SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2023; 40 (4): e2023053 DOI: 10.36141/svdld.v40i4.15118

Radiological predictive remission factors of pulmonary involvement in systemic sarcoidosis: A computed tomography scan study

Melek Kechida[1], Mabrouk Abdelali[2], Rym Mesfar[1], Imene Chaabene[1], Rim Klii[1], Sonia Hammami[1], Syrine Daadaa[1], Mezri Maatouk[2], Jamel Saad[2], Ahmed Zrig[2], Ines Khochtali[1]

[1]Internal Medicine and Endocrinology Department, Fattouma Bourguiba University Hospital, University of Monastir, Monastir, Tunisia; [2]Radiology Department A, Fattouma Bourguiba University Hospital, University of Monastir, Monastir, Tunisia

Abstract. *Introduction:* As little is known about the prognostic value of CT scan findings at onset in patients presenting with sarcoidosis, we aimed to identify factors independently associated with radiological remission of pulmonary involvement in systemic sarcoidosis on CT scan findings. *Methods:* We conducted a retrospective descriptive and analytic study of patients with biopsy-proven systemic sarcoidosis. We compared patients on radiological remission (group 1) to those on stabilization or progression (group 2). Multivariate analysis of variables significantly associated with radiological remission in univariate analysis was performed using binary logistic regression. *Results:* Out of 65 records of systemic sarcoidosis, 43 were analyzed. 18.6% were male and 81.6% were female, with a sex ratio of 0.22 and a mean age at diagnosis of 47.2 ± 13.6 years. We found atypical lesions in CT scan findings in 16 patients (37.2%). Comparative pulmonary CT scan findings at admission and at 12-month follow-up revealed 13 patients (30.2%) in remission (group 1) and 30 patients in radiological stabilization or progression (group 2). On multivariate analysis, lymphopenia, calcifications, and typical CT scan findings at presentation were predictive factors of remission of pulmonary involvement in systemic sarcoidosis (aOR = 27.57; 95% CI = 2.67–284.63; p = 0.005), (37.2; 95% CI = 2.08–663.89; p = 0.014), and (47.1; 95% CI = 1.79–1238.5; p = 0.021), respectively. *Conclusion:* In patients with symptomatic systemic sarcoidosis with no lymphopenia at onset, calcifications, or typical CT scan findings at presentation, we suggest a close follow-up as well as an intensive treatment.

Key words: sarcoidosis, pulmonary manifestations, computed tomography scan

Introduction

Systemic sarcoidosis is a rare granulomatosis characterized by pulmonary involvement in 90% of the cases (1). The computed tomography (CT) scan improved lung investigation as it showed better sensitivity and specificity compared to chest X-rays (2). Treatment options for sarcoidosis are based on corticosteroids as first-line treatment. Immunosuppressors and biologics may be prescribed as second-line treatments. Treatment options are still dependent on extra-pulmonary findings (3). There are no recommended treatment options according to the pulmonary radiological pattern, although clinical manifestations and respiratory functional impact are closely linked to pulmonary involvement. Knowing predictive factors associated with the radiological remission of systemic sarcoidosis at its onset may enable better-customized therapeutic options. In this study, we aimed to identify factors independently associated with radiological remission of pulmonary involvement in systemic sarcoidosis based on CT scan findings.

Received: 17 August 2023
Accepted: 13 October 2023
Correspondence: Melek Kechida,
Internal Medicine and Endocrinology Department, Fattouma Bourguiba University Hospital, Monastir, Tunisia
E-mail: kechidamelek@gmail.com

