Characterisation of the coexistence between sarcoidosis and Sjögren's syndrome. Analysis of 43 patients

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Abstract

Objective

To characterise the key epidemiological, clinical, immunological, imaging, and pathological features of the coexistence between sarcoidosis and Sjögren's syndrome (SS).

Methods

All centres included in two large multicentre registries (the Sjögren Syndrome Big Data Consortium and the Sarco-GEAS-SEMI Registry) were contacted searching for potential cases of coexistence between SS and sarcoidosis seen in daily practice. Inclusion criteria were the fulfilment of the current classification criteria both for SS (2016 ACR/EULAR) and sarcoidosis (WASOG). The following features were considered for evaluating a coexisting immunopathological scenario between the two diseases: non-caseating granulomas (NCG), focal lymphocytic sialadenitis (FLS) and positive anti-Ro antibodies.

Results

We identified 43 patients who fulfilled the inclusion criteria (38 women, with a mean age of 53 years at diagnosis of SS and of 52 years at diagnosis of sarcoidosis). In 28 (65%) cases, sarcoidosis was diagnosed concomitantly with SS, or during the follow-up of patients with an already diagnosed SS, while in the remaining 15 (35%), SS was diagnosed during the follow-up of an already diagnosed sarcoidosis. Patients in whom sarcoidosis was diagnosed first showed a lower mean age (43.88 vs. 55.67 years, p=0.005) and were less frequently women (73% vs. 96%, p=0.04) in comparison with those in whom sarcoidosis was diagnosed concomitantly with SS, or during the follow-up of an already diagnosed SS. We identified the following immunopathological scenarios: a combination of NCG involving extrasalivary tissues and anti-Ro antibodies in 55% of patients, a coexistence of both pathological scenarios (extrasalivary NCG and FLS in MSGB) in 42% (with positive anti-Ro antibodies in two thirds of cases), and NCG involving salivary glands and anti-Ro antibodies in 3% of cases.

Conclusion

We have characterised the largest reported series of patients who fulfilled the current classification criteria for both SS and sarcoidosis. This implies that sarcoidosis (and not just the presence of isolated NCG on salivary gland biopsy) may, like other systemic autoimmune diseases, coexist with SS, and that a sarcoidosis diagnosis does not preclude the development of SS in the future.

Key words

sarcoidosis, Sjögren's syndrome, coexistence of autoimmune diseases

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Received on June 2, 2022; accepted in revised form on August 26, 2022.

Competing interests: J. Sellarés has received honoraria from Boehringer, Roche, Astra-Zeneca, and grants from Boehringer and Roche.
The other authors have declared no competing interests.

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease that usually presents as a persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands (1). Although the histologic hallmark is a focal lymphocytic infiltration of the exocrine glands, the spectrum of the disease extends from an autoimmune exocrinopathy to a systemic process (2). Patients with SS can also be diagnosed with additional systemic autoimmune diseases reflecting a clinical situation of coexistence or overlap, a phenomenon named as polyautoimmunity (3) or autoimmune clustering (4), that has been reported in patients with either systemic or organ-specific autoimmune diseases in a frequency ranging from 8% to 53% (5). For the practical management of SS patients, it makes no sense to separate between patients with or without associated autoimmune diseases since the key target should be the same, the management of SS in all of them (6).

Sarcoidosis is another systemic autoimmune disease with a clinical phenotype overwhelmingly dominated by thoracic involvement in more than 90% of patients (7). The diagnosis is established when clinical and radiologic findings are supported by histological evidence of non-caseating granulomas (8), and the therapeutic approach is complex (9). Patients with sarcoidosis often show a multifaceted clinical scenario due to the frequent coexistence of other chronic diseases, including autoimmune diseases (10), and a recent study has found that 1 out of 6 patients with sarcoidosis have associated autoimmune diseases (5).

Sarcoid involvement of the salivary glands was described more than 70 years ago (11) and since then, sarcoidosis has been traditionally considered a disease mimicking SS ever since. Therefore sarcoidosis has been considered an exclusion criteria for classifying a patient as having SS in all the international classification criteria sets, including the more recently proposed by the American-European study group on the Classification criteria for SS (12). However, some authors have supported a true coexistence between sarcoidosis and SS in at least half the reported cases in the literature (13).

In this study, we have launched an international study with the aim to collate patients with confirmed coexistence between sarcoidosis and SS and to characterise the key epidemiological, clinical, immunological, imaging and pathological features that could help physicians to differentiate a mimicry of SS by sarcoidosis from a true coexistence of both diseases.

