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Features of sarcoidosis associated with chronic disease

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Abstract. *Background:* The clinical outcome of sarcoidosis is variable. Several features have been proposed as predictive of chronic sarcoidosis. *Objectives:* To examine the predictive role of clinical features on the clinical outcome score (COS) of sarcoidosis patients five years after initial diagnosis. *Methods:* A cohort of newly diagnosed sarcoidosis patients seen at one clinic were re-evaluated five years after initial diagnosis. The COS was determined at this five year time point and compared to initial age, race, sex, forced vital capacity (FVC) and chest roentgenogram. We also compared COS to whether patients had Lofgrens syndrome, lupus pernio, or cardiac disease and what treatment they received during the five years of observation. Patients with neurologic disease were divided into those with seventh cranial nerve paralysis alone versus those with other neurologic disease (CNS). *Results:* Of the 335 newly diagnosed patients seen over a three year period, 213 (64%) were evaluated five years after initial diagnosis. Of these patients 168 (79%) were still requiring systemic therapy at five years (COS 7, 8, or 9). Seven features were associated with chronic disease: CNS alone (Odds Ratio (OR)=19.24, $p<0.05$); CNS, cardiac, and/or lupus pernio (OR=5.86, $p<0.02$); FVC<80% (OR=7.04, $p<0.02$); treatment with prednisone (OR=6.35, $p<0.0001$); methotrexate (OR=7.2, $p<0.0001$); azathioprine (OR=19.24, $p<0.05$); anti-tumor necrosis therapy (OR=13.98, $p>0.05$). *Conclusion:* In our study, the majority of sarcoidosis patients were receiving systemic therapy five years after initial diagnosis. Patients with reduced lung function, neurologic disease, lupus pernio, and cardiac disease were more likely to require prolonged treatment. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 275-281)*

Key words: sarcoidosis, clinical outcome score, chronic disease

Introduction

Sarcoidosis is a multi organ disease associated with a variable clinical outcome (1). Some patients resolve their disease within two years of presentation, while others have chronic disease lasting for more than five years (2). Several factors have been associated with chronic disease. These include neurologic, cardiac, and bone disease (2). Also, patients with posterior uveitis (3), nephrocalcinosis (4), lupus pernio (5, 6), and requiring systemic therapy (7, 8) usually have chronic disease. On the other hand, Caucasian patients who present with hilar adenopathy and erythema nodosum (Lofgren's syndrome) often resolve within two years (9).

A clinical outcome status (COS) for sarcoidosis was developed by a World Association of Sarcoidosis and Other Granulomatous disease (WASOG) task force (10). Figure 1 summarizes the nine groups for COS. We analyzed the effect of various parameters versus COS for a cohort of newly diagnosed sarcoidosis patients seen at out institution over a three year period in whom a five year follow up was available.

