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SHORT COMMUNICATION

Coexisting primary Sjögren's syndrome and sarcoidosis: coincidence, mutually exclusive conditions or syndrome?

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Abstract Herein, we describe a 44-year-old female diagnosed with histologically proven coexistence of primary Sjögren's syndrome and sarcoidosis with pulmonary and muscular involvement. The differential diagnosis may be difficult, but this is not an exceptional case, which highlights the need to critically revise the consideration of sarcoidosis as an exclusion for primary Sjögren's syndrome, as established in current classification criteria.

Keywords Primary Sjögren's syndrome · Sarcoidosis · Lung · Muscle

Case report

A 44-year-old Caucasian female was referred to our Department due to a 2-week history of dyspnea, persistent dry cough, arthralgia, and fatigue. Four years previously, primary Sjögren syndrome (pSS) had been diagnosed on the presence of *sicca* symptoms associated with SSA and SSB auto-antibodies, and a salivary gland biopsy demonstrating lymphocytic infiltrates (Chisholm-Mason classification grade IV). She had been successfully treated with hydroxychloroquine 400 mg/day and an ophthalmic emulsion. Her family and occupational and environmental histories were not contributory.

Physical examination showed normal vital signs, and cardiovascular, pulmonary, and musculoskeletal clinical examinations were unremarkable. No peripheral adenopathies were noted.

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The initial laboratory evaluation revealed an erythrocyte sedimentation rate (ESR) of 61 mm/h (normal value <10) and a serum C-reactive protein (CRP) level of 12 mg/L (normal value <5). Rheumatoid factor was 184 UI/mL (normal range <20), and serum angiotensin-converting enzyme (SACE) was 65 U/I (normal value 8–52 U/L). Full blood count and blood chemistry were all within the normal range. Immunoglobulin G levels were 21.3 g/L (normal values 7.0–16.0 g/L); kappa light chain 18.58 g/L (6.66–14.65 g/L); and lambda light chain 7.43 g/L (2.99–6.99 g/L), with no detection of monoclonal component. Purified protein derivative test result was negative (an induration <5 mm).

Her chest radiograph (Fig. 1a) and high-resolution computed tomography (HRCT) (Fig. 2a) showed hilar and mediastinal lymphadenopathy and multiple small pulmonary nodules. Lung function tests and carbon monoxide diffusing capacity were normal. Bronchoalveolar lavage demonstrated an increase in CD4+/CD8+ T cell ratio (12.4). Mycobacterial and fungal cultures were negative. To investigate the pulmonary nodules, a mediastinoscopy-directed biopsy was performed. The histological exam revealed multiple noncaseating granulomas.

The diagnosis of sarcoidosis (stage II) was established based on the clinical, imaging, and pathological findings. The patient was diagnosed with coexisting pSS and sarcoidosis.

Because the respiratory symptoms and fatigue worsened over time, the patient was empirically treated with prednisolone 0.3 mg/kg/day for 6 weeks, with a slow tapering over 6 months, associated with calcium supplementation and alendronic acid/colecalciferol (70 mg/5,600 UI, weekly) [1].

Gradually, all the symptoms improved, and 1 year later, the patient denied any respiratory or systemic symptoms.

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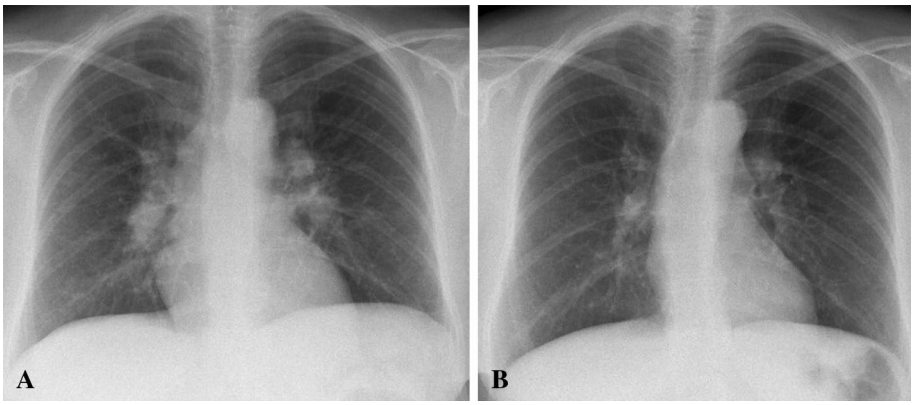