Methods

We conducted a retrospective descriptive and analytic study of patients followed up for systemic sarcoidosis at the Internal Medicine Department of Fattouma Bourguiba University Hospital, Monastir, Tunisia, between January 2008 and December 2020. We only included patients with histologically proven systemic sarcoidosis associated with pulmonary involvement. Patients with no follow-up CT scan or those with a CT scan not performed after 12 months ± 2 months or performed in a different hospital center were excluded. The demographic, clinical, and biological characteristics of patients were recorded. Pulmonary CT scan findings on admission and at 12-month follow-up were reviewed and compared by an experienced radiologist. Were considered typical sarcoidosis lesions: [1] bilateral, symmetrical, not necrotic and not compressive mediastinal, and/or hilar lymphadenopathies (the lymph node location is described according to the International Association for the Study of Lung Cancer (4)). [2] Nodular or reticulo-nodular lesions, hard-edged, sometimes confluent, bilateral, and symmetrical (diameter 3 mm to 1 cm) with typical distribution in the upper and middle fields, and peri-lymphatic (peri-bronchovascular sleeve, subpleural, and along interlobular septa), are associated with frosted glass hyperdensities. Atypical sarcoidosis lesions are: [A1] unilateral or isolated mediastinal lymphadenopathy; [A2] nodules or lung masses (diameter 1-4 cm); [A3] airspace consolidation when the small pulmonary parenchymal nodules appear very close together, tending to merge into a large nodule; [A4] confluent alveolar opacities; [A5] tracheobronchial abnormalities; and [A6] pleural lesions. We defined radiological remission as the disappearance of all pathological parenchymal lesions on the control CT scan, associated with a decrease in lymph nodule size (small diameter < 15mm). Stabilization was defined by the persistence, on the control CT scan, of the parenchymal lesions assessed at diagnosis (with a possible decrease in the size of the lymph nodule while keeping a small diameter of ≥15mm). Progression was defined by the worsening of at least two initial radiological abnormalities and/or the appearance of new ones.

We performed a comparative study between patients on radiological remission (group 1) and those on stabilization or progression (group 2). Statistical analyses were performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Categorical data were expressed in proportions and absolute values, while continuous variables were expressed as the mean (± standard deviation). Comparisons of radiological findings were analyzed by the chi-square test (or Fisher's exact test), the two-group t-test, or the Mann-Whitney U-test, as appropriate. Multivariate analysis of variables significantly associated with radiological remission in univariate analysis was performed using binary logistic regression. Results are expressed as odds ratios (OR) with an accompanying 95% confidence interval (95% CI). The significance level was set at $p<0.05$.

Results

Out of 65 records of systemic sarcoidosis, 43 were analyzed. There were 18.6% males and 81.6% females, with a sex ratio of 0.22 and a mean age at diagnosis of 47.2 ± 13.6 years. In 65.1% of the patients, extra-pulmonary manifestations revealed the disease, while pulmonary manifestations were the onset symptoms in 25.6% of the cases. Extra-pulmonary localizations were diagnosed in 36 patients (83.7%) (Table 1). Typical findings were bilateral and symmetric mediastinal adenopathies (74.7%), hilar adenopathies (72.1%) without mass effect on adjacent structures, parenchymal nodules (62.8%), and peri-lymphatic micronodules (74.4%) with associated

Table 1. Clinical and biological findings of the patients.

Characteristics	Results (n)(%)
Onset symptoms	
- Pulmonary symptoms	11(25.6)
- Extra-pulmonary symptoms	28(65.1)
Extra-pulmonary localization	36 (83.7)
Respiratory functional symptoms	28(65.1)
Pulmonary function tests	
- FVC (l)	2.17
- FEV (l)	2.89
- PaO_2 (kPa)	12
- FEV/FVC <0.7	8(18.6)
- FEV/FVC >0.7	22(48.8)
- Restrictive pattern	12(27.9)
- Obstructive pattern	8(18.6)
- Mixed pattern	10(23.3)
Biological findings	
- Hypercalcemia	12(27.9)
- Angiotensin converting enzyme	30(69.8)
- Lymphopenia (<1500 elements/mm^3)	18(41.9)

FVC: forced vital capacity; FEV: forced expiratory volume; PaO_2: partial pressure of oxygen.

Table 2. Atypical findings of radiological pulmonary findings.

