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Original article

Coexistence of immune-mediated diseases in sarcoidosis. Frequency and clinical significance in 1737 patients

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ABSTRACT

Objective: To analyze whether immune-mediated diseases (IMDs) occurs in sarcoidosis more commonly than expected in the general population, and how concomitant IMDs influence the clinical presentation of the disease.
Methods: We searched for coexisting IMDs in patients included in the SARCOGEAS-cohort, a multicenter nationwide database of consecutive patients diagnosed according to the ATS/ESC/WASOG criteria. Comparisons were made considering the presence or absence of IMD clustering, and odds ratios (OR) and their 95% confidence intervals (CI) were calculated as the ratio of observed cases of every IMD in the sarcoidosis cohort to the observed cases in the general population.
Results: Among 1737 patients with sarcoidosis, 283 (16%) patients presented at least one associated IMD. These patients were more commonly female (OR: 1.98, 95% CI: 1.49–2.62) and were diagnosed with sarcoidosis at an older age (49.6 vs. 47.5 years, $P < 0.05$). The frequency of IMDs in patients with sarcoidosis was nearly 2-fold higher than the frequency observed in the general population (OR: 1.64, 95% CI: 1.44–1.86). Significant associations were identified in 17 individual IMDs. In comparison with the general population, the IMDs with the strongest strength of association with sarcoidosis (OR > 5) were common variable immunodeficiency (CVID) (OR: 431.8), familial Mediterranean fever (OR 33.9), primary biliary cholangitis (OR: 16.57), haemolytic anemia (OR: 12.17), autoimmune hepatitis (OR: 9.01), antiphospholipid syndrome (OR: 8.70), immune thrombocytopenia (OR: 8.43), Sjögren syndrome (OR: 6.98), systemic sclerosis (OR: 5.71), ankylosing spondylitis (OR: 5.49), IgA deficiency (OR: 5.07) and psoriatic arthritis (OR: 5.06). Sex-adjusted ORs were considerably higher than crude ORs for eosinophilic digestive disease in women, and for immune thrombocytopenia, systemic sclerosis and autoimmune hepatitis in men.
Conclusion: We found coexisting IMDs in 1 out of 6 patients with sarcoidosis. The strongest associations were found for immunodeficiencies and some systemic, rheumatic, hepatic and hematological autoimmune diseases.

1. Introduction

Immune-mediated diseases (IMDs) are a broad spectrum of non-communicable diseases related to an abnormal function of the immune system and that, according to the predominant clinical phenotype, are classified into two main groups: organ-specific (in which immune-mediated damage specifically involves a single organ or tissue) and systemic (characterized by multiorgan immune-mediated damage) [1]. Sarcoidosis is considered a T cell-mediated systemic disease [2] like some rheumatic (rheumatoid arthritis, psoriatic arthritis), endocrine (type 1 diabetes mellitus), cutaneous (psoriasis, vitiligo), neurological (multiple sclerosis) and liver (primary biliary cholangitis) diseases [3]. Among them, sarcoidosis is mainly diagnosed in adults aged between 40 and 50 with a slight predominance in women [4], with an estimated of 6 cases per 10,000 people [1]. The most commonly organs involved are located in the thorax (the lungs and regional lymph nodes), but the range of extrathoracic involvement is wide, mainly including extrathoracic lymph nodes, the skin, the liver and the eyes [5]. Since sarcoidosis may mimic a wide variety of processes, the diagnosis is established when clinical and radiologic findings are supported by a specific histological finding [non-caseating granulomas (NCG)] after discarding other etiologies [6]. Although the natural history of sarcoidosis is highly variable, spontaneous remission may occur in up to two thirds of patients, while the remaining cases may follow a chronic and progressive disease course or may even present with life-threatening features [7].

Patients with sarcoidosis may present with a complex clinical scenario due to the frequent coexistence of other chronic diseases, mainly neoplasic, cardiovascular and autoimmune/immune-mediated diseases [8]. Clustering of IMDs in a single patient has been reported in a wide variety of diseases, both systemic and organ-specific, in a frequency ranging 8–53% [9–14]. The coexistence of sarcoidosis with other IMDs has not been well established as in other diseases [15] and has been analyzed from three different approaches. First, there is a large number of isolated reported cases, included in small case series or reported in individual patients. Second, some population-based studies have identified IMDs as one of the most frequently identified comorbidities in large cohorts of patients with sarcoidosis [16–18]. And third, only three studies have specifically investigated coexisting IMDs in sarcoidosis, including a small Turkish cohort of 131 patients [19], and two large population-based studies from UK [20] and Taiwan [21] that evaluated 1510 and 1237 patients with sarcoidosis, respectively, that were identified using ICD diagnostic codes.

The aim of this study was to investigate whether IMDs occurs in sarcoidosis more commonly than expected in the general population, and how concomitant IMDs influence the clinical presentation of the disease, in one of the largest clinical cohorts of patients with sarcoidosis from southern Europe.

2. Methods

2.1. Patients

The SARCOGEAS-Study Group was founded in 2015 with the aim of collecting a large series of patients with sarcoidosis from Spanish hospitals with substantial experience in the management of autoimmune diseases. Both incident and prevalent cases were included. By January 2021, the multicenter database included 1737 consecutive patients diagnosed with sarcoidosis according to the criteria proposed by the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) 1999 statement on sarcoidosis [22]: (a) clinical or radiologic 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;

and (c) absence of other causes of granulomatous disease. Patients lacking the histopathological criteria (b) were 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 [4,23]. The study was conducted in accordance with the amended Declaration of Helsinki. The Clinical Research Ethics Committee of the coordinating center (HCB2016/0181) approved the protocol, and written informed consent was obtained from patients with current follow-up.

2.2. Variables

Epidemiological variables included age, gender, ethnicity (classified according to FDA) and concomitant associated diseases collected according to previous definitions [24]; IMDs were specifically identified on the basis of being diagnosed by the corresponding specialist involved in the multidisciplinary management of patients with sarcoidosis, according to the international classification or diagnostic criteria used in daily practice [Appendix A, Table S1; See the supplementary material associated with this article online]. Extrathoracic involvement at diagnosis was defined according to the 2014 WASOG organ assessment instrument, including only the clinical scenarios classified as highly probable or at least probable [23]. Clinical patterns of extrathoracic involvement were evaluated as follows:

- frequency (patients with at least one extrathoracic organ involved), frequency of multisystemic involvement (patients with ≥ 2 extrathoracic organs involved) and mean number of organs involved;
- individual organ-by-organ WASOG involvements.

