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Diagnostic dilemma between sarcoidosis and primary Sjögren syndrome: mimicry, concomitance or coincidence? An up-to-date clinician's perspective
(Review article)

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Abstract: Both sarcoidosis and primary Sjögren syndrome (pSS) are multisystem disorders of unknown etiology, which share certain clinical features, making the differential diagnosis a real challenge in clinical practice. Several published case reports and case series have posed the question as to whether there is a real association — mimicry between the two diseases or it is just coincidence. We attempt, after systematic and comprehensive research of the relevant published literature, to present all those data, clinical or paraclinical, which could be useful in the diagnostic approach and the distinguishment of the two diseases. It is certain that, besides the classic diagnostic methods, emerging is the role of immunology and genetics on this direction, although not established yet.

Key words: sarcoidosis, primary Sjögren syndrome, granulomas, exocrinopathy, mimicry, biomarker, immunity.

Introduction-Definitions

Sarcoidosis is a multisystem disease of unknown etiology, characterized by the formation of non-caseating granulomas, found in the affected organs. Diagnosis is based upon clinical and radiologic features, while, histopathologic examination consistent with the presence of non-caseating granulomas establishes the diagnosis. It is classified as acute (≤2 years) and chronic (≥3–5 years), based upon the duration of disease's course and the remission. Disease is characterized as refractory, when it progresses despite the therapeutic intervention [1].

Sjögren syndrome (SS) is an exocrinopathy, mainly affecting ocular and salivary glands. In more than 30% of all cases, other organs are also involved during disease's course [2]. SS is divided into primary and secondary. Secondary SS appears along with another autoimmune disease, mainly SLE (15–36%), rheumatoid arthritis (20–32%) and systemic sclerosis (11–24%) [3]. Multisystem involvement is not rare in patients with pSS, increasing significantly morbidity and mortality.

These two diseases share certain clinical features, making the differential diagnosis sometimes really challenging. According to 2016 ACR/EULAR classification criteria for pSS, prior exclusion of sarcoidosis is a definite diagnostic criterion for pSS [4]. Several published case reports and case series have correlated the two diseases, while the discussion is still continued, as to whether there is mimicry between sarcoidosis and pSS or it is just a coincidence and whether the two diseases can both be manifested in the same patient.

Differential diagnosis between the two diseases is significant, based on the fact that therapeutic regimen may share first and second line agents in both diseases, but therapeutic strategy differs substantially. Emerging drugs, such as monoclonal antibodies, although not well established in therapeutics yet, may offer significant help in clinicians, improving disease's course, modifying systemic involvement and thus leading to better prognosis.

Until now, there are no certain clinical features and paraclinical values, in order to distinguish sarcoidosis from pSS. After systematic and thorough research of the relevant literature, we aim, through this review article, to summarize the clinical data that correlate the two diseases, to present potential biomarkers that could be useful in differential diagnosis, new perspectives in the well established diagnostic methods and to emerge the role of immunology and genetics in clinical practice.

Epidemiology

Estimated incidence of sarcoidosis is 4.7–64/100,000, while prevalence is as high as 1–35.5/100,000/year. Northern European and African American individuals exhibit the highest risk of sarcoidosis manifestation [1]. It usually affects adolescents and

young adults, between 10 and 40 years of life. African-Americans have a 3-fold increased risk for sarcoidosis clinical manifestation during life [5].

Prevalence of pSS is 61/100,000 inhabitants, with female to male ratio ranging from 9 : 1 to 19 : 1. It is more frequent in Europe, while the mean age of diagnosis is 56 years [6]. This disease practically affects 0.5% of general population [7].

Clinical manifestations

Spectrum of clinical manifestations in patients with sarcoidosis include: lung involvement in up to 90% of all patients, low-grade fever, malaise, weight loss (up to one third of all patients), skin, joint and eye involvement, lymphadenopathy, hepatomegaly and splenomegaly [8]. CNS (Bell's palsy, multiplex mononeuritis, lymphocytic meningitis), cardiovascular (cardiomyopathy, atrioventricular block, pulmonary hypertension, arrhythmias) and renal (interstitial nephritis, nephrotic syndrome, neprhocalcinosis) involvement are also seen [9]. Extrapulmonary involvement is seen in 30–50% of all patients with sarcoidosis.

Sicca symptoms constitute the main clinical manifestation of pSS. Usual extraglandular manifestations include: arthralgia, non-erosive polyarthritis, cutaneous lesions due to vasculitis involving the small and medium vessels, annular erythema, urticaria and hypergammaglobulinemic purpura. Renal involvement is much rarer, including tubulointersitial involvement along with distal renal tubular acidosis. Neurologic manifestations, due to CNS or PNS involvement are much more challenging in clinical practice [6]. Ten to 20% of all patients will finally develop interstitial lung disease [10].

