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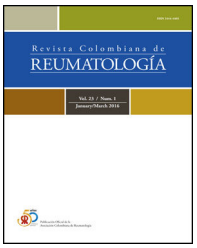

Case report

Haematological complication with pulmonary impact in a patient with Sjögren's syndrome

Laura Gallego[a,*], *Jhon Buitrago*[a], *Diana Guavita-Navarro*[a], *Jairo Cajamarca-Barón*[a], *Ana María Arredondo*[a], *José Fernando Polo Nieto*[b], *Juan Pablo Castañeda-González*[c], *Alejandro Escobar*[a]

[a] *Departamento de Reumatología, Hospital Universitario de San José, Fundación Universitaria de Ciencias de la Salud (FUCS), Bogotá, Colombia*

[b] *Departamento de Patología, Hospital Infantil Universitario de San José, Hospital Universitario de San José, Fundación Universitaria de Ciencias del a Salud (FUCS), Bogotá, Colombia*

[c] *Departamento de Medicina Interna, Hospital Universitario de San José, Fundación Universitaria de Ciencias de la Salud (FUCS), Bogotá, Colombia*

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ABSTRACT

Sjögren's Syndrome (SS) is an autoimmune pathology with glandular and/or extraglandular compromise, secondary to the infiltration of lymphoid cells. The clinical course varies depending on genetic susceptibility, comorbidities, patient's age, and environmental risk factors. Lymphoid proliferation and differentiation are key factors in the progression of SS to haematological malignancies or amyloidosis. Amyloidosis is a secondary entity to the aberrant accumulation of soluble plasma proteins, derived from chronic infectious, inflammatory, neoplastic and haematolymphoid processes. The clinical manifestations vary and depend on the constitutive protein and the age of the patient; and may have glandular or extraglandular, local, or systemic compromise. Among the affected organs, pulmonary involvement poses a diagnostic and therapeutic challenge due to its variable course and clinical manifestation. The following is a case report of a woman over 70 years old, with SS and amyloidosis with glandular and extra glandular manifestations at pulmonary level.

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* *Corresponding author.*
E-mail address: lauragallego14@hotmail.com (L. Gallego).

Complicación hematológica con impacto pulmonar en una paciente con síndrome de Sjögren

Palabras clave:
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RESUMEN

El síndrome de Sjögren (SS) es una patología autoinmune, con compromiso glandular o extraglandular, secundario a la infiltración de células linfoides. La evolución clínica es variable, depende de la susceptibilidad genética, las comorbilidades, la edad del paciente y los factores de riesgo ambientales. La proliferación y diferenciación linfoide es pieza fundamental en la progresión del SS hacia las neoplasias hematoncológicas o la amiloidosis. Esta última es una entidad secundaria al acumulo aberrante de proteínas solubles del plasma, derivadas de procesos crónicos infecciosos, inflamatorios, neoplásicos y hematolinfoides. Las manifestaciones clínicas son variables y dependen de la proteína constitutiva y la edad del paciente, de manera que puede haber un compromiso glandular o extraglandular, local o sistémico. De los órganos afectados, el compromiso pulmonar representa un desafío diagnóstico y terapéutico por su curso y manifestación clínica tan variable. A continuación, se reporta el caso de una mujer mayor de 70 años, con SS y amiloidosis con manifestaciones glandulares y extraglandulares a nivel pulmonar.

Introduction

Sjögren syndrome is an autoimmune disease characterized by glandular or extraglandular involvement secondary to the infiltration of lymphoid cells.[1] Clinically, glandular affection may be associated with unilateral or bilateral parotid enlargement and sicca symptoms (xerophthalmia, xerostomia, and xeroderma). Among the extraglandular manifestations, pulmonary involvement can be insidious or progressive, linked to disorders such as amyloidosis or lymphoproliferative disease, constituting a multidisciplinary diagnostic and therapeutic challenge.[2]

The association between local or systemic amyloidosis with SS is rare; its clinical manifestations may vary, depending on the time of evolution, comorbidities, patients' age, and the systems involved.[3] The case of a woman with SS who presented with systemic amyloidosis is presented.

Case description

A 72-year-old female presented with a 2-year history of progressive parotid enlargement, associated with occasional sensation of dry eyes, deterioration of the mMRC functional class (grade 1–2), along unintentional, unquantified subjective weight loss. The patient denied nocturnal diaphoresis or symptoms suggestive of gastrointestinal, genitourinary, or cutaneous involvement. Subsequently, due to clinical suspicion of SS, she was referred to the Rheumatology service, which confirmed the diagnosis based on the clinical characteristics and laboratory testing (Table 1).

