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Systemic sarcoidosis and primitive Gougerot-Sjörgen syndrome: a rare, complex yet intriguing association

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Abstract

Primary Sjogren's syndrome is a chronic autoimmune disease affecting mainly the exocrine glands, typically presenting with sicca syndrome, but systemic multi-organ manifestations are possible. The diagnosis is based on the 2016 ACR-EULAR criteria. On the other hand, sarcoidosis, which is also a chronic systemic disease, is characterized by tissue infiltration with noncaseating granulomas. The granulomas may occur in any organ, but the most frequently affected sites are the lungs, lymph nodes, skin, eyes, and liver. Traditionally, sarcoidosis is considered to be an exclusion criterion for the diagnosis of primary Sjogren's syndrome, mainly because of overlapping clinical features.

We report the case of a 60-year-old female patient of North African descent, hospitalized initially for chronic dyspnea associated with other systemic manifestations such as sicca syndrome, and in whom we have objectified biological and histological features of both systemic sarcoidosis and systemic primitive Sjogren's syndrome at the same time.

The coexistence of sarcoidosis and Sjogren's syndrome is not frequent and has been rarely reported. We aim to bring more attention to the possibility of an association of these two systemic diseases despite what is typically recommended. Subsequently, it might be of interest to remove sarcoidosis from the elimination criteria in order to avoid the possibility of misdiagnosis.

Introduction

Systemic sarcoidosis is a common but not well-known disease, it is characterized by a granulomatous inflammation that can affect all organs but particularly implicates the lungs and the lymph nodes. The Caucasian population is less likely to be affected with sarcoidosis in comparison to African Americans and Scandinavians, and it usually starts in adults 25 to 50 years of age (70% of cases), with a second peak of incidence in women over 50 years old [1, 2]. Systemic sarcoidosis is currently considered to be an elimination criterion for primitive Sjogren's syndrome following the 2016 ACR-EULAR criteria [3], but it has been reported in some extremely rare cases that their association is indeed possible [4, 5].

We report the case of a North African female patient with many comorbidities who presented with clinical, biological, and histological features of both systemic sarcoidosis and systemic primitive Sjogren's syndrome simultaneously. Our objective is to shine a light on this exceptional case so that it can be explored and thought of more often.

Case report

We present the case of a 60-year-old North African female patient, menopausal for 4 years with no history of gravidity, who had vitiligo since the age of 12, she was diabetic under anti-diabetic oral treatment for 27 years and then under dual-acting human insulin for the past 3 years, history of pulmonary tuberculosis, treated and declared cured 14 years ago, arterial hypertension under triple therapy:

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Amlodipine of 10 mg, Ramipril of 10 mg, and Rilmenidine of 1 mg; Vitamin B12 deficiency anemia treated with hydroxocobalamin; and chronic articular rheumatism for 4 years on hydroxychloroquine 400mg. There is also a history of neoplasia in the family: hematological malignancy in the mother and breast cancer in the aunt.

The patient had chronic bilateral and symmetrical inflammatory arthralgia of the small and medium joints, xerophthalmia, and xerostomia with progressive loss of eyesight over 5 years. She was hospitalized for progressive onset stage 4 of sadoul dyspnea that appeared 2 months before, associated with skin lesions of the 4 limbs appearing 2 weeks after the dyspnea, fever, night sweats, asthenia, anorexia, and weight loss.

The clinical examination revealed digital clubbing, pain on palpation of the small and medium joints of the hands, wrists, and ankles without signs of arthritis, purple papules in all 4 limbs with subcutaneous nodules on the median face of the forearms, and livido on the lower limbs. Ophthalmological examination revealed reduced lacrimal flow on the Schirmer test and moderate bilateral diabetic retinopathy with bilateral nuclear cataracts (Figs. 1 and 2).

Investigation

Given the respiratory symptoms, a thoracic–abdominal–pelvic computed tomography (CT) scan revealed confluent bilateral mediastinal lymphadenopathies without necrosis, calcification, or compression of the tracheobronchial tree, a few scattered small bilateral pulmonary nodules of hematogenous distribution, and signs of localized bronchiectasis. No other abdominal, pelvic, or bone abnormalities were observed (Figs. 3 and 4).