Pathogenesis: the role of genetics

HLA DR3, 11, 12, 14, 15, 17 alleles are positively associated with sarcoidosis manifestation [11, 12]. MHC class II coding alleles, in particular B8, B13, B35, and A9, are also associated with sarcoidosis [13]. HLA DRB1*03 allele is associated with a more favorable disease course, while HLA DRB1*14/15 alleles are associated with chronic disease course [14]. Manifestation of acute sarcoid arthritis with spontaneous remission is typical in HLA-B8 (+) patients [13]. On the other hand, HLA DRI and DR4 seem to be protective against sarcoidosis clinical expression [11].

Hoffmann *et al.* identified annexin A11 (ANXA11) as a non-HLA locus associated with high risk for sarcoidosis manifestation [15]. BTNL2 gene in the MHCII region on chromosome 6 is considered as strongly associated with sarcoidosis development in German and white US populations [9]. Genetic polymorphisms inducing susceptibility for sarcoidosis development include the loci for TNF-a, CD80, CD86 and chemokines receptors CCR2 and CCR5 as well [16, 17].

Regarding the field of epigenetics, Novosadova *et al.* attempted to assess the expression of 35 different extracellular miRNAs in 13 healthy controls and 24 sarcoidosis patients. The latter group was divided into two subgroups, according to the presence or not of Lofgren syndrome (LS). They found: a) dysregulated expression of miR-146, miR-16, miR-425-5p, miR-93-5p in both sarcoidosis subgroups, compared to controls, b) dysregulated expression of miR-1, miR-212 and miR-150-5p in sarcoidosis patients without LS, c) dysregulated expression of miR-340-5p and miR-21-5p in patients with LS. They conclude that: a) the miRNAs that differ between the two sarcoidosis subgroups modify the TGF-β signaling pathway, b) taken into account the profibrotic action of TGF-β, evaluation of miRNAs may serve as a predictor for disease progression towards pulmonary fibrosis and c) more investigation on the field of extracellular miRNAs is required, as they are potential biomarkers for diagnosis and prognosis in patients with sarcoidosis [18].

On the other hand, HLA-DRB1*0301 and HLA-DQB1*0201 alleles are positively associated with pSS manifestation [19], while HLA-B8 is also associated with pSS, besides sarcoidosis [13]. In their study, Kang and colleagues attempted to determine HLA class II alleles in patients with pSS, in comparison with healthy controls, based upon their ethnicity. They documented: a) increased frequency of the predicted haplotype HLA-DRB1*0301-DRB3*0101-DQA1*0501-DQB1*0201 in Caucasian patients ($p < 0.001$), b) increased frequency of the predicted haplotype HLA-DRB1*040 5-DRB4*0101-DQA1*0301-DQB1*0401 in Japanese patients $p < 0.05$) and c) increased frequency of the predicted haplotype DRB1*0803-DQA1*0103-DQB1*0601 in Chinese patients ($p < 0.05$) [20]. In another study by Miyagawa *et al.*, increased frequency of the the HLA class II DRB1*08032/DQA1*0103/DQB1*0601 and DRB1*08032 alleles was shown in patients with pSS and positive anti-Ro and anti-La antibodies, compared with patients with negative anti-La antibodies or with healthy controls in Japanese subjects. The authors conclude that presence or absence of anti-La antibodies in patients with pSS may determine the HLA class II allele distributions that are observed [21].

In their recent review article, Ferro *et al.* tried to summarize all the current insights into pSS pathogenesis. PTPN22W* variant in association with IFN type I response and rs2230926 exonic variant of TNFAIP3 seem to be candidate genes, implicated in the pathogenesis of the discussed syndrome. DNA hypomethylation surrounding PSMB8 and TAP1 genes also seem to be associated with the involvement of minor salivary glands during the disease's course. The levels of TMEVPG1 in $CD4^+$ T-cells were also found to correlate positively with the manifestation of pSS and the levels of "classic" disease markers, such as anti-SSA and ESR [22].

Other genetic associations include susceptibility loci in BLK and CXCR5, which regulate B-cell activation and action, in STAT4, IL-12A and IRF5, which regulate

adaptive and innate immunity as well, and, except for TNFAIP3, TNIP also, which modifies NF-kB signaling [23].

Pathogenesis: the aspect of immunology

In sarcoidosis, Th1 lymphocytes and macrophages are mainly involved in the inflammatory cascade. Tissue permeability, cellular influx and local cell proliferation are crucial for the formation of granulomas. $CD14^+$ alveolar macrophages in patients with sarcoidosis are hyperactive and exhibit certain antigen presenting capacity. Influx of Th1 cells is also seen in the affected organs in the acute phase of sarcoidosis, triggered by CXCR3 chemokines. The latter leads to a Th1 polarized immune response [1]. Within the granulomatous lesion, $CD4^+$ T lymphocytes are predominant, while epithelioid cells represent transformed monocytes with secretory activity [16, 17, 24]. Fractions of $CD4^+$ T-helpers Th1 lymphocytes are found in involved organs in patients with sarcoidosis, while $CD4^+$ T-helpers Th17 lymphocytes may be crucial for the sarcoid granulomas formation [11, 25].