First-line therapeutic management was classified as the need for systemic therapy (glucocorticoids, immunosuppressive agents and/or biological agents), and need for aggressive systemic therapy (first-line use of immunosuppressive agents and/or biological agents) following the definitions proposed by Inoue et al. [25]. Scadding radiographic stages were evaluated in all cases with available chest X-ray at diagnosis, and 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) [26].

2.3. Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. Comparisons were made considering the presence or absence of concomitant IMDs, defined as the coexistence of at least one IMD in patients with sarcoidosis. The Chi-square test was used to study the association between concomitant IMDs and the main epidemiological, clinical, extrathoracic and therapeutic variables. One-way ANOVA tests were used to compare continuous variables. All significance tests were two-tailed and bilateral values of $P < 0.05$ were considered significant. Crude odds ratios (OR) and their 95% confidence intervals (CI) were calculated as the ratio of observed cases of every IMD in the sarcoidosis cohort to the observed cases of that IMD in the people with public health coverage in Catalonia (MASCAT Big Data Project, Appendix A, Table S2 for IMD codification) [1]; a specific adjusted analysis by sex was also carried out. A OR > 1 (with lower 95%CI being > 1 and $P < 0.05$) was interpreted as a higher strength of association (the frequency of IMD was significantly higher in patients with sarcoidosis in comparison with the general population), while a OR < 1 (with upper 95% CI being < 1) was interpreted as a lower strength of association. Statistical analyses were performed using SPSS software ver. 23.0 (IBM, Armonk, NY, USA).

Table 1
Characterization of sarcoidosis in 1737 patients: epidemiological, clinical, radiological and histopathological features, and therapeutic management.

Variables	Patients($n = 1737$)
Gender (women)	1036 (59.6)
Mean age ± SD (years)	47.8 ± 15.1
Ethnicity	
White	1533 (88.3)
Latin American	118 (6.8)
Asian	26 (1.5)
Black/African-American	58 (3.3)
Other	2 (0.1)
Scadding radiological stage	
0	190/1716 (11.1)
1	653/1716 (38.1)
2	663 (38.6)
3	178 (10.4)
4	32 (1.9)
Clinical presentation	
Thoracic involvement	1547 (89.1)
Extrathoracic involvement	1239 (71.3)
Multiple extrathoracic involvement	599 (34.5)
Number of extrathoracic involved organs (mean ± SD)	1.28 ± 1.21
WASOG organ involvement	
Lungs	894 (51.5)
Skin	624 (35.9)
Extrathoracic lymph node	379 (21.8)
Eye	185 (10.7)
Liver	227 (13.1)
Spleen	141 (8.1)
Salivary glands	91 (5.2)
ENT	46 (2.6)
Bone/joint	140 (8.1)
Muscle	23 (1.3)
Kidney	63 (3.6)
Calcium/vitamin D	137 (7.9)
Nervous system	118 (6.8)
Heart	50 (2.9)
Bone marrow	71 (4.1)
Diagnostic features	
Raised ECA levels	788/1407 (56.0)
Histopathological confirmation	1430 (82.3)
Therapeutic management	
Need for therapy	954 (54.9)
Aggressiveness of therapy	175 (10.1)
Drugs	
Glucocorticoids	936 (53.9)
Immunosuppressive agents	164 (9.4)
Biological agents	37 (2.1)

WASOG: World Association of Sarcoidosis and Other Granulomatous Disorders.

3. Results

3.1. General cohort

Of the 1737 patients included in the cohort, there were 1036 (60%) women and 701 (40%) men, with a mean age at diagnosis of sarcoidosis of 47.8 years (SD: 15.12); 1533 (88%) patients were classified as White. Clinical presentation consisted of thoracic involvement in 1547 (89%) patients, with 894 (51%) having pulmonary involvement. Extrathoracic disease was reported in 1239 (71%) patients, and 599 (34%) patients had involvement of at least 2 extrathoracic organs. According to the WASOG extrathoracic classification, the most frequent extrathoracic organs involved included the skin (36%), extrathoracic lymph nodes (22%), liver (13%) and the eyes (11%). Scadding radiologic stage at diagnosis consisted of stage 0 (11%), stage I (38%), stage II (39%), stage III (10%) and stage IV in (2%). Raised levels of angiotensin-converting enzyme were

Table 2
Comparison of the main features of sarcoidosis between patients with and without concomitant immune-mediated diseases (IMDs).

Variables	Concomitant IMDs(n = 283) (%)	Only sarcoidosis(n = 1453) (%)
Gender (women)	206 (72)**	830 (57)
Mean age (years)	49.6 ± 15.1*	47.5 ± 15.1
Ethnicity (white)	257 (90.8)	1276 (87.8)
Scadding radiological stage		
0	38 (13.7)	152 (10.6)
I or II	211 (75.9)	1105 (76.8)
III or IV	29 (10.4)	181 (12.6)
Clinical presentation patters*		
Thoracic involvement	245 (86.6)	1302 (89.5)
Extrathoracic involvement	211 (74.6)	1028 (70.7)
Multiple extrathoracic involvement	110 (38.9)	489 (33.6)
Number of involved organs (mean ± SD)	1.39 ± 1.22	1.26 ± 1.20
Organ-by-organ involvement		
Lungs	147 (51.9)	747 (51.4)
Skin	105 (37.0)	519 (35.7)
Extrathoracic lymph node	74 (26.1)*	302 (20.8)
Eye	32 (11.3)	150 (10.3)
Liver	39 (13.8)	183 (12.6)
Spleen	22 (7.8)	114 (7.8)
Salivary glands	20 (7)	66 (4.5)
ENT	3 (1.1)	38 (2.6)
Bone/joint	28 (9.9)	108 (7.4)
Muscle	5 (1.8)	15 (1.0)
Kidney	6 (2.1)	54 (3.7)
Calcium/vitamin D	18 (6.4)	116 (8.0)
Nervous system	19 (6.7)	94 (6.5)
Heart	8 (2.8)	37 (2.5)
Bone marrow	16 (5.7)	50 (3.4)
Histopathological confirmation	228 (80.6)	1202 (82.7)
Therapeutic management		
Need for therapy	161 (56.7)	793 (54.6)
Aggressiveness of therapy	37 (13.1)	138 (9.5)
Drugs		
Glucocorticoids	157 (55.5)	779 (53.6)
Immunosuppressive agents	32 (11.3)	132 (9.1)
Biological agents	10 (3.5)	27 (1.3)

* $P < 0.05$.
** $P < 0.001$.

reported in 56% of patients. Diagnosis of sarcoidosis was biopsy-proven in 1430 (82%) patients. First-line therapies included oral glucocorticoids in 936 (54%) patients; immunosuppressive agents were required in 164 (9%) patients and biological agents in 37 (2%) due to severe clinical presentations (Table 1).