Methods

During the first week of April 2022, all centres included in two large multicentre registries (the Sjögren Syndrome Big Data Consortium and the Sarco-GEAS-SEMI Registry) (7, 14) were contacted via e-mail by MRC asking for patients seen in clinical practice with a potential coexistence between SS and sarcoidosis. The inclusion criterion was defined as the fulfilment of the current classification criteria for both SS and sarcoidosis:

Sarcoidosis was diagnosed according the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) 1999 statement on sarcoidosis (15) ensuring the fulfilment of the following 3 criteria: a) clinical or radiological findings consistent with sarcoidosis, such as pulmonary disease, uveitis, mediastinal bilateral hilar lymphadenopathy (BHL), or erythema nodosum; b) tissue biopsy with histologic evidence of non-caseating granulomas (NCG); and c) absence of other causes of granulomatous disease. Patients lacking the histopathological criteria (b) could be included if they presented at least one of the following features: elevated serum angiotensin-converting enzyme, organ-specific abnormal uptake on gallium-67 citrate scintigraphy, elevated lymphocyte count or elevated CD4/CD8 ratio in bronchoalveolar lavage fluid, or active extrathoracic involvement classified as highly probable according to the WASOG extrathoracic classification (15).

SS was diagnosed according to the 2016 ACR/EULAR classification criteria (12). Diagnostic tests for SS (ocular tests, oral tests and minor salivary gland biopsy

(MSGB) were carried out according to the recommendations of the European Community Study Group (16).

Epidemiological variables included age at diagnosis of each disease (defined as the time where patient fulfilled the current classification criteria), gender and ethnicity (classified according to FDA) (17). Specific variables for characterise the phenotypic expression of sarcoidosis included thoracic involvement evaluated according to the Scadding radiographic stages that were defined as stage 0 (normal), stage I (BHL without pulmonary infiltrates -PI-), stage II (BHL plus PI), stage III (PI without BHL) and stage IV (extensive fibrosis with distortion or bullae) (18), extrathoracic involvement (defined according to the 2014 WASOG organ assessment instrument, including only the clinical scenarios classified as highly probable or at least probable) (15), and systemic therapies (glucocorticoids, immunosuppressive agents and/or biological agents) (19). With respect to SS, the following variables were collected: ocular and oral dryness, ocular and oral diagnostic tests, minor salivary gland biopsy, antinuclear antibodies, anti-Ro/SSA and anti-La/SSB antibodies, rheumatoid factor, C3 and C4 levels, cryoglobulins, and systemic involvement defined according to the ESSDAI definitions (20). The two international registries were approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, HCB/2015/0869 and HCB/2016/0181).

The following features were specifically analysed to characterise the coexistence of the two diseases:

a) Time of diagnosis of sarcoidosis: prior to SS (diagnosed >1 year before SS diagnosis) or concurrent with/after SS diagnosis (diagnosed within <1 year of SS diagnosis, concomitantly, or during the follow-up of patients already diagnosed with SS).

b) Immunopathological scenarios: the following three features were considered to assess a coexisting immunopathological scenario between the two diseases: NCG, focal lymphocytic sialadenitis (FLS) and positive anti-Ro/SSA antibodies. A definitive immunopathological scenario of coexistence was defined as the presence of the 3 features (concomitant or sequentially), the coexistence of both pathological features (NCG and FLS) in Ro-negative patients, or the coexistence of NCG and anti-Ro antibodies. Patients with a MSGB disclosing NGC were included only in case they showed other sarcoidosis features defined according to the WASOG classification criteria (15).

c) Characterisation of systemic involvement. We specifically analysed the systemic phenotype resulting by the coexistence of the two diseases using the WASOG (15) and ESSDAI (20) definitions for sarcoidosis and SS, respectively. We focused on those organs that are more commonly affected by the two diseases, analysing their synchronous or metachronous development of each organ-specific involvement, as well as the pathological and imaging features that define whether the systemic involvement can be related to sarcoidosis or to SS.