Tondel *et al.* collected bronchoalveolar lavage fluid (BALF) from 30 patients with sarcoidosis, 18 patients with diffuse parenchymal lung diseases (DPLD) other than sarcoidosis and 15 healthy controls. They found that: a) the fractions of $FoxP3^+$ $CD4^+$ T-cells and Th17 cells were both lower in sarcoidosis and in controls ($p = 0.017$ and $= 0.011$ respectively), b) the fractions of IFN-γ^+ Th17 cells were greater in sarcoidosis patients than controls ($p = 0.0005$), positively correlating with Th1 cells ($p = 0.001$) and radiologic stage ($p = 0.03$), and c) increased ratio IFN-γ^+ Th17 cells/ $FoxP3^+$ $CD4^+$ T-cells in sarcoidosis patients compared to controls. The authors suggest that a polarized strong Th1 cytokine mediated response is present in sarcoidosis patients, and that high fractions of IFN-γ^+ Th17 cells may represent a result of the above polarized Th1 response. Evaluation of IFN-γ^+ Th17 cells/ $FoxP3^+$ $CD4^+$ T-cells ratio in BALF could possibly become substantial for the diagnosis of sarcoidosis [26].

According to Tercelj *et al.*, fungal exposure and induced suppression of IL-10 production, one of the most well-known anti-inflammatory and immunosuppressive cytokines, may play a crucial, alternative role in the formation of granulomas in patients with sarcoidosis. Exposure to other microbial agents can possibly modify IL-10 production, a cytokine, which — in experimental models — suppresses granulomatous inflammation and chronic fibrosis [27].

It has been shown in animal models that induced deficiency in TNF-a expression or blockade of its receptors results in impaired formation of new granulomas and regression of the pre-existing granulomas. This fact has emerged anti-TNF agents as promising in therapeutics of patients with sarcoidosis. However, all these factors have been implicated in the development of new, sarcoidosis-like, inflammatory process [28].

Pathogenesis of pSS is still ambiguous. The role of Th1 lymphocytes in this process seems substantial. They bind to MHC2 molecules, activating an immune reaction. Pro-inflammatory Th1 cytokines, such as IL-1b, IL-6, TNF-a, IFN-γ are increased in the affected exocrine glands in patients with pSS, indicating the major role of Th1 lymphocytes in pathogenesis. As for the role of B-cells in pathogenesis, a cause that remains still unidentified leads to activation of plasmacytoid dendritic cells. The latter results in overproduction of interferons, associated with increased levels of BAFF. This cytokine promotes irregular B-cell maturation, resulting in autoimmune B-cells and thus in autoantibodies production [10, 29].

In their study, Brkic and colleagues determined the presence of upregulation of 5 interferon type I inducible genes in CD14 monocytes of patients with pSS in comparison with healthy controls. The authors found that the so called "IFN type I signature", including IFI44, IFI44L, IFIT3, LY6E and MX1 genes, was present in 55% of all patients with pSS, compared with 4.5% of controls. The above signature did not alter significantly over the time, while it correlated positively with disease's severity, as estimated by "classic" biomarkers, and the presence of glandular, haematological and cutaneous involvement. Another remarkable finding of their study was the positive correlation between the IFN type I signature and the increased BAFF mRNA expression in monocytes of patients with pSS, compared with controls. The authors conclude that the above findings may help in identifying specific patients' subgroups in clinical practice, which might benefit from targeted therapeutic interventions [30].

According to the study of Mieliauskaite *et al.* main findings were: a) total expression of IL-17 and IL-17R in minor salivary glands in patients with pSS was comparable to those with preclinical pSS ($p < 0.05$), b) total expression of IL-23 and IL-23R in minor salivary glands in patients with pSS was comparable to those with preclinical pSS ($p < 0.05$), c) total expression of IL-17, IL-17R, IL-23 and IL-23R in patients with pSS was higher in comparison with non autoimmune sicca syndrome ($p < 0.05$). IL-23 seems to be significant for the development of Th17 cells, which are involved in autoimmunity. IL-17 is finally produced by pathogenetic clusters of Th17 cells. The authors propose a potential role of IL-17/IL-23 system in pathogenesis of pSS [31].

In another study conducted by Toussirot *et al.*, patients with pSS exhibited higher serum IL-6 and adiponectin levels, in comparison with healthy controls ($p = 0.05$ and 0.04, respectively). It is well known that adiponectin mainly acts as an anti-inflammatory agent. It seems paradoxical, as high levels of proinflammatory factors in autoimmune diseases suppress adiponectin's production by adipocytes. The authors emphasize, based upon their study's results, on the potential effects of high adiponectin levels on the inflammatory progression in such autoimmune diseases. The question that stems from their observation is if adiponectin levels could serve as a biomarker of disease activity, especially after the notice that adiponectin levels increase during immunosuppressive therapy [32].

