Respiratory Medicine 169 (2020) 105998

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Clinical features and outcomes of asymptomatic pulmonary sarcoidosis. A comparative cohort study

Adriana Iriarte [a,*], Manuel Rubio-Rivas [a], Nadia Villalba [a], Xavier Corbella [a,b], Juan Mañá [a]

[a] Autoimmune Diseases Unit, Department of Internal Medicine, Bellvitge University Hospital-IDIBELL. L'Hospitalet de Llobregat, Barcelona, Spain
[b] Faculty of Medicine and Health Sciences, Universitat Internacional de Catalunya, Barcelona, Spain

ARTICLE INFO

Keywords:
Asymptomatic sarcoidosis
Pulmonary sarcoidosis
Prognosis of sarcoidosis

ABSTRACT

Objective: To evaluate the clinical characteristics and outcomes of patients with asymptomatic pulmonary sarcoidosis (APS) detected incidentally and compare them with symptomatic non-Löfgren sarcoidosis (SnLS) patients.

Methods: Patients diagnosed as having APS at a University hospital in Barcelona, Spain, followed prospectively from 1976 to 2018. APS was defined as the presence of bilateral hilar lymphadenopathy (BHL) with or without lung parenchymal involvement discovered incidentally on chest radiograph or CT scan. APS was compared with SnLS.

Results: APS was diagnosed in 50 (13.6%) and SnLS in 317 (86.4%) patients. At diagnosis, stage I chest radiograph was significantly more frequent in APS than in SnLS ($p < 0.001$) and there were no asymptomatic patients with stages III and IV. SnLS showed more severe impairment in FVC ($p = 0.009$) and forced expiratory volume in 1st second (FEV1) ($p = 0.003$) than APS, while DLco was similar in both groups. Extrathoracic involvement at diagnosis and during the follow up was less frequent in APS than in SnLS patients ($p < 0.005$). Endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS) was the most used diagnostic tool. Treatment was more frequently required in the SnLS than in APS ($p < 0.001$). At five years, APS patients showed less presence of active disease than SnLS ($p = 0.054$).

Conclusions: APS showed earlier radiological stages, lesser impairment in lung function, extrapulmonary organ involvement and need for treatment than SnLS. EBUS was the most useful diagnostic tool. In spite of its benign presentation, around one third of patients evolved to persistent disease but usually with mild clinical and functional impairment.

1. Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology that has a wide variety of clinical manifestations and an unpredictable course [1]. The way of presentation of the disease is highly variable and reflects the multisystem nature of sarcoidosis. In general, an acute onset, such as Löfgren's syndrome (LS), is associated with a good-prognosis, while an insidious onset and some extrathoracic manifestations correlate with a later evolution towards chronicity [2,3]. Interestingly, in a significant number of patients, sarcoidosis is asymptomatic and is detected as a casual finding of bilateral hilar lymphadenopathy (BHL), with or without pulmonary infiltrates on a chest radiograph or CT scan performed in a routine checkup or for other reasons [4,5]. In a recent study, Judson et al. [6] reported that symptomatic sarcoidosis patients had a worse prognosis than those with asymptomatic sarcoidosis, whose disease (pulmonary and extrapulmonary) was detected incidentally. However, no other studies have focused on analyzing the clinical characteristics and long-term outcomes of the particular subgroup of patients with asymptomatic pulmonary sarcoidosis (APS) as a mode of onset of the disease. Here, we report the clinical characteristics of our cohort of patients with APS detected incidentally by imaging techniques who were followed-up in our center and compare them with patients with SnLS. LS is a common form of sarcoidosis in Spain [7,8]. Because of their particular genotype and phenotype characteristics, patients with LS were excluded from the study.

* Corresponding author.
E-mail address: adriana.iriarte@bellvitgehospital.cat (A. Iriarte).

https://doi.org/10.1016/j.rmed.2020.105998
Received 3 December 2019; Received in revised form 27 April 2020; Accepted 28 April 2020
Available online 15 May 2020

Abbreviations list

APS	Asymptomatic pulmonary sarcoidosis
BHL	Bilateral hilar lymphadenopathy
CT	Computed tomography
DLco	Diffusing capacity of carbon monoxide
EBUS	Endobronchial ultrasonography-guided transbronchial needle aspiration
FDG PET/CT	Fluorodeoxyglucose F 18 combined positron emission tomography and computer tomography
FEV1	Forced expiratory volume in 1st second
FVC	Forced vital capacity
LS	Löfren's syndrome
PFT	Pulmonary function tests
SACE	serum angiotensin converting enzyme
SD	standard deviation
SnLS	Symptomatic non-Löfgren sarcoidosis
WASOG	World Association of Sarcoidosis and Other Granulomatous Disorders

