Sarcoidosis in Patients with Antisynthetase Syndrome: Presentation and Outcome

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ABSTRACT. ***Objective.*** To investigate the uncommon co-occurrence of antisynthetase syndrome (AS) and sarcoidosis.

Methods. From 2000 to 2015, patients with sarcoidosis were extracted from a retrospective multicentric cohort of 352 patients with AS.

Results. Ten patients (2.8%; 6 men, 8 whites, 5 smokers, median age 50 yrs) had both AS and sarcoidosis. Most of the time, sarcoidosis and AS occurred simultaneously (n = 7). Antibody testing revealed anti-Jo1 (n = 5), anti-PL12 (n = 4), or anti-PL7 (n = 1). Finally, no patient had a worsening of muscular condition, 5 patients presented respiratory deterioration, 3 remained stable, and 2 showed improvement.

Conclusion. Sarcoidosis may be underdiagnosed in patients with AS. (First Release July 1 2018; J Rheumatol 2018;45:1296–1300; doi:10.3899/jrheum.171098)

Key Indexing Terms:
SARCOIDOSIS ANTISYNTHETASE SYNDROME INTERSTITIAL LUNG DISEASE

Antisynthetase syndrome (AS) is an inflammatory myopathy associated with interstitial lung disease (ILD) and autoantibodies to aminoacyl-tRNA synthetase. Other symptoms may occur such as polyarthritis, Raynaud phenomenon (RP), or mechanic hands[1]. AS may constitute an overlap syndrome with other connective tissue diseases (CTD)[2].

Sarcoidosis is an immune disorder with granulomatous reaction to an unknown antigen, with pulmonary involvement in 90% of the cases and extrapulmonary localizations in half of the cases[3]. Co-occurrence of autoimmune diseases and sarcoidosis is uncommon[4,5]. For instance, association of sarcoidosis with systemic lupus erythematosus, systemic sclerosis, primary biliary cirrhosis, autoimmune cytopenia, or Sjögren syndrome has been described[6,7]. However, the combination of AS and sarcoidosis is particularly rare, reported in only 2 cases[8,9]. We conducted a retrospective multicentric study to investigate the presentation and outcome of this co-occurrence of diseases.

MATERIALS AND METHODS

Our study received institutional review board approval and the requirement for signed informed consent was waived according to French legislation (CLEA-2016-028).

From 2000 to 2015, a cohort of 352 patients with AS was assembled from 10 French university hospitals (women/men ratio = 2/8; median age at diagnosis 50 yrs). The diagnosis of AS was based on the presence of compatible ILD and/or inflammatory myopathy with anti-tRNA-synthetase autoantibodies[2,10]. To exclude false-positive patients, we included patients only if they had at least 2 positive tests for myositis-specific antibodies (Luminex and Linear dot for anti-Jo1 or 2 consecutive intense immunodot for anti-PL7/PL12). Fourteen patients with noncaseous granulomas on biopsy were selected from the whole cohort. Four patients did not fulfill sarcoidosis diagnosis according to the American Thoracic Society/European Respiratory Society (ATS/ERS) statement[11]. Thus, 10 patients with sarcoidosis associated with AS were included. Demographic, clinical, and paraclinical data and outcomes were collected from medical records (PC).

For each patient, 2 lung computed tomography (CT) scans were reviewed and analyzed: at diagnosis and at the last medical followup. Finally, the CT pattern of ILD was consensually defined (PYB, PC, and YU) in agreement with international ATS/ERS CT criteria for idiopathic interstitial pneumonia[12].

For outcome analysis, we defined pulmonary progression or improvement according to New York Heart Association stage of dyspnea, pulmonary function tests (> 10% of predicted value of forced vital capacity or in carbon monoxide transfer factor 6 months after the inclusion and/or at

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the end of the study), and/or the occurrence of symptomatic pulmonary hypertension (PH) confirmed by right heart catheterization. Muscular deterioration was defined as increasing muscle weakness according to Muscular Disability Rating Scale, or a rise of creatine kinase (CK) > twice the normal range[2].