Clinical data

Ramos-Casals *et al.* attempted to define whether sarcoidosis and SS co-exist or mimic each other, presenting 5 cases of patients they encountered and the analysis of 54 published cases till 2004, after comprehensive research of the literature. After histopathologic examination of the exocrine glands in 53 patients, coexistence was confirmed in 28 cases, while concomitance in 25. The authors conclude that when the 2 diseases co-exist, there is a higher prevalence of systemic manifestations, especially articular and ocular involvement ($p = 0.001$ and 0.024 respectively), as well antinuclear antibodies (ANA) and anti-Ro/SSA antibodies ($p = 0.005$ and 0.001 respectively), in comparison with cases of mimicry. They also document that in cases of concomitance, extrapulmonary sarcoid manifestations, especially adenopathy ($p = 0.01$), are more common in comparison with cases in which sarcoidosis is the only subject disease ($p < 0.001$). Thus, they finally conclude that the 3 major aspects that should be determined in cases when differential diagnosis is ambiguous are: a) extraglandular manifestations, b) immunologic profile and c) performance of minor salivary gland biopsy, histopathologic and immunohistochemical examination. They emphasize on the interpretation of mild lymphocytic infiltration found in the lip biopsy; it may be indicative for SS, but in can represent a progranulomatous stage of sarcoidosis [33].

Ahmad *et al.* report a case of a 29 year old male patient who presented complaining of symptoms such as fatigue, low grade fever, night sweats, dry cough, weight loss, dry eyes, dry mouth, rashes, difficulty in swallowing and vomiting after meal. Previous laboratory findings (ANA negative, Rheumatoid Factor — RF — positive, FNA and cytology of the right submandibular swelling which revealed polymorphic populations of lymphoid cells) were consistent of a systemic vasculitis and patient was referred for further investigation. Enlargement of parotid glands, submandibular lymphadenopathy and vasculitic lesions in both limbs were the main clinical findings. Main laboratory findings were: eosinophilia, elevated WBC, elevated levels of ESR and CRP, renal impairment, positive anti-Sm antibodies, elevated serum IgE, normal levels of Angiotensin Converting Enzyme (ACE), hypocomplementemia. Ophthalmological examination was negative for SS or uveitis. After CT scan of chest and abdomen (high suspicion of sarcoidosis), biopsies were taken: skin biopsy from the left leg revealed resolving vasculitis, lower lip biopsy showed chronic inflammation and left cervical lymph node biopsy revealed non-caseating granulomas. Although initial impression was consistent of SS diagnosis, the latter biopsy led to the diagnosis of sarcoidosis. The authors conclude that in atypical cases, as above, the reference standard for the diagnosis is full tissue biopsy from more than one involved sites [34].

Gonzalez Garcia *et al.* report a case of a 62 year old female patient with medical history of SS during the last 5 years, who presented as an outpatient complaining of progressively worsening dyspnea and dry cough over the last 4 months. Bibasilar

crackles constituted the main clinical finding. Elevated levels of IgG in serum electrophoresis was the main laboratory finding, while restrictive pattern of lung involvement was documented, after notice of important decline in DLCO. Chest HRCT showed multiple nodules, multiple cystic changes and peripheral septal thickening on middle to upper lung fields. Differential diagnosis included lung involvement of SS, or concomitant sarcoidosis or pulmonary Langerhans histiocytosis (PLH). BALF examination revealed normal value of the CD4/CD8 ratio, which, along with normal levels of serum ACE, excluded sarcoidosis. Proportion of CD1a stained cells was 15% in BALF. That finding led to the diagnosis of PLH. The authors conclude that when lung involvement in SS patients is suspected, PLH and sarcoidosis should always be excluded [35].

Santiago *et al.* report a case of a 44 year old female, previously diagnosed with primary SS due to sicca symptoms, who presented 4 years later with dyspnea, dry cough, arthralgia and fatigue. Elevated values of ACE, depiction of hilar and mediastinal lymphadenopathy and multiple small nodules in chest HRCT and increased CD4/CD8 ratio in BAL raised the clinical suspicion for concomitant sarcoidosis. A mediastinoscopy- directed biopsy of the nodules was performed, which revealed the presence of multiple non caseating granulomas, thus the patient was diagnosed with sarcoidosis as well. Two years later and after persistent recession of sarcoidosis, patient presented with symptoms of acute inflammatory myopathy. MRI and biopsy revealed the presence of sarcoid myopathy. The authors conclude that: a) when a patient suffering from primary SS presents with symptoms involving lungs and exocrine glands, then sarcoidosis should be taken into account as a concomitant disease and b) when a patient with concomitant sarcoidosis and SS present with muscular symptoms, then a comprehensive diagnostic work-out and even a tissue biopsy may be required. They also emphasize on the need for tissue biopsy beyond the exocrine glands, when there is high suspicion for sarcoidosis, in order to affirm or exclude this diagnosis [36].