Blood tests showed low lymphocyte levels at 780 cells/mm^3 (normal range: 1000 to 4800/mm^3, and serum protein electrophoresis revealed hyper-alpha-globulinemia (Fig. 5). Immunological tests showed elevated antinuclear antibodies at 1/640 (mixed fluorescence) and elevated anti-SSA antibodies. AntiDNA antibodies and rheumatoid factor dosage were normal. The dosage of cryoglobulinemia was negative, and complement C3/C4 dosages were normal. On the other hand, the angiotensin conversion enzyme level was elevated, and the phosphocalcic dosages were normal in both blood and urine, but there was a glomerular proteinuria at 2.75 g/24H (Table 1).

The interferon-gamma release assay (IGRA) test was negative. HIV, hepatitis B, hepatitis C, and tuberculosis were all eliminated.

A biopsy of the accessory salivary glands revealed stage 3 Chisholm–Masson lymphocytic sialadenitis with a focus score at 1 focus /4 mm^2, indicating primitive Gourgerot-Sjogren syndrome. Skin biopsy showed inflammatory infiltrates associated with lymphocytes and histiocytes with the presence of small gigantocellular epithelioid granulomas, confluent and without caseous necrosis, surrounded by slight fibrosis and a few lymphocytes in favor of sarcoidosis.

We completed the investigation with bronchoscopy and bronchial biopsy, which showed nonspecific subacute inflammation.

A renal biopsy showed signs of diabetic nephropathy with sometimes nodular mesangial fibrosis and the presence of moderate tubulointerstitial repercussions, fibrosis, and minimal interstitial inflammation, without signs of sarcoidosis or amyloidosis or Sjogren's syndrome. In view of all the intriguing biological and histological findings, it was decided to perform a mediastinoscopy with a lymph node biopsy that confirmed the histological aspect of gigantocellular epithelioid

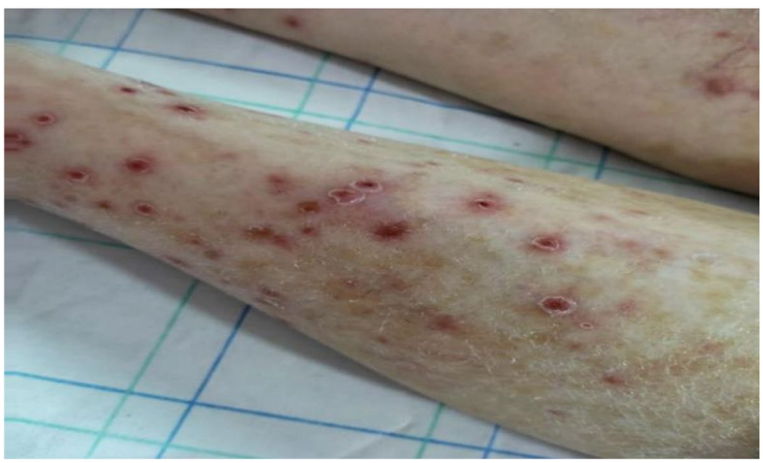

Fig. 1 Purple papules in the lower limbs with an oval or circular shape, firm to the touch, and can be scaly

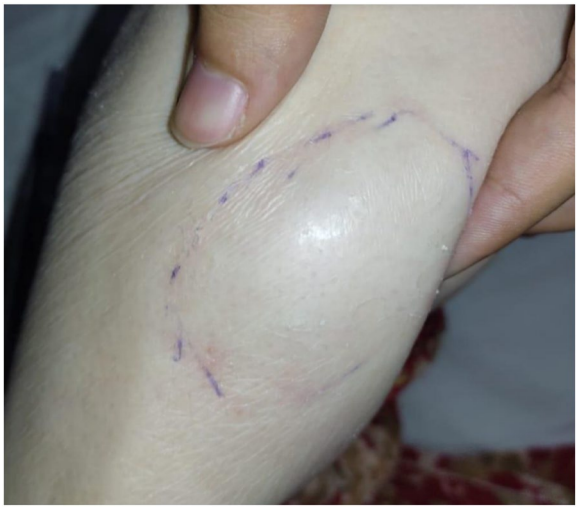

Fig. 2 Subcutaneous nodules in the forearm area, firm, non-painful, mobile, oval, skin-colored nodules (a biopsy of this lesion revealed non-caseating granulomatosis)