Typical features	**N (%)**
- Bilateral and symmetric adenopathies	32 (74.4)
- Hilar adenopathies	31 (72.1)
- Parenchymal nodules	27 (62.8)
- Perilymphatic micronodules	32 (74.4)
- Frost glass hyperdensities	16 (37.2)
Atypical features	
- (A1) Unilateral or isolated mediastinal lymphadenopathy	4(9.3)
- (A2) Nodules or lung masses (diameter 1-4 cm)	3(6.9)
- (A3) Airspace consolidation when the small pulmonary parenchymal nodules appeared very close together, tending to merge into a large nodule	1(2.3)
- (A4) Confluent alveolar opacities	1(2.3)
- (A5) Tracheobronchial abnormalities	4(9.3)
- (A6) Pleural lesions	3(6.9)

frosted glass hyperdensities in 37.2% of the cases. We found atypical lesions in CT scan findings in 16 patients (37.2%), as described in Table 2.

Treatment was based on corticosteroids in 35 patients (81.4%), which were associated with methotrexate in 9 patients (20.9%), cyclophosphamide in 7 patients (16.3%), and hydroxychloroquine in 7 patients (16.3%). In 8 patients (18.6%), no treatment was prescribed.

Comparative pulmonary CT scan findings on admission and at 12-month follow-up revealed 13 patients (30.2%) in remission (group 1) and 30 patients in radiological stabilization or progression (group 2).

Univariate analysis between the 2 groups showed significantly less obesity (0% vs. 23.3%; p = 0.05), less ocular involvement (7.7% vs. 53.3%; p = 0.005), less pulmonary function test abnormalities (38.5% vs. 83.3%; p = 0.006), less declined carbon monoxide diffuse capacity (7.7% vs. 46.7%; p = 0.014), and less atypical CT scan lesions (15.4% vs. 46.7%; p = 0.05) in patients from group 1. Conversely, these patients were significantly more likely to have anergic Mantoux tests (76.9% vs. 36.7%; p = 0.015), to present with lymphopenia (76.9% vs. 26.7%; p = 0.02), and to have normal levels of angiotensin converting enzyme (ACE) (61.5% vs. 16.7%; p = 0.03) (Table 3). Patients from group 2 have significantly more unilateral or isolated mediastinal lymphadenopathy (A1) and significantly more pleural lesion (A6) (13% each) (p=0.01). Multivariate analysis revealed that lymphopenia, calcifications or typical CT scan findings at presentation were predictive factors of remission of pulmonary involvement in systemic sarcoidosis (aOR=27.57; 95%IC=2.67-284.63; p=0.005) (aOR= 37.2; 95% IC= 2.08-663.89; p=0.014) (aOR=47.1; 95% IC= 1.79-1238.7; p=0.021) respectively (Table 4).

Discussion

We reviewed the CT scan findings of 43 patients with systemic sarcoidosis associated to pulmonary involvement. Typical findings were bilateral and symmetric mediastinal adenopathies (74.7%), hilar adenopathies (72.1%) without mass effect on adjacent structures, parenchymal nodules (62.8%), and perilymphatic micronodules (74.4%) with associated frosted glass hyperdensities in 37.2% of the cases. Atypical findings were observed in 37.2% of the cases too. We found a radiological remission in 13 patients (30.2%), out of whom 25.5% were diagnosed with typical radiological pulmonary findings. Conversely, 69.8% of the patients were either on stabilization or on radiological progression.

Radiological remission-associated factors include lymphopenia, calcifications, and typical radiological lesions in CT scan findings. Typical CT scan findings in sarcoidosis are mediastinal adenopathies reported, likewise our findings, in 75% of the patients according to the literature (5). Typically, they are bilateral, symmetric, non-necrotic, and non-compressive, predominantly located on the right side. These adenopathies may show calcifications in 20% of the cases, similarly to our findings (6, 7). Besides, parenchymal micronodules are the most typical parenchymal findings located in the perihilar regions, interlobular septa, and peribronchovascular interstitium. They can merge, likewise with our findings, in 20 to 55% of the cases (8). Other findings like nodular opacities, peri-broncho-vascular interstitial thickening, and ground glass opacities may be associated. The three latter findings are reversible lesions. Other irreversible lesions like pulmonary fibrosis, linear opacities, and traction bronchiectasis are also described. Atypical findings may occur in 25 to 30% of the cases, consisting of unilateral adenopathies in 6.3% of the patients, similarly to our findings (9).

