition/covariates

We reviewed clinical and imaging data at baseline and all follow-up visits from rheumatologists and pulmonologists as well as any other notes relevant to covariates or outcomes. Clinical radiographic reports on imaging procedures of the chest (including plain radiographs, computed tomography [CT] scans, magnetic resonance imaging [MRI]) as well as musculoskeletal imaging (plain radiographs, CT scans, MRI, bone scans, and positron emission tomography [PET] scans) were reviewed by a single abstractor (ERM), and used to determine progression related to sarcoidosis over time. In addition, clinical data were collected including encounter type, clinician type (pulmonology, rheumatology, other), baseline and follow-up laboratory data (ACE, ESR, CRP, calcium, hemoglobin, and 25-hyrdoxy vitamin D), PFT results, and organ involvement, and treatment. We also collected data on emergency department visits as well as hospital admissions (including intensive care unit admissions), fractures overall and at sites of sarcoidal involvement, and death.

Outcomes

Follow-up notes and objective data were reviewed to determine each patient's disease status. For every visit, medical records were reviewed to classify improvement, stability, or worsening in osseous sar-

coidosis (symptoms and musculoskeletal imaging) and pulmonary sarcoidosis (chest imaging and PFT results). Osseous sarcoidosis symptoms were considered to have worsened if, after reviewing medical record notes, the treating provider documented that patient reported worsening pain or other symptoms attributable to osseous sarcoidosis. Progression in PFTs was determined using the impression of the pulmonologist who interpreted the results, PFTs were considered worsening if there was a significant change (defined as ≥12% and ≥200 ml) in forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) typically referring to new or worsened obstruction or restriction respectively, as per current ATS recommendations (22). Imaging was considered worsening, based on review of the clinical radiologist's interpretation. In cases where comparison either across modality (for imaging), or between time points (for imaging and/or PFTs), was not explicitly interpreted, worsening was decided by the medical record reviewer (ERM) based on clinical reports.

As our primary outcome, we created a 4-component composite measure to capture the overall disease course. A worsening composite outcome was defined as any worsening compared to baseline in one or more of: 1) osseous sarcoidosis symptoms, 2) musculoskeletal imaging, 3) chest imaging, or 4) PFTs. To more specifically evaluate the musculoskeletal disease course, we also investigated a composite osseous outcome, which we defined as any worsening compared to baseline in either osseous sarcoidosis symptoms or musculoskeletal imaging. We also investigated each component of the composite overall measure separately. Since data were obtained from routine clinical care, patients had varying durations of follow-up without fixed intervals. We considered their 1-year and last follow-up time points, since all patients had these time points for outcomes available. We also analyzed other follow-up time points as a sensitivity analysis (2 years and 5 years), but these analyses had restricted sample size and did not meaningfully change the results. We also performed a sensitivity analysis of patients who received no treatment as a proxy for the natural history of osseous sarcoidosis.

Statistical analysis

We report descriptive statistics of patients at baseline and follow-up visits using frequencies and proportions for categorical variables, mean and standard deviation for continuous normally distributed variables, and median, range, and interquartile range for continuous non-normally distributed variables. We report the number and proportion of the worsening composite outcomes as well as the components classified as improved, stable, or worsening at 1-year and last follow-up.

We investigated whether baseline factors were associated with worsening composite overall and osseous outcomes at 1-year and last follow-up in separate analyses. In these analyses, the composite outcomes were binary variables indicating that there was or was not worsening in any of the components at that follow-up time point compared to baseline. We used Fisher's exact tests for categorical variables given cells with low frequencies, *t*-tests for normally distributed continuous variables, and Wilcoxon rank-sum tests for non-normally distributed continuous variables. We did not include multivariable regression models due to the limited numbers of outcomes and few statistically significant results in univariate models. Patients with missing data were not included in analyses pertaining to that variable.

We considered a two-sided p value <0.05 as statistically significant in all analyses. Analyses were performed using SAS v9.4 (Cary, NC).

Results

Description of cohort

We identified 24 patients with osseous sarcoidosis and at least one year of follow-up. A summary of their baseline characteristics at the time of osseous sarcoidosis diagnosis is presented in Table 1. Patients were predominately white (96%); 54% were female; and mean age at diagnosis was 50.0 years (SD 10.2). Fifty-eight percent of patients were diagnosed by bone biopsy revealing non-caseating granulomas, and 67% of patients had osseous sarcoidosis as part of their initial presentation for sarcoidosis. Most (75%) had hilar lymphadenopathy, with pulmonary parenchymal involvement in 83%, and nearly all (83%) had evidence of involvement in more than one bone. A minority (21%) had involvement only in the peripheral skeleton while most had axial involvement (75%).

Table 1. Baseline characteristics at diagnosis of osseous sarcoidosis (n=24)

Characteristic			% (n/N), mean (SD), or median (range)
Demographics			
Female			54%
White			96%
Mean age at osseous sarcoidosis, years (SD)			50.0 (10.2)
Presentation			
Median time between osseous detection and diagnosis, days (range)			99 (0-1095)
Diagnosed by bone biopsy			58%
Osseous sarcoidosis at sarcoid presentation			67%
Osseous sarcoidosis only			8%
Ever smoker			17%
Symptoms and distribution of involved bones			
Symptomatic from osseous involvement			54%
>1 bone involved			83%
Any axial skeleton involvement			75%
Any spinal involvement			67%
Any peripheral skeleton involvement			67%
Only axial involvement			29%
Only peripheral skeleton involvement			21%
Spirometry			
Spirometry measured			71%
Obstructive pattern			6% (1/17)
Restrictive pattern			18% (3/17)
Laboratory measures	Range	Median	% Abnormal
Serum ACE, units/mL	10-162	67.5	57 (8/14)
ESR, mm/hr	5-62	12.5	50 (6/12)
CRP, mg/L	0.2-51.0	2.1	40 (4/10)
Serum calcium, mg/dL	8.9-10.7	9.7	0 (0/19)
25-hydroxy vitamin D, ng/mL	13-39	31	29 (2/7)
Hemoglobin, g/dL	12.3-18.2	14.1	26 (5/19)
Any abnormal test			58 (14/24)
Imaging modality performed at diagnosis			% (n/N), mean (SD), or median (range)
Plain film			42%
Computed Tomography			33%
Bone scan at diagnosis			13%
MRI			63%
PET scan			50%
Other sarcoidosis organ involvement			
Pulmonary			83%
Lymphatic			75%
Cutaneous			8%
Ocular			8%
Cardiac			8%
Splenic			4%
Neurologic			4%
Current medication use			
DMARD or glucocorticoid			13%
DMARD			4%
Glucocorticoid			8%

Abbreviations: ACE, angiotensin-converting enzyme; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging; PET, Positron Emission Tomography; DMARD, disease-modifying antirheumatic drug;

Of the 17 (71%) patients with spirometry measured at the time of initial diagnosis, 3 (18%) had a restrictive pattern, and 1 (6%) had an obstructive pattern. Laboratory values available at time of diagnosis revealed 14 (58%) patients with at least one abnormal laboratory test in serum ACE, ESR, CRP, calcium, hemoglobin, or 25-hydroxy vitamin D levels. Half of the patients had at least one comorbidity (hypertension, cancer, coronary artery disease, asthma, or chronic obstructive pulmonary disease). Three patients (13%) were already being treated with medications (DMARDs or glucocorticoids) for other sarcoidosis manifestations at the time of osseous diagnosis.

Table 2 shows the distribution of outcomes, including clinical and laboratory findings, at the 1-year

Table 2. Characteristics of patients with osseous sarcoidosis at each specified follow-up time point

	1-year follow-up (n=24)			Last follow-up[a] (n=24)		
Follow-up duration and outcomes						
Total follow-up, person-years	34.3			149.2		
Number of visits, median (range)	5.5 (2-11)			13 (2-85)		
Follow-up, median years (range)	1.0 (0.4-6.1)			5.3 (1-26.3)		
Death	0%			4%		
Fracture in bone affected by sarcoidosis during follow-up*	0%			0%		
Worsening composite overall outcome[b]	38%			21%		
Worsening composite osseous outcome[c]	25%			13%		
Worsening osseous symptoms	13%			0%		
Worsening osseous imaging	21%			13%		
Worsening chest imaging	17%			8%		
Worsening spirometry	8%			4%		
	Range	Median	% Abnormal	Range	Median	% Abnormal
Laboratory values						
ACE level, units/L	6-113	54	50 (4/8)	16-114	49	29 (2/7)
ESR, mm/hr	4-27	8	37.5 (3/8)	5-79	16.5	70 (7/10)
CRP, mg/L	0.04-8.1	5.4	57 (4/7)	0.04-50	4	57(4/7)
Calcium, mg/dL	8.6-10.2	9.4	0 (0/15)	7.7-10.1	9.4	0 (0/19)
25-hydroxy vitamin D, ng/mL	15-32	23	40 (2/5)	12-31	24	33 (1/3)
Any abnormal test[d]	38% (9/24)				33% (8/24)	
Current medication use						
DMARD or glucocorticoid use	46%				33%	
Glucocorticoid only	17%				8%	
Median dose, mg/day (range)	7.5 (2.5-15)				8.8 (5-20)	
DMARD use	29%				25%	
Methotrexate use only	13%				4%	
Median dose, mg/week (range)	12.5 (10-20)				22.5 (20-25)	
Methotrexate and infliximab use	4%				4%	
Hydroxychloroquine use only	8%				8%	
Azathioprine use only	4%				4%	
Current infliximab use only	0%				8%	
Current NSAID use	8%				17%	

Abbreviations: ACE, angiotensin converting enzyme; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; DMARD, disease-modifying antirheumatic drug; NSAID, Non-steroidal anti-inflammatory drug;

[a] Last follow-up was defined as the most recent follow-up visit up to the study completion date of July 1, 2016.

[b] Any worsening over time in any of: 1. Osseous sarcoidosis-related symptoms 2. Osseous sarcoidosis imaging 3. Pulmonary function tests 4. Chest/pulmonary imaging

[c] Any worsening over time in any of: 1. Osseous sarcoidosis-related symptoms or 2. Osseous sarcoidosis imaging

[d] Any abnormal serum ACE, ESR, CRP, calcium, or vitamin D level

* There were no fractures at sites of osseous sarcoidosis involvement in any patients; 1 fracture did occur and was recorded as a stress fracture. The patient was on prednisone throughout the course of follow up.

and last follow-up time points. There were a total of 149.2 person-years of follow-up for all patients, with a median follow-up time of 5.3 years per patient. One patient died due to massive hemoptysis in the setting of pulmonary hypertension and diffuse pulmonary involvement with sarcoidosis. There was one bone fracture during follow-up. This was a stress fracture of the foot which had no prior evidence of sarcoid involvement. The median total number of clinic visits to rheumatology or pulmonary providers was 5.5 and 13 at the 1-year and last follow-up, respectively. Rates of treatment for systemic sarcoidosis increased from 13% at baseline to 46% at 1-year follow-up, and 29% at last follow-up. Methotrexate and hydroxychloroquine were the most commonly prescribed DMARDs at all time points.

Composite overall and osseous outcomes

At 1-year follow-up, most patients had either stability or improvement compared to baseline in the individual components of the composite overall outcome (Figure 1A). At 1-year follow-up, 38% and 25% of patients had worsening composite and composite osseous outcomes, compared to 21% and 13% at last follow-up. Only three (13%) patients had worsening symptoms attributable to osseous sarcoidosis at 1-year follow-up. Osseous sarcoidosis lesions were evaluated by imaging for all 24 patients at least once in the first year of follow up. Six (25%) patients had objective radiographic improvement in osseous sarcoidosis lesions, 13 (54%) had stable osseous lesions and 5 (21%) had worsening in imaging of osseous lesions at 1-year follow-up. Pulmonary imaging remained stable for 16 (67%) patients, worsened in 4 (17%), and improved in 4 (17%). PFTs remained stable for 16 (88%) patients at 1 year, with only 1 (4%) and 2 (8%) patients in the group either having improved or worsened pulmonary function tests, respectively.

