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AA Amyloidosis Secondary to Primary Sjögren Syndrome: Can It Be Developed without Chronic Inflammation?

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Abstract

Background: The association of primary Sjögren syndrome (PSS) and AA amyloidosis is a rare occurrence. **Objective:** To describe the phenotype of patients with this association through our two cases and a literature review. **Materials and methods:** A report of two cases of AA amyloidosis complicating primary Sjögren syndrome with a literature review. **Results:** Eight patients of Primary Sjögren's Syndrome complicated by AA amyloidosis were studies. Six cases were reported in the literature by consulting several databases. 50% of patients had a positive immunological assessment, three cases with kidney damage, and three cases lung damage. **Conclusion:** The immunological activity in the Primary Sjogren's Syndrome requires the search not only a lymphoma but also AA amyloidosis apart from any clinical or biological chronic inflammation.

Keywords

AA Amyloidosis, Amyloid, Primary Sjögren Syndrome

1. Introduction

AA amyloidosis is a rare complication of chronic inflammatory rheumatism and exceptional in primary Sjögren syndrome (PSS). Primary Sjögren's syndrome is a rare systemic autoimmune disease, in which B cells play a central role in its pathogenesis [1]. In patients with PSS, the hypergammaglobulinemia and the presence of autoantibodies (rheumatoid factor, anti-Ro/SSA and anti-La/SSB) support the main function of B cells. Many hypotheses have linked the activation

of these cells to both the risk of developing lymphoma and the risk of AA amyloidosis [2].

The objective of this article is to describe the phenotype of patients followed for primary Sjögren's syndrome complicated by AA amyloidosis, based on two cases reported and a review of the literature regarding this association.

2. Material and Methods

A retrospective review of the medical records of all patients with primary Sjögren's syndrome that presented to the rheumatology department at the Ibn Rochd University Hospital in Casablanca from January 2010 to June 2020 was conducted. The inclusion criteria were all patients over 16 years of age who had a diagnosis of primary Sjögren's syndrome confirmed histologically (sialadenitis stage 3 or 4) and/or immunologically (anti-Ro/SSA and/or anti-La/SSB) and complicated by AA amyloidosis, as confirmed by anatomopathological examination and immunohistochemistry. Patients less than 16 years of age, patients followed for Sjögren syndrome associated with other chronic inflammatory rheumatism, and those associated with AL amyloidosis were excluded. We conducted a literature review in several databases: PubMed, sciencedirect, embase, and scopus, since their creation until August 2020 as to obtain information on this complication. The keywords used were: AA amyloidosis, Sjögren.

3. Results

Two cases of primary Sjögren's syndrome complicated by AA amyloidosis were identified in the retrospective review conducted in our department for the period between January 2010 and August 2020, which are presented below. Six cases were found in the literature. All the cases are summarized in Table 1.

Case 1

A 54-year-old woman with a history of ocular, buccal and cutaneous dryness that has been evolving over the past year, associated with mechanical arthralgia, myalgia, generalized fatigue, skin hyperpigmentation and paroxysmal parotidomegaly. All this conditions occurred in a context of deterioration of general condition. The physical examination during hospitalization revealed joint pain involving the shoulders, diffuse skin pigmentation and a bluish spot on the right jugal side. Biologically, she had a normal blood count, negative inflammatory assessment (ESR at 21 mm/h, CRP at 2.4 mg/L), positive antinuclear antibody (titer 1:640; speckled pattern), positive anti-Ro (SS-A) antibodies, normal muscle mass, serum protein electrophoresis C3 and C4 returned to normal. The ophthalmologic consultation revealed bilateral superficial punctate keratitis. Salivary gland biopsy showed a lymphoplasmacytic infiltrate of grade I according to Chisholm's classification with amyloid deposits identified by Congo Red staining (**Figure 1(a)**), which reveals apple-green birefringence consistent with amyloid deposition under polarized light (**Figure 1(b)**). The immunohistochemistry was consistent with an amyloid AA protein (**Figure 1(c)**). The renal, cardiac, neurological and pulmonary assessments were unremarkable. The patient was started

Table 1. Demographic, clinical and paraclinical characteristics of the eight patients followed for primary Sjögren syndrome complicated by AA amyloidosis.