2. Methods

2.1. Diagnosis of sarcoidosis and definitions

The diagnosis of sarcoidosis was established according to ATS/ERS/WASOG criteria [9]. Chest radiographs were classified according to Scadding's criteria [10]. Extrapulmonary organ involvement was defined according to the previously reported criteria by *Judson* et al. [11,12]. APS was defined as the presence of typical BHL with or without pulmonary parenchymal involvement discovered incidentally on chest radiograph or CT scan performed in a routine check-up or for another reason. Extrapulmonary asymptomatic presentations, such as abnormal liver function tests, hypercalcemia and others, were not included in this group as they had been classified in our database as presentations according to the corresponding organ involvement and not as asymptomatic abnormal chest imaging.

2.2. Study design and data collection

From 1976 to 2018, 668 patients were diagnosed with sarcoidosis at Bellvitge University Hospital, an 800-bed tertiary university hospital in Barcelona, Spain. The patients diagnosed with sarcoidosis were submitted to a prospective study protocol at diagnosis that has been widely reported [8]. This protocol included variables concerning demographic and clinical data, imaging, extrapulmonary organ involvement, biopsies, follow-up, treatment and outcome. During 2015, the protocols were transferred to a recently created ACCES database (Microsoft Office Access Database 2003). According to the mode of onset of sarcoidosis, patients were classified into two groups depending on their asymptomatic or symptomatic presentation. It is worth noting that LS is a common form of presentation of sarcoidosis in Spain [7,8]. Because of LS's particular genetic and clinical characteristics, some authors consider it a well differentiated clinical entity from non-Löfgren sarcoidosis [3,13]. Therefore, and in order to avoid bias, patients with LS were excluded from this study. There were no other reasons for excluding patients. The study therefore compared patients with APS with those with SnLS.

2.3. Outcomes

APS and SnLS patients were followed up every 3–6 months until the disease became inactive, and thereafter, once a year. No specific therapeutic schedule was followed, and corticosteroids and other immunosuppressive agents were given at the discretion of the physician according to indications recommended in medical literature. Those patients who visited just once and without follow-up could not be classified, but they were included in the analyses concerning mode of onset and clinical characteristics at the time of diagnosis. Sarcoidosis was classified as resolving if the disease presented remission in less than 5 years, and persistent, when the disease remained active (symptomatic disease and/or persistence of radiological findings and/or decline in pulmonary function) for more than 5 years from diagnosis [8,14]. Persistent sarcoidosis was subclassified as having mild and moderate to severe organ damage according to previously reported criteria [15]. Remission was defined as the disappearance of symptoms and radiological findings [8,16,17].

2.4. Statistical analysis

A descriptive analysis was performed, by expressing the results as means and standard deviations for continuous variables, and absolute values and percentages for categorical variables. A T-test (and Mann–Whitney *U* test in the absence of parametric distribution) was performed for the comparison between continuous variables, and the chi-square test or Fisher exact test, when appropriate, for the comparison of categorical variables. SPSS (SPSS 15.0. 2009, Chicago, IL) was used for statistical analyses ($P < 0.005$).

3. Results

3.1. Demographic data and clinical presentation

Three hundred and sixty-seven patients were classified as non-Löfgren's sarcoidosis. Of these, 50 (13.6%) patients were asymptomatic and pulmonary sarcoidosis was discovered by chance in an imaging test performed for another reason. The remaining 317 (86.4%) patients were symptomatic at disease onset. Initial demographic features between APS and SnLS are shown in Table 1. Female and Caucasian patients were more common in the APS group without reaching statistical significance. The median age at diagnosis was similar in both groups. There were no differences regarding smoking behavior. The most common presenting manifestations in the SnLS group were respiratory symptoms (32.5%), specific granulomatous cutaneous lesions (19.6%), constitutional symptoms (fever and/or articular involvement) (13.2%), ocular involvement (6.9%), and neurosarcoidosis (6.6%). The remaining patients presented with a variety of other extrapulmonary manifestations.

Table 1
Demographic data.

	APS n (%) or mean (SD)	SnLS n (%) or mean (SD)	p-value
Patients	50 (13.6)	317 (86.4)	
Age at diagnosis (years)	46.2 (14.3)	46.4 (14.6)	0.916
Female gender	27 (54)	133 (42)	0.110
Ethnicity			0.548
Caucasian	48 (96)	292 (92.1)	
North African	1 (2)	15 (4.7)	
Hispanic	1 (2)	2 (0.6)	
Black	0	6 (1.9)	
Asian	0	2 (0.6)	
Smoking behavior			0.499
Never smoked	33 (67.3)	224 (72.7)	
Current smoker	6 (12.2)	41 (13.3)	
Former smoker	10 (20.4)	43 (14)	

SD: standard deviation. APS: Asymptomatic pulmonary sarcoidosis. SnLS: symptomatic Non-Löfgren sarcoidosis.