Fig. 1 **a** At admission to rheumatology: bilateral hilar and right paratracheal lymphadenopathy, with right paratracheal enlargement. **b** Six months later: resolution of lymph node enlargement

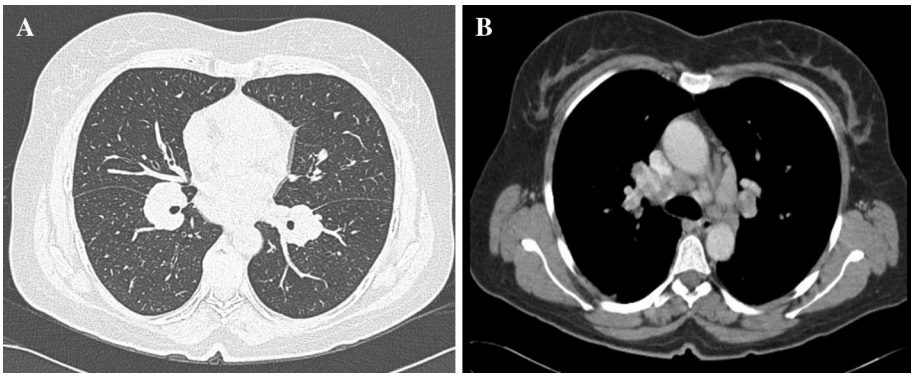

Fig. 2 **a** Contrast-enhanced axial chest HRCT image showing bilateral multiple micronodular lesions; **b** mediastinal window: hilar and subcarinal lymphadenopathy

Repeat HRCT of the chest demonstrated complete resolution of hilar and mediastinal lymphadenopathy (Fig. 1b).

Two years after the diagnosis of pulmonary sarcoidosis, the patient presented with acute inflammatory myopathy. She described an insidious proximal symmetrical weakness of the upper limbs. Laboratory studies showed serum creatine kinase of 562 U/L (normal value <145 U/L) and raised ACE to 115 U/L. Electromyographic examination was considered normal. The magnetic resonance imaging of both arms showed features suggesting myositis (Fig. 3). Pathological examination of a biopsy of the deltoid muscle revealed epithelioid granulomas, consistent with granulomatous myositis (Fig. 4).

The patient was treated with prednisolone (1 mg/kg/day). At present, 6 months after the diagnosis of granulomatous myositis, the patient is still on prednisolone (0.1 mg/kg/day), which has achieved improvement on the muscular weakness and normalization of serum creatine kinase levels and ACE activity.

Discussion

The most recent classification criteria for pSS exclude this diagnosis in the presence of sarcoidosis [2]. This exclusion criterion was retained from the previous American-European Consensus Criteria from 2002 [3]. If such classification criteria were taken as "the truth" in clinical practice, sarcoidosis and pSS would be regarded as mutually exclusive conditions and their coexistence regulated as "impossible" or at least "unlawful." However, the prevalence of sarcoidosis in large series of patients with pSS ranges from 1 to 2 % [4–6]. Although classification criteria are not to be taken as diagnostic criteria, they are bound to affect clinicians' decisions and perceptions in clinical practice and induce diagnostic error or suboptimal management. The risk of circularity in the establishment of classification criteria also is a cause of concern: "Virtual reality" becomes modeled by factors used in its definition.