The descriptive clinical outcomes at last follow-up were similar to the 1-year follow-up (Figure 1B). Thirteen (52%) patients had improvements in symptoms related to osseous sarcoidosis and the remaining 11 (48%) had unchanged symptoms. Most patients had improvement or stability of osseous lesions on musculoskeletal imaging at last follow-up compared to baseline, with 12 (50%) improving, 9 (38%) remaining stable, and 3 (13%) worsening at time of last follow-up. Pulmonary imaging revealed improvement in pulmonary sarcoidosis in 7 (28%) patients, stability in 15 (60%) and worsening in 2 (8%) patients at last follow up. There were few PFT changes at last follow-up, with 22 (88%) remaining unchanged, 1 (4%) showing improvement and 1 (4%) worsening.

Figure 2 panels A-D shows a representative patient with improved osseous sarcoidosis on musculoskeletal and chest imaging over a 3-year period compared to baseline. The patient was treated initially with prednisone, methotrexate, and infliximab and was gradually weaned off all medications at the follow-up time point. Figure 2 panels E-H shows a representative patient with worsening osseous lesions on musculoskeletal imaging and pulmonary infiltrates that were read as stable over 1.5 years compared to baseline. This patient was treated with azathioprine and rituximab for nearly 1 year due to intolerance of corticosteroids.

Associations of baseline factors with worsening outcomes at follow-up

At 1-year follow-up, 9 (38%) patients had worsening composite overall outcome, and 6 (25%) had worsening osseous outcome. Few baseline characteristics were statistically associated with worsening outcome at 1 year (Table 3). While these results did not reach statistical significance (likely due to small sample size), female sex, older age at osseous diagnosis, symptoms related to osseous sarcoidosis at time of diagnosis, and treatment for sarcoidosis all showed a trend toward an association with worsening composite overall outcome. Patients tended to be older at baseline (mean 54.3 vs. 47.5 years, p=0.11) for those with a worsening composite outcome at 1 year. Current DMARD or glucocorticoid use at baseline was associated with a lower proportion of patients with positive worsening composite outcome (22% vs. 60%, p=0.10). A worsening composite overall outcome was also more common in patients with a restrictive pattern on PFTs (43% vs. 0%), p=0.05). In addition, having a worsening composite osseous outcome at 1 year showed a trend toward association with older age at baseline (p=0.10), and the presence of musculoskeletal symptoms at time of diagnosis (p=0.17).

Table 4 shows the associations of baseline factors with outcomes at the last follow-up visit, simi-

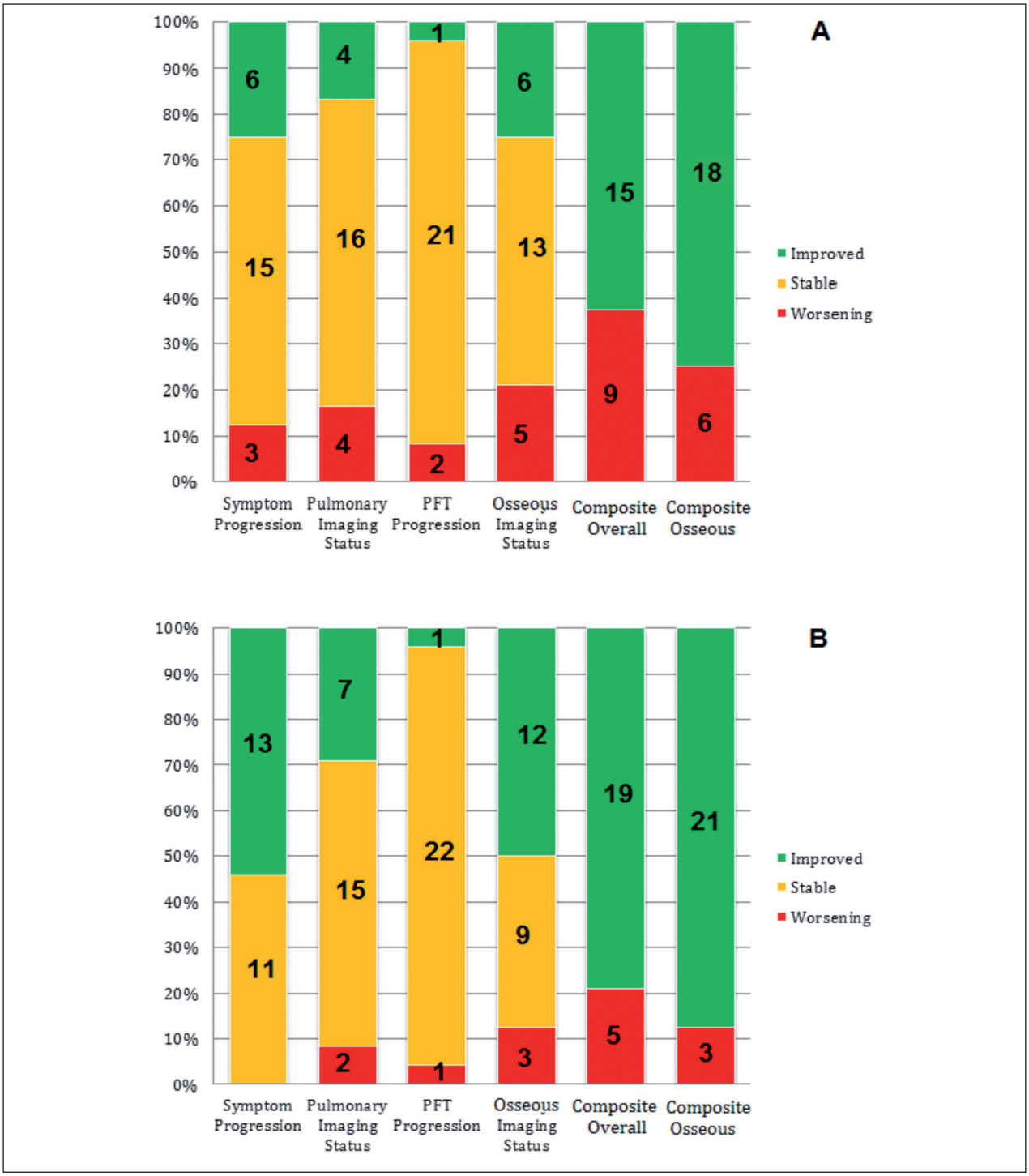

Fig. 1. Clinical outcomes at (A) 1-year follow-up and (B) last follow-up compared to baseline. For Symptom Progression, Pulmonary Imaging Status, PFT Progression, and Osseous Imaging Status, the numbers in green refer to absolute number of patients with improvement, numbers in yellow refer to absolute number of patients with stability, and numbers in red refer to absolute number of patients with worsening. The Y-axis shows percentage for each category. For Composite Overall, numbers in red refer to a positive composite outcome of any worsening in Symptom Progression, Pulmonary Imaging, PFT Progression, or Osseous Imaging. Numbers in green refer to negative Composite outcome. For Composite Osseous, numbers in red refer to a positive composite osseous outcome of any worsening in Symptom Progression or Osseous Imaging

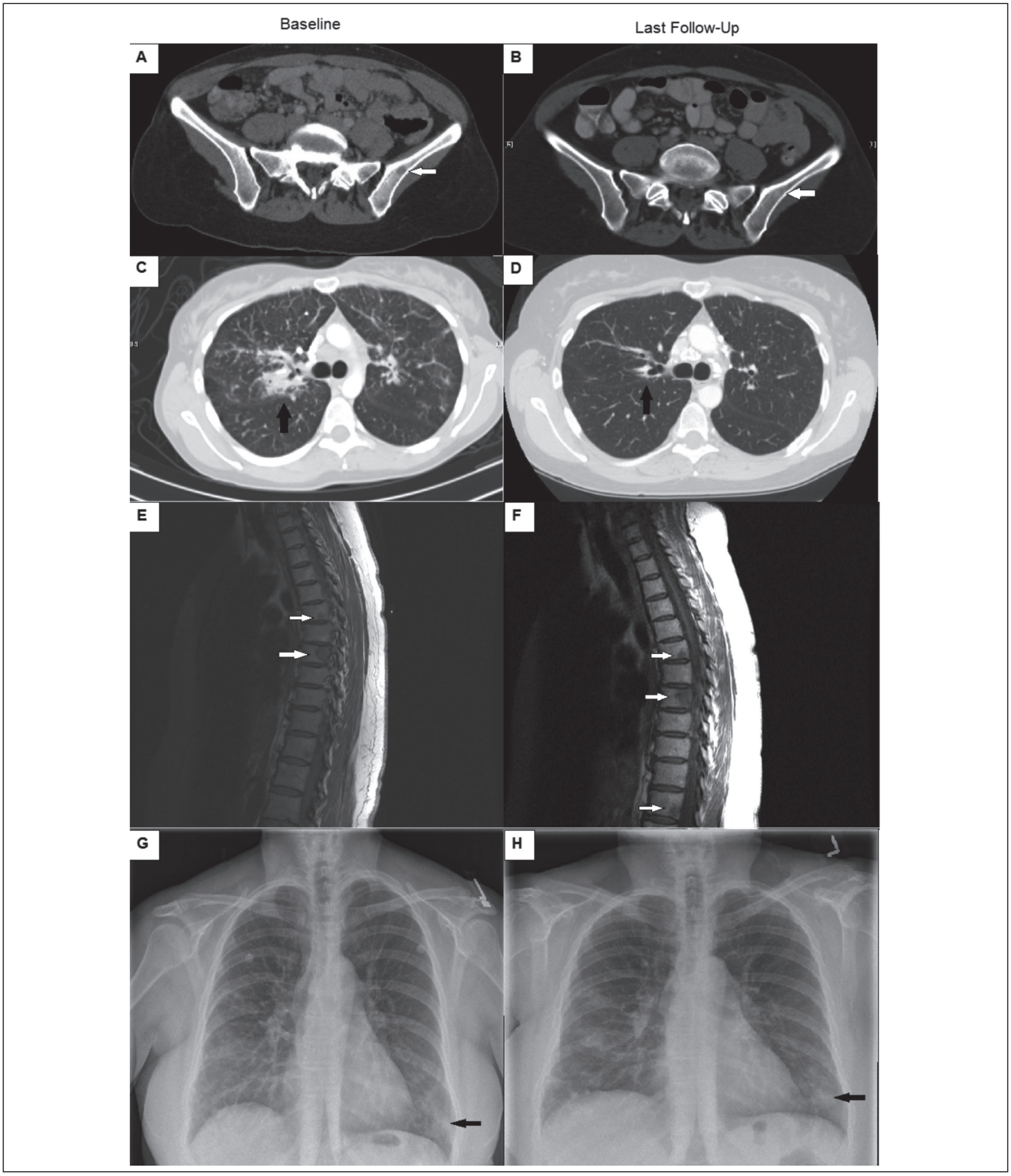

Fig. 2. Panels A-D show representative images of radiographic features of a patient with improving osseous sarcoidosis. Panel A (baseline) and panel B (follow-up) show osseous sarcoidosis improvement on pelvic computed tomography imaging of the left iliac bone (white arrows). Panel C (baseline) and panel D (follow-up) show improvement in chest imaging, particularly in peribronchiovascular consolidation (black arrows) on chest computed tomography imaging. Panels E-H show a patient with worsening osseous sarcoidosis. Panel E (baseline) and panel F (follow-up) show larger osseous lesions in the thoracic spine (white arrows) on T1-weighted magnetic resonance imaging. Panels G (baseline) and panel H (follow-up) show stable lower lobe nodular opacities (black arrows) on chest plain film.