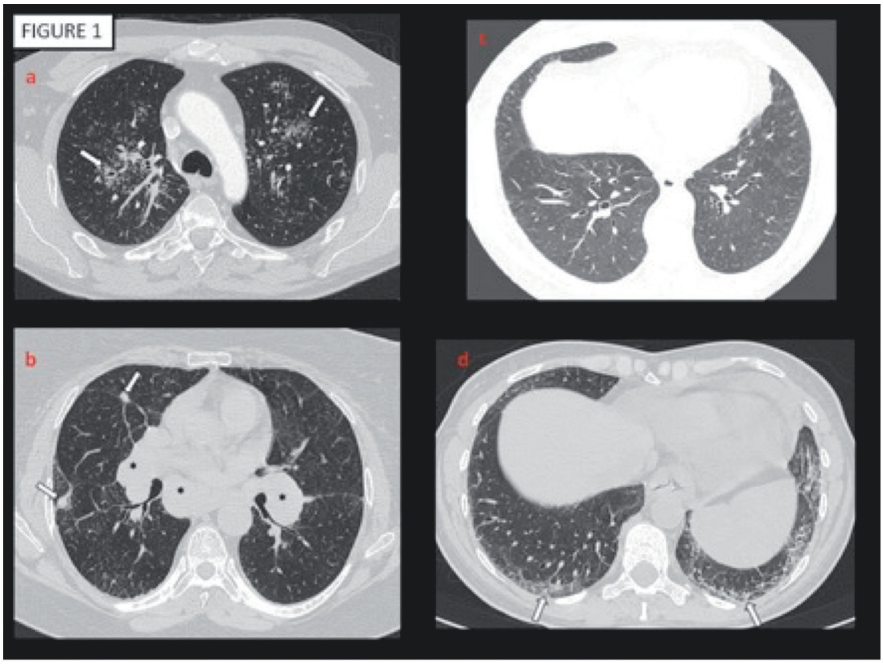

Fig. 1. Pulmonary involvement in patients with coexisting sarcoidosis and SS.
a) Axial contrast material-enhanced CT scan showing clusters of micronodules with perilymphatic distribution in both upper lobes suggestive of sarcoidosis (arrows). **b)** Axial high-resolution CT scan with pulmonary sarcoidosis shows solid pulmonary nodules (arrows) in the right upper lobe with some micronodules in a perilymphatic distribution and irregular thickening of the fissures. Bilateral hilar and subcarinal lymphadenopathies (*) are observed. **c)** Axial high-resolution CT scan showing mild bronchiectasis in lower lobes associated with mosaic attenuation pattern. This finding is present in airways disease in Sjögren's patients. **d)** Axial high-resolution CT scan shows non-specific interstitial pneumonia (NSIP) pattern with basal predominance distribution (arrows). This is one of the most common patterns of lung disease in patients with Sjögren's disease.

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. We used Chi-square/Fisher tests and t-test, according to the type of variable. All tests were two-tailed and *p*-values <0.05 was considered statistically significant.

Results

By April 30, we received the data from 54 patients with coexisting SS and sarcoidosis that were evaluated for inclusion in the study. Among them, 43 fulfilled the inclusion criteria (38 women and 5 men; 36 patients were classified as White, 2 as Asian, 3 as Hispanic and 2 as Black/African American).

Sarcoidosis was diagnosed at a mean age of 52 years (range 21–81 years, SD 13.41), in 5 (12%) patients due to incidental radiological findings (asymptomatic cases). Scadding radiologic stage at diagnosis was available in 39 patients and consisted of stage 0 in 6

Table I. Main epidemiological, clinical, immunological, imaging, and pathological features of 43 patients with proven coexistence between sarcoidosis and Sjögren's syndrome (SS).

Variable	N=43 n (%)
Sarcoidosis	
Age at diagnosis, mean (range) ± SD	52 (21-81) ± 13.4
Women	38 (88.4)
Ethnicity	
White	36 (83.7)
Hispanic	3 (6.9)
Asian	2 (4.6)
BAA	2 (4.6)
Clinical presentation	
Asymptomatic patients	5 (11.6)
Thoracic involvement	37 (86)
Pulmonary involvement	25 (58)
Chest radiographic or CT scan staging	
0	6 (14)
I	12 (28)
II	22 (51)
III	3 (7)
Biopsy location confirming NCG (n=40)	
Mediastinum lymph nodes	13 (30.2)
Lung	10 (23.2)
Extrathoracic lymph nodes	7 (16.2)
Skin	6 (13.9)
Liver	2 (4.6)
Brain	1 (2.3)
Salivary gland	1 (2.3)
Bone marrow	1 (2.3)
Muscle	1 (2.3)
Laboratory findings	
Raised serum angiotensin converting enzyme levels	14/32 (43.8)
Hypergammaglobulinemia	12/39 (30.8)
Raised serum transaminases	9/39 (23.8)
Hypercalcemia	6 (14)
Sjögren's syndrome	
Age at diagnosis, mean (range) ± SD	53 (31-80) ± 12.4
Clinical features	
Dry eye	43 (100)
Dry mouth	42 (97.7)
Abnormal ocular tests	32/33 (96.9)
Abnormal scintigraphy/ salivary flows test	19/20 (95)
MSGB disclosing FLS	19/24 (79.1)
Laboratory findings	
Anti-Ro/SSA antibodies	30 (69.8)
Anti-La/SSB antibodies	16 (37.2)
Antinuclear antibodies	29 (67.4)
Rheumatoid Factor	7/42 (16.2)
Low C3 complement levels	2/40 (5)
Low C4 complement levels	1/41 (2.4)
Cryoglobulins	1/28 (3.5)

(14%) patients, stage I in 12 (28%), stage II in 22 (51%), and stage III in 3 (7%) patients. Therefore, 86% presented with thoracic involvement and 58% with pulmonary involvement (Fig. 1a, 1b). Diagnosis of sarcoidosis was biopsy-proven in all patients, although specific data on biopsy location was available in 40 cases; the most frequent biopsied sites included the mediastinum lymph nodes (30%), lungs (23%), extrathoracic lymph nodes (16%) and skin (14%). The main abnormalities in the laboratory tests included raised serum angiotensin-converting enzyme levels (40%), hypergammaglobulinaemia (31%), raised serum transaminases (23%) and hypercalcaemia (14%) (Table I).