Sarcoidosis and pSS share pathogenic, immunogenetic, and clinical features. Both chronic inflammatory conditions of unknown origin are characterized by an intense cellular immune infiltrate at disease sites, predominantly composed of T lymphocytes [4, 5]. The similarity of the underlying immunopathogenetic mechanisms has been argued as an explanation for the coexistence of both diseases. Other authors suggest the immunological derangement caused by one disorder may result in the other, and a third perspective suggests that this is a mere coincidence. The first hypothesis is supported by findings in lung biopsy specimens from 10 patients with SS [7]. There were significant elevations in CD4-positive lymphocytes in the bronchial mucosa, an

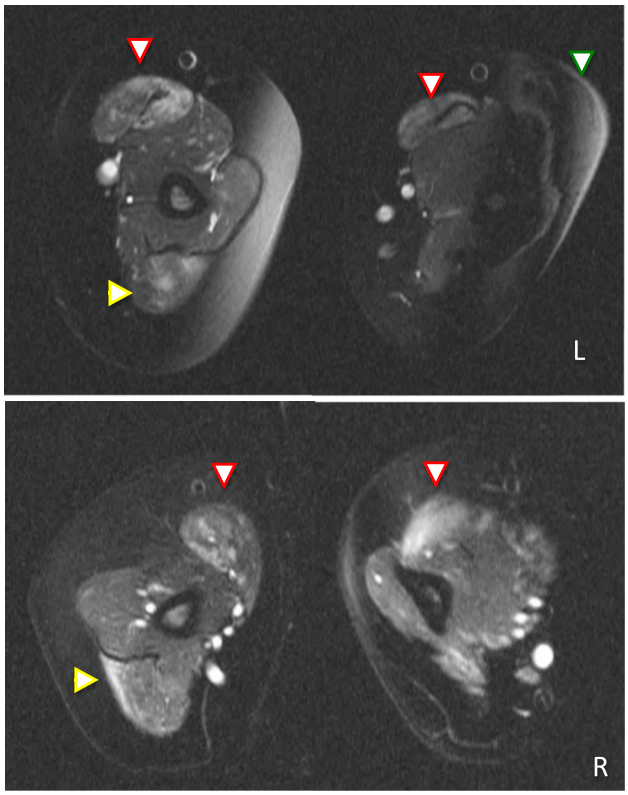

Fig. 3 MRI images (coronal STIR) showing abnormal symmetrical signal with a moderate intensity, with a major relevance in biceps (*red arrowhead*), triceps (*yellow arrowhead*), and proximal portion of the deltoids (*green arrowhead*) suggesting edema and myositis

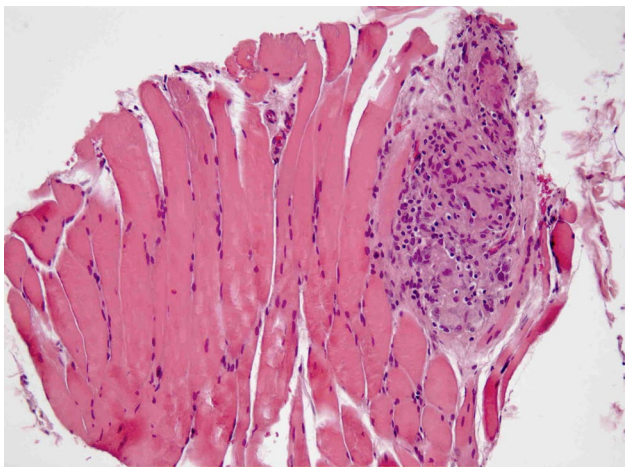

Fig. 4 Histological aspect of the muscle biopsy, showing the presence of an endomysial lymphocytic infiltrates and an epithelioid noncaseating granuloma between muscle fibers. (H and E, ×200, paraffin). Courtesy of Dr. Olinda Rebelo (Neuropathology Laboratory, Neurology Department, Centro Hospitalar e Universitário de Coimbra)

abnormality that is also described in sarcoidosis. In addition, the HLA-DR3 phenotype is associated with pSS and with a subgroup of patients with sarcoidosis [8].