RESULTS

Patients' characteristics at diagnosis are reported in Table 1. There were 10 patients, including 4 men, 8 whites, 5 smokers. Thus, 2.8% of patients with AS also had a confirmed sarcoidosis. The onset of clinical manifestations occurred at the median age of 50 years (range: 35–69). None had history of neoplasia. Median followup was 47 months (from 18 to 165 mos). Patients' characteristics during followup are reported in Table 2. In most cases, sarcoidosis and AS occurred at the same time (n = 7). Sarcoidosis started first in 2 patients (10 and 24 mos) while AS occurred first in the last case (24 mos).

At sarcoidosis diagnosis, 7 patients complained of fatigue, 4 reported a significant weight loss (from 2 to 9 kg), and 1 had fever. Most patients (n = 8) disclosed an inflammatory syndrome with a median CRP level at 17 mg/l (from 3 to 77).

Initial lung CT scans (Figure 1) showed commonly nonspecific interstitial pneumonia (NSIP; n = 6), NSIP with organizing pneumonia (NSIP-OP; n = 2), and unclassifiable ILD (n = 1). Most patients had mediastinal-hilar lymphadenopathies (n = 7) that were noncompressive (n = 7) and/or noncalcified (n = 5; Table 1).

The bronchoalveolar lavage lymphocyte count was increased in only 1 case. However, noncaseating granulomas were discovered in biopsies: bronchial (n = 5), mediastinal (n = 1), pleural (n = 1), skin (n = 2), or salivary glands (n = 1).

Extrapulmonary features related to AS were as follows: inflammatory polyarthralgia (n = 6), mechanic hands (n = 2), RP (n = 5), and myositis (n = 4). In relation to sarcoidosis, 3 patients had biopsy-proven cutaneous nodules and 3 others had peripheral lymphadenopathies.

Biological findings showed slightly elevated CK and lactate dehydrogenase levels, with median values 1.3 and 2 times the normal range, respectively. Antinuclear antibodies were positive for 6 patients. Antibody testing revealed anti-Jo1 (n = 5), anti-PL12 (n = 4), and anti-PL7 (n = 1), whereas anti-RNP, anti-DNA, anticitrullinated protein antibodies, and rheumatoid factor were negative. The distribution of the AS autoantibody subtypes was not different in AS patients with or without sarcoidosis[2].

At diagnosis, angiotensin-converting enzyme level was increased only twice (median level 33 IU/l; range: 5–150 IU/l).

Inflammatory myopathy was confirmed on muscular biopsies (n = 4/6) and muscle histology never revealed granuloma. All the patients with muscular symptoms fulfilled the European Neuromuscular Centre classification criteria for inflammatory myopathy (n = 5), and 1 additional patient was classified as having dermatomyositis according to a biopsy-proven heliotrope rash[13]. The remaining 4 patients, who were hypomyopathic or amyopathic, fulfilled the additional criteria for overlap myositis from Troyanov, *et al*[14].

When 18F-fluorodeoxyglucose positron emission tomography was performed (n = 4), hypermetabolic activity was always found in place of mediastinal-hilar lymphadenopathies and pulmonary parenchyma.

All patients were treated with steroids. Nine patients needed immunosuppressive therapy, including methotrexate (n = 7), azathioprine (n = 3), IV cyclophosphamide (CYC; n = 2), and mycophenolate mofetil (n = 1; Table 2).

At the end of the study, the median dose of prednisone was 12.5 mg/d (0–30).

Table 1. Characteristics of all patients at diagnosis.