A minor salivary gland biopsy was performed, reporting fibrosis without the possibility of calculating the Focus Score. Due to the histopathological features, the Pathology service considered staining with Congo Red dye, which demonstrated an apple-green coloration, compatible with amyloid material (Fig. 1). Given age, weight loss, and history of bilateral parotid enlargement, a risk profile for lymphoproliferative syndrome

Table 1 – Autoimmune and infectious profiles.

Immune profile	
ANA	1:160 fine granular nuclear pattern (AC-4)
ENA	Anti-La: 73.1 IU/mL Anti-Ro > 200 IU/mL Anti-RNP: Negative Anti-Sm: Negative
Complement	C3: 97.5 mg/dL (90–207) C4: 3.3 mg/dL (17–52)
Anti-dsDNA	Negative
Rheumatoid factor	107.8 U/mL (0–18)
Cryoglobulin	Negative
Infectious profile	
Bacilloscopies	3/3 negative
IGRA	Negative
HIV	Negative
HCV	Reactive
VDRL	Non-reactive
CMV	IgM: Negative IgG: Negative
HBV	HBsAg: Positive HBeAg: Negative HBV DNA: negative ALT: Normal

ANA: Antinuclear Antibodies; ENA: Extractable Nuclear Antigens; IGRA: Interferon Gamma Release Assay; VDRL: Venereal Disease Research Laboratories test; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; CMV: Cytomegalovirus; HBV: Hepatitis B Virus; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase.

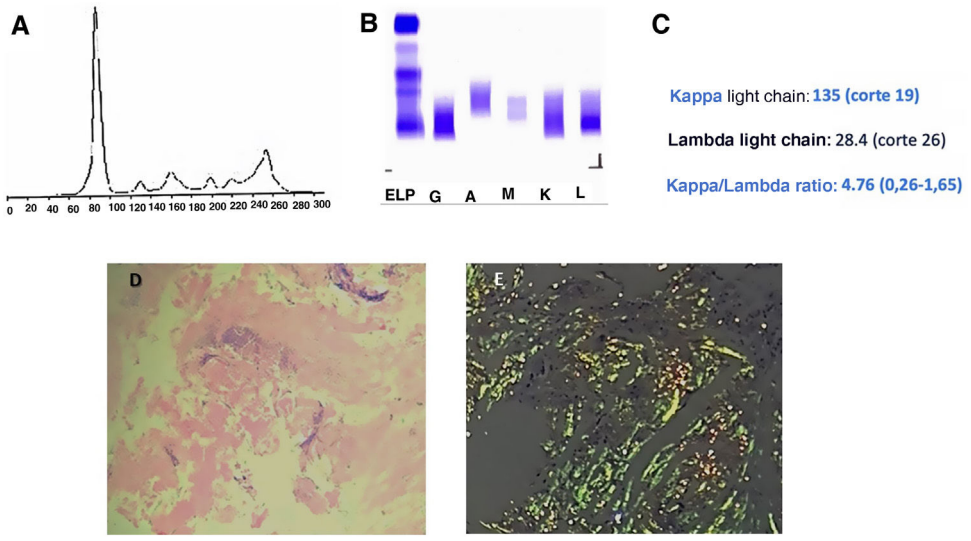

Fig. 1 – A) Protein electrophoresis: Monoclonal peak in gamma region. B) Serum immunofixation: Positive IgG lambda. C) κ/λ light chains. D) Major salivary gland positive for amyloid infiltrate. E) Minor salivary gland positive for amyloid infiltrate; positive Congo Red staining.

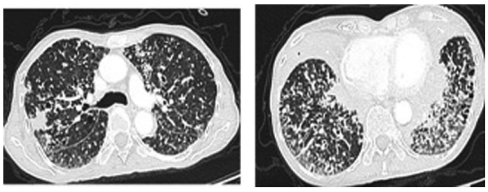

Fig. 2 – Chest CT scan: Multiple nodules with soft tissue density, with random distribution in both lung fields, diameters between 2–14 mm, and tendency to consolidation.

was performed, documenting lymphopenia, elevated rheumatoid factor, serum protein electrophoresis with a monoclonal gamma peak region, and positive serum immunofixation for IgG lambda, associated with increased κ/λ light chain ratio (Fig. 1).