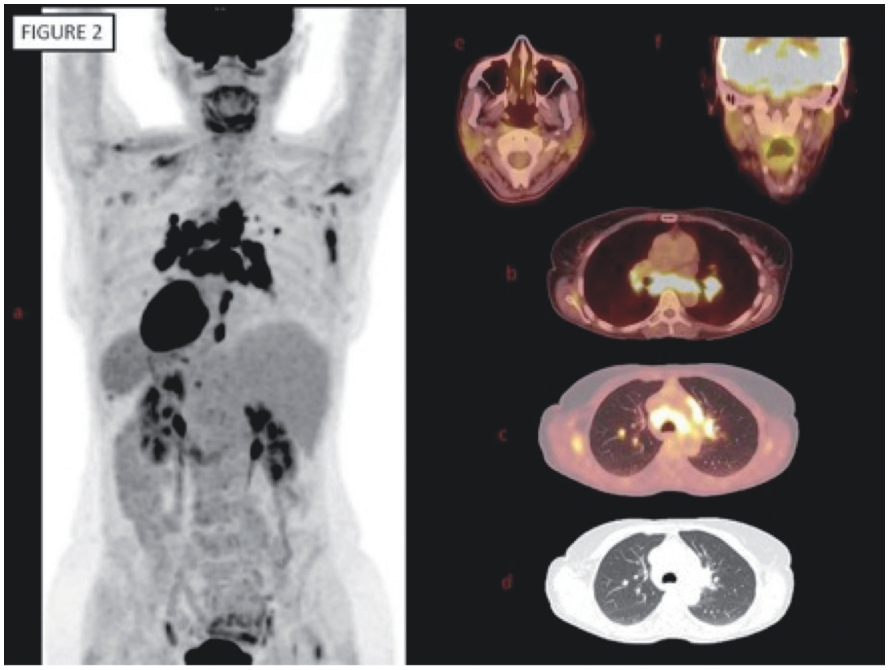

Fig. 2. FDG PET scan in a patient diagnosed with pSS 13 years ago, who presented with fever of unknown origin. Whole-body FDG PET scan (a) shows hypermetabolic mediastinal/hilar lymph (b) and pulmonary (c y d) nodes in axial images. The distribution of active lymph nodes and the presence of active pulmonary nodes suggest active sarcoid inflammation, that has to be confirmed to discard a lymphoproliferative syndrome. PET guide biopsy toward the most hypermetabolic structure (subcarinal node) and the diagnosis of sarcoidosis was made. Moderate hypermetabolism was seen in salivary glands: a) whole body, e) axial and f) coronal images.

With respect to SS, the mean age at diagnosis was 53 years (range 31 to 81 years, SD 12.48), and the main SS-related features were dry eye (100%), dry mouth (98%), abnormal ocular tests (97%), abnormal oral diagnostic tests (95%), MSGB disclosing FLS (79%), anti-Ro/SSA antibodies (70%) and anti-La/SSB antibodies (37%). Other immunological markers included positive antinuclear antibodies (67%), rheumatoid factor (16%), low C3 levels (5%), low C4 levels (2%) and positive cryoglobulins (3%) (Table I).

Epidemiological and phenotypic coexistence

In 28 (65%) cases, sarcoidosis was diagnosed concomitantly with SS, or during the follow-up of patients with an already diagnosed SS. The clinical features that led to the sarcoidosis suspicion were mainly respiratory (in some cases in combination with general features such as fever or fatigue), but also there were non-respiratory features including erythema nodosum (n=6), extrathoracic lymph node involvement (n=6), liver involvement (n=6), uveitis (n=4), hypercalcaemia (n=3) and cardiac involvement (n=1); in two patients, sarcoidosis was incidentally diagnosed in routine imaging studies.

In the remaining 15 (35%) cases, SS was diagnosed during the follow-up of patients with a previous diagnosis of sarcoidosis; in all cases, SS was suspected due to the development of oral and/or ocular dryness alongside the confirmation of glandular dysfunction in the corresponding oral and ocular diagnostic tests. A positive test for anti-Ro/SSA antibodies confirmed the diagnosis in 9 (60%) cases, a MSGB disclosing FLS in

5 (33%), while the remaining case (7%) had positive anti-Ro/SSA antibodies and FLS on MSGB.