Koopmans *et al.* reported a case of a 45 year old man, previously misdiagnosed with sarcoidosis. He first presented with fatigue, dry mouth, dry eyes and Raynaud's phenomenon with depiction of bilateral hilar lymphadenopathy in chest x-ray, thus transbronchial lung biopsy was performed. Histological examination revealed the presence of epitheloid cells and few granulomatous structures, and, in accordance with the elevated ACE, the diagnosis of sarcoidosis was made. Six months later the patient complained of pain in the right upper abdominal quadrant. Diagnostic work-up raised suspicion of a tumor located in the pancreatic head. Due to this fact, laparotomy was performed, in order full tissue biopsies to be taken. Microscopic findings suggestive of chronic pancreatitis were the only pathological sign. When examined in the Department of Internal Medicine, clinical findings such as dry oral mucosa and tender submandibulary glands and laboratory findings such as anemia,

hyperglobulinaemia and positive RF and ANA made the diagnosis of SS possible. Sialography confirmed the presence of sialoadenitis. A sublavial salivary gland biopsy and a new lung biopsy were taken, in order to confirm or not SS or sarcoidosis. Findings were suggestive for SS, thus the authors suggest that sublavial salivary gland biopsy may be very helpful in the differential diagnosis, especially when involvement of major organs is noticed, with clinical manifestations that occur both in sarcoidosis and SS [37].

Van de Loosdrecht *et al.* report a case of a 32 year old woman, who presented at the outpatient department complaining of migratory arthralgia, dry mouth, dry eyes and blurred vision during the last 6 months. Erythema nodosum on both legs was found. Elevated values of ESR and CRP, mild proteinuria, increased serum lysozume and ACE values, positive anti-Ro antibodies and elevated IgM and IgG rheumatoid factor were found. Chest radiograph was suggestive for sarcoidosis, while ophthalmological examination was consistent with keratoconjuctivitis sicca. Sialometric analysis revealed the presence of reduced whole saliva flow rate, while elevated sodium concentration was found via sialochemistry. They then performed sialography, which showed globular sialectasia in the right parotid gland. Due to the presence of findings consistent both with SS and sarcoidosis, the authors conducted parotid gland and labial salivary gland biopsy. Histopathology revealed the presence of epithelioid cell granuloma, but also lymphocytic infiltration and epimyoepthelial islands. Patient was finally diagnosed with concomitant Lofgren's syndrome and SS. During a 2 year follow up period, recession of sarcoidosis, but persistence of SS was confirmed. The authors conclude that, based upon the limited relevant literature, it is unknown if there is mimicry or concomitance, and that the possibility of simultaneous presentation of the two diseases should not be excluded in clinical practice [38].

Daouk *et al.* reported a case of a 53 year old female patient, diagnosed with SS 8 years before, who presented with dyspnea on exertion and dry cough, gradually worsening over the past 2 years before admission. CT scan of the chest revealed the presence of centrilobular ground glass opacities and a bronchovascular pattern of distribution. Transbronchial lung biopsy was then performed. Histopathologic examination showed non caseating granulomas. Liver biopsy was also conducted, and it was also consistent with the diagnosis of sarcoidosis. Immunologic profile reconfirmed the presence of SS. The patient was diagnosed with sarcoidosis and Sjogren's overlap syndrome [39].

Lois *et al.* reported two cases of patients, the one previously diagnosed with SS and the other with sarcoidosis, who presented with severe lung impairment. In patient with sarcoidosis lung tissue biopsy revealed the presence of lymphocytic interstitial pneumonitis, leading to diagnosis of SS, while in patient with a previous diagnosis of SS, lung tissue biopsy showed lymphocytic interstitial pneumonitis, due to the subject

disease, but also the existence of non caseating granulomas. The authors emphasize on the need of aggressive approach with prompt conduction of lung tissue biopsy in patients with pulmonary exacerbation, when neither sarcoidosis nor SS can be excluded. Despite the possibility of coexistence, it is crucial to evaluate timely if lung involvement is due to SS or sarcoidosis, because of different therapeutic intervention, and thus different prognosis [40].

Kohsokabe *et al.* reported a case of a 70 year old woman with a past history of pSS who presented with fever and loss of weight, progressively worsening. Abdominal CT and gallium-67 scan revealed lymphadenopathy within the abdominal cavity. Histopathologic findings after liver and lymph node biopsy were consistent with sarcoidosis (non caseating granulomas). Lip biopsy reconfirmed the presence of SS. The authors emphasized on the possibility of concomitance between the 2 diseases, questioning about potential immunologic mimicry [41]. A similar case was reported by Deheinzelin *et al.* A 57 year old female patient with a past history of SS presented with pulmonary symptoms. A transbronchial lung biopsy was conducted. Histopathologic examination confirmed the coexistence of sarcoidosis. The authors excluded the possibility of TASS clinical manifestation (Thyroiditis, Addison's disease, SS, and sarcoidosis) [42].