3.2. Frequency and significance of concomitant IMDs

Among the 1737 patients, 283 patients presented at least one associated IMD (frequency of 16%, 95% CI: 14.6%–18.0%), mainly thyroiditis (n = 94), Sjögren syndrome (n = 31), psoriasis (n = 29), ankylosing spondylitis (n = 13), combined variable immunodeficiency (CVID) (n = 10) and type-I diabetes mellitus (n = 10); 41/283 (14%) presented two associated IMDs and 6 (2%) three associated AD (Appendix A, Table S3 includes the complete list of IMDs diagnosed in patients with sarcoidosis). The general characteristics of sarcoidosis in patients with and without associated IMDs are presented in Table 2. Patients with associated IMDs were more commonly female (72% vs. 57%, $P < 0.001$, OR: 2.01, 95% CI: 1.52–2.67) and were diagnosed with sarcoidosis at an older age (49.6 vs. 47.5 years, $P < 0.05$). Presence of associated IMDs did not altered the frequency of both thoracic and parenchymal lung involvements. With respect to the extrathoracic phenotypic expression, patients with associated IMDs presented a higher frequency of involvement of extrathoracic lymph nodes (26% vs. 21%, $P < 0.05$, OR: 1.35, 95% CI: 1.01–1.81) and a trend towards higher number of extrathoracic organs involved and a higher frequency of involvement of salivary glands and bone marrow, but the differences were not statistically significant. The presence of concomitant IMDs was not associated with a different therapeutic approach of sarcoidosis except for a non-statistically significant trend for need for aggressive therapy (use of immunosuppressive/biologics agents, p = 0.08).

3.3. Disease associations

The frequency of IMDs in patients with sarcoidosis was nearly 2-fold higher than the frequency observed in the general population (16.3% vs. 10.6%, $P < 0.001$, OR: 1.64, 95% CI: 1.44 to 1.86). Significant associations were identified in 17 individual IMDs (Table 3). In comparison with the general population, the IMDs with the strongest strength of association with sarcoidosis (OR > 5) were common variable immunodeficiency (CVID) (OR: 431.8; 95% CI: 225.1 to 828.5), familial mediterranean fever (OR: 33.9; 95% CI: 4.74 to 242.6), primary biliary cholangitis (OR: 16.5; 95% CI: 8.60 to 31.9), haemolytic anemia (OR: 12.1; 95% CI: 3.91 to 37.8), autoimmune hepatitis (OR: 9.01; 95% CI: 2.90 to 27.9), antiphospholipid syndrome (OR: 8.70; 95% CI: 3.90 to 19.4), immune thrombocytopenia (OR: 8.43; 95% CI: 4.37 to 16.2), Sjögren syndrome (OR: 6.98; 95% CI: 4.89 to 9.96), systemic sclerosis (OR: 5.71; 95% CI: 2.85 to 11.4), ankylosing spondylitis (OR: 5.49; 95% CI: 3.18 to 9.48), IgA deficiency (OR: 5.07; 95% CI: 1.90 to 13.5) and psoriatic arthritis (OR: 5.06; 95% CI: 2.10 to 12.1) (Table 3). When IMDs were clustered, the strongest associations were found for immunodeficiencies, systemic, rheumatic, hepatic and hematological autoimmune diseases (Fig. 1).

The predominance of concomitant IMDs observed in women with sarcoidosis was confirmed in a sex-adjusted, disease-by-

Table 3
Occurrence of immune-mediated diseases (IMDs) in people with sarcoidosis: observed and expected number of people with IMD in the sarcoidosis population, ratio of rates in the sarcoidosis population to that in the reference population (MASCAT study, reference 1), and 95% CIs for the rate ratio.

IMDs	Observed cases	Expected cases	OR	Lower 95% CI	Upper 95% CI
Total IMDs	283	184.2	1.6[a]	1.4[a]	1.9[a]
Individual IMDs					
Thryroiditis	94	83.8	1.1	0.9	1.4
Sjögren syndrome	31	4.5	7.0[a]	4.9[a]	10.0[a]
Psoriasis	29	28.5	1.0	0.7	1.5
Ankylosing spondylitis	13	2.4	5.5[a]	3.2[a]	9.5[a]
Combined variable immunodeficiency	10	0.0	431.9[a]	225.1[a]	828.5[a]
Diabetes mellitus type I	10	9.9	1.0	0.5	1.9
Primary biliary colangitis	9	0.6	16.6[a]	8.6[a]	31.9[a]
Immune thrombocytopenia	9	1.1	8.4[a]	4.4[a]	16.2[a]
Rheumatoid arthritis	9	9.6	0.9	0.5	1.8
Systemic sclerosis	8	1.4	5.7[a]	2.9[a]	11.4[a]
Multiple sclerosis	8	2.4	3.4[a]	1.7[a]	6.9[a]
Glomerulonephritis	8	5.1	1.6	0.8	3.2
Chronic atrophic gastritis	7	2.2	3.2[a]	1.5[a]	6.7[a]
Systemic lupus erythematosus	7	2.7	2.6[a]	1.2[a]	5.4[a]
Celiac disease	7	5.3	1.3	0.6	2.8
Antiphospholipid syndrome	6	0.7	8.7[a]	3.9[a]	19.4[a]
Psoriasic arthritis	5	1.0	5.1[a]	2.1[a]	12.2[a]
Lichen	5	5.1	1.0	0.4	2.4
IgA deficiency	4	0.8	5.1[a]	1.9[a]	13.5[a]
Ulcerative colitis	4	5.7	0.7	0.3	1.9
Haemolytic anemia	3	0.3	12.2[a]	3.9[a]	37.8[a]
Autoimmune hepatitis	3	0.3	9.0[a]	2.9[a]	28.0[a]
Amyloidosis	3	0.7	4.6[a]	1.5[a]	14.4[a]
Vitiligo	3	3.8	0.8	0.3	2.5
Inflammatory myopathies	2	0.5	4.1[a]	1.0[a]	16.5[a]
Addison disease	2	0.5	4.0	1.0	15.9
Familial mediterranean fever	1	0.0	33.9[a]	4.7[a]	242.7[a]
Thrombotic microangiopathy	1	0.2	6.7	0.9	47.4
Eosinophilic digestive disease	1	0.2	5.6	0.8	40.1
Urticaria vasculitis	1	0.2	4.6	0.6	32.6
Guillain–Barré syndrome	1	0.5	2.0	0.3	14.1
Mysthenia	1	0.7	1.5	0.2	10.6
Polymyalgia rheumatica	1	7.0	0.1	0.0	1.0

CI: confidence intervals; OR: odds ratios.
[a] Significant associations.

disease analysis: among the different IMDs, 29 showed a W/M ratio > 1 (including 9 IMD in which all reported cases were women), 3 showed a ratio of 1 (equal sex distribution) and 5 showed a ratio < 1 (predominance in men), highlighting the key role of female sex for driving the association of IMDs with sarcoidosis. However, a subgroup analysis stratified by sex found a specific increased association of some IMDs with sarcoidosis (Table 4), with sex-adjusted ORs being considerably higher than crude ORs for eosinophilic digestive disease in women, and for immune thrombocytopenia, systemic sclerosis and autoimmune hepatitis in men (Fig. 2).