Table 3. Clinical characteristics at baseline and outcomes at 1 year of follow-up (n=24)

	Worsening composite overall outcome at 1 year[a]			Worsening composite osseous outcome at 1 year[b]		
	Yes (n=9)	No (n=15)	p value	Yes (n=6)	No (n=18)	p value
Demographics						
Female	78% (7/9)	40% (6/15)	0.10	67%% (4/6)	50% (9/18)	0.65
White	100% (9/9)	93% (14/15)	>0.99	100% (6/6)	94% (17/18)	>0.99
Mean age at osseous sarcoidosis diagnosis, years (SD)	54.3 (11.5)	47.5 (8.6)	0.11	55.9 (10.1)	48.1 (9.6)	0.10
Presentation						
Ever smoker	11% (1/9)	20% (3/15)	>0.99	0% (0/6)	22% (4/18)	0.54
Diagnosed by bone biopsy	67% (6/9)	53% (8/15)	0.68	83% (5/6)	50% (9/18)	0.34
Osseous sarcoidosis only	0% (0/9)	13% (2/15)	0.51	0% (0/6)	11% (2/18)	>0.99
Pulmonary Involvement	89% (8/9)	80% (12/15)	>0.99	83% (5/6)	83%(15/18)	>0.99
Hilar lymphadenopathy	89% (8/9)	80% (12/15)	>0.99	100% (6/6)	78% (14/18)	0.54
Osseous symptoms and distribution						
Symptomatic at baseline[c]	78% (7/9)	40% (6/15)	0.10	83% (5/6)	44% (8/18)	0.17
Any axial involvement	78% (7/9)	73% (11/15)	>0.99	83% (5/6)	72% (13/18)	>0.99
Any spinal involvement	67% (6/9)	67% (10/15)	>0.99	67% (4/6)	67% (12/18)	>0.99
Any peripheral involvement	56% (5/9)	73% (11/15)	0.41	50% (3/6)	72% (13/18)	0.36
Clinical and laboratory measures						
Baseline spirometry performed	78% (7/9)	67% (10/15)	0.67	83% (5/6)	67% (12/18)	0.63
Obstructive pattern[d]	14% (1/7)	0% (0/10)	0.41	20% (1/5)	0% (0/12)	0.29
Restrictive pattern[e]	43% (3/7)	0% (0/10)	**0.05**	40% (2/5)	8% (1/12)	0.19
Abnormal ACE[f]	20% (1/5)	60% (3/5)	0.52	0% (0/3)	57% (4/7)	0.20
Abnormal ESR[g]	38% (3/8)	83% (5/6)	>0.99	100% (2/2)	86% (6/7)	>0.99
Abnormal CRP[h]	50% (1/2)	40% (2/5)	>0.99	0% (0/1)	50% (3/6)	>0.99
Abnormal 25-hydroxy vitamin D[i]	33% (1/3)	0% (0/3)	>0.99	0% (0/1)	20% (1/5)	>0.99
Any abnormal laboratory value	44% (4/9)	47% (7/15)	>0.99	33% (2/6)	50% (9/18)	0.65
At least 1 comorbidity	33% (3/9)	60% (9/15)	0.40	50% (3/6)	50% (9/18)	>0.99
Medications						
Ever treated[k]	44% (4/9)	67% (10/15)	0.40	50% (3/6)	56% (11/18)	0.67
Current treatment	22% (2/9)	60% (9/15)	0.10	33% (2/6)	50% (9/18)	0.65

ACE, angiotensin converting enzyme; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug;

[a]Composite outcome was defined as worsening at this time-point in any of: Osseous sarcoidosis related symptoms, Osseous sarcoidosis imaging, Pulmonary function tests, or Chest/pulmonary imaging

[b] Any worsening over time in any of: Osseous sarcoidosis related symptoms, or Osseous sarcoidosis imaging

[c] Symptomatic from osseous lesions/sarcoidosis at baseline visit

[d] Out of 17 patients with spirometry performed

[e] Out of 17 patients with spirometry performed

[f] 10/24 patients had ACE levels drawn at 1-year follow-up

[g] 9/24 patients had ESR levels at 1-year follow-up

[h] 7/24 patients had CRP levels at 1-year follow-up

[i] 6/24 patients 25(OH)-vitamin D levels at 1-year follow-up

[j] Presence of at least one of the following: coronary artery disease, chronic obstructive pulmonary disease, asthma, hypertension, systemic lupus erythematosus, or cancer

[k] Ever received medical therapy (DMARD or glucocorticoid) since diagnosis

lar to the results at 1-year follow-up. Patients with peripheral skeletal involvement were significantly less likely to have worsening composite or osseous outcome compared to those with no peripheral involvement (20% vs. 79%, p=0.03, and 0% and 76%, p=0.03). Worsening osseous composite overall outcome was associated with older age at baseline (mean 61.0 years vs. 48.5, p=0.04). Patients who had ever been treated for sarcoidosis at any time between baseline and follow-up were significantly less likely

Table 4. Clinical characteristics at baseline and outcomes at last follow-up (n=24)

	Worsening composite overall outcome at last follow-up[a]			Worsening composite osseous outcome at last follow-up[b]		
	Yes (n=5)	No (n=19)	p value	Yes (n=3)	No (n=21)	p value
Demographics						
Female	80% (4/5)	47% (9/19)	0.33	67%% (2/3)	52% (11/21)	>0.99
White	100% (5/5)	95% (18/19)	>0.99	100% (3/3)	95% (20/21)	>0.99
Mean age at diagnosis, years (SD)	55.0 (14.9)	48.7 (8.6)	0.23	61.0 (11.7)	48.5 (9.2)	**0.04**
Presentation						
Ever smoker	20% (1/5)	16% (3/19)	>0.99	0% (0/3)	19% (4/21)	>0.99
Diagnosed by bone biopsy	60% (3/5)	58% (11/19)	>0.99	67% (2/3)	57% (12/21)	>0.99
Osseous sarcoidosis only	0% (0/5)	11% (2/19)	>0.99	0% (0/3)	10% (2/21)	>0.99
Pulmonary Involvement	100% (5/5)	79% (15/19)	0.54	100% (3/3)	81%(17/21)	>0.99
Hilar lymphadenopathy	80% (4/5)	84% (16/19)	>0.99	100% (6/6)	78% (14/18)	0.54
Osseous Symptoms and Distribution						
Symptomatic at baseline[c]	80% (4/5)	47% (9/19)	0.33	67% (2/3)	52% (11/21)	>0.99
Any axial involvement	80% (4/5)	74% (14/19)	>0.99	100% (3/3)	71% (15/21)	0.55
Any spinal involvement	80% (4/5)	63% (12/19)	0.63	100% (3/3)	62% (13/21)	0.53
Any peripheral involvement	20% (1/5)	79% (15/19)	**0.03**	0% (0/3)	76% (16/21)	**0.03**
Laboratory and clinical measures						
Baseline spirometry performed	80% (4/5)	68% (13/19)	>0.99	100% (3/3)	67% (14/21)	0.53
Obstructive pattern[d]	25% (1/4)	0% (0/13)	0.24	33% (1/3)	0% (0/14)	0.18
Restrictive pattern[e]	25% (1/4)	15% (2/13)	>0.99	33% (1/3)	14% (2/14)	0.46
Abnormal ACE[f]	0% (0/3)	57% (4/7)	0.20	0% (0/2)	50% (4/8)	0.47
Abnormal ESR[g]	100% (2/2)	86% (6/7)	>0.99	100% (1/1)	88% (7/8)	>0.99
Abnormal CRP[h]	50% (1/2)	40% (2/5)	>0.99	0% (0/1)	50% (3/6)	>0.99
Abnormal 25-hydroxy vitamin D[i]	0% (0/2)	25% (1/4)	>0.99	0% (0/1)	20% (1/5)	>0.99
Any abnormal lab	40% (2/5)	47% (9/19)	>0.99	33% (1/3)	48% (10/21)	>0.99
At least 1 comorbidity[j]	60% (3/5)	47% (9/19)	>0.99	100% (3/3)	43% (9/21)	0.22
Medications						
Ever treated[k]	20% (1/5)	74% (14/19)	**0.05**	33% (1/3)	67% (14/21)	0.53
Current treated	0% (0/5)	37% (7/19)	0.27	0% (0/3)	33% (7/21)	0.53

ACE, angiotensin-converting enzyme; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging; PET, Positron Emission Tomography; DMARD, disease-modifying antirheumatic drug; NSAID, Non-steroidal anti-inflammatory drug;

[a] Composite outcome was defined as worsening over time in any of: Osseous sarcoidosis related symptoms, Osseous sarcoidosis imaging, Pulmonary function tests, or Chest/Pulmonary imaging

[b] Any worsening over time in any of: Osseous sarcoidosis related symptoms, or Osseous sarcoidosis imaging

[c] Symptomatic from osseous lesions/sarcoid at baseline visit

[d] Out of 17 patients with spirometry performed

[e] Out of 17 patients with spirometry performed

[f] 10/24 patients had ACE levels drawn at last follow-up

[g] 9/24 patients had ESR levels drawn at last follow-up

[h] 7/24 patients had CRP levels drawn at last follow-up

[i] 6/24 patients Vitamin D 25-OH levels at 1-year follow-up

[j] Presence of at least one of the following: coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), asthma, hypertension (HTN), systemic lupus erythematosus (SLE), and cancer

[k] Ever received medical therapy (DMARD or glucocorticoid) since diagnosis

(20% vs. 74%, p=0.05) to have a worsening composite outcome at last follow-up.

In sensitivity analyses, we found similar results in subgroups restricted to no treatment and at 2-year and 5-year follow-up time points (data not shown).

Discussion

We evaluated the baseline characteristics, clinical features, and outcomes of 24 patients with osseous sarcoidosis followed for at least one year. This

study represents a relatively large clinical cohort whose disease outcomes were investigated over time. Unique to our study was the use of a composite clinical outcome metric to assess the clinically relevant progression of this rare manifestation of an uncommon disease. We found that a majority of patients with osseous sarcoidosis had a stable or improved course of disease during follow-up. Regardless of the distribution of bones involved, patients had mostly favorable outcomes. However, a minority of patients did experience clinical deterioration in terms of symptoms and musculoskeletal and chest imaging.

Unlike previous studies focusing on clinical characteristics of patients with osseous sarcoidosis at diagnosis, we designed our study to investigate relevant subsequent disease outcomes after diagnosis to assess long-term clinical outcomes. We created a composite outcome incorporating both subjective and objective measures of osseous and pulmonary disease to represent clinically relevant outcomes for patients with osseous involvement in sarcoidosis. Similar to the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG) (23) classifications, we incorporated clinician evaluation of symptoms and objective reports of imaging modalities in order to determine worsening, stability, or improvement. At baseline, just over half of the patients in our cohort were symptomatic from their osseous sarcoidosis based on review of provider notes. This is similar to rates of symptoms in larger series (5, 18). At 1-year and last follow-up, most patients remained with stable or improved composite disease or osseous-specific disease outcomes. This finding is consistent with our previous descriptive study (19), and also consistent with other case series of osseous sarcoidosis (9, 10). Our study provides reassurance to both patients and clinicians that osseous involvement of sarcoidosis may have a favorable prognosis in terms of imaging and symptoms. However, given the small number of patients in our series and relatively limited follow-up, we cannot comment on risks that may develop in the longer term or that may have been detected with a larger sample size.

In our cohort, we found few baseline demographic or clinical features associated with the composite or osseous outcomes. At 1-year follow-up, only the baseline presence of restrictive spirometry was statistically significantly associated with progression of osseous sarcoidosis by the composite overall outcome. This association disappeared at last follow-up, suggesting that abnormal spirometry may not be associated with worsening osseous sarcoidosis. However, we cannot definitively determine whether or not pulmonary sarcoidosis was the driver of either clinical evaluation or improvement. Ours is the largest study to investigate the pulmonary function of patients with osseous sarcoidosis. A smaller case series involving seven patients with osseous involvement also noted no clear association between spirometry patterns and osseous involvement (12). While we had few statistically significant associations, the detailed description of patients at baseline, 1-year, and last follow-up will be useful to provide counseling to patients who present with osseous sarcoidosis.