Characteristics	Patients									
	1	2	3	4	5	6	7	8	9	10
Age at diagnosis, yrs	64	64	69	44	50	45	57	35	48	50
Sex	Male	Female	Male	Female	Male	Male	Female	Female	Female	Female
Geographic origins	White	White	White	White	White	White	White	Afro-Caribbean	Afro-Caribbean	White
Dyspnea (NYHA)	1	1	0	3	2	0	2	2	2	3
Dry cough	Yes	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Crackles	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes
Antisynthetase antibody	JO1	PL12	JO1	PL7	JO1	JO1	PL12	PL12	PL12	JO1
Sarcoidosis stage at diagnosis	2	4	1	3	2	2	4	4	2	1
Lymphadenopathy, location	Paratracheal, hilar, mediastinal	Paratracheal, mediastinal	Mediastinal	0	0	Paratracheal, hilar, mediastinal	0	Paratracheal, hilar, mediastinal	Hilar, mediastinal	Hilar, mediastinal
CT findings at diagnosis	NSIP	NSIP	Emphysema	Unclassified	NSIP	NSIP	NSIP-OP	NSIP-OP	NSIP	NSIP
FVC (%)	85	88	70	52	69	83	60	23	45	60
TLCO (%)	46	55	39	42	53	54	56	75	54	42
BAL (%) (macrophages/ neutrophils/ lymphocytes/ eosinophils)	—	57/40/2/1	90/10/4/0	31/11/53/4	—	71/7/12/10	90/1/9/0	90/6/4/0	70/19/10/1	69/22/7/2

NYHA: New York Heart Association; CT: computed tomography; FVC: forced vital capacity; TLCO: carbon monoxide transfer factor; BAL: bronchoalveolar lavage; NSIP: nonspecific interstitial pneumonia; NSIP-OP: NSIP with organizing pneumonia.

Table 2. Characteristics of all patients during followup.

Characteristics	Patients									
	1	2	3	4	5	6	7	8	9	10
Followup, mos	45	120	18	165	46	47	51	20	18	114
FVC (%) at 6 mos	85	90	—	52	80	98	45	26	45	51
TLCO (%) at 6 mos	46	45	—	39	70	72	40	80	46	31
FVC (%) at end of followup	61	88	75	33	130	96	63	35	46	70
TLCO (%) at end of followup	40	48	42	29	43	73	65	75	46	30
ILD progression at end of study	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes
Fibrosis at end of followup	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PH, confirmed with RHC	Yes	No	No	No	No	No	No	No	No	Yes
mPAP, mmHg	37	—	—	—	—	—	—	—	—	51
PWP, mmHg	17	—	—	—	—	—	—	—	—	8
Death	Yes	No	No	No	No	No	No	No	No	No
No. treatment lines	2	4	2	3	3	1	3	2	3	3
Cumulative treatment	Steroid CYC	Steroid, MTX, AZA, HCQ	Steroid, MTX	Steroid, MTX, CYC	Steroid, MTX, AZA	Steroid	Steroid, AZA, HCQ	Steroid, MTX	Steroid, MTX, HCQ	Steroid, MTX, MMF
Pulmonary evolution	Worsened	Stable	Stable	Worsened	Worsened	Improved	Worsened	Improved	Stable	Worsened

FVC: forced vital capacity; TLCO: carbon monoxide transfer factor; ILD: interstitial lung disease; MMF: mycophenolate mofetil; MTX: methotrexate; CYC: cyclophosphamide; AZA: azathioprine; HCQ: hydroxychloroquine; PH: pulmonary hypertension; RHC: right heart catheterization; mPAP: mean pulmonary arterial pressure; PWP: pulmonary wedge pressure.

No patient experienced a worsening of muscular condition. Deterioration in respiratory status occurred in 5 patients, while 3 remained stable and only 2 improved (Table 2). In 4 cases, lung fibrosis appeared (n = 2) and/or worsened (n = 2) during the followup. Accordingly, 9 patients had fibrosis at the end of the followup. One patient underwent lung transplantation. Further, signs of pulmonary hypertension were found on cardiac ultrasonography in 4 patients: 1 case at diagnosis and the others during the followup. By right heart catheterization (n = 4), PH was confirmed in 2 patients: 1 with group 3 precapillary PH and the other with postcapillary PH (Table 2). This last patient died from cardiac failure: although initial heart investigations were normal, the patient developed at Year 1 right bundle branch block concomitantly with lung function worsening. Echocardiography found a severely dilated cardiomyopathy, with 40% of left ventricular ejection fraction. Steroid pulses and IV CYC failed to improve the patient's condition.