3.2. Pulmonary sarcoidosis

Table 2 shows the radiological stages at diagnosis. Stage I was significantly more frequent in APS than in SnLS ($p < 0.001$). There were no asymptomatic patients with stages III and IV at the beginning of the disease. Symptomatic patients demonstrated more advanced Scadding radiographic stages than the asymptomatic group ($p = 0.003$). Five (10%) patients with APS were categorized as stage 0 on chest radiograph. In these cases, sarcoidosis was detected by the presence of BHL on thoracic CT scan performed for other reasons (Table 3). At diagnosis, SnLS patients had significantly more severe pulmonary function impairment in FVC ($p = 0.009$) and FEV1 ($p = 0.003$) than APS patients, while DLco was similar in both groups (Table 4).

3.3. Extrapulmonary sarcoidosis

The extrapulmonary organ involvement at diagnosis or at any time during the follow-up is displayed in Table 5. Overall, symptomatic patients at onset showed extrapulmonary involvement more often than those with asymptomatic disease (84.5% vs. 52% patients) ($p < 0.005$). In particular, arthralgia/arthritis other than periarticular ankle inflammation, fever, granulomatous skin lesions, disabling asthenia, hypercalcemia, neurosarcoidosis and ocular involvement were significantly more prevalent in the SnLS group.

3.4. Ancillary tests and histological confirmation

There were no statistical differences between groups on the presence of positive tuberculin skin test (PPD) (9.5% vs. 16.2%, $p = 0.436$), hypergammaglobulinemia (30.3% vs. 38.4%, $p = 0.358$), and increased serum angiotensin converting enzyme (SACE) levels (42% vs.50.8%, $p = 0.248$) at diagnosis. Table 6 summarizes the histological diagnosis of sarcoidosis in both groups. In APS patients, mediastinoscopy (24% vs. 8.2%, $p < 0.003$) and endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS) (34% vs. 6.9%, $p < 0.001$) were the most used diagnostic tools, while skin (10% vs. 32.8%, $p < 0.005$) and Kveim-Siltzbach skin test (6% vs. 17%, $p < 0.026$) were more frequently used in the SnLS group.

3.5. Treatment, follow-up and outcomes

A total of 332 patients, 47 (94%) in APS vs. 285 (89.9%) in SnLS group, were followed up. The mean follow-up time for both groups was 6.5 (SD 5.9) in APS vs. 9.2 (SD 9) years in SnLS ($p < 0.006$). Fifteen patients (30%) in the APS group were treated vs. 205 (64.6%) in SnLS ($p < 0.001$). In particular, corticosteroid therapy was administered to 15 patients in the APS group, while two also received methotrexate, and one, azathioprine. In the SnLS group, corticosteroid therapy was administered in 197 (62.1%) patients, and steroid sparing agents (usually with a low dose of corticosteroids) were administered as follows: methotrexate in 29 (9.1%) patients, antimalarials in 25 (7.9%) and azathioprine in 20 (6.3%). Other agents were used in a few cases: mycophenolate mofetil in 8 (2.5%), cyclosporine in 2 (0.6%), cyclophosphamide in 2 (0.6%) and anti-TNF blockers (infliximab and adalimumab) in 4 (1.2%) patients.

Table 2
Radiological stages at diagnosis.

Chest radiograph stage	APS n = 50	SnLS n = 317	p-value
Stage 0	5 (10%)	48 (15.1%)	0.336
Stage I	35 (70%)	115 (36.3%)	**<0.001**
Stage II	10 (20%)	98 (30.9%)	0.115
Stage III/IV	0	56 (17.7%)	**0.003**

APS: Asymptomatic pulmonary sarcoidosis. SnLS: symptomatic Non-Löfgren sarcoidosis.

Table 3
Thoracic CT at diagnosis in 246 patients.

	APS n = 43	SnLS n = 203	p-value
Normal	0	16 (7.9%)	0.118
Mediastinal lymph nodes	24 (55.8%)	67 (33%)	**0.005**
Mediastinal lymph nodes plus pulmonary parenchyma	19 (44.2%)	103 (50.7%)	0.435
Pulmonary parenchyma alone	0	17 (8.4%)	0.102

CT: Computed tomography. APS: Asymptomatic pulmonary sarcoidosis. SnLS: symptomatic Non-Löfgren sarcoidosis.