The distribution of affected bones did not appear to correlate with long-term outcomes. At 1-year follow-up, there were more patients who either improved or did not worsen in both composite outcomes and osseous outcomes with any peripheral involvement. At last follow-up, peripheral involvement was statistically significantly associated with stability or improvement in composite or osseous outcomes. However, other patterns were not associated with differences in outcomes. Axial or spinal involvement was not associated with worsening osseous sarcoidosis outcomes in our study.

We previously reported on the clinical characteristics of patients at our center with osseous sarcoidosis at diagnosis and this current report adds more cases (19). Our results are also similar to another case series (18) finding that a majority of osseous sarcoid patients were middle-aged, and have involvement of the axial skeleton with multiple bone lesions. Another case series reported a majority of patients were African American and diagnosed at a younger age than our cohort (5). Our results likely reflect the local selection of our patient population, rather than a true difference in prevalence of osseous sarcoidosis across different populations.

Most of our patients had involvement of the axial skeleton, including 67% with spinal involvement, including the vertebrae. There are conflicting data on the typical distribution of skeletal involvement in osseous sarcoidosis. Larger case series describe axial involvement ranging from 51%-88% (5, 6, 18, 24). In one of these series, none of the 17 patients identified with osseous sarcoidosis by MRI had involvement of the vertebrae (24). Involvement of the axial skeleton

is of particular clinical concern as it can be difficult to distinguish radiographically from metastatic cancer (9).

In our cohort, laboratory measurements were available for most patients. Just over half had at least one abnormal laboratory test, and approximately half had elevated serum inflammatory markers. None of the patients had an abnormal serum calcium level. This finding suggests that, unlike the lytic lesions of metastatic cancer (25), the osseous lesions in sarcoidosis generally present without hypercalcemia. We found that baseline laboratory abnormalities were not associated with worsening composite or osseous outcomes over time, suggesting that abnormal serum levels of ACE and inflammatory markers are not reliable predictors for worsening clinical outcomes for patients with osseous sarcoidosis.

Osseous sarcoidosis can mimic metastatic bone lesions (9, 13) and for this reason is often heavily evaluated by physicians. Patients in our cohort had a median of 5.5 and 13 visits at 1 year and last follow-up, respectively. This high level of resource utilization in a cohort with, on average, favorable outcomes, may suggest that less aggressive follow-up may be warranted for some patients with osseous sarcoidosis. However, the timing and frequency of clinical follow-up should be determined based on clinical expertise since it is unclear that osseous involvement alone was responsible for this utilization of health care.

We found that treatment at baseline and during follow-up was associated with favorable clinical outcomes. Patients who were undergoing treatment with DMARDs or glucocorticoids at baseline were more likely to have stability or improvement than those patients who were never treated for osseous sarcoidosis during follow-up. Despite reports suggesting that osseous sarcoidosis is resistant to treatment (26), our data, along with other case reports and case series, (5, 6, 11, 18, 19, 27) demonstrate that patients with osseous sarcoidosis requiring treatment do respond favorably to systemic anti-inflammatory drugs. It is unclear whether the natural history of osseous sarcoidosis portends a relatively benign clinical course or whether some of the favorable clinical outcomes observed were related to treatment. Our study provides a rationale for future, prospective studies to further investigate the role of treatment in osseous sarcoidosis.

There are several limitations to our study. While ours is one of the largest studies of patients with osseous sarcoidosis and the first to concentrate on outcomes after initial presentation, our sample size was small and the length of follow-up was relatively limited. Therefore, we may have been unable to detect true associations and may not have observed clinically relevant outcomes that require larger sample size and longer follow-up, such as bone fractures or death. We created a composite measure to detect any worsening on three objective tests (musculoskeletal/chest imaging and PFTs) and one subjective measure (symptoms). However, this composite measure has not been validated, and it may not fully capture the burden of disease. We created this measure since no other outcome measures currently exist, and we utilized criteria that clinicians and patients are likely to consider important metrics for success and/or initiating treatment. In our analysis, an abnormality in any one of four outcome measures resulted in a positive composite outcome, indicating overall deterioration. We find the relatively small number of patients who experienced this broad definition of a worsening composite outcome, to be reassuring information for providers and patients.

Although we collected detailed data on a variety of clinically relevant characteristics, our study was retrospective, and so not all data were available at all time points. We included patients through electronic medical record search and case specialist case referral. This process may bias our sample, and may account for the rate of biopsies performed to diagnose osseous sarcoidosis. The frequency of follow-up visits was determined by routine clinical care and was inevitably variable. It is possible that clinically meaningful outcomes may have occurred and were not noted in our medical record. However, most patients received all their care at our institution. While we collected a large list of laboratory, imaging, and clinical data, there was a relatively large amount of missing data since not all of these measurements were clinically indicated for all patients. Also, patients with active disease requiring close clinical follow-up may have been seen more often and received more clinical measures than patients with more stable disease. However, since we found that most patients had a relatively stable course during follow-up, we find this unlikely to explain our results. While our intent was to describe the natural history of patients with os-

seous sarcoidosis, some patients were treated with DMARDs and glucocorticoids. When we restricted the sample size to patients who received no treatment, we found overall similar results.

Those who were treated with glucocorticoids or DMARDs were slightly more likely to have improvement at last follow-up compared to those who did not receive treatment. However, we found no association at the 1-year follow-up time point, so this result may be due to chance. Larger, prospective observational and interventional studies are needed to further describe the natural history of osseous sarcoidosis and to determine the role of treatment. Finally, we only included patients at a large tertiary care hospital so our results may not be generalizable to other patients owing to the care setting and demographics of our population. We encourage collaborative efforts to further investigate rheumatic manifestations of sarcoidosis on a larger scale across institutions.

Conclusion

In this study of patients with 5-year median follow-up, we found that most patients with osseous sarcoidosis have a favorable clinical course. After initial diagnosis, most patients with osseous sarcoidosis were either stable or improved as measured by symptoms, musculoskeletal/chest imaging, and PFTs. Notably, the distribution and number of osseous sarcoidal lesions was not associated with worsened clinical outcomes, including among those presenting with widespread axial involvement. We found no association between pulmonary burden at baseline and subsequent osseous sarcoidosis outcomes. While many patients did not require treatment with DMARDs or glucocorticoids, those who were treated also had favorable response. Our findings suggest that osseous sarcoidosis often has a favorable clinical course, though further prospective research is needed for definitive conclusions.

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Study Design: Miller, Fanta, McSparron, Coblyn, Sparks
Acquisition, analysis or interpretation of the data: Miller, Fanta, McSparron, Pan, Coblyn, Sparks.
Critical revision of the manuscript for important intellectual content: Miller, Fanta, McSparron, Pan, Coblyn, Sparks.
Statistical analysis: Miller, Pan, Sparks
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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 74-78

Association of low body surface area with dose reduction and/or discontinuation of nintedanib in patients with idiopathic pulmonary fibrosis: a pilot study

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Abstract. *Background:* We have often encountered adverse events requiring dose reduction and/or discontinuation of nintedanib in patients with idiopathic pulmonary fibrosis. *Objectives:* The objectives of this study were to clarify the incidence of dose reduction and/or discontinuation following the commercialization of nintedanib and to investigate predictors of dose reduction and/or discontinuation of nintedanib at our hospital. *Methods:* We retrospectively identified 25 patients who had received nintedanib 150 mg twice daily at Sendai Kousei Hospital and categorized them into two groups according to whether they had or had not required dose reduction and/or discontinuation and sought to identify predictors of dose reduction and/or discontinuation. *Results:* Seventeen patients developed adverse events, which included diarrhea (n=10, 44%), hepatotoxicity (n=7, 28%), and anorexia (n=2, 16%). No adverse event-related deaths occurred during the study period. Patients who required dose reduction and/or discontinuation were significantly older than those who did not (72 years vs 67 years; *P*=0.047). Body surface area (BSA) was significantly lower in the group that needed dose reduction and/or discontinuation than in the group that did not (1.63 m^2 vs. 1.78 m^2; *P*=0.028). Multivariate logistic regression revealed that the association of low BSA with dose reduction and/or discontinuation was statistically significant. *Conclusions:* A low BSA was associated with dose reduction and/or discontinuation of nintedanib in patients with idiopathic pulmonary fibrosis. Further studies in larger patient samples are needed to validate these findings. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 74-78)*

Key words: body surface area, discontinuation, dose reduction, idiopathic pulmonary fibrosis, nintedanib

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing interstitial pneumonia that occurs primarily in the elderly population and is characterized by increasing dyspnea and loss of lung function (1-3). IPF is ultimately fatal and has a median survival time of only 2-4 years from diagnosis (3).

Nintedanib is an intracellular tyrosine kinase inhibitor of the receptors for fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor (4, 5) and was approved in Japan for use in IPF in September 2015.

Recently, the results of the two replicate Phase III INPULSIS trials demonstrated that nintedanib slowed disease progression in patients with IPF by

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significantly reducing the rate of decline in forced vital capacity (FVC) (6). In these trials, the most common adverse events (AEs) were gastrointestinal; these AEs accounted for the majority of discontinuations of nintedanib (6).

We have often encountered AEs that require dose reduction and/or discontinuation of nintedanib. The objectives of this study were to clarify the incidence of dose reduction and/or discontinuation of nintedanib since its commercialization and to identify predictors of dose reduction and/or discontinuation of this agent at our hospital.

Methods

This retrospective study was performed at the Sendai Kousei Hospital. All consecutive patients with IPF newly treated with nintedanib 150 mg twice daily from October 2015 to April 2017 were enrolled. The diagnosis of IPF was made according to the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement of 2011 (3). The clinical severity of AEs was graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (7). The criteria for dose reduction and/or discontinuation of nintedanib were the same as those used in a previous clinical trial (8).

All patients were evaluated by spirometry (CHESTAC-55V; Chest, Tokyo, Japan) in accordance with the American Thoracic Society/European Respiratory Society Task Force guidelines (9).

The study protocol was approved by the Sendai Kousei Hospital Ethics Committee (IRB.30-14) and was carried out in accordance with the Declaration of Helsinki. The requirement for patient consent was waived in view of the retrospective nature of the study and the anonymity of the data.

Statistical analysis

Univariate and multivariate logistic regression analyses were used to identify patient variables related to dose reduction and/or discontinuation of nintedanib. Categorical variables were tested for significance using the chi-squared test, Student's *t*-test, Mann-Whitney *U* test, or Welch's *t*-test, as appropriate. Variables identified to be significant prognostic indicators in univariate analysis ($P<0.05$) were evaluated by forward selection stepwise multivariate logistic regression. A *P*-value < 0.05 was considered statistically significant. All *P*-values were two-sided. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander and is designed to add statistical functions frequently used in biostatistics (10).

Results

Patient characteristics

The patient characteristics are summarized in Table 1. Nineteen (76%) of the 25 patients with IPF enrolled in the study were male and the median patient age was 69 years. The median body surface area (BSA) was estimated to be 1.69 m^2 using the Du Bois formula. All patients showed the usual interstitial pneumonia pattern on computed tomography scans. The median %FVC and percent diffusing capacity for lung carbon monoxide (DL_{CO}) at baseline were 67.2% and 52.6%, respectively. The median follow-up duration was 244 days (the data cut-off date was June 30, 2017).