granulomas without caseous necrosis. The diagnosis was set as systemic sarcoidosis associated with a primary Sjogren's syndrome, and the patient was started on hydroxychloroquine 400 mg/day and prednisolone 40 mg/day with satisfying clinical response, objectified by an improvement of the dyspnea and regression of the lymph nodes volume in the standard chest radiography.

Discussion

Gougerot-Sjögren's syndrome (GSS) is an autoimmune disorder that leads to dry mucous membranes and may involve other organs. The diagnosis is based on many elements ranging from clinical to histological features and with the presence of some exclusion criteria, using the 2016 ACR/EULAR classification [6]. They require various items such as ocular and oral dryness symptoms, reduction of lacrimal or salivary flow, abnormal labial gland biopsy, and/or the presence of anti-SSA-Ro autoantibodies.

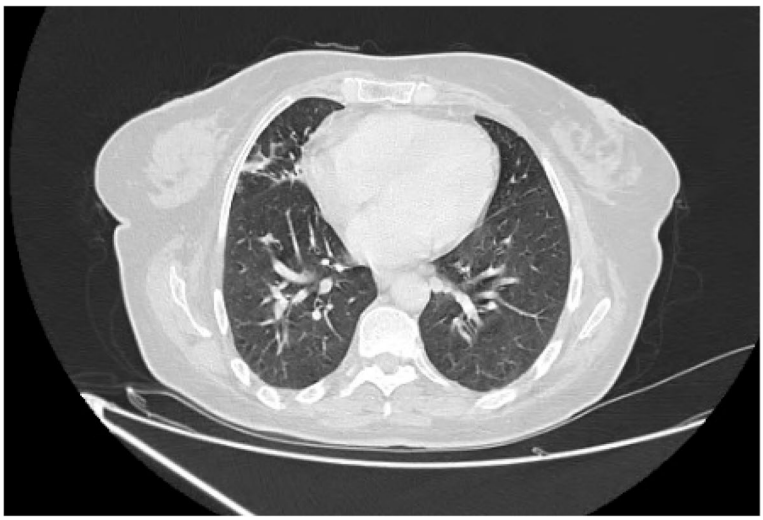

Fig. 3 Chest CT scan: parenchymal window showing various lesions including small bilateral pulmonary nodules of hematogenous distribution and signs of localized bronchiectasis in favor of ILD

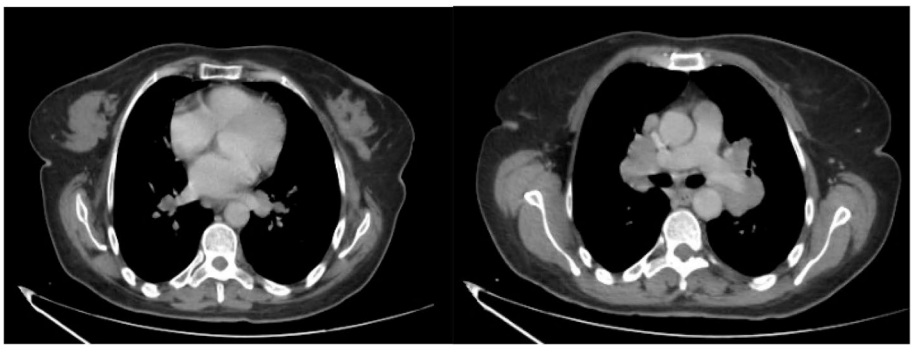

Fig. 4 Chest CT scan: mediastinal window revealing confluent bilateral mediastinal lymphadenopathies without necrosis, calcification, or compression of the tracheobronchial tree