DISCUSSION

Our study showed several important findings: (1) sarcoidosis is probably underdiagnosed in patients with AS; (2) lung manifestations were those usually seen in AS rather than those found in sarcoidosis; (3) intrathoracic lymphadenopathies were often typical of sarcoidosis; and (4) pulmonary severity resulted from AS rather than from sarcoidosis.

The evaluated prevalence of sarcoidosis in patients with AS may be underlined in this series because 2.8% is far higher than common findings. Some biases are to be considered, however. First, having a systemic disease necessitates multiple investigations allowing the recognition of asymptomatic diseases, which might have been overlooked in other contexts. Then, the age tended to be higher than is usually seen in sarcoidosis. This finding must be all the more underscored considering that both diseases were often concomitant.

We can hypothesize that the 2 diseases may share some similar immunological background. Sarcoidosis involves adaptive Th1 response and production of interleukin 2 + interferon (IFN)-γ. Likewise, AS involves a Th1 response with activation of the type I IFN pathway[3]. Further, sarcoidosis-like granulomatosis as well as AS have been described in patients treated with exogenous IFN-α[15,16].

Concerning the presentation, all cases were typical for both diseases. Sarcoidosis was typical according to thoracic lymphadenopathy, perilymphatic micronodules, cutaneous nodules, and peripheral lymphadenopathy, and all cases had evidence of noncaseating granulomatous lesions, mostly from the thoracic sphere. On the other hand, extrapulmonary features and the biologic profile were typical of AS. Because the lungs may often be involved in both diseases, it was interesting to search for signs to indicate one disease or the other. The phenotype of our patients was complex and taught us to be careful with unusual presentations.

When a diagnosis of sarcoidosis is made, we must pay attention to untypical extrapulmonary features. NSIP pattern during sarcoidosis should lead the physician to search also for CTD, including AS. Obviously, concomitant AS diagnosis has to be taken into account for the specific treatment management. Finally, as is often observed in these "overlapping patients," pulmonary evolution may be severe, requiring screening for PH[17].