The coexistence of the two conditions may be a cause of concern for the clinician faced with this challenging clinical scenario. Differentiating between pSS and sarcoidosis can raise difficulties when the symptoms are common to both conditions, as in the case of lung and exocrine gland involvement. The occurrence of features more typical of sarcoidosis, such as muscle involvement in the current case, facilitates the differential diagnosis.

To our knowledge, reports of a coexistence of both conditions with histological proof of sarcoidosis are relatively scarce [4–7]. Our case underlines how important pathology can be to establish the true coincidence of sarcoidosis with pSS.

With this case, the authors wish to highlight two main points.

- *Sarcoidosis should be considered in the differential diagnosis for lung and exocrine gland involvement in pSS,* thus requiring a complete workout including tissue biopsy where appropriate.

In a patient with pSS, the differential diagnosis of dyspnea and cough includes xerotrachea, pulmonary vascular disease, and interstitial lung diseases that may present with sicca symptoms or salivary gland involvement (e.g., sarcoidosis, IgG4-related systemic disease) [9–11]. Sarcoidosis may also present with lacrimal and salivary gland involvement, as well as diffuse parenchymal lung disease.

The histological exam distinguishes the two conditions, since noncaseating granulomas are present in sarcoidosis, while lung involvement by pSS is characterized by lymphocytic interstitial pneumonitis. The correct diagnosis has important therapeutic and prognostic implications. Lung sarcoidosis frequently resolves spontaneously, whereas lymphocytic interstitial pneumonitis frequently requires immunosuppressive treatment beyond glucocorticoids.

In a literature review published in 2004, Ramon-Casals et al. [6] identified 53 case reports of patients with suspected coexistence of Sjögren syndrome and sarcoidosis, submitted to definitive histological investigation. True coexistence of these conditions was confirmed in 28 patients, by the demonstration of histological features specific to each disease: focal sialadenitis in the exocrine glands and noncaseating granulomas in the exocrine glands or in other tissues. In the remaining 25 cases, sarcoidosis mimicked Sjögren's syndrome [6]. Overall, noncaseating granulomas were found in extraglandular tissues in 45 of the 53 patients (76 %), predominantly in the lung (24–53 %) and in hilar and/or mediastinal lymph nodes (7–16 %). Biopsies of the exocrine glands performed in all 53 patients only revealed noncaseating granulomas in 22 (42 %). Focal sialadenitis coexisted with noncaseating granulomas in only six cases. In this review, the American-European Consensus Criteria

for pSS [3] retained a high sensitivity and specificity in the presence of sarcoidosis.

As in our case, in patients first diagnosed with pSS, the presence of clinical features such as hilar and mediastinal adenopathies, uveitis, or hypercalcemia should raise the possibility of coexisting sarcoidosis. Minor salivary gland biopsies, usually included in the workout for pSS, may show noncaseating granulomas in 38–58 % of the patients with sarcoidosis [12, 13]. Therefore, the clinician needs to consider other tissues when these biopsies are negative.

In patients first diagnosed with sarcoidosis, especially when disseminated outside the lungs, the presence of antinuclear antibodies, rheumatoid factor, and/or anti-Ro/La should alert to the possible coexistence of pSS. If the case remains unclear on clinical and immunological grounds, biopsies should be performed, including the minor salivary glands.

- *When pSS coexists with sarcoidosis, sarcoid myopathy should be considered in the differential diagnosis for muscular involvement,* thus requiring a complete workout including muscle biopsy.

In the reported cases of sarcoidosis coexisting with pSS, a higher prevalence of extrapulmonary sarcoidosis seems to occur [6]. Muscular involvement is present in 50–80 % of individuals with sarcoidosis but is rarely (0.5–2.5 %) symptomatic. The finding of granulomatous myositis is highly suggestive of sarcoid myopathy. However, this is not a common finding: In a literature review of 26 patients with pSS and coexisting sarcoidosis, only one patient had sarcoid involvement of the muscles [14, 15].