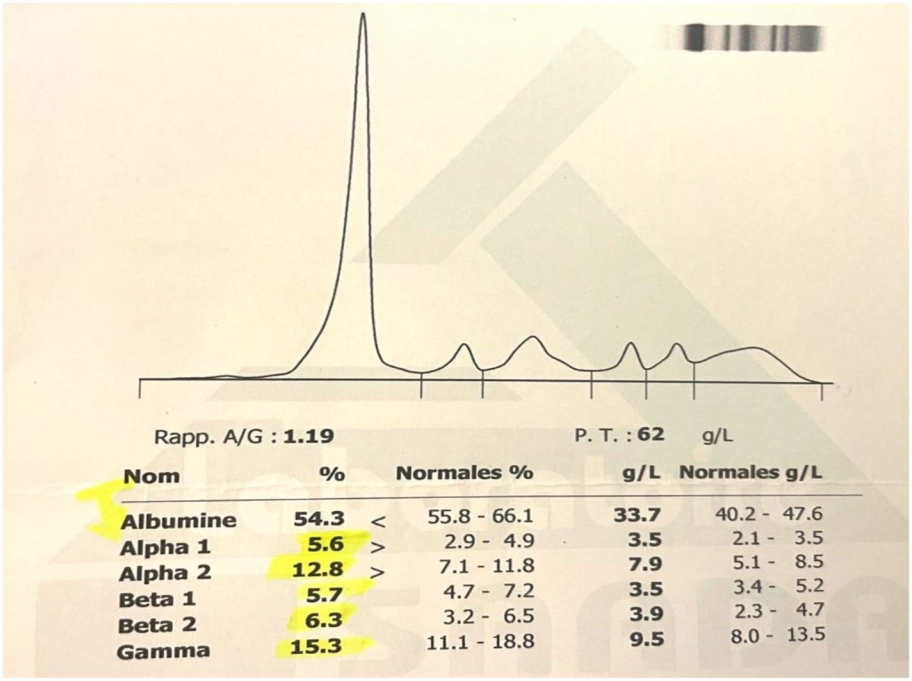

Fig. 5 Serum protein electrophoresis showing elevated alpha 1 and 2 globulins

Table 1 Summary of the blood work with lab references

Study	Interpretation	Result	Reference range
Anti-nuclear antibodies	Positive	1/640 with mixed fluorescence	< 1/80
Anti SSA antibody	Positive	60 UA	< 30 UA
Anti SSA/Ro 52kD antibody	Positive	44 UA	< 30 UA
Anti DNA antibody	Negative	8.30 U/mL	< 25 U/mL
C3 complement	Normal	1.21 g/L	0.90–1.80 g/L
C4 complement	Normal	0.42 g/L	0.10–0.45 g/L
Rheumatoid factor	Normal	6.1 UI/mL	< 14 UI/mL
Cryoglobulinemia	Normal	Negative	
Angiotensin conversion enzyme	High	85 U/I	13.3–63.9 UI/L
Blood phosphorus	Normal	34 mg/L	27–45 mg/L
Blood calcium	Normal	94 mg/L	88–102 mg/L
Urinary phosphorus	Normal	915 mg/24H	400–1300 mg/24H
Urinary calcium	Normal	335 mg/24H	100–400 mg/24H
Proteinuria	High	2.75 g/24H	< 0.14 g/24H

Histologically, a diagnosis is made if there is focal or diffuse lymphocytic infiltration. The presence of more than 50 periductal lymphocytes (histiocytes and plasma cells) in 4 mm^2 of salivary gland tissue defines a focus [7]. The Chisholm and Mason scoring system is based on the degree of lymphocyte infiltration per 4 mm^2 of salivary tissue: 0 = absent, stage 1 = mild infiltration, stage 2 = moderate infiltration or less than one foci/4 mm2, stage 3 = 1 focus/4mm^2, and stage 4 = > 1 foci/4mm^2 [8]. This grading system is the one used in the primary Sjogren's syndrome diagnostic criteria, with a sensitivity and specificity of 72.1% and 80%, respectively [3, 8].