4. Discussion

In this study, we have evaluated the presence of concomitant IMDs in 1737 patients diagnosed with sarcoidosis in a clinical setting using the current international diagnostic criteria. Concomitant IMDs were identified in 1 out of 6 patients, confirming the frequent coexistence of IMDs in the largest cohort of patients with sarcoidosis analyzed so far. In comparison with previous studies, the rate was very similar to that reported in Taiwan (17.6%) [21] but lower than that reported in the UK study (9.5%) [20]. The frequency of IMDs in our patients with sarcoidosis was 1.64-fold higher than that reported in general population [1], a similar figure to that reported by the two population-based studies (1.66 and 2.23, respectively) [20,21]. However, we must acknowledge the limitation linked to the use of the Catalonian healthcare database that does not allow to identify the age of patients and, therefore, we were unable to provide age-adjusted ORs.

In previous studies, the list of IMDs significantly associated with sarcoidosis included chronic active hepatitis, myxedema, thyrotoxicosis, celiac disease, type I diabetes, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, Sjögren syndrome and ankylosing spondylitis; however, only 3 showed a OR higher than 5 (chronic active hepatitis, SLE and Sjögren syndrome) [20,21]. In our study, we confirmed a strong strength of association for some of these diseases, but also for additional IMDs that were not investigated in these studies. The different results we obtained could be explained by the significant methodological differences between our study (a clinical study that used individually, clinically-confirmed cases on the basis of the current classification criteria) and the above-mentioned population-based studies (that used ICD codification for both sarcoidosis and IMDs cases), especially considering the IMDs selected (the UK study included chronic active hepatitis, myxedema or thyrotoxicosis, which may be related to non-autoimmune etiologies) and, especially, with the number of IMDs evaluated (58 in our study vs. less than 25 in the two population-based studies). This approach led us to identify 5 different clusters of IMDs strongly associated with sarcoidosis (OR > 5): immunodeficiencies and autoinflammatory diseases, systemic autoimmune diseases, inflammatory arthritis, autoimmune liver diseases and autoimmune cytopenias.

The IMD more strongly associated with sarcoidosis in our cohort was CVID, which was not evaluated in previous studies. The association between sarcoidosis and CVID has been largely considered controversial, with most studies considering that a patient with CVID presenting with NCG involvement should be considered as having a “granulomatous” variant of CVID, especially in those

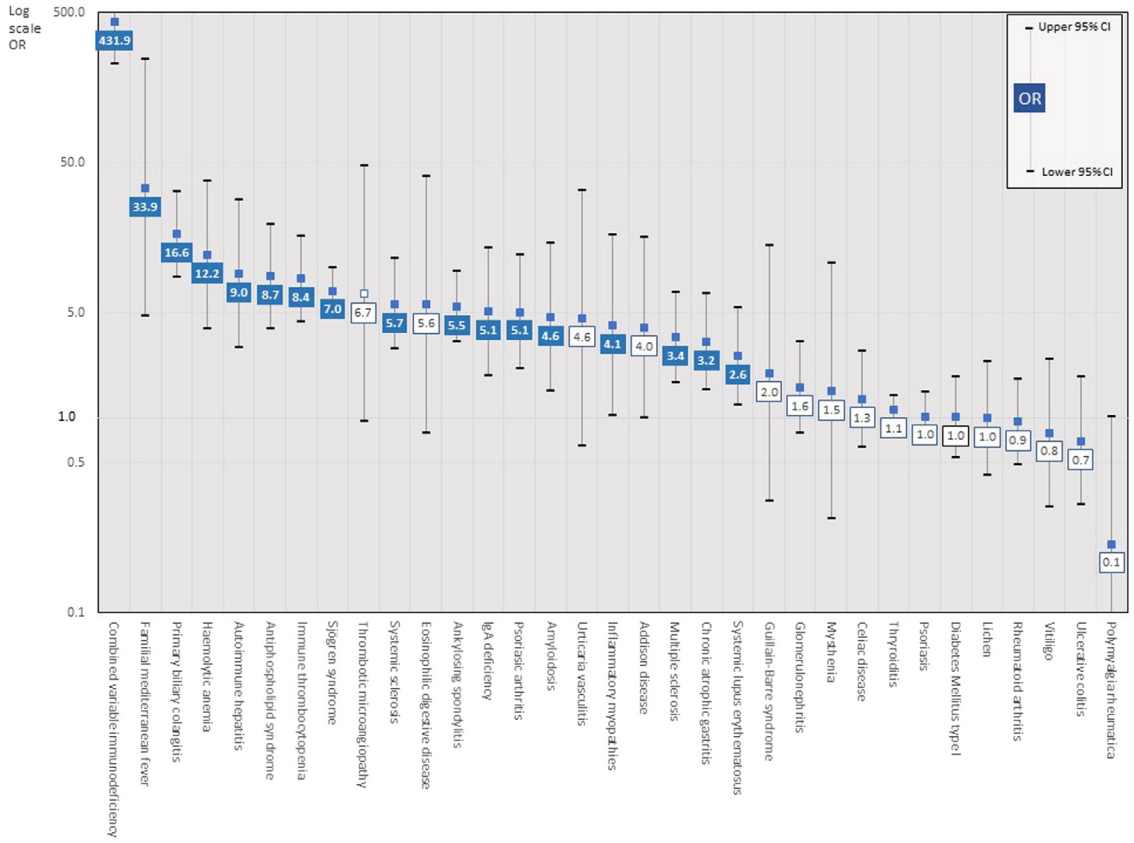

Fig. 1. Odds ratios (OR) and 95% confidence intervals (CI) of coexisting immune-mediated diseases in patients with sarcoidosis, using a logarithmic scale.

