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Case reports

Reversed halo sign as initial manifestation of interstitial pneumonitis associated with Sjögren's syndrome

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ABSTRACT

Introduction: Sjögren's syndrome (SS) is a chronic autoimmune multisystemic disease. Respiratory manifestations of SS are polymorphic and vary in severity. Among the possible manifestations, organizing pneumonia (OP) is a rare entity. Reversed halo sign (RHS) is an unusual radiological finding classically related to OP but it is also reported in other forms of interstitial pneumonitis (IP).

Case presentation: We report a case of a 65-year-old woman with dyspnoea and persistent-cough of 2-month duration. She presented with RHS as an initial manifestation of IP related to SS. Chest radiography and computer tomography showed multiple well defined lesions with a central ground glass area and peripheral rim of consolidation. No pathological lymph nodes were found. After investigations, the associated diagnosis of SS was confirmed. The patient started steroids (0.5 mg/kg/day) and after 10 weeks of steroid tapering a significant clinical improvement was observed, with radiological resolution of lung lesions. We make some general considerations about differential diagnosis, conditions related to RHS and different patterns of lung involvement in SS. A report of the literature emphasizes this case as an exceptional way of presentation.

Conclusion: To the best of our knowledge this is the second reported OP case associated with SS manifesting as RHS. RHS as an expression of IP related to SS is exceptional, either in the pattern of OP or non-specific IP.

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1. Introduction

Sjögren's syndrome (SS) is a chronic autoimmune multisystemic disease featured by progressive dysfunction of exocrine glands due to lymphocytic infiltration [1]. SS is the second most common autoimmune disease after rheumatoid arthritis (RA). The prevalence of clinically significant lung disease in SS is 9–20% with a female predominance. Respiratory manifestations of SS are polymorphic and vary in severity, explaining this wide variability of prevalence [2]. SS is associated with interstitial pneumonitis (IP) which can also be the first manifestation of the disease, resulting in impaired quality of life and decreased survival. Among IP secondary to SS, organizing pneumonia (OP) is a relatively rare disorder compared to other patterns such as nonspecific

interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) or lymphocytic interstitial pneumonia (LIP).

Connective tissue diseases (CTD) are known to be one of the causes of OP. However, this association is rare and signs of OP usually occur in the context of an already diagnosed disease. It has been suggested that exhaustive investigations should be considered when OP is diagnosed, including antinuclear antibodies (ANA) and investigations for SS, even when there are no clinical signs suggesting an underlying CTD [3]. Even though the association of COP with primary SS is extremely rare it may be an early manifestation [4]. It has been reported that no remarkable differences in clinical and radiologic manifestations were present between patients with cryptogenic organizing pneumonia (COP) and those with CTD related OP (CTD-OP), except that the proportion of women and ANA positive rate were higher in CTD-OP including those with SS [5].

The unusual presence of a focal ring-shaped area of ground-glass opacity within a peripheral rim of consolidation called *reversed halo sign* (RHS) or *atoll sign* is a radiological finding

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strongly suggestive but no exclusive of OP. We report a case of SS presenting with RHS.

1.1. Case report

A 65-year-old woman with no significant medical history born at the Dominican Republic but living for more than 10 years in Spain with no recent travels, was admitted to our Department with dyspnoea and persistent-cough of 2-month duration. She denied haemoptysis, fever, chest pain or weight loss. No digestive, articular or urinary symptoms were developed. Her clinical examination on admission was unremarkable. The patient gave an informed consent in accordance with the Declaration of Helsinki.

Chest radiography and computer tomography showed multiple well defined lesions with a central ground glass area and peripheral rim of consolidation, showing the RHS pattern (Fig. 1a and b). No pathological lymph nodes were found.

No laboratory findings were noted in the complete blood count, liver and renal functions or coagulation. Elevated erythrocyte sedimentation rate (ESR: 73 mm/1st hour, normal 0–30 mm/1st) and C reactive protein level (CRP: 1.22 mg/dL, normal 0.1–0.5 mg/dL) were observed. Immunoglobulin G level was also high (1909 mg/dL, normal: 700–1600 mg/dL) and serum protein electrophoresis showed a gammaglobulin polyclonal increase. Serological tests for human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, hepatitis C virus and *Toxoplasma* were all negative. Past hepatitis B infection was found.

A bronchoscopy was performed without noteworthy results. Microbiological tests in sputum, bronchoalveolar lavage and bronchial aspirate (including Gram staining, auramine-rodamine, direct exam for fungi and *P. jiroveci* detection) were all negative. A *Paracoccidioides brasiliensis* polymerase chain reaction (PCR) in bronchial aspirate sample was also negative. While performing transbronchial biopsy whose results were ultimately inconclusive, iatrogenic pneumothorax was developed so we desist from making a new attempt to get histological samples.

Antinuclear antibody (ANA) screening (1:160) and anti-Ro/SS-A were positive, with normal levels of C3-C4 complement, cryoglobulins, anti-neutrophil cytoplasmic antibody and angiotensin converting enzyme (ACE). Based on this antibody profile, the patient was asked about dry eye or dry mouth previous history. She admit-

ted presence of long-standing xerostomia and xerophthalmia had never been studied. Schirmer's test was positive and reduced global saliva secretion was demonstrated by gammagraphy. Diagnosis of SS was established according to the revised version of classification criteria [6].