Our patient was diagnosed with SS on the basis of this classification. She had dry eye and dry mouth symptoms, the presence of characteristic autoantibodies (anti-Ro/

SS-A), and focal lymphocytic sialadenitis defined by a focus score ≥ 1 foci/4 mm^2 in labial salivary gland biopsy samples. However, the diagnosis of sarcoidosis could not be excluded in the presence of all the clinical, radiological, biological, and histological findings.

The risk of malignant transformation into lymphoma is possible and should always be considered. SS-associated lymphomas are mostly low-grade B cell non-Hodgkin lymphomas. It should be suspected in the presence of swelling of the salivary glands, lymphadenopathies, palpable purpura, cryoglobulinemia, lymphopenia, hypocomplementemia, and a serum and/or urinary monoclonal component [9]. In our case, the cryoglobulinemia and complement test were negative; however, lymphopenia was present, along with mediastinal adenopathy, for which a biopsy was performed showing no sign of lymphoma, but instead revealed an epithelia-cellular granuloma without caseous necrosis.

Sarcoidosis is a multisystemic disease that can affect almost all organs. A diagnosis is made if the clinical features are confirmed by histological examination and the elimination of other causes of granulomatous diseases [1]. Sarcoidosis granulomas are composed of tightly clustered epithelioid histiocytes and occasionally multinucleated giant cells with few lymphocytes and are often surrounded by fibrosis. An outer layer of loosely organized lymphocytes, mostly T cells, is often observed accompanied by a few dendritic cells [1, 2].

Concerning the dermatological manifestations of sarcoidosis, subcutaneous sarcoidosis is the least common among the specific lesions of cutaneous sarcoidosis. Subcutaneous lesions are usually round or oval, firm to the touch, and can occur in a bilateral and asymmetric pattern on the extremities [10], which is similar to our patient's dermatological lesions.

All the main differential diagnoses of sarcoidosis were eliminated in our patient's case, starting from the most common one: tuberculosis was eliminated by TB PCR test and histologically as there was no necrosis in the histological examination in all the biopsied organs. Lymphoma and other inflammatory diseases were eliminated such as granulomatosis with eosinophilia and polyangiitis, hypersensitivity pneumonitis, pneumoconiosis, and drug-induced granulomatosis.

Primary Sjogren syndrome–Sarcoidosis Overlap Syndrome is extremely rare, but over the past few years, many studies and cases have reported their coexistence [5, 10, 11]. The coexistence of sarcoidosis with SS can only be confirmed when the patient shows the histopathologic features of both diseases, simultaneously or at different times [4], which is the case in our presentation. Some even recommend that sarcoidosis should not be considered as an exclusion criterion for the diagnosis of SS [4, 11].

Conclusion

The presence of both systemic sarcoidosis and primitive Sjogren's syndrome is possible but not well known. The pathophysiology has not yet been determined, and further studies are needed to facilitate the diagnosis and treatment of these difficult cases.

Abbreviations

ACR	American College of Rheumatology
Anti-Ro/SS-A	Anti–Sjögren's syndrome-related antigen A autoantibodies
C3/C4	Complements 3 and 4
CT	Computed tomography
EULAR	European League of Associations for Rheumatology
HIV	Human immunodeficiency virus
GSS	Gougerot-Sjögren's syndrome
PCR	Polymerase chain reaction
SS	Sjogren's syndrome
TB	Tuberculosis

Other relationships

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

HI and FE were involved in the diagnosis and surveillance of the patient, analysis of the data and the literature search and wrote the manuscript. HS helped with the patient management, supervision of diagnosis and treatment of the patient and also revision of the manuscript. All the authors have read and approved the final version of the manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

I confirm in my own words that there is no legal conflict, the consent was obtained and declare that the family was informed of all the written information related to the patient's medical case, and accepted it to be published.

Competing interests

The authors declare that they have no competing interests.

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