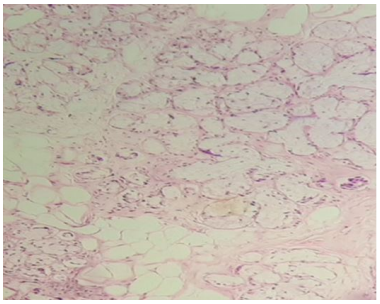
Author (References)	Age (year) gender	Time after the diagnosis of Sjögren's syndrome	Articular Symptomatology	Extra articular symptomatology	Immunology	AA Amyloidosis (Systemic/Localized)	Lymphomatous degeneration	Treatment	Outcome after treatment
Costa *et al.* [3]	79 F	22 days	**NA**	Rapidly progressive renal failure asthenia, anorexia and generalized oedema	ANA+ (1:80) Anti-SSA+ (>200 UI/ml) Anti-SSB+ (40 U/ml) RF+ (88.6 IU/ml)	Renal	No	Corticosteroids haemodialysis	Death
Motegi *et al.* [4]	58 F	8 years	NA	Ocular, buccal dryness	NA	Pulmonary	NA	NA	NA
Wong *et al.* [5]	29 F	At the time of diagnosis	NA	NA	NA	Pulmonary	No	NA	NA
Parambil *et al.* [6]	NA	NA	NA	Dyspnea	NA	Pulmonary	No	Corticosteroids Immunosuppression	NA
Ooms *et al.* [9]	53 M	18 years	NA	Acute renal failure and nephrotic syndrome	NA	Renal	No	Corticosteroids	Favorable
Katsikas *et al.* [7]	62 F	NA	Polyarthritis	Mild mixed sensory-motor axonal polyneuropathy	ANA+ (1:640) Anti-SSA+ Anti-SSB+ RF+ (3600 IU/ml)	Cutaneous	No	Corticosteroids hydroxychloroquine	Favorable
Case 1	54 F	1 year	Mechanical arthralgia	Ocular, buccal and cutaneous dryness Myalgia, generalized fatigue, skin hyperpigmentation and paroxysmal parotidomegaly	ANA+ Anti-SSA+ (200 IU/ml) Anti-SSB-	Accessory Salivary Glands	No	Rituximab	Favorable
Case 2	55 F	6 years	Inflammatory arthralgia	Renal failure	ANA+ Anti-SSA+ Anti-SSB-RF+ (252 IU/ml)	Accessory Salivary Glands Renal (inconclusive biopsy)	No	Rituximab Corticosteroids	Stationary

F: female; M: male; ANA: antinuclear antibodies; RF: rheumatoid factor; NA: data not available.

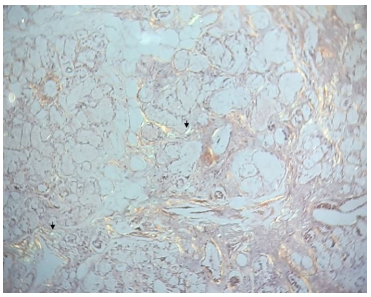
on Hydroxychloroquine but was stopped after a month of use due to palpitations, then she was switched to Rituximab (course of 2 g: 1 g administered every 15 days) with a favorable response (ESSDAI-Fatigue).

Case 2

The patient is 55 years old and has no particular pathological history. She was hospitalized for a picture of chronic inflammatory polyarthralgia progressing



(a)



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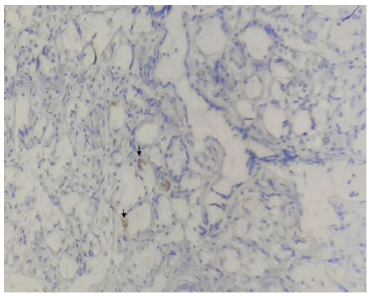


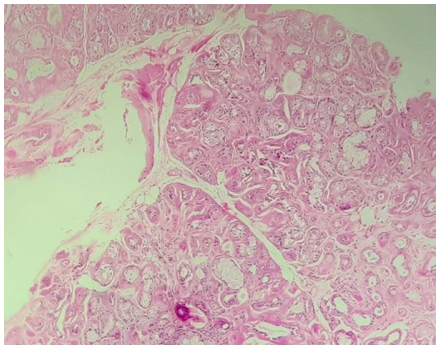
(c)

Figure 1. (a) Salivary glands biopsy showing a minimal eosinophilic deposits located along basement membranes and in the interstitium. Hematein eosin staining (HE × 100); (b) Apple-green birefringence character of amyloid deposits when viewed in polarized light. (Congo red stain × 100); (c) Immunochemistry: Amyloid deposits strongly express the AA protein (×40).