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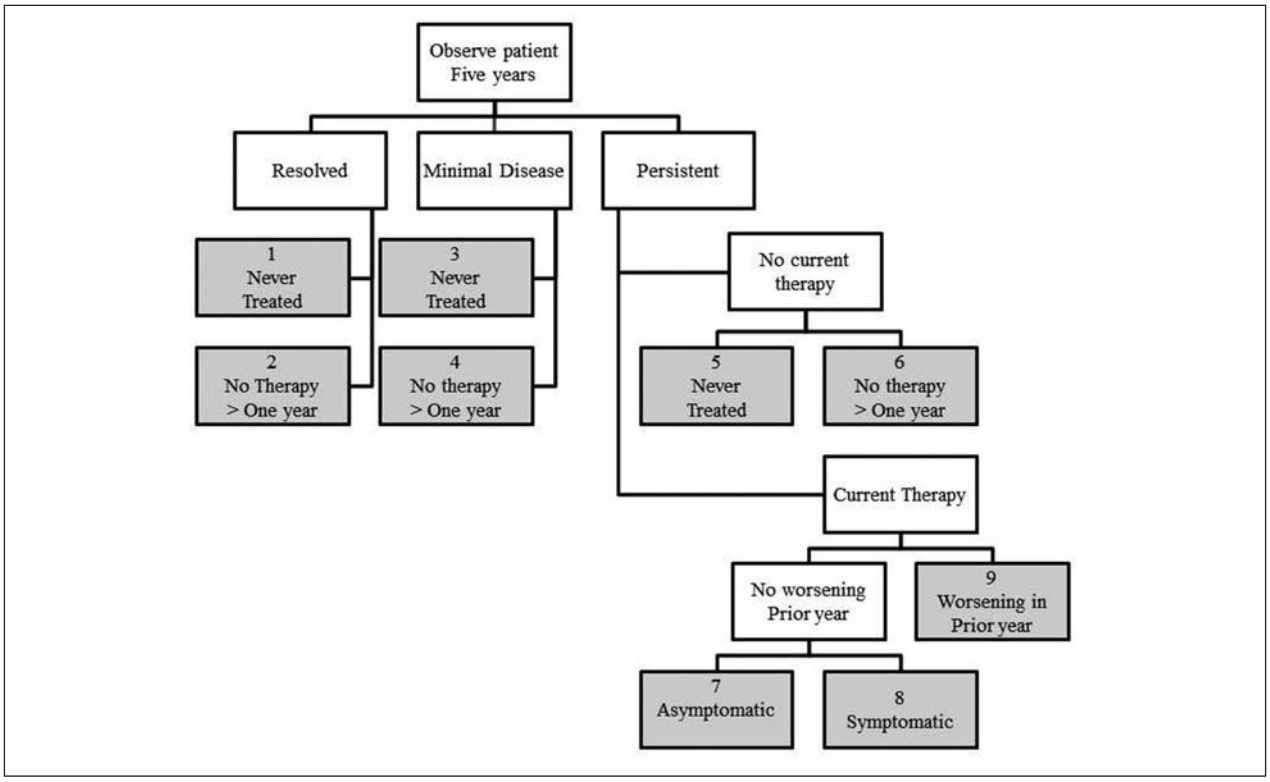

Fig. 2. The clinical outcome status (COS) for patients with sarcoidosis. From Baughman et al (10), reprinted with permission.

Methods

Patients seen at the University of Cincinnati Interstitial Lung Disease and Sarcoidosis clinic over a three year period (2002 to 2005), seen within a year of diagnosis, and followed for at least five years were eligible for inclusion in the study. Clinical features identified within the first year of diagnosis were recorded in an electronic database. These included age, race, and sex. Organ involvement was considered present if a patient had definite or probable involvement using a standard definition (11). Patients with neurologic involvement were divided into those who had seventh cranial nerve involvement (with or without other neurologic disease) versus those with neurologic disease but no history of seventh cranial nerve involvement. Patients were felt to have cardiac involvement if they had either arrhythmias, reduced ejection fraction, or both. Patients with chronic cutaneous facial lesions consistent with *lupus pernio* were noted (12). Patients were classified as Lofgren's syndrome if they had hilar adenopathy on chest imaging and either erythema nodosum or peri ankle edema (13). Systemic treatment for the patients over the five year period of observation was noted. The study was approved by the University of Cincinnati Institutional Review Board.

The clinical status of patients five years after initial diagnosis was determined using previously described criteria (14) (Figure 1). Patients were considered chronic if they were still requiring therapy at years five (COS scores 7, 8, or 9). Patients were considered acute if they never required systemic therapy (COS score 1, 3, or 5) or had been on therapy but had not received systemic treatment in the previous year (COS 2, 4, or 6). Subsequent comparisons were made between acute patients, who had not been on therapy within the past year (COS 1 through 6) versus chronic patients still on therapy in the prior year (COS 7, 8, or 9).

We also noted spirometry and chest imaging that was available within six months of initial evaluation. Spirometry was performed to capture the forced vital capacity (FVC) and the predicted values

as per Hankinson (15). Chest x-rays were staged using the criteria proposed by Scadding et al (16). Therapy for sarcoidosis was prescribed for patients using general guidelines established by our clinic (17).