In conclusion, the available evidence suggests that the association between pSS and sarcoidosis may be more than casual. The growing number of reported cases suggests that the exclusion of pSS in the presence of sarcoidosis should be reconsidered. Of note, the coexistence of the two diseases seems to be related to a higher frequency of extrapulmonary involvement of sarcoidosis.

Clinicians should be aware of and explore the possibility of coexistence of both entities. A detailed clinical history (enquiring for systemic and respiratory symptoms, uveitis, and arthritis), the evaluation of ACE, calcium levels, and immunological profile, together with the tissue biopsy, are pivotal to this end and to the optimal treatment approach. In the presence of findings suggestive of sarcoidosis, the clinician needs to be ready to extend histological examination beyond the exocrine glands.

Classification criteria should still be applied, but sarcoidosis should not be taken as an exclusion criterium for the diagnosis of pSS in clinical practice. The persistence of this exclusion in classification criteria needs to be reconsidered.

References

1. Hoes JN, Jacobs JW, Boers M et al (2007) EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 66(12):1560–1567
2. Shiboski SC, Shiboski CH, Criswell L et al (2012) American college of rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's international collaborative clinical alliance cohort. Arthritis Care Res (Hoboken) 64(4):475–487
3. Vitali C, Bombardieri S, Jonsson R et al (2002) Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61(6):554–558
4. Mansour MJ, Al-Hashimi I, Wright JM (2007) Coexistence of Sjogren's syndrome and sarcoidosis: a report of five cases. J Oral Pathol Med 36(6):337–341
5. Gal I, Kovacs J, Zeher M (2000) Case series: coexistence of Sjogren's syndrome and sarcoidosis. J Rheumatol 27(10):2507–2510
6. Ramos-Casals M, Brito-Zeron P, Garcia-Carrasco M, Font J (2004) Sarcoidosis or Sjogren syndrome? Clues to defining mimicry or coexistence in 59 cases. Medicine (Baltimore) 83(2):85–95
7. Travis WD, Galvin JR (2001) Non-neoplastic pulmonary lymphoid lesions. Thorax 56(12):964–971
8. Hansen SR, Hetta AK, Omdal R (2008) Primary Sjogren's syndrome and sarcoidosis: coexistence more than by chance? Scand J Rheumatol, pp 485–486
9. van de Loosdrecht A, Kalk W, Bootsma H, Henselmans JM, Kraan J, Kallenberg CG (2001) Simultaneous presentation of sarcoidosis and Sjogren's syndrome. Rheumatology (Oxford) 40(1):113–115
10. Schutt AC, Bullington WM, Judson MA (2010) Pharmacotherapy for pulmonary sarcoidosis: a Delphi consensus study. Respir Med 104(5):717–723
11. Takemura T, Hiraga Y, Oomichi M et al (1995) Ultrastructural features of alveolitis in sarcoidosis. Am J Respir Crit Care Med 152(1):360–366
12. Giotaki H, Constantopoulos SH, Papadimitriou CS, Moutsopoulos HM (1986) Labial minor salivary gland biopsy: a highly discriminatory diagnostic method between sarcoidosis and Sjogren's syndrome. Respiration 50(2):102–107
13. Marx RE, Hartman KS, Rethman KV (1988) A prospective study comparing incisional labial to incisional parotid biopsies in the detection and confirmation of sarcoidosis, Sjogren's disease, sialosis and lymphoma. J Rheumatol 15(4):621–629
14. Le Roux K, Streichenberger N, Vial C et al (2007) Granulomatous myositis: a clinical study of thirteen cases. Muscle Nerve 35(2):171–177
15. Fayad F, Liote F, Berenbaum F, Orcel P, Bardin T (2006) Muscle involvement in sarcoidosis: a retrospective and followup studies. J Rheumatol 33(1):98–103