In light of these findings, the patient was referred to the Hematology service, which suspected systemic amyloidosis and indicated bone marrow, abdominal fat pad, and parotid gland biopsies. In the latter, findings suggestive of amyloidosis were reported. To assess multisystem involvement, various paraclinical tests were ordered, including a transthoracic echocardiogram, NT-proBNP levels, troponins, azoates, and urinary albumin; cardiac and renal involvement were ruled out.

During the clinical course, the patient's functional class worsened. For this reason, a neck, abdominal, and chest CT scan with contrast was performed. A random micronodular pattern was documented in the lung parenchyma (Fig. 2), with variable diameters between 2–14 mm, and a tendency towards basal consolidation. The patient was assessed by the Pulmonology service, which ordered fiberoptic bronchoscopy with transbronchial biopsy for etiological characterization of the lesions. Despite the support care provided during hospitalization, the patient presented ventilatory failure, subsequent multi-organ failure, and died. Based on the progression, along with the biochemical and imaging findings, it was considered that the final diagnosis was systemic light chain amyloidosis (AL) secondary to SS.

Discussion

In SS, genetic susceptibility, comorbidities, patient age, infectious processes, and environmental factors damage epithelial cells, which enter in apoptosis, are detected by antigen-presenting cells and presented to T-lymphocytes. The latter triggers the TH1 and TH17 effector response, with the consequent production of cytokines such as IL-6, IL-22, IL-17, Interferon-gamma (IFNγ), and Tumor Necrosis Factor (TNF).[4] This inflammatory response, in the liver, induces the secretion of high-density lipoproteins (HDL), acute-phase reactants, and amyloidogenic proteins, whose conformational changes favor pathological folding, form antiparallel beta sheets, and are oligomerized, producing deficient proteolysis and aggregates in the liver, giving way to reactive, localized, or systemic amyloidosis. If accumulation in the spleen or gastrointestinal tract occurs, the risk of developing malabsorption syndrome, pseudo-obstruction, vomiting, diarrhea, and bleeding with or without gastrointestinal perforation increases.[5]

The association between SS and AA is rare; however, it can occur both at the onset and during the disease, with gastrointestinal or splenic involvement; pulmonary, renal, or cardiac affection is unlikely, as reported in the case series published by Zaher et al.[6] In these subjects, systemic manifestations secondary to amyloid infiltrate are controlled by suppressing the inflammatory process[7]; however, there may be relapses with rapid formation of the amyloid deposit, since the proteins behave like "nucleating seeds" after inflammatory relapse.[8]

On the other hand, IFNγ may have an additional effect on glands, as it induces the production of B-cell activating factor,

increases the production of antibodies, and favors lymphoid proliferation, which is benign in the case of lymphoepithelial sialadenitis and malignant in hematological neoplasia due to clonal proliferation of plasma cells and accelerated production of κ and λ light chains, which, due to deficient proteolysis, forms amyloid fibrils and leads to the development of AL.[9] Individuals with SS and AL may present with lymphoproliferative disorders, monoclonal gammopathies, multiple myeloma, or the formation of plasma cell tumors.[10] Hernández et al.[11] published one of the largest series, with 55 patients with SS and significant elevation of rheumatoid factor, anti-Ro/SSA, and anti-La/SSB antibodies. Of these subjects, 52 had AL amyloidosis localized to the lung, skin, breast, and kidney without a monoclonal component, while three presented with systemic amyloidosis with glandular, pulmonary, and renal involvement associated with parotid enlargement, monoclonal component, IgG hypergammaglobulinemia, elevated κ/λ ratio, and bone marrow biopsy that reported <10% plasma cells, similar to the case report previously described, in which participants were treated with cyclophosphamide, thalidomide, or autologous stem cell transplantation.