Statistics: Comparison between acute and chronic outcome was performed using Chi Square analysis. A p value of less than 0.05 was considered significant. In addition, sensitivity, specificity, negative and positive predictive value, and odds ratio were calculated using standard formulas (18).

Results

A total of 335 new sarcoidosis patients were seen over the three year period. Of these 213 (64%) were seen at five years after the original diagnosis. There was no difference in terms of race, gender, or age between those who were seen at five years and those who were lost to follow up. However, of the 122 patients not seen at five years, only 72 (59%) had received prednisone versus 169/213 (79%) who were seen at five years (Chi square=7.915, P<0.005). Table 1 summarizes the clinical features of the 213 patients seen at five years follow up. Results of spirometry and/or chest roentgenogram available within six months of initial evaluation are also noted in the table.

Table 1. Features of Sarcoidosis Patients seen Five years after Initial Diagnosis

	Number	Percent
Total number	213	
Age, years	50 (22-79)	
Female	148	69.5%
Black	83	39.0%
Had Spirometry at initial evaluation	114	53.5%
FVC		
>80%	74	64.9%
70-80%	17	14.9%
<70%	23	20.2%
Had chest roentgenogram at initial evaluation	195	91.5%
stage 0-1	117	60.0%
stage 2-3	64	32.8%
stage 4	14	7.2%
Treated at any time with Prednisone	169	79.3%
Methotrexate	117	54.9%
Azathioprin	29	13.6%
Leflunomide	18	8.5%
Hydroxychloroquine	54	25.4%
Infliximab/adalimumab *	22	10.3%
Lofgren	12	5.6%
CNS (not including seventh cranial nerve paralysis)	29	13.6%
Seventh cranial nerve paralysis	9	4.2%
Cardiac	9	4.2%
Lupus pernio	4	1.9%

*Only one patient treated exclusively with adlimumab

Patients were classified at five years based on the COS (Figure 1). Table 2 shows the different rates clinical features of patients comparing those who never received systemic therapy (COS 1, 3, or 5), those who had received treatment but had been off treatment for more than a year (COS 2, 4, or 6), versus those still receiving therapy (COS 7, 8, 9). The presence of neurologic sarcoidosis, excluding seventh nerve paralysis, was the only feature that was statistically different between the three groups.

Forty-five (21%) of the sarcoidosis were classified as acute disease with resolution within five years (COS 1through 6). These were compared to those with chronic disease (COS 7, 8, and 9) in Tables 3. There was no significant difference between acute and chronic patients in terms of race or gender. Of the clinical features studied, only the presence of neurologic disease excluding seventh nerve paralysis was significantly more likely in chronic disease. It should be noted that there were only four patients with *lupus pernio* in this series. All had chronic disease. Spirometry at presentation was associated with long term outcome, with a significant difference in outcome between the three categories of FVC at time of presentation (Chi square=8.104, p<0.02). Only two of the forty patients (5%) with a FVC of less than 80% at presentation had acute disease. This was significantly different from 20 of 74 (27%) of those with a normal FVC at presentation who had acute disease (Chi Square=6.737, p<0.01). While only one of fourteen (7%) patients who presented with stage 4 pattern had acute disease, the chest x-ray stage at presentation was not associated with a significant difference in proportion of acute versus chronic disease.

Table 4 reports the effect of treatment during the five year course for those with acute versus chronic disease. Nearly eighty percent of patients were treated with prednisone and 86% of these developed chronic disease (Chi square=25.603, p<0.0001). Nearly half of the patients were treated