with pulmonary involvement [27,28], rather than a coexistence of two different diseases, as has been supported by other authors [29,30]. The reason why a patient with CVID presenting with clinical, laboratory and histopathological findings indistinguishable from sarcoidosis is not considered as a sarcoidosis is difficult to understand from a clinical point of view. It is true that the clinical phenotype of sarcoidosis may differ according to the presence or absence of an associated CVID, with hepatosplenomegaly being more frequently found in those with concomitant CVID, and that even pulmonary scan findings may differ with respect to isolated sarcoidosis [27]. But it seems reasonable to find a different clinical phenotype in patients having two different diseases in comparison with the phenotype of patients affected by a single disease, as has been reported in other similar clustered autoimmune diseases [31,32]. Since all our patients with CVID fulfilled the classification criteria internationally accepted for the diagnosis of sarcoidosis, it seems that the current criteria for sarcoidosis are not able to distinguish between sarcoidosis and granulomatous CVID. In addition, we also found a strong association with selective IgA deficiency, that is the most common primary immunodeficiency [33], and that although was firstly reported in 1972 [34], less than 10 isolated cases have been reported since then, suggesting that this association could be underdiagnosed in patients with sarcoidosis. The association with autoinflammatory diseases (familial mediterranean fever, amyloidosis) may be overstated since is based on the identification of very few coexisting cases (1 and 3, respectively) and deserves further analysis in larger populations, since the association of sarcoidosis with these diseases has been very rarely reported [35,36].

The second cluster of IMDs especially associated with sarcoidosis are systemic autoimmune diseases, especially Sjögren syndrome, antiphospholipid syndrome and systemic sclerosis, and less strongly, inflammatory myopathies and SLE. Among them, Sjögren syndrome share significant pathogenic, immunogenetic and clinical features with sarcoidosis [37]. Differentiating sarcoidosis and primary Sjögren syndrome may be difficult when the initial symptoms of sarcoidosis are sicca symptoms or parotid enlargement, reported in 3–6% of patients with sarcoidosis [37]. Autoantibody analysis may be very useful, since patients with sarcoidosis are usually negative for anti-Ro/SS-A and anti-La/SS-B antibodies [37]. When the clinical and immunological features do not allow clear differentiation between coexistence or mimicry, salivary gland biopsy may be highly discriminatory between sarcoidosis (NCG infiltration) and Sjögren syndrome (focal sialadenitis) [37]. Our study strongly supports that sarcoidosis may, like other IMDs, coexist with Sjögren syndrome, and that a pre-existing sarcoidosis does not rule out a concomitant diagnosis of Sjögren syndrome [37]. With respect to the other diseases associated with sarcoidosis, the evidence in previous studies is mainly limited to descriptive series of associated antiphospholipid syndrome [38], systemic sclerosis [39], or antisynthetase syndrome [40], among others, while in the case-control studies, only Sjögren syndrome and SLE had a higher frequency than that expected in the general population [20,21].

Autoimmune cytopenias are the third cluster of IMDs overrepresented in our cohort of patients with sarcoidosis in comparison with the general population, but there are very few previous studies analyzing this association. The largest study described 20 patients with sarcoidosis and immune thrombocytopenia, most presenting with a platelet count $< 30 \times 10$/L and a therapeutic response overwhelmingly favorable, with no severe bleeding and no deaths [41]. The association between sarcoidosis and autoimmune hemolytic anemia has been even less investigated, despite the first case of association was reported in 1954 [42], with several isolated

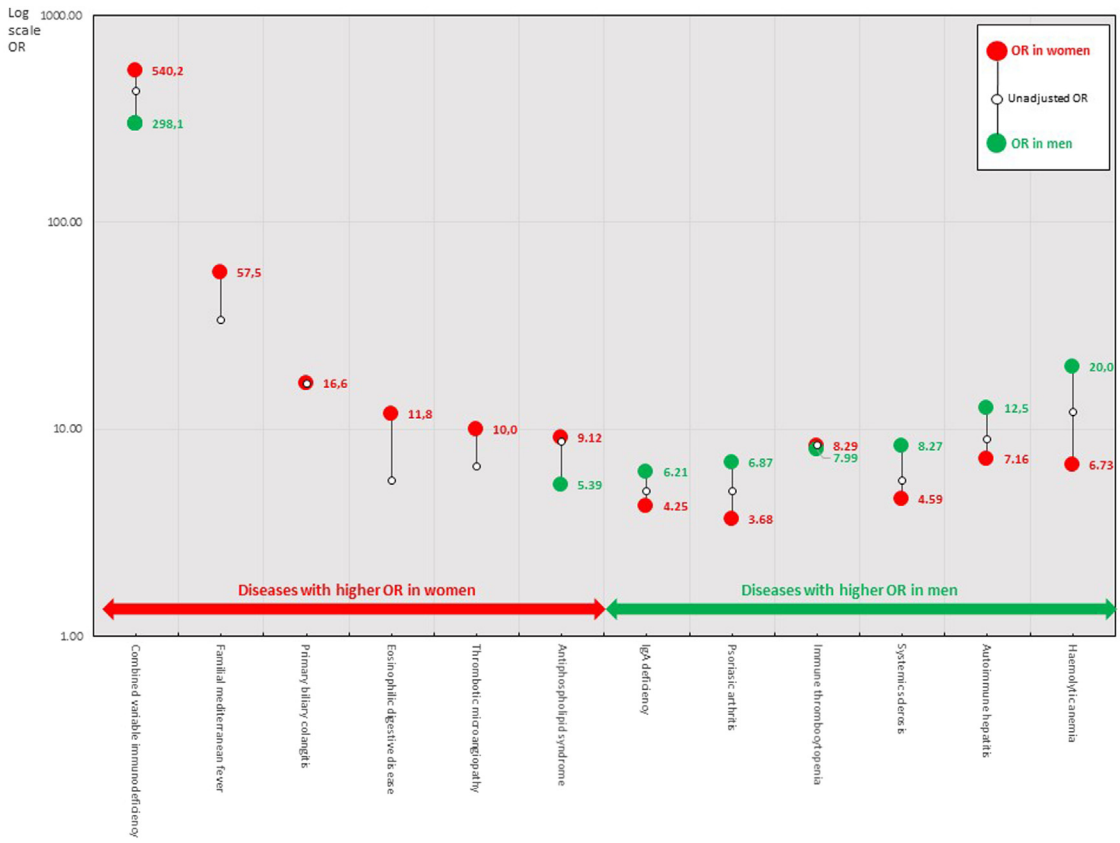

Fig. 2. Sex-adjusted odds ratios (OR) of coexisting immune-mediated diseases in patients with sarcoidosis: unadjusted OR (black circle), adjusted OR in women (red circle), adjusted OR in men (green circle).

cases predominantly reported during the last century, and only 3 reported in the last 20 years [43–45].