Table 4
Pulmonary function tests at diagnosis.

PFT at diagnosis	APS n (%)	SnLS n (%)	p-value
FVC			
≥80%	35/37 (94.6%)	188/249 (75.5%)	**0.009**
<80%	2/37 (5.4%)	61/249 (24.5%)	
FEV1			
≥80%	34/37 (91.9%)	173/249 (69.5%)	**0.003**
<80%	31/37 (8.1%)	76/249 (30.5%)	
DLco			
≥80%	20/32 (62.5%)	135/220 (61.4%)	0.902
<80%	12/32 (37.5%)	85/220 (38.6%)	

PFT: pulmonary function tests. FVC: forced vital capacity. FEV1: forced expiratory volume in 1st second. DLco: diffusing capacity of carbon monoxide. APS: Asymptomatic pulmonary sarcoidosis. SnLS: symptomatic Non-Löfgren sarcoidosis.

Table 5
Extrapulmonary sarcoidosis at diagnosis or at any time during the follow-up. Some patients presented diverse manifestations affecting the same organ, so the total count on each organ involvement does not add up.

Extrapulmonary manifestations	APS n = 50	SnLS n = 317	p-value
Erythema nodosum	0	5 (1.6%)	1.000
Arthralgia/itis other than periarticular ankle inflammation	3 (6%)	59 (18.6%)	**0.025**
Fever	0	51 (16.1%)	**0.001**
Specific granulomatous skin lesions	5 (10%)	98 (30.9%)	**0.002**
Maculopapules	3 (6%)	50 (15.8%)	0.082
Plaques	2 (4%)	33 (10.4%)	0.198
Subcutaneous nodules	1 (2%)	19 (6%)	0.497
Scar sarcoidosis	0	13 (4.1%)	0.230
Lupus pernio	0	8 (2.5%)	0.605
Peripheral lymph nodes	12 (24%)	84 (26.5%)	0.709
Abdominal/retroperitoneal lymph nodes	8 (16%)	58 (18.3%)	0.694
Liver involvement	9 (18%)	77 (24.3%)	0.329
Disabling asthenia	1 (2%)	38 (12%)	**0.027**
Neurological involvement	1 (2%)	40 (12.6%)	**0.027**
Isolated VII cranial nerve palsy	0	12 (3.8%)	0.383
Neurological involvement other than VII cranial nerve palsy	1 (2%)	28 (8.8%)	0.153
Ocular involvement	1 (2%)	54 (17%)	**0.003**
Anterior uveitis	1 (2%)	33 (10.4%)	0.065
Intermediate/posterior uveitis	0	10 (3.2%)	0.369
Splenic involvement	4 (8%)	45 (14.2%)	0.272
Hypercalcemia	0	26 (8.2%)	**0.034**
Parotid/salivary glands/lacrimal	4 (8%)	24 (7.6%)	1.000
SURT	2 (4%)	22 (6.9%)	0.756
Bone involvement	3 (6%)	19 (6%)	1.000
Renal involvement (Chronic renal failure, nephritis or proteinuria)	0	15 (4.7%)	0.239
Muscular involvement	0	5 (1.6%)	1.000
Cardiac involvement	0	7 (2.2%)	0.600

APS: Asymptomatic pulmonary sarcoidosis. SnLS: symptomatic Non-Löfgren sarcoidosis. SURT: Sarcoidosis of upper respiratory tract.

Table 6
Histological diagnosis of sarcoidosis.

Biopsies	APS n = 50	SnLS n = 317	p- value
Diagnosis without biopsy	2 (4%)	12 (3.8%)	1.000
Diagnosis with biopsy	48 (96%)	305 (96.2%)	1.000
Mediastinal node (EBUS)	17 (34%)	22 (6.9%)	**<0.001**
Mediastinal node (mediastinoscopy)	12 (24%)	26 (8.2%)	**0.003**
Transbronchial	6 (12%)	50 (15.8%)	0.425
Peripheral node	5 (10%)	59 (18.6%)	0.310
Skin	5 (10%)	104 (32.8%)	**0.005**
Kveim-Siltzbach skin test	3 (6%)	54 (17%)	**0.026**
Daniels	3 (6%)	14 (4.4%)	0.664
Lacrimal gland	2 (4%)	5 (1.6%)	0.245
Liver	1 (2%)	34 (10.7%)	0.075
Thoracotomy/videothoracoscopy	1 (2%)	22 (6.9%)	0.374
Conjunctiva	1 (2%)	12 (3.8%)	0.766
Parotid/salivary	1 (2%)	6 (1.9%)	0.618
SURT	1 (2%)	11 (3.5%)	0.862
Abdominal node	1 (2%)	13 (4.1%)	0.703
Bone	1 (2%)	6 (1.9%)	1.000
Kidney	0	7 (2.2%)	0.600
Muscle	0	9 (2.8%)	0.173
Endobronchial	0	14 (4.4%)	0.311
Spleen	0	6 (1.9%)	0.570
CNS	0	2 (0.6%)	1.000
Others	1 (2%)	9 (2.8%)	0.898

APS: Asymptomatic pulmonary sarcoidosis. SnLS: symptomatic Non-Löfgren sarcoidosis. SURT: Sarcoidosis of upper respiratory tract. CNS: central nervous system.