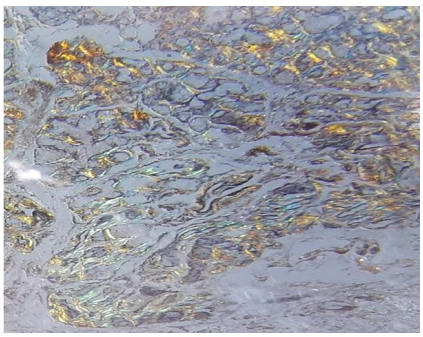
over 6 years associated with a subjective ocular and oral dryness. A bilateral superficial punctate keratitis was found in the assessment with positive anti-SSA and positive rheumatoid factors at 252 IU/ml. Histological examination of salivary gland biopsy showed a lymphoplasmacytic infiltrate of grade I of Chisholm, the Congo Red stain demonstrate amyloid deposits (**Figure 2(a)**), with typical apple-green birefringence of amyloid deposition under polarized light (**Figure 2(b)**). The immunohistochemistry was consistent with an AA amyloid protein (**Figure 2(c)**). The assessment of renal function revealed renal failure with a glomerular filtration rate of 30 mL/min. Renal biopsy was performed but the results were inconclusive. Serum and urinary ionogram, and electrophoresis of serum proteins C3 and C4 were normal. Serology for hepatitis B and C was normal. Pulmonary function tests demonstrate a diffuse lung disease with non-septal thickening on the right side with nonspecific pattern and a slight decrease in the DLCO. Cardiovascular and neurologic examination findings were normal. Treatment with Rituximab has been proposed, which is not yet received and corticosteroids with a dose of 7.5 mg per day with a stationary evolution.

4. Discussion

AA amyloidosis is a systemic acquired disease, characterized by the presence of extracellular tissue deposits of protein fibrils, and recognized by specific properties such as the green-yellow birefringence after Congo red staining, affecting all



(a)



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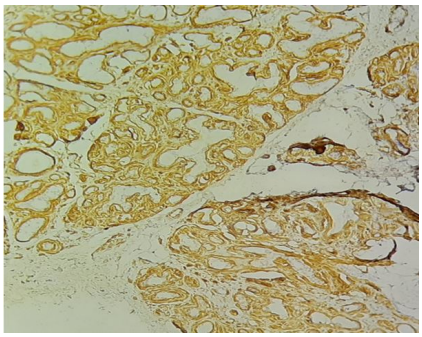

(c)

Figure 2. (a) Salivary glands biopsy showing eosinophilic deposits located along basement membranes and in the interstitium. Hematein eosin staining (HE × 40); (b) Apple-green birefringence character of amyloid deposits when viewed in polarized light. (Congo red stain × 100); (c) Immunochemistry: Amyloid deposits strongly express the AA protein (×40).

organs except the central nervous system, and complicating any chronic inflammatory disease or infection [8]. AA amyloidosis rarely complicates PSS. The risk of developing AA amyloidosis is related to persistent subclinical inflammation and, therefore, to the degree and duration of elevated AA amyloid protein levels [9]. In our first case, the patient did not have a biological inflammatory syndrome, while the second case had a mild inflammatory syndrome. When associated to PSS, amyloidosis is diagnosed 1 to 25 years after the diagnosis of the disease, although in some cases they were diagnosed simultaneously. This may be the consequence of a delayed diagnosis of PSS in patients who previously had only mild symptoms related to the disease [10], which seems to be the case among these patients. Despite being a common complication of chronic inflammatory disease, few studies have evaluated the natural history, prognostic markers and treatment of AA amyloidosis [11]. The first known successful treatments for systemic amyloidosis were described in the context of AA amyloidosis. Amyloid deposits are derived from the proteolysis of serum amyloid A that mainly synthesized by the liver, and almost invariably affect the kidneys [12]. Studies on experimental murine AA amyloidosis show that AA amyloid can indeed be spontaneously eliminated when inflammation is stopped by redundant innate immune mechanisms [13] [14]. They also demonstrate that after

apparent resolution of AA amyloid deposits, a relapse of inflammation can lead to a rapid and dramatic exacerbation of amyloid deposits, presumably due to residual AA amyloid fibrils that are resistant to compensatory mechanisms and serve as nucleator seeds, further emphasizing the importance of maintaining low serum amyloid A levels throughout the course of the disease [15]. 50% of the reported cases of PSS complicated by AA amyloidosis had a high immunological activity (Positive serum anti-SSA/anti-SSB, positive rheumatoid factor). For the other cases, the serological profile was not specified, which agrees with Hernandz-molina *et al.* regarding the systematic search for amyloidosis in patients with consistently high serological activity with suggestive lesions [2].

5. Conclusion

The immunological activity in the Primary Sjogren's Syndrome requires the search not only a lymphoma but also AA amyloidosis apart from any clinical or biological chronic inflammation.

Conflicts of Interest

The authors declare that they have no competing interest.

Ethics Approval and Consent to Participate

The case report was approved by the Ethics Committee of the University Hospital of Ibn Rochd.

Consent for Publication

Patient's written consent was obtained.

Availability of Data and Material

Data concerning the patient's record are available from the corresponding author on reasonable request.

Authors' Contributions

SZ: conception, data curation, interpretation, and writing of the manuscript.
KN, IR, MR, MK, SJ: conception, data curation, and supervision of the draft.

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