Autoimmune liver diseases are the fourth cluster of IMDs strongly associated with sarcoidosis. Few studies have specifically analyzed the coexistence between primary biliary cholangitis (PBC) and sarcoidosis, mainly estimating the frequency of sarcoidosis in patients with PBC (sarcoidosis was identified in 18 out of 1990 patients included in 3 studies, a frequency of 0.1%) [46–48]. Sarcoidosis may cause a cholestatic liver damage similar to PBC, which should be ruled out on the basis of a negative panel of PBC-related antibodies, and the lack of histological features specific of PBC (in addition to hepatic granulomas, plasma and lymphocyte rich, non-suppurative cholangitis) [49]. With respect to autoimmune hepatitis, evidence of association with sarcoidosis is limited to isolated cases [50,51], as well as with sclerosing cholangitis (SC) [52], with one study reporting a frequency of sarcoidosis in 4% of SC patients [47]. In our study, we cannot calculate the OR since SC was not evaluated in the MASCAT project [1], but considering that the prevalence of SC in general population has been estimated in around 8 cases per 100,000 people [53], we could estimate a 7-fold higher frequency of SC in our patients with sarcoidosis.

The fifth cluster of IMDs associated with sarcoidosis are inflammatory arthritis, including ankylosing spondylitis and psoriatic arthritis, but not rheumatoid arthritis. Sacroiliitis in patients has been reported in around 10% of patients with sarcoidosis, most of whom being HLA B27 negative [54,55], and when inflammatory back pain is the major clinical complaint, it may be difficult to differentiate from ankylosing spondylitis. The coexistence of sarcoidosis and ankylosing spondylitis has been reported in around 20 cases on the basis of the fulfillment of the Assessment of SpondyloArthritis International Society/European Spondylarthropathy Study Group criteria of spondyloarthritis [55–57]. With respect to psoriatic arthritis, patients with sarcoidosis may present with articular involvement of the small joints of hands and feet (dactilytis) that may be similar to patients with psoriatic arthritis, often associated with sarcoid bone involvement [58,59]. Due to the reported cases of sarcoidosis triggered by anti-TNF therapies in psoriatic arthritis [60], the use of anti-TNF should always be investigated in patients with psoriatic arthritis who develop sarcoidosis.

The reason why some IMDs are more frequently reported than others in patients with sarcoidosis is unknown, but it could be hypothesized that at least for the diseases more strongly associated, common immunopathogenic mechanisms could be involved in increasing the risk for developing more tan one IMD in a single people, as has been suggested for SS [37], CVID [28] or antisynthetase syndrome [40]. However, the presence of associated IMDs did not altered the clinical pattern of sarcoidosis, and although we found that patients with concomitant IMDs had an older age and a higher frequency of extrathoracic lymph nodes, the differences were not enough sizeable for being considered as useful in a clinical setting. In contrast, the coexistence between IMDs and sarcoidosis may have significant implications for the clinical practice in terms of differential diagnosis considering the large list of signs and symptoms related to IMDs that are overlapped with sarcoidosis. Therefore, to ascertain whether a patient may have 2 different diseases or whether sarcoidosis is mimicking an IMD (either systemic or organ-specific) may be a diagnostic challenge. This is especially difficult for some extrathoracic involvements such as hepatic sarcoidosis or inflammatory joint involvement, because treatment and outcomes are significantly different if the damage is related to sarcoidosis or to an additional IMD. The key message should be the active search for coexisting IMDs in patients with sarcoidosis presenting with some specific clinical profiles, especially when they

Table 4
Subgroup analysis stratified by sex of the occurrence of immune-mediated diseases (IMDs) in people with sarcoidosis.

IMDs	W/M ratio in sarcoidosis	W/M ratio in general population	Non-adjusted OR	Sex-adjusted OR	Lower 95% CI	Upper 95% CI	Sex-adjusted OR	Lower 95% CI	Upper 95% CI
Combined variable immunodeficiency	2.3	0.9	431.9	540.3[a]	243.9[a]	1196.8[a]	298.1[a]	92.9[a]	956.3[a]
Familial Mediterranean fever	All W	1	33.9	57.6[a]	8.0[a]	415.2[a]	nc	nc	nc
Primary biliary colangitis	All W	5.5	16.6	16.7[a]	8.6[a]	32.2[a]	nc	nc	nc
Haemolytic anemia	0.5	1	12.2	6.7	1.0	47.9	20.1[a]	5.0[a]	80.6[a]
Autoimmune hepatitis	2.0	2.5	9.0	7.2[a]	1.8[a]	28.7[a]	12.6[a]	1.8[a]	89.7[a]
Antiphospholipid syndrome	5.0	2.1	8.7	9.1[a]	3.8[a]	22.0[a]	5.4	0.8	38.4
Immune thrombocytopenia	2.0	1.4	8.4	8.3[a]	3.7[a]	18.5[a]	8.0[a]	2.6[a]	24.9[a]
Sjögren syndrome	9.3	6	7.0	6.3[a]	4.3[a]	9.1[a]	5.7[a]	1.8[a]	17.7[a]
Thrombotic microangiopathy	All W	1.3	6.7	10.0[a]	1.4[a]	71.3[a]	nc	nc	nc
Systemic sclerosis	3.0	3.8	5.7	4.6[a]	2.1[a]	10.3[a]	8.3[a]	2.1[a]	33.2[a]
Eosinophilic digestive disease	All W	0.7	5.6	11.9[a]	1.7[a]	84.7[a]	nc	nc	nc
Ankylosing spondylitis	0.9	0.6	5.5	5.8[a]	2.6[a]	12.9[a]	5.7[a]	2.7[a]	12.0[a]
IgA deficiency	1.0	1	5.1	4.3[a]	1.1[a]	17.0[a]	6.2[a]	1.6[a]	24.9[a]
Psoriasic arthritis	0.7	0.9	5.1	3.7	0.9	14.8	6.9[a]	2.2[a]	21.4[a]
Amyloidosis	2.0	1	4.6	5.3	1.3	21.4	3.7	0.5	26.2
Urticaria vasculitis	All W	0.9	4.6	8.3[a]	1.2[a]	58.9[a]	nc	nc	nc
Inflammatory myopathies	All W	1.5	4.1	5.8[a]	1.4[a]	23.1[a]	nc	nc	nc
Addison disease	1.0	1.1	4.0	3.3	0.5	23.1	5.0	0.7	35.2
Multiple sclerosis	7.0	2.1	3.4	3.7[a]	1.8[a]	7.9[a]	1.6	0.2	11.4
Chronic atrophic gastritis	6.0	1.5	3.2	2.3[a]	1.0[a]	5.0[a]	1.4	0.2	9.9
Systemic lupus erythematosus	6.0	4.8	2.6	2.3[a]	1.0[a]	5.0[a]	2.6	0.4	18.3
Guillain–Barré syndrome	All W	0.7	2.0	4.2	0.6	29.9	nc	nc	nc
Glomerulonephritis	1.0	1.1	1.6	1.3	0.5	3.4	1.9	0.7	5.2
Mysthenia	0.0	1	1.5	nc	nc	nc	3.7	0.5	26.3
Celiac disease	All W	2.2	1.3	1.7	0.8	3.5	nc	nc	nc
Thryroiditis	6.2	4.6	1.1	1.0	0.8	1.3	1.1	0.6	1.8
Psoriasis	0.6	0.8	1.0	0.7	0.4	1.3	1.4	0.9	2.3
Diabetes mellitus type I	1.5	0.8	1.0	1.2	0.5	2.6	0.9	0.3	2.3
Lichen	1.5	1.7	1.0	0.8	0.3	2.5	1.3	0.3	5.2
Rheumatoid arthritis	2.0	2.5	0.9	0.7	0.3	1.7	1.3	0.4	4.1
Vitiligo	1.5	1.1	0.8	1.3	0.4	4.0	1.3	0.3	5.3
Ulcerative colitis	3.0	1	0.7	0.9	0.3	2.8	0.4	0.1	3.0
Polymyalgia rheumatica	All W	2	0.1	0.2	0.0	1.3	nc	nc	nc