Table 7
Patients' classification. Part of the cohort cannot be classified since they are patients yet on activity and others due to lack of follow-up, so that numbers do not add up. Different severe organ damage can be present in the same patient, so numbers do not add up as well.

Outcome	APS n = 50	SnLS n = 317	p-value
Patients diagnosed and without follow-up	3 (6%)	32 (10.1%)	0.511
Classifiable patients	47 (94%)	285 (89.9%)	0.511
Classifiable patients in < 5 years from diagnosis	32 (68%)	151 (53.0%)	**0.032**
Spontaneous remission	11 (23.4%)	41 (14.4%)	0.088
Remission under treatment	4 (8.5%)	31 (10.9%)	0.889
Patients with follow-up < 5 years and still active	17 (36.1%)	79 (27.7%)	0.175
Persistent sarcoidosis (activity > 5 years)	15 (32%)	134 (47%)	0.054
Mild organ damage	13 (27.7%)	71 (24.9%)	0.688
Moderate to severe organ damage	2 (4.3%)	63 (22.1%)	**0.008**
Pulmonary damage	1 (2.1%)	42 (14.7%)	**0.032**
Fibrosis + functional pulmonary impairment	1 (2.1%)	41 (14.4%)	
Pulmonary hypertension	0	1 (0.3%)	
Neurosarcoidosis	0	10 (3.5%)	0.399
Lupus pernio	0	8 (2.8%)	0.516
Chronic posterior uveitis	0	3 (1.1%)	0.900
Liver cirrhosis/portal hypertension	0	3 (1.1%)	0.900
Bone involvement	1 (2.1%)	0	0.303
Cardiac involvement	0	2 (0.7%)	0.659
Chronic renal failure	0	3 (1.1%)	0.900

APS: Asymptomatic pulmonary sarcoidosis. SnLS: symptomatic Non-Löfgren sarcoidosis.

Table 7 summarizes the clinical outcomes of patients that were followed-up. 23.4% asymptomatic patients vs. 14.4% symptomatic patients showed spontaneous remission without treatment in the first 5 years from diagnosis (p = 0.088). There was no difference between the asymptomatic and symptomatic groups regarding remission of the disease with treatment at 5 years (p = 0.889). 32% of asymptomatic and 47% of symptomatic patients (p = 0.054) showed active disease over 5 years after diagnosis and were classified as persistent sarcoidosis. Of them, 27.7% in the APS group vs. 24.9% in the SnLS group (p = 0.688) were classified as having mild persistent activity. 4.3% of patients in the APS group (one with pulmonary fibrosis and other with symptomatic extent bone involvement) vs. 22.1% in the SnLS group were classified as having moderate to severe organ damage (p = 0.008).

4. Discussion

One of the most characteristic diagnoses of sarcoidosis is the fortuitous detection of BHL with or without pulmonary parenchymal involvement on a chest radiograph or CT-scan performed in a routine medical exam in asymptomatic patients [1,2]. However, there are few available studies on the clinical characteristics and outcomes of this subgroup of sarcoidosis patients. In the present study, we describe the clinical characteristics and long-term outcomes of 50 patients with APS from a large cohort of patients with sarcoidosis at a tertiary referral center in Barcelona, Spain, over a 42-year period.

4.1. Demographic data and clinical presentation

APS represented 13.6% of our cohort of non-Löfgren's sarcoidosis patients. Although most of our population was Caucasian, there were no significant differences of race, age and sex distribution in the two groups. Different clinical patterns of disease presentation, organ involvement and prognosis have been observed depending on ethnic origin. In particular, asymptomatic presentation was reported to be more common in Caucasian patients compared to black and Asian patients, who suffered more severe and symptomatic forms [6,18]. The real prevalence of APS is unknown due to the lack of reliable epidemiological records in many countries. In historical worldwide series, asymptomatic sarcoidosis at presentation was reported in frequencies that ranged from 10% to 48.5% [4,6,19–21]. These high frequencies were in part due to the performance of general survey examinations. No cases in our study were detected by radiographic screening exams. This way of presentation, however, has decreased in comparison with earlier series because of the withdrawal of mass radiograph screening programs [5]. There are probably an increasing number of patients with sarcoidosis which has been detected incidentally since the introduction of PET-CT scans performed in the follow-up of patients with cancer. However, we have not included this new form of detection in our study because we consider this particular subgroup of patients deserves a separate analysis. As reported in most series, respiratory symptoms and granulomatous skin lesions were the most frequent way of presentation in the SnLS group.