Table 3. Univariate analysis comparing patients with radiological remission with those with stabilization or progression.

		Group 1 n=13	Group 2 n=30	P value
Mean age at diagnosis (years)		45.53 +/- 16,63	47.96 +/- 1.38	0.126
BMI		24.11+/- 2.36	27.36+/-4.84	**0.005**
Smoking		0(0)	3(10)	0.23
Uveitis		1(7.7)	15(50)	0.08
Cutaneous involvement		3(23.1)	12(40)	0.28
Anergic Mantoux test		10(76.9)	11(36.7)	**0.015**
FVC(l)		85.8	94.33	**0.04**
FEV(l)		106.6	105	0.9
PaO_2		12	13	0.9
Low CMDC		1(7.7)	14(46.7)	**0.014**
Function tests pattern - **Restrictif** - **Obstructif** - **Mixed**		2(15) 3(23) 0	10(33) 5(16) 10(33)	0.009
Lymphopenia (<1500 elements/mm^3)		10(76.9)	8(26.7)	**0.02**
Mean calcium levels (mmol/l)		2.53 +/- 0.150	2,50 +/- 0.159	0.59
Mean ACE (UI/l) levels		53.07 +/- 16.33	96.03 +/- 47.08	**0.01**
Initial lymph nodes calcifications		5(38.5)	4(13.3)	0.1
Ground glass pattern		3(23.1)	13(43.3)	0.27
Typical CT scan findings		11(84.6)	16(53.3)	0.08
Atypical CT scan findings				
- A1: Unilateral or isolated mediastinal lymphadenopathy		0	4 (13)	**0.001**
- A2: Nodules or lung masses (diameter 1-4 cm)		2	1(3)	**0.001**
- A3: Airspace consolidation when the small pulmonary parenchymal nodules appeared very close together, tending to merge into a large nodule		0	3(9)	**0.001**
- A4: Confluent alveolar opacities		0	1(3)	**0.001**
- A5: Tracheobronchial abnormalities		0	1(3)	**0.001**
- A6: Pleural lesions		0	4(13)	**0.001**
Treatment	**Yes**	10(76)	25(83)	**0.01**
	No	3(23.1)	5(16)	

ACE: angiotensin converting enzyme; BMI: body mass index; CMDC: carbone monoxide diffuse capacity; CT: computed tomography

Table 4. Predictive factors of pulmonary radiological remission on CT scan findings on systemic sarcoidosis.

	Adjusted Odds Ratio (aOR)	95% IC	P value
Lymphopenia (<1500 elements/mm^3)	27.57	2.67-284.69	0.005
Initial lymph node calcifications	37.2	2.08-663.89	0.014
Typical radiological pattern	47.1	1.79-1238.7	0.021

Other atypical lesions are macronodular lesions and alveolar shape lesions (alveolar sarcoidosis), reported, unlike our findings, in up to 25% and up to 20% of the cases, respectively (10, 11).

Compared to 12-month follow-up CT scan findings, we found lower radiological remission compared to other published data with similarly typical radiological features. This could be a confounding bias as our study interested patients with systemic manifestations with a high prevalence of extra

pulmonary manifestations, probably more difficult to treat. Radiological stabilization occurred in 44.1% of our patients; likewise, in the literature, we found more progressive radiological features (9, 10).

According to our findings, calcifications on CT scan findings were independently associated with the radiological remission of sarcoidosis. Calcifications, resulting from a local production of vitamin D, are suggested to limit the disease progression (12). This local production is also suggested to modulate the inflammation, favoring thus the disease remission (13).