OR: odds ratios; CI: confidence intervals. "nc" denotes too few cases for odds ratio to be calculated in.
[a] Statistically significant OR ($P < 0.05$).

present with features considered out of the clinical extrathoracic scenario typical of sarcoidosis.

Disclosure of interest

The authors declare that they have no competing interest.

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Author contributions

MRC had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. The remaining authors contributed substantially to the study design, data collection, data analysis and interpretation, and the writing of the manuscript.

Appendix A. Supplementary data

Supplementary data (Tables S1–S3) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2021.105236.

References

[1] Sisó-Almirall A, Kostov B, Martínez-Carbonell E, et al. The prevalence of 78 autoimmune diseases in Catalonia (MASCAT-PADRIS Big Data Project). Autoimmun Rev 2020;19:102448.
[2] Korsten P, Tampe B, Konig MF, et al. Sarcoidosis and autoimmune diseases: differences, similarities and overlaps. Curr Opin Pulm Med 2018;24:504–12.
[3] Sakaguchi S, Toda M, Asano M, et al. T cell-mediated maintenance of natural self-tolerance: its breakdown as a possible cause of various autoimmune diseases. J Autoimmun 1996;9:211–20.
[4] Brito-Zeron P, Sellares J, Bosch X, et al. Epidemiologic patterns of disease expression in sarcoidosis: age, gender and ethnicity-related differences. Clin Exp Rheumatol 2016;34:380–8.
[5] Valeyre D, Prasse A, Nunes H, et al. Sarcoidosis. Lancet (London, England) 2014;383:1155–67.
[6] Pereira CAC, Dornfeld MC, Baughman R, et al. Clinical phenotypes in sarcoidosis. Curr Opin Pulm Med 2014;20:496–502.
[7] Gerke AK. Morbidity and mortality in sarcoidosis. Curr Opin Pulm Med 2014;20:472–8.
[8] Brito-Zeron P, Acar-Denizli N, Siso-Almirall A, et al. The burden of comorbidity and complexity in sarcoidosis: impact of associated chronic diseases. Lung 2018;196:239–48.
[9] Ordoñez-Cañizares MC, Mena-Vázquez N, Redondo-Rodriguez R, et al. Frequency of polyautoimmunity in patients with rheumatoid arthritis and systemic lupus erythematosus. J Clin Rheumatol Pract Reports Rheum Musculoskelet Dis 2020, http://dx.doi.org/10.1097/RHU.0000000000001574 [Online ahead of print].
[10] Botello A, Herrán M, Salcedo V, et al. Prevalence of latent and overt polyautoimmunity in autoimmune thyroid disease: a systematic review and meta-analysis. Clin Endocrinol (Oxf) 2020;93:375–89.
[11] Kalkan Ç, Soykan I. Polyautoimmunity in autoimmune gastritis. Eur J Intern Med 2016;31:79–83.
[12] Deretzi G, Kountouras J, Polyzos SA, et al. Polyautoimmunity in a Greek cohort of multiple sclerosis. Acta Neurol Scand 2015;131:225–30.
[13] Amador-Patarroyo MJ, Arbelaez JG, Mantilla RD, et al. Sjögren's syndrome at the crossroad of polyautoimmunity. J Autoimmun 2012;39:199–205.
[14] Hudson M, Rojas-Villarraga A, Coral-Alvarado P, et al. Polyautoimmunity and familial autoimmunity in systemic sclerosis. J Autoimmun 2008;31:156–9.
[15] Terwiel M, Grutters JC, van Moorsel CHM. Clustering of immune-mediated diseases in sarcoidosis. Curr Opin Pulm Med 2019;25:539–53.
[16] Martusewicz-Boros MM, Boros PW, Wiatr E, et al. What comorbidities accompany sarcoidosis? A large cohort (n = 1779) patients analysis. Sarcoidosis Vasc Diffus Lung Dis 2015;32:115–20.
[17] Pohle S, Baty F, Brutsche M. In-hospital disease burden of sarcoidosis in Switzerland from 2002 to 2012. PLoS One 2016;11:e0151940.
[18] Nowiński A, Puścińska E, Goljan A, et al. The influence of comorbidities on mortality in sarcoidosis: a observational prospective cohort study. Clin Respir J 2017;11:648–56.
[19] Yildiz F, Kobak Ş, Semİz H, et al. Concomitant autoimmune diseases in patients with sarcoidosis in Turkey. Arch Rheumatol 2020;35:259–63.
[20] Rajoriya N, Wotton CJ, Yeates DGR, et al. Immune-mediated and chronic inflammatory disease in people with sarcoidosis: disease associations in a large UK database. Postgrad Med J 2009;85:233–7.
[21] Wu C-H, Chung P-I, Wu C-Y, et al. Comorbid autoimmune diseases in patients with sarcoidosis: a nationwide case-control study in Taiwan. J Dermatol 2017;44:423–30.
[22] Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffus Lung Dis 1999;16:149–73.
[23] Judson MA, Costabel U, Drent M, et al. The WASOG Sarcoidosis Organ Assessment Instrument: an update of a previous clinical tool. Sarcoidosis Vasc Diffus Lung Dis 2014;31:19–27.
[24] Brito-Zeron P, Perez-Alvarez R, Pallares L, et al. Sarcoidosis: an update on current pharmacotherapy options and future directions. Expert Opin Pharmacother 2016;17:2431–48.
[25] Inoue Y, Inui N, Hashimoto D, et al. Cumulative incidence and predictors of progression in corticosteroid-naive patients with sarcoidosis. PLoS One 2015;10:e0143371.
[26] Scadding JG. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. Br Med J 1961;2:1165–72.
[27] Gupta S, Pattanaik D, Krishnaswamy G. Common variable immune deficiency and associated complications. Chest 2019;156:579–93.