4.2. Pulmonary sarcoidosis

The most significant differences between APS and SnLS were in the higher frequency of stage I in asymptomatic patients and in the absence of stages III and IV. Although in both groups most of our patients showed normal pulmonary functional tests at diagnosis, restrictive and obstructive patterns were significantly more frequent in SnLS, probably because of the presence of more advanced radiological stages. Winterbauer and Hutchinson [22] reported that about 20% of patients with stage I and 40–70% with stage II to IV had abnormal pulmonary function tests at presentation. This suggests that the classical clinical, radiographic and functional dissociation described in sarcoidosis is rather limited to the first radiological stages and that the more advanced the radiological stage, the greater the probability of it being symptomatic and presenting impairment in lung function.

4.3. Extrapulmonary sarcoidosis

The presence of extrapulmonary involvement was more frequent in symptomatic than in APS patients. In particular, constitutional symptoms, disabling asthenia, specific skin lesions, neurosarcoidosis, ocular involvement and hypercalcemia were significantly more frequent in SnLS patients. However, it should be noted that up to 52% of asymptomatic patients showed extrapulmonary involvement at some point of their disease, which reinforces the systemic nature of sarcoidosis. Judson et al. [6] also reported significantly more organ involvement in symptomatic patients, particularly skin, eye and neurologic.

4.4. Ancillary tests and histological confirmation

Diagnosis was proven histologically in 96% of patients with APS. Several studies have suggested that in asymptomatic stage I when discovered incidentally, the diagnosis of sarcoidosis can be accepted without histologic confirmation [2,23]. In patients with presumptive stage I sarcoidosis, a balance between the use of aggressive diagnostic procedures for a usually relatively benign disease and the assumption of a diagnosis without histology has been controversial [24]. Winterbauer et al. [25] reported that BHL, either in asymptomatic patients or in association with erythema nodosum or uveitis, was highly suggestive of sarcoidosis and biopsy confirmation of the diagnosis was not mandatory. In contrast, patients with neoplastic hilar adenopathy were always symptomatic [25]. Likewise, in asymptomatic patients with typical BHL, an increased SACE level and a negative tuberculin skin test may strongly support the diagnosis [26].

In our series, the most used diagnostic techniques in patients with APS were mediastinoscopy and EBUS. Currently, EBUS has displaced the use of mediastinoscopy to evaluate mediastinal lymphadenopathy [27,28]. In consequence, although the diagnosis of sarcoidosis is highly likely in the majority of asymptomatic patients with typical BHL, we strongly recommend the use of EBUS as the diagnostic procedure of choice in these patients. However, it should be emphasized the importance of systemic examination in order to check for other more accessible extrapulmonary involvements, such as skin, conjunctiva and others, which avoid the need of invasive biopsy procedures.

4.5. Treatment, follow-up and outcomes

In concordance with the Judson et al. study [6], treatment was more frequently required in the symptomatic group than in APS patients. Particularly controversial is the administration of treatment in the case of persistence of asymptomatic pulmonary involvement on chest imaging without functional derangement for more than 6–12 months. In our series, the frequency of spontaneous remission without treatment at five years from diagnosis was more frequent in the APS group (a trend towards significance). However, complete remission was achieved during treatment in only a small number of patients in both groups, without statistically significant differences. These findings, once again, question the real efficacy of treatment of sarcoidosis in inducing the remission of the disease. They suggest that treatment is merely useful in helping keep the disease under relative control. In fact, most patients do not require treatment, as they have spontaneous remission or have persistent disease for years, but with few clinical and functional repercussions in affected organs.

Persistent disease is accepted when the disease remains active for over 5 years [14]. In our series, SnLS patients showed an almost statistically significant trend to higher frequency of persistent disease than APS patients. However, patients with persistent sarcoidosis may show a mild degree of activity without clinically significant organ dysfunction or with moderate to severe organ damage. The rates in both groups with mild persistent disease were similar. Some of these patients do not require therapy but should be monitored periodically. Instead, persistent disease with moderate to severe organ damage, both pulmonary and extrapulmonary, was significantly more frequent in SnLS patients.