Table 2. Comparison of features versus COS

	Never Treated	No Therapy in prior year	Current Therapy	Total	Percent of total	Chi Square	p
Status							
Total Number	21	24	168	213			
Female	11	16	121	148	69.5%	3.498	p>0.05
Black	4	9	70	83	39.0%	4.040	p>0.05
Number with							
Lofgren	2	1	9	12	5.6%	0.719	p>0.05
Seventh cranial nerve paralysis	1	2	6	9	4.2%	1.193	p>0.05
Neurologic (not seventh cranial nerve paralysis)	0	0	29	29	13.6%	8.992	0.00112
Cardiac	0	2	7	9	4.2%	1.929	p>0.05
Lupus pernio	0	0	4	4	1.9%	1.092	p>0.05
Neurologic (not seventh cranial nerve paralysis), Cardiac, and/or *lupus pernio*	0	2	36	38	17.8%	7.516	0.0233
Eye	8	7	56	71	33.3%	0.402	p>0.05
FVC						8.665	p>0.05
>80%	9	11	54	74	64.9%		
70-79%	0	1	16	81	79.8%		
<70%	0	1	22	23	20.2%		
<80%	9	2	54			8.642 *	0.0133
CXR						3.463	p>0.05
stage 0-1	14	16	87	117	60.0%		
stage 2-3	5	7	52	64	32.8%		
stage 4	0	1	13	14	7.2%		

*Compared to >80%

Table 3. Acute versus chronic

	Acute		Chronic		Total	Percent of total	Chi Square	p
Number of patients	45		168		213			
Feature:	Present	Absent	Present	Absent				
Female	27	18	121	47	148	69.50%	1.886	p>0.05
Black	13	32	70	98	83	39.00%	1.929	p>0.05
Lofgren	3	42	9	159	12	5.60%	0.001	p>0.05
Seventh cranial nerve paralysis	3	42	6	162	9	4.20%	0.249	p>0.05
Neurologic (not seventh cranial nerve paralysis)	0	45	29	139	29	13.60%	7.584	0.0059
Cardiac	2	43	7	161	9	4.20%	0.112	p>0.05
Lupus pernio	0	45	4	164	4	1.90%	0.182	p>0.05
Neurologic (not seventh cranial nerve paralysis), Cardiac, and/or *Lupus pernio*	2	43	36	132	38	17.80%	5.874	0.0154
Eye	15	30	56	112	71	33.30%	0.032	p>0.05
FVC							8.104	0.0174
>80%	20		54		74	64.90%		
70-80%	1		16		17	14.90%		
<70%	1		22		23	20.20%		
<80% *	2		38		40	35.1%	6.737 *	0.0094
CXR							3.093	p>0.05
stage 0-1	30		87		117	60.0%		
stage 2-3	12		52		64	32.8%		
stage 4	1		13		14	7.2%		

*Compared to >80%

Table 4. Clinical outcome at five years versus therapy

	Acute With	Acute Without	Chronic With	Chronic Without	Total	Percent With	Chi Square	P value
Prednisone	23	22	146	22	169	79.34%	25.603	<0.0001
Methotrexate	9	36	108	60	117	54.93%	26.357	<0.0001
Azathioprine	0	45	29	139	29	13.62%	7.584	0.0059
Leflunomide	2	43	16	152	18	8.45%	0.618	>0.05
Hydroxychloroquine	9	36	45	123	54	25.35%	0.542	>0.05
Anti-TNF therapy *	0	45	22	146	22	10.33%	5.234	0.0222

* Anti-tumor necrosis factor (TNF) therapy: only one patient treated with only adalimumab, others treated with infliximab +/- adalimumab

Table 5. Sensitivity, specificity, positive and negative predictive value, and odds ratio of clinical features

	Chronic	Acute	Total	Percent of total	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Odds Ratio	95% CI	p-value
Number	168	45	213								
Feature											
CNS *	29	0	29	13.6%	100.0%	82.7%	100.0%	75.5%	19.24	1.15-321.31	<0.05
CNS Cardiac, and/or *lupus pernio*	36	2	38	17.8%	4.4%	78.6%	5.3%	75.4%	5.86	1.36-25.37	<0.02
FVC<80%	20	2	22	10.3%	5.0%	73.0%	9.1%	58.7%	7.04	1.55 to 31.91	<0.02
Prednisone	146	23	169	79.3%	51.1%	13.1%	13.6%	50.0%	6.35	3.04 to 13.26	<0.0001
Methotrexate	108	9	117	54.9%	20.0%	35.7%	7.7%	62.5%	7.2	3.25 to 15.96	<0.0001
Azathioprine	29	0	29	13.6%	100.0%	82.7%	100.0%	75.5%	19.24	1.15 to 321.31	<0.05
Anti-TNF therapy*	22	0	22	10.3%	100.0%	86.9%	100.0%	76.4%	13.98	0.83 to 234.98	>0.05