Table 1. Baseline characteristics of the study population (n=25)

Characteristic	Value*
Age, years	69 [53-79]
Sex (male), n (%)	19 (76)
Body surface area (Du Bois, m^2)	1.69 [1.36-1.79]
Findings on CT (UIP pattern), n (%)	25 (100)
Laboratory data	
Aspartate aminotransferase (IU/L)	22.7 (15.0-36.0)
Alanine aminotransferase (IU/L)	20.8 (8.0-47.0)
Total bilirubin (mg/dL)	0.84 (0.29-2.07)
Creatinine (mg/dL)	0.76 (0.39-1.48)
Krebs von den Lungen-6 (U/mL)	1131 (523-2394)
Pulmonary function tests	
FVC, L (n=23)	2.19 (0.94-3.84)
%FVC, L (n=23)	67.2 (42.0-112.0)
% DL_{CO}, % (n=16)	52.6 (27.0-89.0)
6MWT	
Lowest SpO_2, % (n=20)	86.4 (75-91)
Walking distance, m (n=20)	355.0 (130-465)

* The values are presented as the median [range] or as the number (percentage). 6MWT, six-minute walk test; CT, computed tomography; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; UIP, usual interstitial pneumonia

Table 2. Categorization of adverse events

	n (%)	CTCAE grade, n 1/2/3/4
Diarrhea	10 (40)	3/7/0/0
Hepatotoxicity	7 (28)	3/4/0/0
Anorexia	4 (16)	2/2/0/0

CTCAE, Common Terminology Criteria for Adverse Events

Table 3. Reasons for dose reduction and/or discontinuation

	n (%)
Dose reduction, n (%)	11 (44)
Diarrhea, n	4
Hepatotoxicity, n	7
Discontinuation, n (%)	4 (16)
Diarrhea, n	2
Anorexia, n	1
Progression of IPF, n	1

IPF, idiopathic pulmonary fibrosis

Categorization of AEs

Table 2 shows the incidence and nature of the AEs. Seventeen patients developed AEs, consisting of diarrhoea (n=10, 40%), hepatotoxicity (n=7, 28%), and anorexia (n=4, 16%). No AE-related deaths occurred during the study period.

Dose reduction and/or discontinuation of nintedanib

Table 3 shows the reasons for dose reduction and/or discontinuation of nintedanib. Eleven patients required dose reduction because of diarrhoea (n=4) or hepatotoxicity (n=7). Of the 4 patients in whom nintedanib was interrupted, 2 had diarrhoea, 1 had anorexia, and 1 had progression of IPF.

Characteristics and examination findings in patients who did and did need dose reduction/discontinuation

The characteristics of patients who did and did not require dose reduction and/or discontinuation are compared in Table 4. There were no significant differences in patient sex, %FVC, $\%DL_{CO}$, 6MWT (six-minute walk test), %min SpO_2 during the 6MWT, or any of the laboratory results between the two groups. Patients who required dose reduction and/or discontinuation were significantly older than those who did not (72 years vs 67 years; P=0.047). Furthermore, BSA was significantly smaller in the group that required dose reduction and/or discontinuation than in the group that did not (1.63 m^2 vs 1.7 8 m^2; P=0.028).

In univariate analysis, older age and a low BSA were significant predictors of dose reduction and/or discontinuation of nintedanib. In multivariate analysis, the only independent predictor of a treatment response was low BSA (odds ratio 0.53, 95% confidence interval 0.29-0.97, P=0.040; Table 5).

Table 5 Multivariate analysis of predictors of dose reduction and/or discontinuation of nintedanib (n = 25)

Variable	OR	95% CI	*P*-value*
Body surface area	0.53	0.29-0.97	0.040

*Result calculated by logistic regression. CI, confidence interval; OR, odds ratio

Table 4. Comparison of characteristics between the group that required dose reduction and/or discontinuation and the group that did not

Variable	Dose reduction and/or discontinuation (n=15)	No dose reduction and/or discontinuation (n=10)	*P*-value
Male sex, n (%)	10 (67%)	9 (90%)	0.390*
Age, years	72 [58-79]	67 [53-72]	0.047†
Body surface area, m^2	1.63 [1.36-1.95]	1.78 [1.55-1.95]	0.028†
%FVC, %	65.6 [42.0-78.0] (n=13)	69.4 [45.0-112.0]	0.877‡
$\%DL_{CO}$, %	51.8 [40.0-70.0] (n=6)	53.1 [45.0-89.0]	0.897†
6MWT, m	339 [130-415] (n=10)	370 [305-465]	0.705‡
%min SpO_2 during 6MWT	86.3 [80-90] (n=10)	86.5 [75-91]	0.760‡
Krebs von den Lungen-6	974 [523-1520]	1368 [656-2394]	0.081§
Albumin	3.9 [3.1-4.4]	4.0 [3.5-4.6]	0.328†
Serum creatinine	0.76 [0.39-1.48]	0.76 [0.56-0.95]	0.853§
Total bilirubin	0.81 [0.29-2.07]	0.88 [0.38-1.62]	1.000‡
Aspartate aminotransferase	22.5 [15.0-36.0]	23.1 [15.0-26.0]	0.738‡
Alanine aminotransferase	19.5 [8.0-47.0]	22.6 [10.0-26.3]	0.374‡

FVC, forced vital capacity; 6MWT, six-minute walk test; min SpO_2, minimal oxygen saturation measured by pulse oximetry.
*Chi-squared test. †Student's *t*-test. ‡Mann-Whitney *U* test. §Welch's *t*-test.

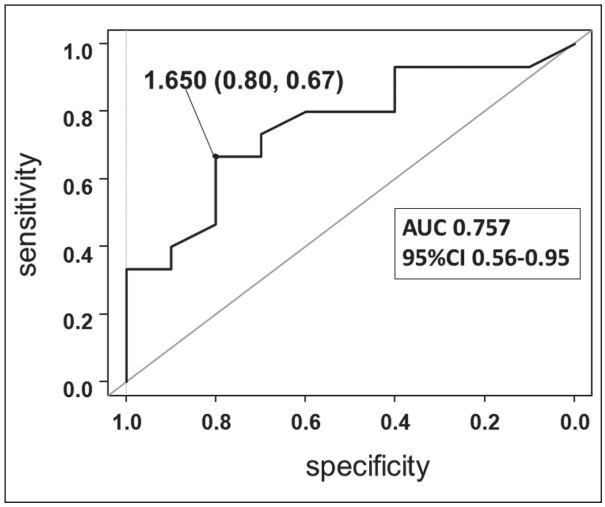

Fig. 1. Receiver-operating characteristic curve analysis used to determine the cut-off values for body surface area. The area under the curve was 0.757 (95% confidence interval 0.56-0.95) and the cut-off value for which sensitivity and specificity was maximal was 1.650 m^2 (67.0% sensitivity and 80.0% specificity)

Figure 1 shows the results of the receiver-operating characteristic (ROC) curve analysis used to determine the cut-off values for BSA. The area under the curve was 0.757 (95% confidence interval 0.56-0.95) and the cut-off value for which sensitivity and specificity was maximal was 1.650 m^2 (67.0% sensitivity and 80.0% specificity).

Discussion

This single-center, retrospective study sought to identify predictors of dose reduction and/or discontinuation of nintedanib in patients with IPF. These predictors have hitherto been unknown. Multivariate analysis revealed that low BSA was the only independent predictor of dose reduction and/or discontinuation of nintedanib 150 mg twice daily. To the best of our knowledge, this is the first study to report this association.

Seven of our 25 patients developed hepatotoxicity, which was grade 2 in 4 cases and grade 1 in 3 cases. No patient developed hepatotoxicity that was more severe than grade 3. In all cases, the hepatotoxicity was completely reversible with dose reduction. Therefore, it may be unnecessary to hesitate when administering nintedanib because of concerns over hepatotoxicity. However, close monitoring and appropriate management according to the guide for appropriate use of nintedanib was required.

The incidence of dose reduction in the present study was considerably higher than that in the INPULSIS trials (44% vs 26.5%-29.2%). The reason for the higher incidence in our study is unclear but could be related to physical or ethnic differences in the study populations. Ikeda et al reported an association of low BSA with hepatotoxicity in patients with IPF receiving nintedanib 150 mg twice daily (11). Of note, the present study included only Japanese patients. A sub-analysis of the INPULSIS trials revealed that elevated hepatic enzymes of any CTCAE grade were more common in the Japanese population than in the non-Japanese population (39.5% vs 10.1%; $P<0.001$); however, the incidence of elevation of aspartate aminotransferase and/or alanine aminotransferase to a CTCAE grade ≥2 was not significantly different between the Japanese and non-Japanese populations (6.6% and 4.8%; $P=0.572$) (12).

Sixteen percent of our patients required discontinuation of nintedanib. In the INPULSIS trials, nintedanib was discontinued in 18.8%-21.0% of patients. We speculate that the reason for this low incidence of discontinuation was prompt dose interruption when hepatotoxicity developed. Furthermore, diarrhoea could be controlled by anti-diarrheal medication.

In patients with a small body habitus, particularly Japanese and Eastern Asian patients with a BSA <1.65m^2, a good option would be to start nintedanib at a dose of 100 mg twice daily and then increase the dose to 150 mg twice daily if safety permits. However, the effectiveness of low-dose nintedanib in Japanese patients is unclear. In the TOMORROW trial, low-dose nintedanib was not demonstrated to be effective; however, that study did not contain Japanese patients (13) and dose reduction was not evaluated in the INPULSIS trials (6). Therefore, the data on dose reduction of nintedanib in the Japanese population are inconclusive.

This study has some limitations in that it had a retrospective single-center design and included a small number of patients. Furthermore, the observation period was too short to assess long-term safety.

In summary, a low BSA was associated with dose reduction and/or discontinuation of nintedanib 150 mg twice daily in patients with IPF. Further studies in larger patient samples are needed to validate these findings.

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Competing interests:
Dr. Kimura reports lecture fees from Boehringer Ingelheim.
Dr. Sugawara reports lecture fees from Boehringer Ingelheim.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 79-85

A case of relapsing isolated neurosarcoidosis in an 18-year-old male patient successfully treated by corticosteroids

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Abstract. Sarcoidosis is a granulomatous multisystemic disease of unknown cause most often affecting the lungs, lymph nodes of the pulmonary hilus, eyes, skin, and other structures including central (CNS) or peripheral nervous system (PNS). Isolated neurosarcoidosis is extremely rare. The diagnosis of isolated neurosarcoidosis is challenging because of its rarity, variety of manifestations, and the lack of systemic signs. We report relapsing and remitting isolated intracranial neurosarcoidosis in an 18-year-old male patient who undervent complex diagnostics including cerebral and meninges biopsy. Patient was succesfully treated with corticosteroids. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 79-85)*

Key words: isolated neurosarcoidosis, biopsy, treatment

Introduction

Sarcoidosis is a granulomatous multisystemic disease of unknown cause most often affecting the lungs, lymph nodes of the pulmonary hilus, eyes, skin, and other structures including central (CNS) or peripheral nervous system (PNS). Simultaneous affection of CNS or PNS with other systems is estimated to 5-10% of cases (1, 4, 6, 8). Isolated neurosarcoidosis is extremely rare, with an estimated incidence in Caucasians of 0.2/100,000 (2). The diagnosis of isolated neurosarcoidosis is challenging because of its rarity, variety of manifestations, and the lack of systemic signs. To reach a definitive diagnosis of neurosarcoidosis, a biopsy must be obtained in order to demonstrate the typical histological picture of sarcoidosis in the nervous system and to exclude other granulomatous diseases (3, 5). We report relapsing and remitting isolated intracranial neurosarcoidosis in an 18-year-old male patient. Tissue from the frontal lobes and meninges of the patient were taken for biopsy.

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Case report

An 18-year-old male patient presented in July 2014 with intensive temporal bilateral headache accompanied by vomitting, photophobia, and dehydration. Neurologic examination revealed quadruhyperreflexia and slowed psychomotoric tempo, without

meningeal signs and involvement of the cranial nerves. The patient had a 6-year history of headache, which was unilateral, mild intensity, well controlled with analgetics. Brain MRI imaging performed in 2009 was negative.