Supplementary Figure S1 shows a comparison of the main epidemiological and phenotypic features of sarcoidosis according to the time of diagnosis of the two diseases. Patients in whom sarcoidosis was diagnosed first were younger (43.88 *vs*. 55.67 years, p=0.005) and less likely women (73% *vs*. 96%, p=0.04) in comparison with those in whom sarcoidosis was diagnosed concomitantly with SS or during the follow-up of an already diagnosed SS. In addition, there was a statistical trend for a higher frequency of thoracic involvement (100% *vs*. 79%, p=0.053) in patients firstly diagnosed with sarcoidosis.

Systemic involvement

With respect to sarcoidosis, 31 (72%) patients showed extrathoracic systemic involvement according to the WASOG extrathoracic classification, the most frequent extrathoracic organs involved included the skin in 10 (23%) patients, extrathoracic lymph nodes in 10 (23%), the liver in 9 (21%) and the eyes in 7 (16%) patients (Fig. 2, 3).

With respect to SS, 37 (86%) patients showed systemic involvement according to the ESSDAI definitions. The ESSDAI clinical domains more frequently involved included the articular domain in 11 (26%) patients, the lymph node domain in 9 (21%), the glandular domain in 6 (14%), and the pulmonary domain in 3 (7%) patients (Fig. 1c, 1d).

There were 9 (21%) patients in whom a potential involvement of the same organ by the two diseases was reported, including pulmonary involvement (n=3), extrathoracic lymph node involvement (n=4), skin involvement (n=3), glandular involvement (n=2), articular involvement (n=1) and peripheral nervous system involvement (n=1). A specific case-by-case re-evaluation finally confirmed this dual organ-specific involvement in only 4 cases: two were diagnosed concurrently with pulmonary and skin involvements attributed to both diseases, and the remaining two presented with organ-specific involvements that were diagnosed separately (one patient showed vasculitis after being diagnosed with primary SS, and several years later was diagnosed with sarcoidosis after developing erythema nodosum; the other patient had a first diagnosis of bronchiectasis related to SS (Fig. 1c) and then presented with pulmonary interstitial involvement related to sarcoidosis).

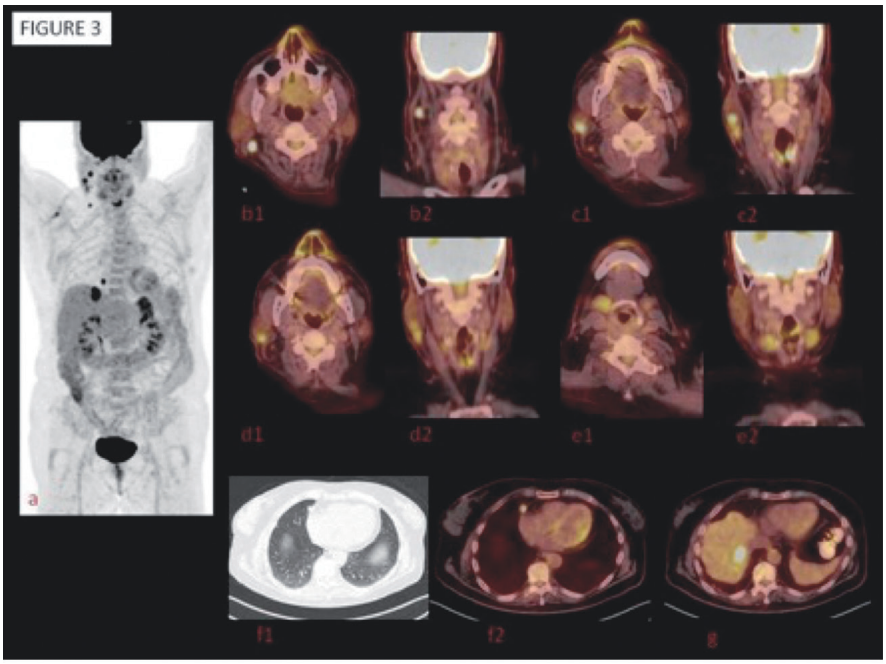

Fig. 3. FDG PET scan in a patient presenting with asthenia and cervical lymph nodes. Whole-body FDG PET scan (a) shows hypermetabolic cervical lymph nodes in axial (b1, c1 d1, and e1) and coronal (b2, c2, d2 and e2) images. Moreover, pulmonary paracardiac lymph nodes (f1 and f2) nodes hypermetabolic hepatic (g) and were also seen. A diagnosis of sarcoidosis was confirmed after a lymph node and hepatic biopsy disclosing non-caseating granulomas.