Sato *et al.* reported a case of a 63 year old man who presented complaining of worsening dyspnea and dry cough, low grade fever and edematous erythema on his face, anterior chest and dorsal region. Chest HRCT suggestive of interstitial lung disease (ILD), pulmonary function test indicative of restrictive disorder, documentation of absence of myogenic changes in EMG in accordance with laboratory findings (negative Rheumatoid factor, antinuclear autoantibodies, and anti-Jo-1 antibodies) raised the suspicion on diagnosis of Clinically Amyopathic Dermatomyositis — ILD (CADM-ILD). They excluded the possibility of rapidly progressive ILD, after the negative results for anti-CADM-140/MDA5 antibodies. Transbronchial lung biopsy and BALF analysis led to the diagnosis of sarcoidosis. The authors conclude that in cases of lung and skin involvement, when differential diagnosis between connective tissue disorder — especially CADM along with ILD, and sarcoidosis is difficult, anti-CADM-140/MDA5 antibodies can give useful information, crucial for the therapeutic management and the follow up [43].

Differential diagnostic modalities and potential biomarkers

Epithelioid cells found on sarcoid granulomas produce ACE. Elevated serum levels of ACE are observed in 60% of patients with sarcoidosis, reflecting granulomas' mass and disease activity [44, 45]. Cytopenia, eosinophilia, hypergammaglobulinemia, hypercalcemia, hypercalciuria and elevated ACE are the main laboratory findings in

sarcoidosis. Histopathologic examination of the biopsy taken from an involved organ remains the reference method to establish diagnosis of sarcoidosis [46].

Birnbaum *et al.* suggest, through their retrospective study in sarcoidosis patients and after evaluation of serum values of lysozume and ACE and conduction of chest X-ray, that more than 80% of their patients had at least one out of three suggestive for the diagnosis. When a chest HRCT instead of chest X-ray is conducted, then sensitivity rises up to 90% [47].

BALF examination is crucial for the diagnosis of sarcoidosis. CD4/CD8 ratio >4 : 1 and lymphocyte percentage ≥16% are specific for sarcoidosis diagnosis. Transbronchial lung biopsy is usually required to confirm the diagnosis. Elevated D-dimer levels in BALF are also consistent with sarcoidosis [48, 49].

According to the classic study by Winterbauer and colleagues, the triad CD4 : CD8 ratio >2, <1% neutrophils and <1% eosinophils in the BALF analysis features sensitivity of 59%, specificity of 94%, negative predictive value of 90% and positive predictive value of 73% in differential diagnosis between sarcoidosis and non-sarcoidosis disease. Determination of this triad showed almost the same specificity and positive predictive value with transbronchial lung biopsy [50].

HRCT of the chest is considered as the imaging reference method in sarcoidosis, however it is often difficult to differentiate from other interstitial diseases. Major CT features in patients with sarcoidosis include: bilateral, multifocal, poorly defined, peripherally distributed opacities with or without air bronchograms and/or multiple and bilateral nodules, well demarcated or with irregular outline and small surrounding satellite nodules, producing the typical "galaxy sign". Cavitation is a rare finding, and mycetoma formation, as well. The latter develops usually in stage IV disease. Finally, pleural effusion and necrotizing sarcoid angiitis are other rare patterns in sarcoidosis [51].

18F-FDG PET is considered as an alternative imaging method in sarcoidosis. It features high sensitivity, but low specificity. FDG is highly taken up by the granulomas, but the uptake pattern resembles that of lymphoma or other malignant diseases. A pathognomonic finding in cases of sarcoid myopathy is the "tiger-man" sign. Despite its use in diagnosis, it can be also used in the follow up period, as a useful tool for the clinician to evaluate disease's activity and response to the therapy [52]. 18F-FMT PET seems able to differentiate between sarcoidosis and malignancy. Sarcoid lesions are positive on FDG PET but negative on FMT PET, while malignancy is positive on both [53].

Ascites can occur almost in 10% of patients with sarcoidosis, mainly due to pulmonary or portal hypertension, after granulomatous obstruction. In some cases, as the one reported by Baskaran *et al.*, peritoneal sarcoid studding can even cause significant ascites. Those cases are associated with significant increase in serum levels

of CA125. Histopathologic examination after tissue biopsy is necessary in order to exclude the presence of malignancy, especially in females, in whom hepatosplenic sarcoidosis resembles ovarian malignancy [54, 55].