* CNS: Neurologic (not seventh cranial nerve paralysis)
§ Anti-tumor necrosis factor (TNF) therapy: only one patient treated with only adalimumab, others treated with infliximab +/- adalimumab

with methotrexate, with 92% having chronic disease (Chi Square=26.357, p<0.001). All patients treated with azathioprine had chronic disease (Chi square=7.584, p<0.01). There were 22 (10%) of all patients treated with anti-TNF agents infliximab or adalimumab. All of these patients had chronic disease (Chi square=5.234, p<0.05).

Table 5 summarizes the sensitivity and specificity of each of the six factors which were significantly more likely to occur in patients with chronic disease in Tables 3 and 4. We also note the prevalence of the feature as well as the positive and negative predictive value. We also calculated the odds ratio associated with the individual features.

Discussion

Sarcoidosis is associated with a variable clinical outcome. Over the years, several features have been associated with either a good or bad prognosis (2, 14, 19, 20). Genetic markers have been associated with chronic or severe disease (21, 22). In the current study, we were able to confirm that some clinical features at presentation were associated with a prolonged need for treatment. These included the presence of neurologic disease and a reduced FVC. Also, the need for treatment with glucocorticoids, cytotoxic therapy, or anti-TNF antibodies was associated with a need for prolonged therapy.

Several groups have reported that between twenty to eighty percent of their patients require chronic therapy (7, 23-25). In the current study, 168 (79%) of patients were still receiving therapy five years after diagnosis. In a large survey of ten sarcoidosis centers across the world, half of patients were still on therapy five years after diagnosis (10). A third of patients who were initially evaluated were not seen five years after initial diagnosis. We do not know what proportion of these patients would be classified as acute. We do know that almost forty percent of these patients were not treated for their

sarcoidosis initially. That may explain why they were no longer being seen in our clinic.

The presence of neurologic disease has often been associated with chronic disease (2) and a need for chronic therapy (26-28). An exception has been patients who have seventh cranial nerve paralysis. In these patients, the disease may respond to short term treatment (27). The current study also found that most patients who presented with neurologic disease required prolonged therapy. There were three patients with neurosarcoidosis who were no longer receiving systemic therapy after five years. All three had seventh cranial nerve paralysis. While patients with seventh nerve cranial nerve paralysis may do well, some patients may require chronic therapy (29).

Some features associated with chronic disease were not found in the current study to be significantly associated with chronic disease. Cardiac disease has been reported as predictive of chronic disease (2, 20, 21). Cardiac sarcoidosis patients usually require prolonged therapy (30, 31). In our current study, we did find that most patients with cardiac disease at presentation were still on systemic therapy after five years. However, there were two of nine patients who had been successfully weaned off systemic therapy by year five. Sarcoidosis patients with *lupus pernio* usually require chronic therapy (6, 12, 32). In the current study, all four patients with *lupus pernio* at presentation were still on chronic therapy. Because of the low prevalence of both of these features, the study was underpowered to determine if there was a significant associated with chronic disease for either of these individual features. All patients with neurologic, cardiac, or *lupus pernio* were treated. The presence of any of these three features was significantly more likely to be associated with chronic disease. This supports the use of these manifestations as markers for chronic disease.

Patients with fibrotic pulmonary sarcoidosis have a worse prognosis (33). In the current study, we found that patients with abnormal FVC were more likely to require chronic therapy. In a prior study of ten centers, the level of FVC was not associated with the need for chronic therapy (8). However, that study found that the severity of the dyspnea was an independent predictor of chronic disease. In the current study, we did not record systematically the level of dyspnea of our patients. Only one of fourteen (7.1%) of patients with stage 4 disease on initial chest roentgenogram was no longer receiving systemic therapy at five years. However, the proportion of patients who presented with stage 4 disease on chest roentgenogram was probably too low to detect a significant difference in the outcome of this group compared to other chest roentgenogram patterns.