Laboratory findings

Laboratory tests showed hyponatremia of 123 mmol/l (136-146 mmol/L). Results were within normal limits for all remaining laboratory tests including hemogram, CRP, basic metabolic panel, autoimmune screens, endocrine laboratory testing, and imunologic status. The results of extensive serum infectious studies including those for VZV, HSV 1,2, CMV, EBV, Chlamydia pneumoniae, Chlamydia trachomatis, Mycoplasma pneumoniae, Borrelia burgdorferi, HIV, Toxoplasma gondii, Aspergillus fumigatus, Cryptococcus neoformans, Candida, rubeola, and syphilis were negative. The tuberculin reaction (Mantoux II) and the QuantiFERON test were both negative. Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis of 207 lymphocytes, 53 monocytes, and 20 segments, slightly elevated protein levels (0.463 g/l), elevated immunoglobulins (IgM, IgG, IgA), and the presence of oligoclonal bands (Type 3). The results of studies for cerebrospinal fluid infections including bacterial cultivation, cultivation of *Mycobacterium tuberculosis*, polymerase chain reaction (PCR) for the diagnosis of Herpes simplex virus 1/2, Varicella zoster virus, cytomegalovirus, Epstein-Barr virus, Chlamydia pneumoniae, Chlamydia trachomatis, Mycoplasma pneumoniae, Borrelia burgdorferi, and Neisseria gonorrhoeae were all negative. The immunoregulatory CD4/CD8 index was increased to 5 in CSF. Immunophenotyping examination of the CSF did not indicate B-NHL infiltration of the central nervous system. B-lymphocytes were present minimally and showed no pathologic expression of immunological cell markers. Cytologic examination of CSF revealed no blastic forms of T-lymphocytes.

Imaging and additional investigations

Initial computed tomography (CT) revealed bilateral frontal lobe white matter hypodensity. Subsequent magnetic resonance imaging (MRI) of the head with gadolinium contrast demonstrated extensive confluent bilateral frontal white matter hyperintensities on T2-weighted and FLAIR, extending to the optic tracts, chiasma, and adjacent optic nerves, plus leptomeningeal contrast enhancement in these areas (Figure 1). Retinal examination revealed bilateral papilloedema, which was accentuated in the right eye. The patient was treated with methylprednisolone 3000 mg over 6 days. His headaches receded, and on brain MRI in September 2014, regression of the edema and of the postcontrast enhancement of the leptomenings was seen.

Relapse of the disease

In October 2015, the patient developed a fever of unknown genesis. At that time, he was taking antibiotics. He presented with the same symptoms as those in July 2014, namely intensive bilateral temporal headache associated with vomiting and photophobia, but additionally with blurred vision in the right eye followed by one generalized tonic-clonic seizure. Patient complained on blurred vision on the right eye, other clinical symptoms were identical to initial examination. Retinal examination showed bilateral papilloedema. Brain MRI revealed extensive T2 and FLAIR hyperintensities in the frontobasal area bilaterally, and involvement of the ependyme of the lateral ventricles, corpus callosum, medulla oblongata, and cervical and thoracic parts of the spinal cord. Micronodular postcontrast enhancement was present in these areas (Figure 2). MR angiography of the cerebral arteries was negative. Repeat laboratory examination showed mild leukocytosis of $10{,}10\times10^9$/l without elevation of CRP, hyponatremia of 123 mmol/l (136-146 mmol/l), hypochloremia of 87 mmol/l (95-107 mmol/l), and hypokalemia of 3.4 mmol/l (3.8-5 mmol/l). CSF examination revealed 245 lymphocytes, 25 segments, elevated protein levels of 0.86g/l, elevated immunglobulins (IgM, IgG, IgA), and the presence of oligoclonal bands (Type 3). Extensive autoimmune and microbial screenings were negative once again. EEG examination showed non-specific slow waves in the right frontal lobe with a tendency to spread to the left frontal lobe.

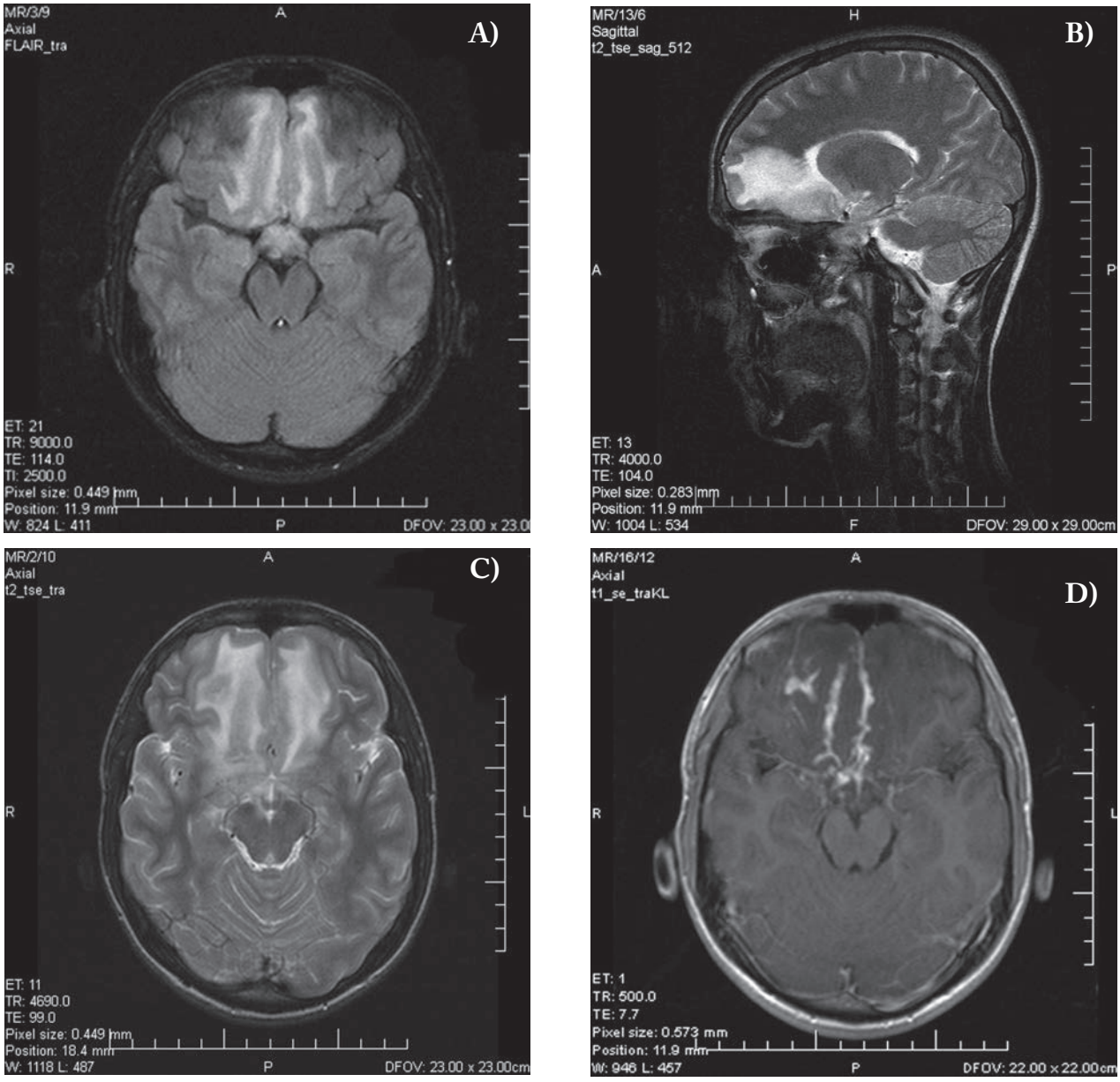

Fig. 1. Magnetic resonance imaging of subcortical white matter and optic chiasm
A: FLAIR diffuse hyperintensity in the bilateral frontal subcortical white matter extending to the chiasma; B, C: T2-weighted image diffuse hyperintensity in the bilateral frontal subcortical white matter extending to the chiasma; D: Postcontrast enahcement of the lesions

Biopsy

The biopsy of frontal lobes demonstrated the typical morphology of chronic non-caseating granulomatous inflammation. The granulomas consisted of dominating histiocytes and epitheloid cells with a few intermingled multinucleated giant cells. The intra- and peri-granulomatous lymphocytes were represented exclusively by a CD3+ T-cell population composed of a mixture of slightly prevailing CD4 and less numerous CD8+ T-lymphocytes. Granulomatous lesions in the subleptomeningeal and meningeal areas were associated with the peri-granulomatous fibrous reaction. The biopsy established the diagnosis of neurosarcoidosis (Figure 3, A-E)).

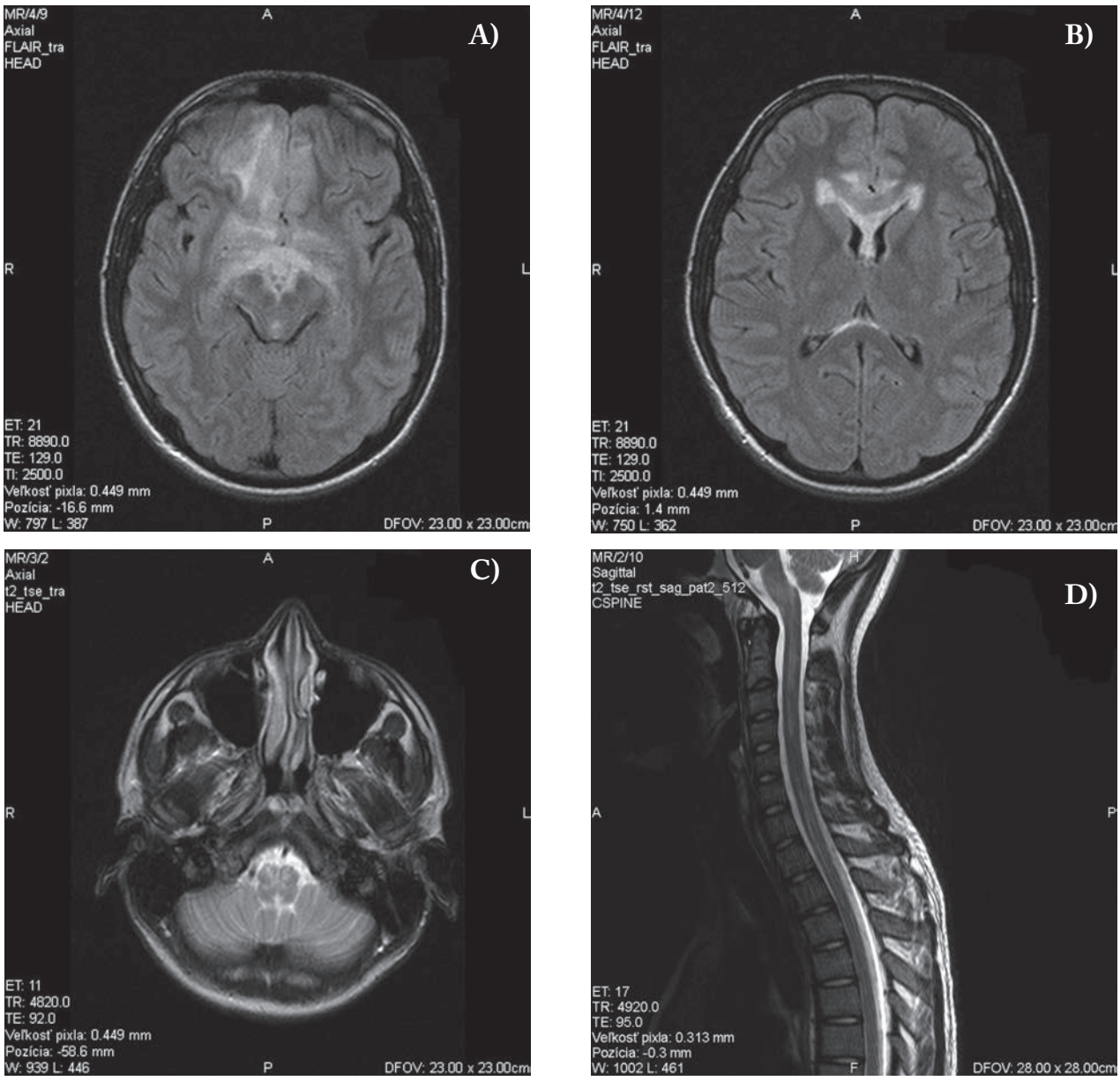

Fig. 2. Magnetic resonance imaging of subcortical white matter, brainstem, and cervical and thoracic spine
A,B: FLAIR diffuse hyperintensity in the bilateral frontal subcortical white matter with involvement of the ependyma of the lateral ventricles and corpus callosum; C: T2-weighted image involvement of the medulla oblongata; D: T2-weighted image involvment of the cervical and thoracal spine