Taking into account the previous findings and patient's immunocompetent status, SS associated IP was suspected and prednisone 0.5 mg/kg/day was started. Neither antibiotics nor antifungals were added to treatment. After 10 weeks of steroid tapering a significant clinical improvement was observed, with radiological resolution of lung lesions.

2. Discussion

The lack of histological confirmation is a serious limitation to ensure the diagnosis in this case. However, we would perform some diagnostic considerations in view of clinical and radiological evolution with steroid treatment (strategy suggested by some authors when histology or focused investigations are inconclusive or cannot be obtained) [7]. In a previously reported case, typical bilateral pulmonary shadows were confirmed as OP by the analysis of bronchoalveolar lavage fluid and transbronchial lung biopsy [8].

Reversed halo sign was first reported in cryptogenic OP and initially considered a hallmark of this disease [9]. Ulterior publications widened the spectrum of conditions associated to this sign [10]. Tuberculosis and some fungal diseases are remarkable infections related to RHS, among which *Paracoccidioides* is singularly important in patients from Latin America and the Caribbean [11]. In our case, infectious diseases were reasonably ruled out due to microbiological negative results, patient's immunocompetent status and favourable response to prednisone.

Regarding non-infectious causes, sarcoidosis seems an unlikely diagnosis due to normal ACE and lack of lymphadenopathy or nodular appearance of ring area. Otherwise, presentation and clinical evolution was not compatible with vasculitis or malignancy. Finally, our case fulfilled the classification criteria for Sjögren's syndrome.

Data from the largest cohort of SS [12] showed NSIP was the most prevalent pattern of IP followed by UIP and LIP, while OP was only present in 7% of patients. RHS was not observed in this cohort so it may be considered an uncommon radiological finding.

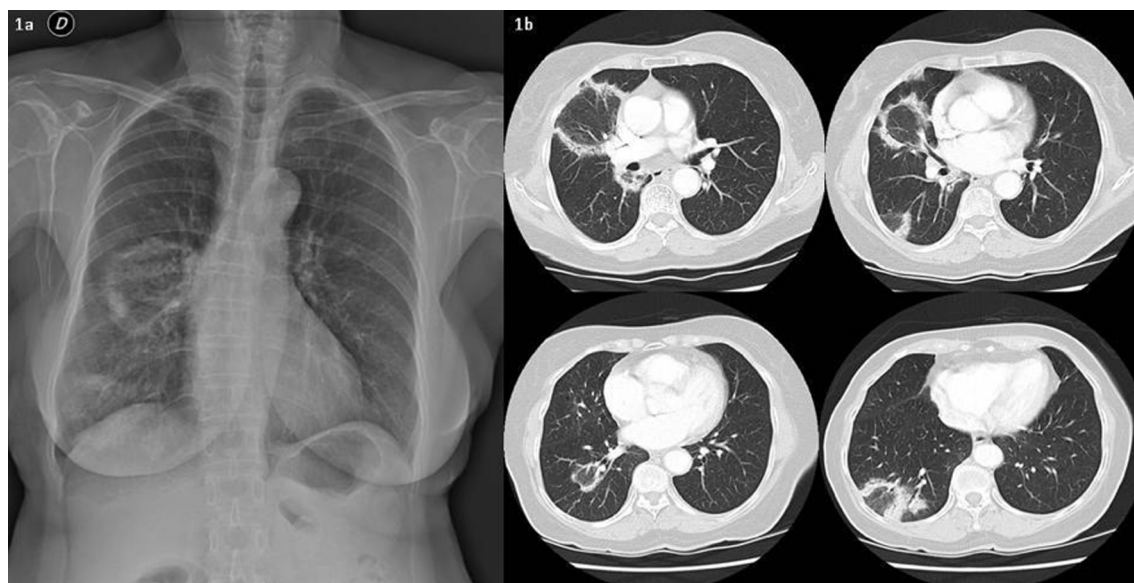


Figure 1. (a). Chest radiography and (b). CT scan shows RHS, a central ground-glass opacity surrounded by a ring-shaped area of consolidation.

However, a recent review concluded that OP still remains as the most common IP associated with RHS [7]. Therefore, in the absence of conclusive histology we consider that presence of RHS suggests more strongly the OP diagnosis given its lower association to NSIP.

The present case showed a significant clinical and radiological improvement after 10 weeks of tapering steroids. Similarly, a patient with COP associated SS improved on steroids. It was recommended that exclusion of SS should be part of a thorough evaluation of patients with COP [4]. Again, high dose steroid treatment resulted in resolution of symptoms and prolonged remission in a case with sicca complex associated with OP [13]. However, it has been suggested that in refractory cases with OP associated with SS, tocilizumab could be an alternative therapeutic option [14].

To the best of our knowledge only one OP case secondary to SS manifesting as RHS has been previously reported [15]. Also one case of RHS related to NSIP has been described in a patient with SS-systemic sclerosis overlap [16]. In summary, RHS as an expression of IP related to SS is exceptional, either in the pattern of OP or NSIP.

Conflict of interest

None.

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