Kobak *et al.* studied 42 patients with sarcoidosis (32 female, 10 male, mean age 45.2 years old). ANA positivity was detected in 12 out of 42 patients (28.5%). Immunoblot analysis revealed that 8 patients were negative, 1 had anti-dsDNA antibody, 1 had anti-Ro antibody, 1 had anticentromere antibody and 1 had anti-Scl-70 antibody. Anti-Ro (+) patient had also a SS diagnosis. Rest laboratory findings in that subgroup included: a) elevated serum ACE in 15 patients (35.7%), b) elevated serum calcium in 6 patients (14.3%) and c) elevated serum 25-hydroxy-vitamin-D3 in 2 patients (4.7%). Twenty five (59.5%) and 23 patients (54.7%) had elevated ESR and CRP levels, respectively. The authors conclude that ANA determination in sarcoidosis patients is necessary, because on the one hand sarcoidosis mimics other autoimmune diseases and on the other hand there is always the possibility of coincidence [56].

In patients with sarcoidosis, although histologic presence of non caseating granulomas after labial salivary gland biopsy (LSGB) is a hallmark for the diagnosis, it is not always the case. Multinucleated giant cells and lymphoplasmacytic infiltrates may also be present. Such histopathologic features are also seen in patients with SS [57, 58].

Histopathologic hallmark for the diagnosis of pSS in biopsies of salivary glands is the infiltration by mononuclear lymphoid cells, replacing the glandular epithelium. Medical history, immunologic profile and labial salivary gland biopsy are crucial for the diagnosis of pSS [59].

Determination of both positive anti-Ro52 and anti-Ro60 antibodies shows the highest positive predictive value for clinical expression of SS, years before the diagnosis, while anti-La antibodies, when found solely, are difficult to be interpreted [60].

There are many promising biomarkers for the diagnosis and the follow-up of SS patients. High profilin levels and low carbonic anhydrase I (CA-I) levels have been found in the saliva of patients with pSS compared to healthy controls. IL-4, IL-5 and clusterin in combination in the salivary proteome may also predict the development of disease. Cathepsin S activity in tears of patients with pSS is elevated in comparison with patients suffering from other rheumatoid diseases and healthy controls thus could be used as a diagnostic but not a prognostic biomarker. IFN-I and myxovirus-resistance protein A (MxA) may offer as diagnostic biomarkers, while the latter correlates positively with disease's activity, thus its levels can be used in the follow up of those patients. Finally, they report that the levels of CXCL13, both in serum and saliva, were elevated in patients with pSS in comparison with healthy controls [61].

According to Kopeć-Mędrek *et al.*, serum calprotectin, a heretodimeric complex of two S-100 calcium binding proteins, MRP-8 and MRP-14, may serve as a more accurate biomarker for the diagnosis and the monitoring of patients suffering from

rheumatoid diseases. It may be also useful for distinguishing those patients, who will be good responders to the therapeutic management. However, data on the use of calprotectin in SS patients are limited, thus further investigation is required [62]. B_2-microglobulin, serum free light chains of immunoglobulins and BAFF positively correlate with SS activity [63]. According to Nakamura *et al.*, prevalence of anti-M3R antibodies is higher in early onset SS than in late onset SS [64].

Sharma *et al.* consider fine needle aspiration cytology (FNAC) as significant in the context of evaluation of a patient with parotid or submandibular or labial salivary gland enlargement. They report a case of a 54 year old woman presenting with bilaterally enlarged parotid glands, dry mouth, dry eyes and dry cough over the past 6 months. After FNA performance, the smears exhibited non caseating granulomas and multinucleated giant cells. The findings raised high suspicion on the presence of a granulomatous disease. Crystalline structures within giant cells made the diagnosis of sarcoidosis more possible. Radiological and laboratory findings were consistent with diagnosis of sarcoidosis. Presence of SS was excluded, because neither lymphocytic infiltration was shown nor anti-Ro and anti-La antibodies were positive. Patient was finally diagnosed with multisystem sarcoidosis. Salivary gland cytology can be very useful in patients with ambiguous clinical manifestations [65].

Baeteman *et al.* presented the results of their retrospective study concerning the usefulness of LSGB in clinical practice. During 2004 they conducted 96 LSGBs in patients with SS, amyloidosis, sarcoidosis and other autoimmune diseases. LSGB's specificity was 100%, while sensitivity was 75% for SS and 60% for sarcoidosis [66]. Ozcakir-Tomruk *et al.* emphasized on the value of immunohistochemistry after performance of LSGB, especially when microscopic findings are not sufficient to differentiate between sarcoidosis and SS. CD3 and CD4 immunoreactivity was confirmed in patients with sarcoidosis, while CD20 immunoreactivity was seen in patients with SS. Thus, they consider immunohistochemistry as substantial for the differential diagnosis between the two diseases [67].

Mansour *et al.* tried to assess usefulness of salivary evaluation in clinical practice, when differential diagnosis is difficult between sarcoidosis and SS. They observed no differences in mean salivary flow rate ($p = 0.768$), total salivary protein ($p = 0.718$) and in electrophoretic profile ($p = 1.000$). They do not recommend salivary evaluation as a crucial differential diagnostic tool between the two entities [68].