Treatment

Throughout the period of illness, no signs of the involvement of any organs other than the brain were seen. An HRCT scan of the thorax, pulmonary function tests, ophthalmological examination, hand radiographs, and abdominal ultrasonogram were all negative. Our patient met the diagnostic criteria for isolated neurosarcoidosis. Glucocorticoid therapy with prednisolone at 40 mg daily and anti-epileptic therapy with karbamazepine was initiated. The patient was treated with prednisolone for 19 months with slow detraction of the dose. The patient complained on occasional headaches. On follow-up MRI

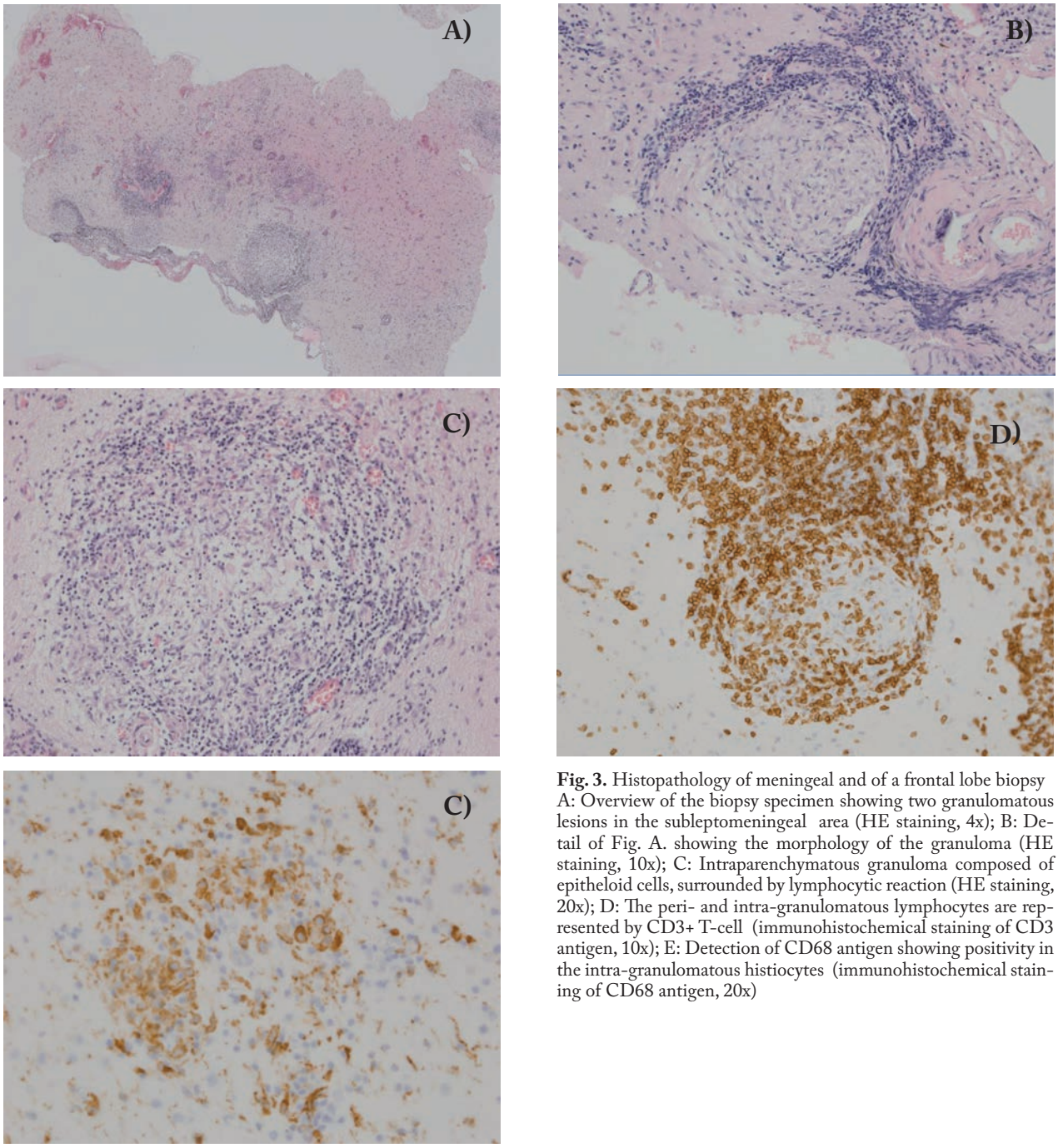

Fig. 3. Histopathology of meningeal and of a frontal lobe biopsy
A: Overview of the biopsy specimen showing two granulomatous lesions in the subleptomeningeal area (HE staining, 4x); B: Detail of Fig. A. showing the morphology of the granuloma (HE staining, 10x); C: Intraparenchymatous granuloma composed of epitheloid cells, surrounded by lymphocytic reaction (HE staining, 20x); D: The peri- and intra-granulomatous lymphocytes are represented by CD3+ T-cell (immunohistochemical staining of CD3 antigen, 10x); E: Detection of CD68 antigen showing positivity in the intra-granulomatous histiocytes (immunohistochemical staining of CD68 antigen, 20x)

scans (4/2016, 10/2017), a marked regression of the hyperintensities and postcontrast enhancement could be seen. Small hyperintensities were still present in frontal lobes, medulla oblongata, and cervical spine with minimal postcontrast enhancement (Figure 4).

Discussion

Based on the MRI findings, the clinical picture, and the laboratory findings, we were able to exclude inflammatory, neoplastic (especially lymphoma, me-

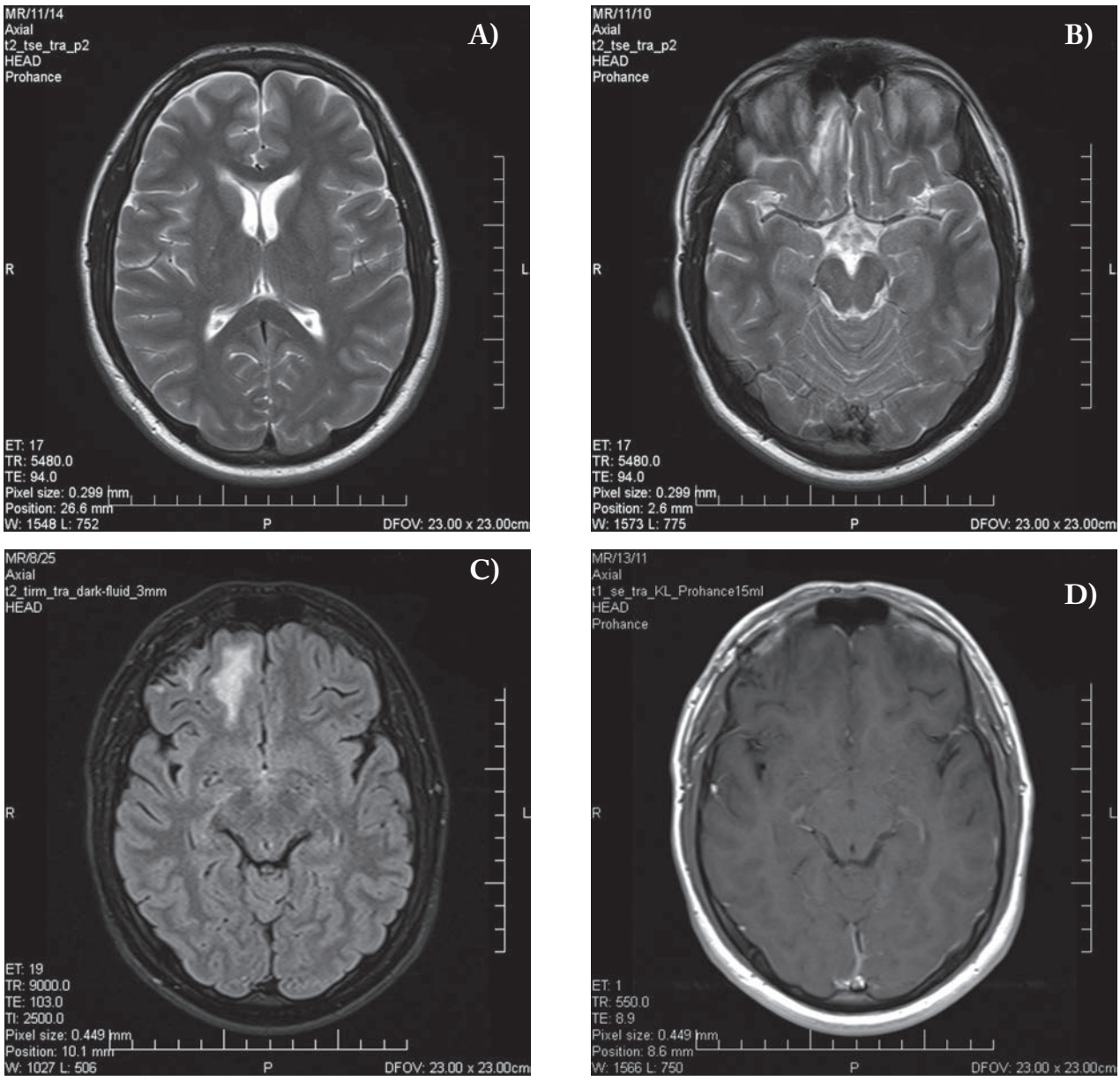

Fig. 4. Magnetic resonance imaging after 19 months of corticosteroid therapy
A, B: T2-weighted image marked regression of hyperintensities in the frontal lobes, corpus callosum, and the ependym of the lateral ventricles; C: FLAIR small hyperintensities are still present in the frontal lobes; D: Minimal postcontrast enhacement, T1-weighted image

tastasis), and infectious etiologies. The good response to intravenous corticosteroids, in addition to the negative extensive infectious studies, excluded infectious etiology but, on the other hand, led us to suspect aseptic meningoencephalomyelitis, neurosarcoidosis, another autoimmune disease, or CNS lymphoma. An important factor to be aware of is the transient but profound response of CNS lymphoma to the use of glucocorticoids (e.g., dexamethasone and prednisolone) (10). More recently, an increase has been reported in the incidence of sporadic primary CNS lymphomas in immunocompetent individuals; this is particularly seen in older patients (50-80 years of age). The vast majority (>90%) of primary CNS lymphoma are of B-cell in origin. Patients with primary CNS lymphoma present similarly to patients

with other central nervous system mass lesions, with symptoms and signs of raised intracranial pressure, focal neurological deficit, and seizures. They can present as solitary (60-70%) or multiple (30-40%) lesions with a predilection for the periventricular white matter, although they can also arise in the cortex or deep gray matter (13, 16). The examination of the CSF including immunophenotyping and cytologic investigations did not establish B-cell lymphoproliferation, the blastic transformation of lymphocytes, or the presence of tumor cells in our patient. The patient's age was also not characteristic for the manifestation of lymphoma. The definitive diagnosis was established after a biopsy. In the present case study, non-caseating granulomatous inflammation was evident in the pathologic analysis. When granulomatous inflammation is discovered through biopsy, other possible etiologies that can cause granulomatous inflammation need to be considered, because it is not specific for sarcoidosis. Tuberculosis, parasitic, fungal infections, and vasculitis should be excluded (12). Our patient fulfilled the diagnostic criteria for the diagnosis of definitive neurosarcoidosis, namely the typical histologic picture of sarcoidosis in the nervous system and exclusion of other granulomatous diseases. Patient presented with optic neuropathy, headache, and one generalised epileptic seizure. According to the literature, the most common symptomps for neurosarcoidosis are cranial nerve deficits (50%) and headache (30%). The facial nerve and the optic nerve are the most frequently affected. Other symptoms that can be present are seizures (10%), sensory and motor deficits (10%), neuropsychological deficits (10%), hydrocephalus (5%), and hypothalamic and pituitary dysfunction (5). The most common anatomic sites of symptomatic involvement are the cranial nerves, the meninges, the brain parenchyma, the spinal cord and its meninges, the hypothalamic-pituitary axis, and the peripheral nerves (14). The MRI picture of our patient, showed white matter hyperintensities on T2-weighted and FLAIR imaging extending to the optic tracts, chiasm, optic nerves, brainstem, and spine, plus leptomeningeal contrast enhancement confirmed the diagnosis of neurosarcoidosis. Lymphocytosis, elevated protein levels, and positive oligoclonal bands were present in our patient; these symptoms are suggestive, but not specific for sarcoidosis (7, 14). Isolated neurosarcoidosis is reported to have a better clinical prognosis compared with systemic neurosarcoidosis. A good clinical course could thus be a typical feature of isolated neurosarcoidosis (7).