Immunopathological scenarios

Among the 40 patients for whom we had specific data about the location of biopsy confirming NCG, we defined the following immunopathological scenarios:

- 22 (55%) patients had a combination of NCG involving extrasalivary tissues and anti-Ro/SSA antibodies; MSGB was carried in 2 patients showing a non-specific lymphocytic infiltration classified as Chisholm-Mason grades 1 or 2;
- 17 (42%) patients showed a coexistence of both pathological scenarios (extrasalivary NCG and FLS in MSGB); anti-Ro/SSA antibodies were positive in 12 patients and negative in the remaining 7;
- 1 (3%) patient showed NCG in MSGB without concomitant FLS, together with positive anti-Ro/SSA antibodies and a clinical and radiological picture suggestive of sarcoidosis.

In the 3 patients whose information about the location of biopsy demonstrating NCG was not available, the clinical picture was clearly suggestive of sarcoidosis according to the WASOG recommendations (15); and with respect to SS, all the three had anti-Ro/SSA antibodies and 2 showed FLS without concomitant NCG in their MSGB. None of our patients showed concomitant NCG and FLS in MSGB.

Outcome

First-line systemic therapies for sarcoidosis were required in 28 (65%) patients, including oral glucocorticoids (n=26), immunosuppressive agents (n=11) and biological agents (n=4). Therapeutic response was collected in 27 cases, and was classified as complete response in 14 (52%) patients (Fig. 4), partial response in 6 (22%), and stable disease/no response in the remaining 7 (26%). Two patients developed a haematological neoplasia. The first case was firstly diagnosed with SS and developed a parotid mucosa-associated lymphoid tissue (MALT) lymphoma (achieving a complete remission with

rituximab and chlorambucil), she was diagnosed with sarcoidosis 10 years after being diagnosed with SjS and two years after sarcoidosis diagnosis, died due to a T-cell lymphoma (Fig. 5). The second patient developed SS 13 years after being diagnosed with sarcoidosis and chronic lymphocytic leukaemia subsequently occurred. Seven patients died during the follow-up due to haematological neoplasia (n=1), sepsis (n=1), and non-autoimmune processes in 2 (no aetiology was known for the remaining 3).

Discussion

We have reported a detailed description of 43 patients that fulfil the current classification criteria for both SS and sarcoidosis and this is the largest series of coexisting cases reported to date. Our data help to better understand how the two diseases may coexist in daily practice with the delineation of two overlapping specific clinical scenarios. In two thirds of cases, sarcoidosis was diagnosed concomitantly with SS or during the follow-up of patients with an already diagnosed SS while a superimposed diagnosis of SS during the follow-up of patients firstly diagnosed with sarcoidosis was less frequently observed. To date, less than 39 cases of coexisting SS with sarcoidosis had been reported (Supplementary Table S1) (13, 21-28). Therefore, the coexistence of the two diseases should be considered a rare event. The prevalence of sarcoidosis in large series of patients with primary SS has been estimated around 1% (13, 29) while, the estimated frequency of SS in population-based studies including 2974 patients with sarcoidosis is 1.7% (5, 30).

In two of every three cases of coexistence, sarcoidosis was diagnosed in patients with SS, either concomitantly or during the follow-up. In these patients, the mean age at diagnosis of sarcoidosis was around 56 years, significantly higher in comparison with patients included in large series of sarcoidosis (7), but closer to the mean age at diagnosis of primary SS (30). In addition, the frequency of women was significantly higher than that reported for sarcoidosis, and closer to that reported in patients with primary SS. Unfortunately, no information about environmental factors has recorded, considering the significant role of occupational exposures and smoking in sarcoidosis pathogenesis (31).