In summary, APS is a characteristic and probably underestimated presenting form of sarcoidosis. Asymptomatic patients show less advanced radiological stages, functional impairment and extrathoracic involvement than SnLS patients. Although in cases with typical chest radiograph or CT scan, histological confirmation may not be mandatory, EBUS has become a high yield and less aggressive diagnostic procedure. Although most of the patients with APS showed remission of the disease within 5 years, around one-third evolved to persistent disease usually with mild clinical and functional impairment. We recommend periodic follow-up of these patients and a more thorough assessment of treatment indications in order to avoid the side effects, which not infrequently produce more discomfort than the disease itself. Moderate to severe organ damage was more frequent in symptomatic than in asymptomatic disease.

Declaration of competing interest

I declare that all the authors have read and agreed with the content and interpretation of the submitted article. On behalf of all the other authors, I declare that there are no financial agreements that may constitute a potential conflict of interest with the subject matter dealt with in the article.

CRediT authorship contribution statement

Adriana Iriarte: Conceptualization, Methodology, Investigation, Resources, Data curation, Visualization, Writing - original draft. **Manuel Rubio-Rivas:** Methodology, Formal analysis. **Nadia Villalba:** Data curation. **Xavier Corbella:** Supervision. **Juan Mañá:** Conceptualization, Writing - review & editing.

References

[1] J. Grunewald, J. Grutters, E. Arkema, L. Saketkoo, D. Moller, J. Muller-Quernheim, Sarcoidosis, Nat. Rev. Dis. Prim. 5 (1) (2019) 45, https://doi.org/10.1038/s41572-019-0096-x.

[2] D. Valeyre, A. Prasse, H. Nunes, Y. Uzunhan, P.Y. Brillet, J. Muller-Quernheim, Sarcoidosis, Lancet 383 (9923) (2014) 1155–1167, https://doi.org/10.1016/S0140-6736(13)60680-7.

[3] P. Spagnolo, H. Sato, J. Grunewald, B. Brynedal, J. Hillert, J. Mañá, A.U. Wells, A. Eklund, K.I. Welsh, R.M. Du Bois, A common haplotype of the C-C chemokine receptor 2 gene and HLA-DRB1*0301 are independent genetic risk factors for Löfgren's syndrome, J. Intern. Med. 264 (2008) 433–441, https://doi.org/10.1111/j.1365-2796.2008.01984.x.

[4] G. Hillerdal, E. Nou, K. Osterman, B. Schmekel, Sarcoidosis: epidemiology and prognosis: a 15-year European study, Am. Rev. Respir. Dis. 130 (1984) 29–32, https://doi.org/10.1164/arrd.1984.130.1.29.

[5] D. Valeyre, J.F. Bernaudin, F. Jeny, B. Duchemann, O. Freynet, C. Planès, M. Kambouchner, H. Nunes, Pulmonary sarcoidosis, Clin. Chest Med. 36 (4) (2015) 631–641, https://doi.org/10.1016/j.ccm.2015.08.006.

[6] M.A. Judson, S. Preston, K. Hu, R. Zhang, S. Jou, A. Modi, I. Sukhu, F. Ilyas, G. Rosoklija, R. Yucel, Quantifying the relationship between symptoms at presentation and the prognosis of sarcoidosis, Respir. Med. 152 (2019) 14–19, https://doi.org/10.1016/j.rmed.2019.03.012.

[7] J. Mañá, F. Badrinas, J. Morera, E. Fité, F. Manresa, F. Fernández-Nogués, Sarcoidosis in Spain, Sarcoidosis 9 (2) (1999) 118–122.

[8] J. Mañá, M. Rubio-Rivas, N. Villalba, et al., Multidisciplinary approach and long-term follow-up in a series of 640 consecutive patients with sarcoidosis, Medicine (Baltim.) 96 (29) (2017), e7595, https://doi.org/10.1097/MD.0000000000007595.

[9] G.W. Hunninghake, U. Costabel, M. Ando, et al., ATS/ERS/WASOG statement on sarcoidosis. American thoracic society/European respiratory society/world association of sarcoidosis and other granulomatous disorders, Sarcoidosis Vasc, Diffuse Lung Dis. 16 (2) (1999) 149–173.

[10] J.G. Scadding, Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation, Br. Med. J. 2 (5261) (1961) 1165–1172, https://doi.org/10.1136/bmj.2.5261.1165.

[11] M.A. Judson, R.P. Baughman, A.S. Teirstein, M.L. Terrin, H. Yeager Jr., Defining organ involvement in sarcoidosis: the ACCESS proposed instrument. ACCESS research group. A case Control etiologic study of sarcoidosis, Sarcoidosis Vasc, Diffuse Lung Dis. 16 (1) (1999) 75–86.