We also found that lymphopenia and typical radiological findings were associated with the radiological findings. No published data reported such results. Lymphopenia is strongly associated with active sarcoidosis and is considered according to the literature as a marker of disease activity as it was correlated to features of inflammation in PET/CT scan (13,14). So we think that patients having lymphopenia, and thus having an active disease will be more sensitive to the treatment and will achieve remission whereas those without lymphopenia have probably a chronic disease course poorly responding to the treatment. We suggest that, as lymphopenia is a marker of disease activity, the more active the disease is, the more likely it is to achieve radiological remission. Typical radiological findings might be more responsive to treatment, leading to radiological remission.

In terms of acknowledged limitations, this study was confined to a retrospective analysis of a limited number of patient records. Nevertheless, this is, to the best of our knowledge, the first North African study aiming at studying factors associated with pulmonary radiological remission in systemic sarcoidosis.

Conclusion

In systemic sarcoidosis with pulmonary involvement, lymphopenia, typical radiological findings, and calcifications seem to be associated with radiological remission. For those patients without any of the abovementioned criteria, we suggest a close follow-up as well as intensive treatment when they are symptomatic.

References

1. Akira M, Kozuka T, Inoue Y, Sakatani M. Long-term follow-up CT scan evaluation in patients with pulmonary sarcoidosis. Chest Janv 2005;127(1):185-91.
2. Miller BH, Rosado-de-Christenson ML, McAdams HP, Fishback NF (1995) Thoracic sarcoidosis: radiologic-pathologic correlation. Radiographics 1995 Mar;15(2):421-37.
3. Fazzi P. Pharmacotherapeutic management of pulmonary sarcoidosis. Am J Respir Med 2003;2(4):311-20.
4. Hostettler KE, Studler U, Tamm M, et al. Long-term treatment with infliximab in patients with sarcoidosis. Respiration 2012;83(3):218-24
5. Augier A, Brillet PY, Duperon F, Nunes H, Valeyre D, Brauner M. Analyse en tomodensitometrie de 500 cas de sarcoidose pulmonaire. J Radiol 2005;86(10):1385.
6. Fabry A, Cohen JG, Reymond E, Jankowski A, Ferretti G. Verre dépoli pulmonaire en tomodensitométrie thoracique. J Imag Diagn Interv 2018;1(2):102-5.
7. Calandriello L, Walsh SLF. Imaging for Sarcoidosis. Semin Respir Crit Care Med 2017 Aug;38(4):417-436.
8. Polverosi R, Russo R, Coran A, et al. Typical and atypical pattern of pulmonary sarcoidosis at high-resolution CT: relation to clinical evolution and therapeutic procedures. Radiol Med 2014 Jun;119(6):384-92
9. Susam S, Ucsular FD, Yalniz E, et al. Comparison of typical and atypical computed tomography patterns regarding reversibility and fibrosis in pulmonary sarcoidosis. Ann Thorac Med 2021 Jan-Mar;16(1):118-125
10. Criado E, Sánchez M, Ramírez J, et al. Pulmonary Sarcoidosis: Typical and Atypical Manifestations at High-Resolution CT with Pathologic Correlation. Radiographics 2010 Oct;30(6):1567-86
11. Sharma SK, Soneja M, Sharma A, Sharma MC, Hari S. Rare manifestations of sarcoidosis in modern era of new diagnostic tools. Indian J Med Res May 2012;135(5):621-9.
12. Reichel H, Koeffler HP, Barbers R, Norman AW. Regulation of 1,25-dihydroxyvitamin D3 production by cultured alveolar macrophages from normal human donors and from patients with pulmonary sarcoidosis. J Clin Endocrinol Metab 1987; 65: 1201–1209.
13. Vagts C, Ascoli C, Fraidenburg DR, et al. Unsupervised Clustering Reveals Sarcoidosis Phenotypes Marked by a Reduction in Lymphocytes Relate to Increased Inflammatory Activity on 18FDG-PET/CT. Front Med 2021; 8: 595077
14. El Jammal T, Dhelft F, Pradat P, et al. Diagnostic value of elevated serum angiotensin-converting enzyme and lymphopenia in patients with granulomatous hepatitis. Sarcoidosis Vasc Diffuse Lung Dis 2023;40(3):e2023031