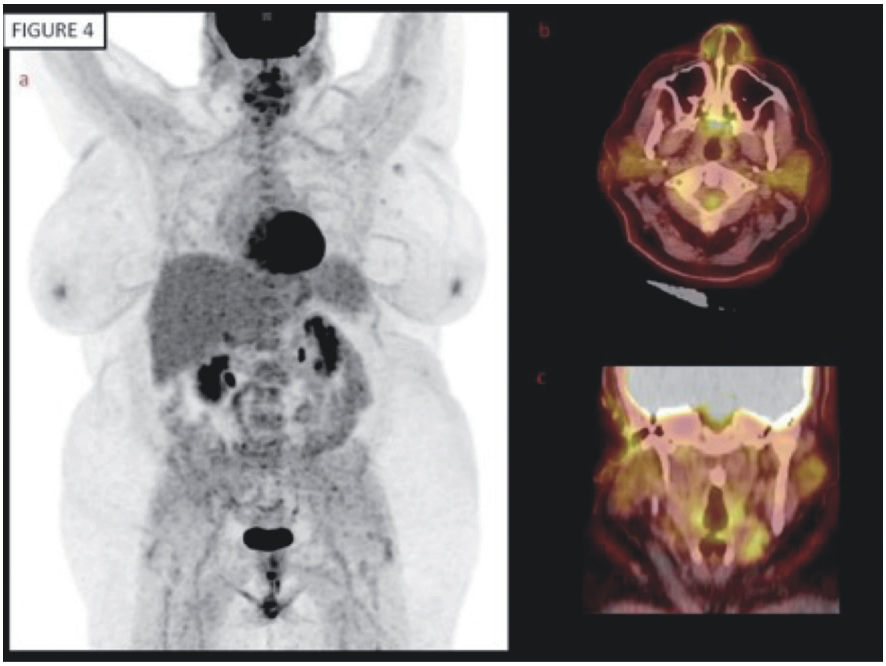

Fig. 4. A post treatment (Prednisone) FDG pet scan in a patient with sarcoidosis and Sjögren syndrome. Physiological uptake was seen, with an uptake less than the blood pool, suggesting a favourable treatment response. Moderate hypermetabolism was seen in salivary glands: a) whole body, b) axial and c) coronal images.

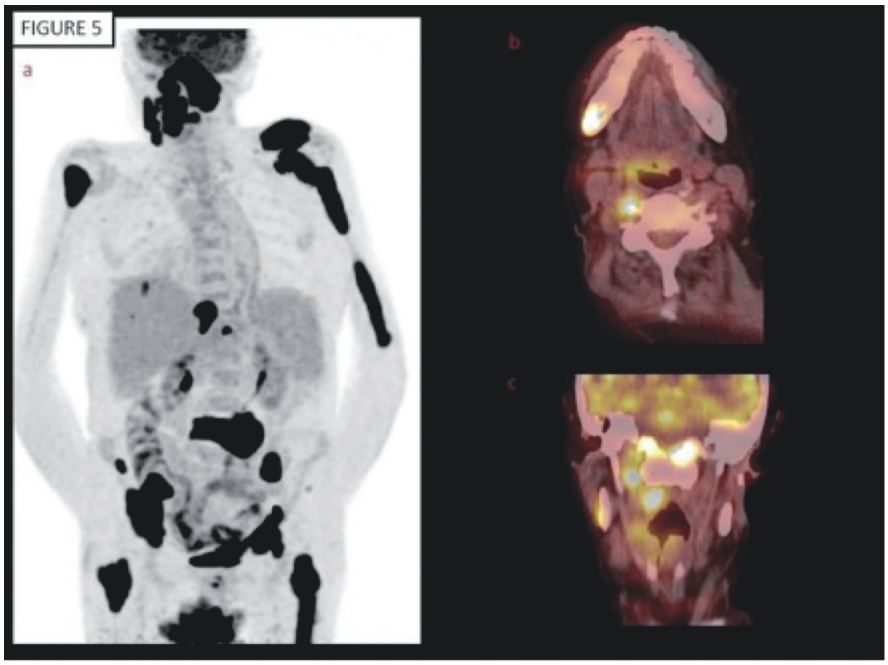

Fig. 5. Patient with pulmonary sarcoidosis, Sjögren's syndrome, history of parotid gland MALT lymphoma and L4 pathological fracture. FDG PET scan was done and demonstrated hepatic and bone dissemination: a) whole-body scan, b) axial and c) coronal images. Bone marrow biopsy disclosed T-cell lymphoma. No pathological hypermetabolism was seen in salivary glands.

In patients concomitantly diagnosed with the two diseases, the most frequently observed clinical scenario was a patient investigated for a possible diagnosis of sarcoidosis in the multidisciplinary interstitial lung disease (ILD)

committee, in whom the autoimmune screening detected sicca symptoms and diagnostic and immunological tests finally confirmed the coexistence of SS. Therefore, the careful application of classification criteria for SS was very useful in confirming a true coexistence of the two conditions in these patients. In fact, previous studies reported that in case of concomitant SS and sarcoidosis the application of the American-European criteria correctly identified the coexistence with a sensitivity of 93% and a specificity of 92% (13). Analysis of the autoantibodies may be very useful for distinguishing mimicry or coexistence since the immunological pattern is clearly different in the two diseases. Patients with sarcoidosis usually lack autoantibodies, although in some cases, low titres of antinuclear antibodies (ANA) or rheumatoid factor (RF) may be detected (32), while anti-Ro/SS-A and anti-La/SS-B antibodies are negative (33). Superimposed diagnosis of sarcoidosis in primary SS patients due to the emergence of features highly suggestive of sarcoidosis (hilar adenopathy with or without ILD, erythema nodosum, uveitis, hypercalcaemia) was more frequent than the concomitant diagnosis of the two diseases. The diagnosis of sarcoidosis was finally confirmed by a biopsy showing NCG and in fact, we found in these patients a higher frequency of sarcoidosis without extrathoracic involvement, especially skin and ocular features.