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 86-88

A composite score to assess treatment response in pulmonary sarcoidosis: the Sarcoidosis Treatment Score (STS)

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To the editor:

Assessing response to treatment for pulmonary sarcoidosis can be difficult (1). As more expensive agents are being considered for treatment of sarcoidosis, it is important that studies employ adequate and clinically relevant endpoints. A World Association of Sarcoidosis and other Granulomatous disease (WASOG) task force report on clinical trial endpoints examined those parameters reported in clinical trials of pulmonary sarcoidosis (2). The panel noted that several single endpoints had been used. With therapy, changes in forced vital capacity (3, 4) and DLCO (3) have been reported. Chest imaging has also been shown to improve with therapy (4). Two sarcoidosis specific quality of life instruments have been developed: the King's sarcoidosis questionnaire (KSQ) (5) and fatigue assessment scale (FAS) (6). In addition, some treatments have been shown to be steroid sparing (7). The task force recommended that a composite score be developed to capture the many facets of pulmonary sarcoidosis (2). To date, no reports utilize composite scores to assess treatment efficacy in pulmonary sarcoidosis. We recently reported a prospective study of repository corticotropin injection (RCI) for chronic pulmonary sarcoidosis (8). In that study, many of the features were prospectively collected and allowed for the development of a composite score – Sarcoidosis Treatment Score (STS).

Sixteen patients were enrolled in a single blind, prospective study. They underwent physiological, imaging, patient reported quality of life questionnaires, and prednisone tapering evaluations. These included: forced vital capacity (FVC) and diffusion lung of carbon monoxide (DLCO) measurement, high resolution computer tomography (HRCT) scan, King's sarcoidosis health questionnaire - general health (KSQ-GH) (5), FAS, and prednisone dosage tapering at baseline and after 7 and 24 weeks of therapy. A composite score was developed (STS) using these parameters with scoring ranging from -6 to +6 points (Table 1). Absolute change of FVC and DLCO % predicted of both 5% and 10% were calculated. The composite score was then compared to the individual features of the composite score and to six minute walk distance (6MWD).

There was better correlation between the components of composite score and an absolute change of 5% versus 10% for FVC and DLCO percent predicted (data not shown). Therefore, further analysis used absolute change of 5%.

Response (R) was defined as scores of ≥ 3/6 points; Partial Response (PR) was defined as scores of 2/6 points or stable with corticosteroid reduction (i.e., a total score of +1 due to ≥50% reduction in corticosteroid dosage); and Non Response (NR) was defined as scores of ≤1/6 points without significant corticosteroid taper (stable or deterioration).

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Table 1. Composite score and 6MWD determinations

Parameter	FVC	DLCO	HRCT	KSQ GH	FAS	Steroid Taper	Total Score
Improved							
+1 point	≥5%	≥5%	Improved	≥4	≤-4	≥50% reduction	
Unchanged							
0 point	>-5 to <5%	>-5 to <5%	Unchanged	>-4 to <4	>-4 to <4	<50% reduction or ≥5 mg increase for less than 2 weeks	
Deterioration							
-1 point	≤-5%	≤-5%	Worse	≤-4	≥4	≥5 mg increase for more than 2 weeks	
Patient number							
1-001	1	1	1	1	1	1	6 R
1-002	-1	1	1	1	0	0	2 PR
1-003	1	0	0	1	1	1	4 R
1-004	0	-1	0	0	0	1	0 NR
1-005	0	1	1	1	0	0	3R
1-008	0	Not done	1	0	1	0	2 PR
1-009	-1	-1	0	0	0	1	-1 NR
1-010	0	-1	0	1	1	0	1NR
1-011	1	1	0	1	1	1	5 R
1-012	0	1	-1	1	0	1	2 PR
1-014	0	1	0	0	0	0	1 NR
1-015	1	1	0	0	1	0	3 R
1-016	0	0	0	1	1	1	3 R
2-001	0	1	1	1	1	1	5 R
2-002	0	0	0	1	0	0	1 NR

R=response; PR=partial response; NR=no response

Of the sixteen patients studied, fifteen patients had sufficient information available to be evaluates. Seven (46.6%) were responders, three (18.8%) were partial responders, and five (31.2%) were non responders. The final composite score and individual values are shown in Table 1.

The mean composite post treatment score was 3, with only five patients having a composite score of -1 to 1. There was a significant correlation between the composite score and all of its components. A significant positive correlation existed between change in 6MWD at week 7 with composite score (rho=0.588, p=0.0344), change in FVC % predicted (rho=0.628, p=0.0216) and KSQ-GH (rho=0.583, p=0.0364). For change in 6MWD at 24 weeks, there was a borderline correlation with composite score (rho=0.523, p=0.0666) and borderline negative correlation with change in prednisone dose (rho=-0.542, p=0.0566). No correlation existed at either time point for changes in DLCO % predicted, HRCT, or FAS.

A composite score to assess the value of angiotensin converting enzyme in monitoring sarcoidosis was used by DeRemee et al (9). To date, composite scores have not been employed as end points of clinical trials. In this study, we examined a composite score which consisted of physiology, radiology, quality of life, and steroid sparing parameters. The composite score confirmed the value of the RCI in treating advanced sarcoidosis. In a prospective study (8), RCI treatment was associated with significant steroid sparing, improvement in DLCO, and KSHQ-GH and FAS scores. In addition, some patients had improvement of their HRCT when scored in a blinded fashion. The composite score mirrored the positive results seen for the individual parameters. As none of the previous randomized clinical trials in sarcoidosis have collected all of these parameters, validating the STS would require future studies. We also compared the composite score to the 6MWD. Previous studies in sarcoidosis have demonstrated that 6MWD is independently affected by lung function and patient's reported quality of life (10). In this study, we found that the composite score was associated with changes in 6MWD at 7 and 24 weeks of treatment.

Using a composite score consisting of physiology, radiology, and quality of life parameters as well

as changes in prednisone dosing, as recommended by WASOG (2), may prove useful in assessing treatment for pulmonary sarcoidosis. This endpoint is being explored in an upcoming double blind placebo controlled trial of RCI which may help to validate the STS.

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Sarcoidosis: an orphan disease needs to be adopted

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Sarcoidosis, a multi-organ granulomatous disorder, continues to remain an elusive entity. It is generally under diagnosed and overshadowed by the presence of tuberculosis, a close mimic (1). Although potentially a curable disease, diagnostic delays may adversely impact not just the lungs but other bodily organs as well. In April 2016, US Senate Resolution 443 designated April 2016 as "National Sarcoidosis Awareness Month" and stated a few facts as "Many sarcoidosis patients struggle to find knowledgeable physicians and emotional support resources relating to sarcoidosis; and treatment options for sarcoidosis are limited due in part to the lack of informative research and funding specific to sarcoidosis." Sarcoidosis is a challenge for both the clinician and the patient. For a clinician, timely and accurate diagnosis is of utmost essence, whereas for patients, it is a matter of understanding a disease which is not heard before they encounter it. The disease sarcoidosis is abundant with diagnostic imprecision, unfavorable outcomes, therapeutic after effect and a great deal of psychological stress but lacks any clinical and therapeutic model or dedicated specialty clinics for its better management.

The prevalence of sarcoidosis varies with respect to countries and ethnicity. African Americans are the commonest affected ethnic group in the United States and have a prevalence four times that of for Caucasians (2.4% vs 0.85% respectively) (2). The reported prevalence of sarcoidosis in India is estimated to be 10-12 cases per 1,000 new registrations in a respiratory unit at Kolkata and 61.2/100,000 new cases at a center in New Delhi (3). However, these figures are unlikely to be a true representation as sarcoidosis is usually unidentified due to the high burden of tuberculosis here. Real figures are anticipated to be much higher. At the All India Institute of Medical Sciences, a tertiary referral health care center at Delhi, approximately 100 new cases of pulmonary sarcoidosis are being diagnosed every year. The number is quite noticeable for a disease otherwise considered rare.

Regarding diagnosis of sarcoidosis, clinicians usually lack any confident explanation about disease cause and course to satisfy the anxiety of patients. Patients make themselves to read and search as much information as possible to give them the understanding and knowledge of the disease so as to obtain some security and trust that they are receiving the appropriate treatment and care to prevent any further damage to their health. However, self-gathered knowledge might be catastrophic for their mental health. For sarcoidosis patient care, it is advisable that clinicians should also include mental as well as emotional health in their treatment protocol.

Disease course in sarcoidosis is generally self-limiting but many patients face an uncertain future with chronic illness. Complete remission is not always certain and if, it is only possible with the long course of steroids treatment. To survive with a disease of unexplained reasons and unpredictable outcomes is physically as well as psychologically tiring. There are studies that have examined the psychiatric

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aspect of sarcoidosis and the results are really concerning. Depression, perceived stress, anxiety, fatigue and decreased quality of life are on the higher side in patients with sarcoidosis (4-8). All the reverberations associated with this disease necessitated the establishment of multispecialty center as well as a dedicated sarcoidosis patient care facility for catering their symptomatic and psychometric aspect.

Almost no country has such clinical setups that exclusively deal with the problems of sarcoidosis patients. Apart from a nationwide survey of pulmonary sarcoidosis clinics in the United States, no other study reported the status of sarcoidosis clinics in any part of the world. In this study, a minority of academic medical centers were found to have a dedicated sarcoidosis clinic, and the minority of dedicated sarcoidosis clinics used a concurrent multidisciplinary model (9). In India, sarcoidosis is gaining recognition slowly but of course is not privy to speciality treatment. The disease-specific clinical model usually proves beneficial for improved disease management. We believe that the health care providers should create a standard multidisciplinary model for evaluation, diagnosis, and treatment of sarcoidosis which will improve the outpatient care of disease bearer.

Although lacking in clinical model, UK and USA both have support and welfare groups that are helping sarcoidosis patients through their education programs, fund raising awareness camps, and other clinical facilities. Additionally, these organizations are also filling the research gaps by encouraging funding to acclaimed research groups. Foundation of Sarcoidosis Research (FSR); Bernie Mac Foundation in USA and Sarcoidosis and Interstitial Lung Disease (SILA or Sarcoidosis UK) in the UK are the awareness groups working in this direction.

In India as well as in other countries, we also need similar groups so we can make people aware of the disease and its outcomes. There is a need to establish a platform that can give people confidence to sustain with the disease, a platform where people can share their struggle with the disease and inspire others to tackle it. Through such organization, we can also assemble clinical and research groups together to find actual prevalence of sarcoidosis and to arrange funds for better research in this field.

Sarcoidosis, a disease without consistent definitions and practice patterns requires special consideration rather a casual approach. Multidisciplinary clinical model and in-person support groups may work favorably to cure the disease and to inform the public about the disease so the patients do not go through undue trauma. Furthermore, extensive research is indeed required to find some breakthroughs which will provide answers to etiology, diagnosis, treatments and a cure for the disease.

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