Therapeutic strategy: does differential diagnosis still make difference?

Indications of therapy in pulmonary sarcoidosis are: a) granulomatous inflammation proven by tissue biopsy, b) pulmonary dysfunction and c) clinical manifestations that affect patient's daily activity. Initial treatment for acute pulmonary sarcoidosis requires 20–40 mg of prednisone daily. After 1–3 months of therapy, the dose should be

tapered to 5–10 mg/daily, for at least one year before discontinuation of prednisone. Relapse occurs in 20–70% of all patients after discontinuation of corticosteroids [69]. Although the role of corticosteroids remains ambiguous in sarcoidosis, this class of drugs remains the first-line treatment. Patients with systemic manifestations and organ dysfunction, mainly pulmonary symptoms, usually require long-term treatment with corticosteroids, with a minimum at 2 years. Follow-up of the patient on a 4–6 month basis is required. Alternative agents are initiated when a patient is corticosteroid dependent or relapses at a high rate after corticosteroids discontinuation or tapering. Second-line agents usually reach their peak activity 3–9 months after initiation. They include: hydroxychloroquine, methotrexate, azathioprine, cyclosporine and thalidomide. The latter agents are more useful as dose-reductants in patients that are on a corticosteroid-based regimen, rather than substitutes [9]. Methotrexate is useful as a corticosteroid sparing agent in sarcoidosis, when given in doses similar with those administered in refractory rheumatoid arthritis. Results are comparable with those achieved with azathioprine, but with a lower risk of infection. Hydroxychloroquine at a single dose 200–400 mg daily achieves a dose reduction of corticosteroids up to 50%. Anti-TNF agents, namely inflixmab and adalimumab may serve also as corticosteroid sparing agents in patients with refractory sarcoidosis, mediating the lung inflammatory response [14]. Pulmonary hypertension related to sarcoidosis should be treated with epoprostenol, sildenafil or bosentan.

In patients with pSS, management of sicca symptoms is mainly symptomatic, while systemic manifestations require usually corticosteroids or DMARDs, as second-line treatment option. Regarding lung involvement, which is really challenging in differential diagnosis from sarcoidosis, corticosteroids are the treatment of choice, while cyclophosphamide for active alveolitis, pirfenidone and nintedanib are alternative approaches [6].

Gottenberg and colleagues estimated the efficacy of rituximab in 78 patients with pSS and systemic involvement. Another immunosuppressive agent was co-administered in 17 patients. The authors observed overall efficacy after the first circle of rituximab in 60% of all patients, with decrease in median ESSDAI score from 11 (2–31) to 7.5 (0–26) ($p < 0.0001$) and in median dosage of corticosteroid from 17.6 mg/day (3–60) to 10.8 mg/day ($p = 0.1$) [70]. In another study conducted by Ramos-Casals *et al.*, the rates of complete or partial response after rituximab administration in 196 patients with autoimmune diseases with systemic involvement (including 15 patients with pSS) were 51% and 26%, respectively. Forty four patients, who initially responded to rituximab, relapses after 28 months (29%) [71]. Patients with pSS treated with rituximab may further benefit by the addition of anti-BAFF treatment in their therapeutic regimen, as BAFF levels increase during rituximab therapy and this cytokine's role is well established in pSS pathogenesis [72].

Prognosis

Main causes of death in patients with sarcoidosis in Western countries are: pulmonary fibrosis, CNS, cardiac and hepatic involvement. Cardiac sarcoidosis is the main cause of death in Japanese subjects [73].

On the other hand, patients with pSS usually die due to progressing cardiovascular disease, infections, solid tumors or lymphoma development [6]. Regarding the latter mentioned, we should emphasize on the fact that SS is associated with a 6.6-fold increase in risk of non-Hodgkin lymphoma (NHL) development, 250-fold increase in risk of parotid gland NHL and a 1000-fold increase in risk of parotid gland MALT lymphoma [74]. Patients with sarcoidosis are not on the same risk of lymphoma manifestation during disease's course.

Conclusion

The discussed diseases are multifactorial, with multisystem involvement. Concomitance of sarcoidosis and pSS cannot be excluded in clinical practice. Increasing data substantiate the correlation between them. As they share certain clinical features, but pathogenesis subsequently therapeutic strategy and prognosis differ, high index of suspicion is required in clinical practice. We attempted, after comprehensive research of the relevant literature, to shed light on pathogenesis of the two diseases and the modalities of differential diagnosis in daily routine.

We believe that the role of immunology and genetics is emerging and seems attractive for the better understanding of the subject pathophysiology. Implementation of those data in daily practice will substantiate this challenging diagnostic dilemma.

Further investigation on the topic is absolutely necessary, in order to clarify the obscure aspects of this clinical issue.

Conflict of interest

None declared.

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