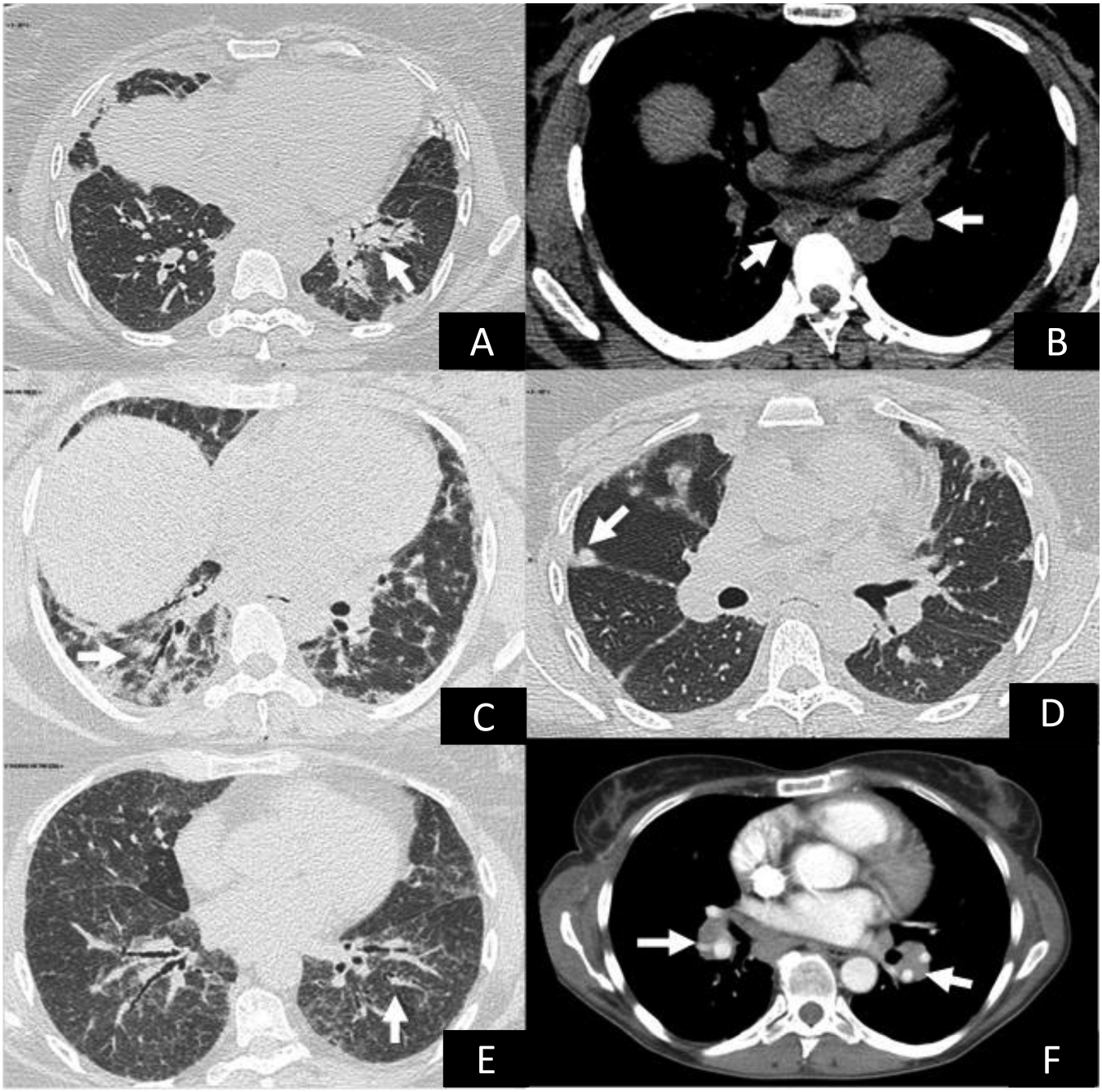

Figure 1. Three examples of lung CT presentations mixing features of AS and sarcoidosis. CT images on the left showed ILD pattern compatible with NSIP pattern, and CT images on the right showed lung lesions and lymph nodes well-matched with sarcoidosis features. Patient number 8 had NSIP-OP pattern with peribronchiolar condensation (A) and hilar calcified lymphadenopathies (B). Patient number 9 had NSIP pattern with proximal bronchiectasis (arrow, panel C), and subpleural reticulations with bibasal distribution; note the characteristic of intraparenchymal lymph node (arrow, panel D) with typical distribution of micronodules including fissural spreading. Patient 10 had NSIP pattern with diffuse ground glass opacities, proximal bronchiectasis, and some reticulations (E) with bilateral and symmetric enlargement of hilar lymph nodes (F). CT: computer tomography; ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; NSIP-OP: NSIP with organizing pneumonia.

In case of atypical signs for AS such as cutaneous nodules or lymphadenopathy (which may suggest cancer in the context of myositis), sarcoidosis should be considered. Physicians might thus look for suggestive clinical findings and histological evidence of granulomas.

The diagnosis of sarcoidosis should lead to a systematic evaluation of all specific organ damage[3], leading to a dedicated therapeutic management. Because rituximab could be promising both in AS and in sarcoidosis separately, its use could theoretically be effective in refractory patients who

have both AS and sarcoidosis[18,19,20]. However, further studies are required to assess this point.

This series showed that clinicians should be aware of possible associations between sarcoidosis and AS. Atypical clinical imaging and biology features may indicate such an association. Both diagnoses are important to establish as they imply particular diagnostic investigation, monitoring, and management.

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