Regarding lung affection and SS, in order of frequency, were interstitial lung disease with non-specific interstitial pneumonia (NSIP) (45%), usual interstitial pneumonia (UIP) (41%), and progressive fibrotic phenotypic (24%–31%). It is remarkable that in none of them, it is usual to find an association with pulmonary micronodules; in cystic lung disease (lymphoid interstitial neoplasia (LIN) and amyloidosis, there are descriptions of pulmonary micronodules in 10% and 2%, respectively.[12]

Three patterns are described in pulmonary amyloidosis: tracheobronchial, which is less common and is distinguished by multifocal submucosal plaques limited to the larynx and trachea, without lung parenchyma affection; the diffuse alveolar septal, with amyloid deposits in blood vessels and interstitium, presenting with thickening of the interlobular septum, micronodules, ground-glass, or traction bronchiectasis with honeycombing; and thirdly, the nodular pattern, which is defined by one or more nodular deposits of variable size, with peripheral and bilateral subpleural location, with predominance of kappa light chain infiltrate in localized involvement, or lambda light chains in systemic affection.[11]

Differential diagnoses include neoplasms, multiple myeloma, monoclonal gammopathy of undetermined significance, and some lymphomas.[12] Histopathological studies should be performed to characterize the cell type, followed by immunohistochemistry to determine the amyloidogenic clone. Mass spectrometry, if available, is the gold standard for typifying the constituent protein.[13] With these studies, the Hematology service discriminates, according to eligibility criteria described in the literature, into high, moderate, or low-risk.[14]

Low-risk comprises those cases in which the age is less than 70 years, and the patient has preserved cardiac and renal function, with no more than two compromised organs; in this scenario, it is estimated that the patient may be a candidate for autologous hematopoietic stem cell transplantation (HDM-SCT). On the other hand, moderate risk include those cases in which the age is over 70 years, without renal or cardiac involvement, like the current case; in this situation, surgical management or the initiation of chemotherapy can be considered as a therapeutic option, with the CyBorD protocol (cyclophosphamide, bortezomib, and dexamethasone) as first-line; in second place, the MDex protocol (melphalan and dexamethasone) is described. If bortezomib or melphalan are not tolerated or have contraindications, cyclophosphamide and dexamethasone can be considered in these individuals.[14]

If there are limitations obtaining histopathological studies, there are some clinical, radiological, and serological clues described in the literature[15] that enable to infer whether the micronodule in patients with SS is associated with disorders such as lymphoma or amyloidosis. In non-Hodgkin's lymphoma (NHL), cases are typically young patients with splenomegaly, lymphadenopathy, vasculitis, purpura, Raynaud's phenomenon, ectopic germinal centers, Focus Score > 3, rheumatoid factor positivity, anti-Ro/SSA, lymphopenia, cryoglobulinemia, and multinodular lung nodule (>10 NP), with apicomedial and bilateral location, nodular size between 20.5–41.5 mm, cystic, and a tendency to consolidation. On the other hand, subjects with amyloidosis were frequently over 67 years of age, presented with peripheral neuropathy, arthralgia, centrilobular, basal, and bilateral pulmonary nodules, stable over time, with nodular size between 13–26 mm, with a trend to progression to cystic lesions or septal thickening whose pattern is very similar to that documented in the current case report.

Therefore, considering the clinical debut of the patient with chronic and bilateral parotid gland enlargement, histopathological findings of amyloidosis in the minor salivary and parotid gland, <10% bone marrow plasma cells, immunohistochemistry without aberrant neoplastic phenotype, monoclonal component in protein electrophoresis, abnormal κ/λ chain ratio immunofixation, associated with organic, pulmonary and progressive affection, led to the diagnosis of systemic amyloidosis secondary to SS.

Conclusion

This case reflects the Sjögren syndrome impact on glandular and extraglandular involvement associated with AL amyloid deposits, especially in the lung. Its identification is a diagnostic challenge that requires high clinical intuition. Histopathological studies, immunohistochemistry, and especially mass spectrometry are ideal for typifying amyloid protein, stratifying the patient, and providing timely treatment.

Ethical considerations

To prepare this case report, the patient received a clear and detailed explanation of the clinical chart, laboratory results, diagnostic images, and pathology report management for scientific dissemination purposes in the context of institutional academic activities. After verbal explanation, an informed consent signature was obtained to participate in different research projects to strengthen knowledge about the disease and positively impact future subjects with the same condition. In this manner, this project complies with current regulations on bioethical research and institutional requirements for the management of personal data. It should be noted that, within

the collection of graphic pieces for diffusion, the anonymity of the patient was always promoted to prevent immediate identification by the reading public. In this way, the patient gave her informed consent to participate in the informed consent to participate in the research projects with the objective of research projects with the aim of strengthening the knowledge her pathology and have a positive impact on future patients with the same condition.

Conflict of interest

The authors declare that they have no conflict of interest in the publication of this article.

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