[28] Verbsky JW, Routes JM. Sarcoidosis and common variable immunodeficiency: similarities and differences. Semin Respir Crit Care Med 2014;35:330–5.
[29] Fasano MB, Sullivan KE, Sarpong SB, et al. Sarcoidosis and common variable immunodeficiency. Report of 8 cases and review of the literature. Medicine (Baltimore) 1996;75:251–61.
[30] Ameratunga R, Becroft DM, Hunter W. The simultaneous presentation of sarcoidosis and common variable immune deficiency. Pathology 2000;32:280–2.
[31] Antonini L, Le Mauff B, Marcelli C, et al. Rhupus: a systematic literature review. Autoimmun Rev 2020;19:102612.
[32] Ramos-Casals M, Brito-Zerón P, Font J. The overlap of Sjögren's syndrome with other systemic autoimmune diseases. Semin Arthritis Rheum 2007;36:246–55.
[33] Swain S, Selmi C, Gershwin ME, et al. The clinical implications of selective IgA deficiency. J Transl Autoimmun 2019;2:100025.
[34] Sharma OP, Chandor SM. IgA deficiency in sarcoidosis. A case report. Am Rev Respir Dis 1972;106:600–3.
[35] Erten S, Erzurum C, Kosker TA, et al. Two cases of familial Mediterranean fever associated with sarcoidosis (Lofgren's syndrome) and rheumatoid arthritis. Int J Rheum Dis 2013;16:373–5.
[36] Ben Abdelghani K, Mahfoudhi M, Hriz A, et al. [AA amyloidosis complicating sarcoidosis: two cases and literature review]. Rev Med Interne 2010;31:369–71.
[37] Ramos-Casals M, Brito-Zeron P, Garcia-Carrasco M, et al. Sarcoidosis or Sjögren syndrome? Clues to defining mimicry or coexistence in 59 cases. Medicine (Baltimore) 2004;83:85–95.
[38] Pathak R, Khanal R, Aryal MR, et al. Sarcoidosis and antiphospholipid syndrome: a systematic review of cases. N Am J Med Sci 2015;7:379–83.
[39] Ueda-Hayakawa I, Nguyen CTH, Kishimoto I, et al. Clinical characteristics of sarcoidosis patients with systemic sclerosis-specific autoantibody: possible involvement of thymus and activation-regulated chemokine and a review of the published works. J Dermatol 2019;46:577–83.
[40] Couture P, Brillet P-Y, Varin S, et al. Sarcoidosis in patients with antisynthetase syndrome: presentation and outcome. J Rheumatol 2018;45:1296–300.
[41] Mahevas M, Chiche L, Uzunhan Y, et al. Association of sarcoidosis and immune thrombocytopenia: presentation and outcome in a series of 20 patients. Medicine (Baltimore) 2011;90:269–78.
[42] Davis AE, Belber JP, Movitt ER. The association of hemolytic anemia with sarcoidosis. Blood 1954;9:379–83.
[43] Chernow K, Donegan T, Milman T, et al. Sarcoidosis, complete heart block, and warm autoimmune hemolytic anemia in a young woman. J Community Support Oncol 2015;13:159–61.
[44] Ghaddar RK, Muzaffar TH. Pulmonary sarcoidosis and autoimmune hemolytic anemia: possible common immune pathogenesis. Arch Iran Med 2011;14:146–8.
[45] Zaina A, Horn I, Manaster O, et al. Sarcoidosis with cholangitis component in a patient with autoimmune hemolytic anemia. Isr Med Assoc J 2000;2:712.
[46] Rupp C, Mummelthei A, Sauer P, et al. Non-IBD immunological diseases are a risk factor for reduced survival in PSC. Liver Int 2013;33:86–93.
[47] Lamberts LE, Janse M, Haagsma EB, et al. Immune-mediated diseases in primary sclerosing cholangitis. Dig Liver Dis 2011;43:802–6.
[48] Efe C, Torgutalp M, Henriksson I, et al. Extrahepatic autoimmune diseases in primary biliary cholangitis: prevalence and significance for clinical presentation and disease outcome. J Gastroenterol Hepatol 2020.
[49] Jouanolle H, Turlin B, Guyader D, et al. [Association of sarcoidosis and primary biliary cirrhosis: review of the literature apropos of a new case]. Rev Med Interne 1990;11:252–5.
[50] Efe C, Wahlin S, Ozaslan E, et al. Autoimmune hepatitis/primary biliary cirrhosis overlap syndrome and associated extrahepatic autoimmune diseases. Eur J Gastroenterol Hepatol 2012;24:531–4.
[51] Teufel A, Weinmann A, Kahaly GJ, et al. Concurrent autoimmune diseases in patients with autoimmune hepatitis. J Clin Gastroenterol 2010;44:208–13.

[52] Jebran AF, Schmidt WE, Kahraman A, et al. Sarcoidosis of the intra- and extrahepatic bile ducts with concomitant cholangitis in a patient with ulcerative colitis. Case Rep Gastroenterol 2019;13:153–8.
[53] Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol 2012;56:1181–8.
[54] Erb N, Cushley MJ, Kassimos DG, et al. An assessment of back pain and the prevalence of sacroiliitis in sarcoidosis. Chest 2005;127:192–6.
[55] Kobak S, Sever F, Ince O, et al. The prevalence of sacroiliitis and spondyloarthritis in patients with sarcoidosis. Int J Rheumatol 2014;2014:289454.
[56] Levy S, Sandhu V. Ankylosing spondylitis and pulmonary sarcoidosis–a case report and discussion of the literature. Rheumatology (Oxford) 2008;47:1733–4.
[57] Rahul CD, Sharma RK, Talwar D. Sarcoidosis with ankylosing spondylitis: changing therapeutic landscape. Sarcoidosis Vasc Diffus Lung Dis 2018;35:285–8.
[58] Mori T, Yamamoto T. Dactylitis in sarcoidosis. J Dermatol 2017;44:e340–1.
[59] Namas R, Meysami A. Sarcoidosis of hands. J Clin Rheumatol 2016;22:278–9.
[60] Ramos-Casals M, Perez-Alvarez R, Diaz-Lagares C, et al. Autoimmune diseases induced by biological agents: a double-edged sword? Autoimmun Rev 2010;9:188–93.