[12] M.A. Judson, U. Costabel, M. Drent, et al., The WASOG sarcoidosis organ assessment instrument: an update of a previous clinical tool, sarcoidosis Vasc, Diffuse Lung Dis. 31 (1) (2014) 19–27.

[13] B. Karakaya, Y. Kaiser, C.H.M. van Moorsel, J. Grunewald, Löfgren's syndrome: diagnosis, management, and disease pathogenesis, Semin. Respir. Crit. Care Med. 38 (4) (2017) 463–476.
[14] R.P. Baughman, E.E. Lower, Features of sarcoidosis associated with chronic disease, Sarcoidosis Vasc. Diffuse Lung Dis. 31 (2014) 275–281.
[15] P. Korsten, K. Strohmayer, R.P. Baughman, N.J. Sweiss, Refractory pulmonary sarcoidosis - proposal of a definition and recommendations for the diagnostic and therapeutic approach, Clin. Pulm. Med. 23 (2) (2016) 67–75.
[16] M. Berlin, A. Fogdell-Hahn, O. Olerup, A. Eklund, J. Grunewald, HLA-DR predicts the prognosis in Scandinavian patients with pulmonary sarcoidosis, Am. J. Respir. Crit. Care Med. 156 (5) (1997) 1601–1605.
[17] J. Grunewald, A. Eklund, Löfgren's syndrome: human leukocyte antigen strongly influences the disease course, Am. J. Respir. Crit. Care Med. 179 (4) (2009) 307–312, 15.
[18] G.E. Westney, M.A. Judson, Racial and ethnic disparities in sarcoidosis: from genetics to socioeconomics, Clin. Chest Med. 27 (3) (2006) 453–462, https://doi.org/10.1016/j.ccm.2006.04.002.
[19] L.E. Siltzbach, D.G. James, E. Neville, J. Turiaf, J.P. Battesti, O.P. Sharma, Y. Hosoda, R. Mikami, M. Odaka, Course and prognosis of sarcoidosis around the world, Am. J. Med. 57 (1974) 847–852, https://doi.org/10.1016/0002-9343(74)90160-0.
[20] P.E. Sartwell, L.B. Edwards, Epidemiology of sarcoidosis in the U. S. navy, Am. J. Epidemiol. 99 (4) (1974) 250–257.
[21] D.G. James, E. Neville, L.E. Siltzbach, A worldwide review of sarcoidosis, Ann. N. Y. Acad. Sci. 278 (1976) 321–334.
[22] R.H. Winterbauer, J.F. Hutchinson, Use of pulmonary function tests in the management of sarcoidosis, Chest 78 (1980) 640–647, https://doi.org/10.1378/chest.78.4.640.
[23] M.C. Iannuzzi, B.A. Rybicki, A.S. Teirstein, Sarcoidosis, N.Engl. J. Med. 357 (21) (2007) 2153–2165, https://doi.org/10.1097/01.ju.0000067820.86347.95.
[24] J.M. Reich, R.E. Johnson, Course and prognosis of sarcoidosis in a nonreferral setting. Analysis of 86 patients observed for 10 years, Am. J. Med. 78 (1985) 61–67, https://doi.org/10.1016/0002-9343(85)90463-2.
[25] R.H. Winterbauer, N. Belic, K.D. Moores, Clinical interpretation of bilateral hilar adenopathy, Ann. Intern. Med. 78 (1973) 65–71, https://doi.org/10.7326/0003-4819-78-1-65.
[26] P.L. Carr, D.E. Singer, P. Goldenheim, J. Bernardo, A.G. Mulley, Noninvasive testing of asymptomatic bilateral hilar adenopathy, J. Gen. Intern. Med. 5 (1990) 138–146, https://doi.org/10.1007/BF02600516.
[27] A. Tremblay, D.R. Stather, P. MacEachern, M. Khalil, S.K. Field, A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis, Chest 136 (2009) 340–346, https://doi.org/10.1378/chest.08-2768.
[28] N. Navani, D.R. Lawrence, S. Kolvekar, M. Hayward, D. McAsey, G. Kocjan, M. Falzon, A. Capitanio, P. Shaw, S. Morris, R.Z. Omar, S.M. Janes, Endobronchial ultrasound-guided transbronchial needle aspiration prevents mediastinoscopies in the diagnosis of isolated mediastinal lymphadenopathy: a prospective trial, Am. J. Respir. Crit. Care Med. 186 (2012) 255–260, https://doi.org/10.1164/rccm.201203-0393OC.