In one of every three cases of coexistence, SS was confirmed in patients already diagnosed with sarcoidosis. The features that led to clinical suspicion of SS were sicca symptoms, with diagnostic tests disclosing salivary gland dysfunction and positive anti-Ro/SSA autoantibodies, finally confirming SS diagnosis. In one third of cases, autoantibodies were negative and MSGB played a key role in the final diagnosis, since it was highly discriminatory for confirming SS (FLS) and ruling out a potential glandular involvement by sarcoidosis (lack of granulomatous infiltration) (13). We found inconclusive pathological results in the MSGB of 2 patients who showed scattered lymphocytic infiltrates, a pathological scenario reported both in SS patients (Chisholm-Mason grades 1–2) as in 37–42% of patients with sarcoidosis in whom a salivary gland biopsy was carried out (33, 34). In these cases, immunophenotypic analysis may be useful, since a predominance of CD8+ lymphocytes is seen in sarcoidosis, whereas CD4+ predominates in SS patients (35). Another rare pathological scenario was the finding of NCG in the salivary glands without concomitant FLS, which was found in only 1 patient, and the coexistence of the two diseases was supported by positive anti-Ro/SSA antibodies and a clinical and radiological picture suggestive of sarcoidosis according to the corresponding classification criteria. We did not find any case with a coexistence of the two pathological scenarios (NCG and FLS) in the MSG specimen, a very rare condition reported in only 9 cases (Supplementary Table S1) (12, 20-22). In these cases, immunophenotypic studies could also help in confirming the coexistence of two differentiated patterns of immune-mediated damage. Gal *et al*. (28) described a moderate $CD8^+$ lymphocytic infiltrate concomitant with non-caseating granulomas in patients with sarcoidosis mimicking SS, while patients with coexisting sarcoidosis and SS showed a mixed population of $CD4^+$ and $CD8^+$lymphocytes together with NCG. Interestingly, MSGB specimens obtained from these patients after glucocorticoid treatment revealed the disappearance of sarcoidosis-related features and the persistence of scattered focal $CD4^+$ lymphocytic infiltrates only (28).

An additional practical message about the coexistence of sarcoidosis and SS is the careful evaluation of organ-specific systemic involvement in these patients, considering that several organs may be affected by both diseases (especially the salivary glands, the lungs and the lymph nodes). Thus, parotid involvement has been reported in around one third of patients with primary SS (34) and in 5% or less of those with sarcoidosis (7). The clinical picture at presentation is seldom helpful in differentiating mimicry or coexistence, except for the development of concomitant extra-salivary features, such as uveitis or facial nerve palsy that outline an infrequent syndromic presentation of sarcoidosis (the so-called Heerfordt syndrome) (33). Unfortunately, it seems that imaging studies are not able to clearly differentiate SS and sarcoidosis in patients with parotid involvement, as a recent study has suggested (13). Therefore, only a pathological study of salivary glands can confirm the underlying immune-mediated mechanisms in these patients. A similar approach may be suggested when extrathoracic lymph nodes are evaluated, with biopsy being highly recommended not only for confirming sarcoidosis, but also to rule out haematological neoplasia (9, 35). With respect to pulmonary involvement, which is more frequent in sarcoidosis (>50%) than in SS (around 10%), the role of pulmonologists and radiologists is essential to characterise parenchymal involvement in detail. In sarcoidosis, ILD is characterised by micronodules with a perilymphatic distribution, fibrotic changes, and bilateral perihilar opacities, especially in the presence of concomitant, bilateral hilar lymph node enlargement at high-resolution computed tomography (HRCT) (Fig. 1). In contrast, there is a wide variety of histopathological diagnoses in SS-ILD, mainly nonspecific interstitial pneumonia (NSIP), bronchiolitis, usual interstitial pneumonia, lymphocytic interstitial pneumonia and organising pneumonia (36). Despite the detailed evaluation of some specific organs in patients with coexisting sarcoidosis and SS, we also recommend the characterisation of systemic involvement through a CT-PET study, expecting a differentiated pattern of activity in internal organs that may be very helpful in determining whether sarcoidosis or SS are responsible for the organ-specific systemic activity (37-39) (Fig. 2).

In conclusion, we have characterised the clinical and immunopathological phenotype of 43 patients who fulfilled the current classification criteria for both SS and sarcoidosis. This implies that sarcoidosis (and not just the presence of isolated NCG on MSGB) may, coexist with SS like other systemic autoimmune diseases, and that a sarcoidosis diagnosis does not preclude

the development of SS in the future, as we found in one third of cases described in this study. Patients with a coexistence of sarcoidosis and SS should be managed at centres of excellence in systemic autoimmune diseases, using a multidisciplinary approach requiring an expert guidance, not only to confirm the complex diagnosis of coexistence, but also to evaluate the extent of organs damaged and to ultimately design a specific personalised therapeutic approach and follow-up.

Sjögren GEAS-SEMI

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