In COS, one can differentiate patients with persistent disease who are or are not receiving ongoing therapy. It has been observed that patients who still require therapy beyond five years have more severe and advanced disease (23). It has also been observed that patients who are begun on therapy within the first six months of diagnosis usually require long term therapy (7, 8). The current study confirmed that patients who had received prednisone were much more likely to require continued therapy. In the current study, we were also able to demonstrate that patients placed on either methotrexate or azathioprine remained on treatment five years later. The fact that most patients treated with either methotrexate or azathioprine required chronic treatment has been previously noted by ourselves (3) and others (34). During the three year period of enrollment into the study, twenty-two newly diagnosed patients were treated with infliximab or adalimumab. All of these patients were still requiring some form of treatment five years after diagnosis. It has been observed by others that most patients require long term treatment with infliximab , since there is a high rate of relapse when the drug is withdrawn (35, 36).

We did not find that race or gender were associated with chronic disease and need for therapy. This is similar to prior observations (8, 10). We also did not find the presence of Lofgren's syndrome was always associated with a good prognosis. This may be because erythema nodosum in blacks is not associated with a high rate of resolution of disease (37). Even in Caucasians, there are some patients with Lofgren's syndrome who have chronic disease (9). We did not study the potential role of biomarkers to predict COS. Bargagli et al found that lowest chitotripidase levels were found in patients with COS score 1 (38).

In conclusion, we found that several features predicted the need for chronic therapy. As summarized in Table 5, none of the factors was associated with a strong negative predictive value. However, the presence of these individual features was associated with a high odds ratio for chronic disease.

References

1. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG Statement on sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16:149-173.
2. Neville E, Walker AN, James DG. Prognostic factors predicting the outcome of sarcoidosis: an analysis of 818 patients. Q J Med 1983; 208:525-533.
3. Baughman RP, Lower EE, Ingledue R, et al. Management of ocular sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2012; 29:26-33.
4. Rizzato G, Colombo P. Nephrolithiasis as a presenting feature of chronic sarcoidosis: a prospective study. Sarcoidosis 1996; 13:167-172.
5. Stagaki E, Mountford WK, Lackland DT, et al. The treatment of lupus pernio: results of 116 treatment courses in 54 patients. Chest 2009; 135(2):468-476.
6. Spiteri MA, Matthey F, Gordon T, et al. Lupus pernio: a clinico-radiological study of thirty-five cases. Br J Dermatol 1985; 112(3):315-322.
7. Gottlieb JE, Israel HL, Steiner RM, et al. Outcome in sarcoidosis. The relationship of relapse to corticosteroid therapy. Chest 1997; 111(3):623-631.
8. Baughman RP, Judson MA, Teirstein A, et al. Presenting characteristics as predictors of duration of treatment in sarcoidosis. QJM 2006; 99(5):307-315.
9. Grunewald J, Eklund A. Lofgren's syndrome: human leukocyte antigen strongly influences the disease course. Am J Respir Crit Care Med 2009; 179(4):307-312.
10. Baughman RP, Nagai S, Balter M, et al. Defining the clinical outcome status (COS) in sarcoidosis: results of WASOG Task Force. Sarcoidosis Vasc Diffuse Lung Dis 2011; 28(1):56-64.
11. Judson MA, Baughman RP, Teirstein AS, et al. Defining organ involvement in sarcoidosis: the ACCESS proposed instrument. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16:75-86.
12. Baughman RP, Judson MA, Teirstein A, et al. Chronic facial sarcoidosis including lupus pernio: clinical description and proposed scoring systems. Am J Clin Dermatol 2008; 9(3):155-161.
13. Grunewald J, Eklund A. Sex-specific manifestations of Lofgren's syndrome. Am J Respir Crit Care Med 2007; 175(1):40-44.
14. Baughman RP, Nagai S, Balter M, et al. Defining the clinical outcome status (COS) in sarcoidosis: results of WASOG task force. Sarcoidosis Vasc Diffuse Lung Dis 2011; 28:in press.
15. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999; 159(1):179-187.
16. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. Br Med J 1961; 4:1165-1172.
17. Baughman RP, Nunes H, Sweiss NJ, et al. Established and experimental medical therapy of pulmonary sarcoidosis. Eur Respir J 2013; 41:1424-1438.
18. Woolf SH. Panel methodology: Analytical principles in evaluating the performance characteristics of diagnostic tests for ventilator-associated pneumonia. Chest 2000; 117(4 Suppl 2):182S-185S.
19. Prasse A, Katic C, Germann M et al. Phenotyping sarcoidosis from a pulmonary perspective. Am J Respir Crit Care Med 2008; 177 (3): 330-336.
20. Wasfi YS, Rose CS, Murphy JR, et al. A new tool to assess sarcoidosis severity. Chest 2006; 129(5):1234-1245.
21. Zhou T, Zhang W, Sweiss NJ, et al. Peripheral blood gene expression as a novel genomic biomarker in complicated sarcoidosis. PLoS ONE 2012; 7(9):e44818.
22. Su R, Nguyen ML, Agarwal MR, et al. Interferon-inducible chemokines reflect severity and progression in sarcoidosis. Respir Res 2013; 14(1):121.
23. Johns CJ, Michele TM. The clinical management of sarcoidosis: a 50-year experience at the Johns Hopkins hospital. Medicine 1999; 78: 65-111.
24. Rizzato G, Montemurro L, Colombo P. The late follow-up of chronic sarcoid patients previously treated with corticosteroids. Sarcoidosis 1998; 15:52-58.
25. Hunninghake GW, Gilbert S, Pueringer R, et al. Outcome of the treatment for sarcoidosis. Am J Respir Crit Care Med 1994; 149(4 Pt 1):893-898.
26. Agbogu BN, Stern BJ, Sewell C, et al. Therapeutic considerations in patients with refractory neurosarcoidosis. Arch Neurol 1995; 52:875-879.
27. Lower EE, Broderick JP, Brott TG, et al. Diagnosis and management of neurologic sarcoidosis. Arch Intern Med 1997; 157:1864-1868.
28. Chapelon C, Ziza JM, Piette JC, et al. Neurosarcoidosis: signs, course and treatment in 35 confirmed cases. Medicine (Baltimore) 1990; 69:261-276.
29. Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis-diagnosis and management. QJM 1999; 92(2):103-117.
30. Chapelon-Abric C. Cardiac sarcoidosis. Curr Opin Pulm Med 2013; 19(5):493-502.
31. Hiramitsu S, Morimoto S, Uemura A, et al. National survey on status of steroid therapy for cardiac sarcoidosis in Japan. Sarcoidosis Vasc Diffuse Lung Dis 2005; 22(3):210-213.
32. Stagaki E, Mountford WK, Lackland DT, et al. The Treatment of Lupus Pernio: The Results of 116 Treatment Courses in 54 Patients. Chest 2008.
33. Nardi A, Brillet PY, Letoumelin P, et al. Stage IV sarcoidosis: comparison of survival with the general population and causes of death. Eur Respir J 2011; 38(6):1368-1373.
34. Vorselaars AD, Wuyts WA, Vorselaars VM, et al. Methotrexate versus azathioprine in second line therapy of sarcoidosis. Chest 2013;10-1728.
35. Vorselaars AD, Verwoerd A, Van Moorsel CH, et al. Prediction of relapse after discontinuation of infliximab therapy in severe sarcoidosis. Eur Respir J 2013;in press.
36. Panselinas E, Rodgers JK, Judson MA. Clinical outcomes in sarcoidosis after cessation of infliximab treatment. Respirology 2009; 14(4):522-528.
37. Mana J, Marcoval J. Erythema nodosum. Clin Dermatol 2007; 25(3):288-294.
38. Bargagli E, Bennett D, Maggiorelli C, et al. Human chitotriosidase: a sensitive biomarker of sarcoidosis. J Clin Immunol 2013; 33(1):264-270.