

# Primary Sjogren syndrome diagnosed simultaneously with localized amyloidosis of the lacrimal gland

## A case report

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### Abstract

**Introduction:** Amyloidosis accompanied by Sjögren's syndrome (SS) has been reported to occur primarily in the skin, lungs, tongue, and mammary gland. However, SS in association with secondary amyloidosis is rarely reported, and knowledge of its relevance is inadequate. Here we report a case of primary SS diagnosed simultaneously with localized amyloidosis of the lacrimal gland.

**Case presentation:** A 45-year-old woman complaining of a left eyelid mass was referred to the hospital and was diagnosed with localized amyloidosis after excisional biopsy. She was then referred to the rheumatology department for additional evaluation for amyloidosis. Subsequently, her diagnosis was primary SS based on the presented symptoms and results of the Schirmer test, serologic testing, and minor salivary gland biopsy. Pilocarpine (10 mg/d) and hydroxychloroquine (200 mg/d) were initiated for the treatment of SS. Six months after the initial diagnosis, the dry eyes and mouth did not worsen and no masses suggestive of localized amyloidosis were reported.

**Conclusion:** This is a rare case of amyloidosis, localized to the lacrimal gland, with SS. Therefore, despite its rarity, physicians should be aware of the potential coexistence of secondary amyloidosis, even in the localized form, in patients with SS.

**Abbreviations:** AA = amyloid A, AL = amyloid light-chain, AS = ankylosing spondylitis, RA = rheumatoid arthritis, SS = Sjogren syndrome.

**Keywords:** amyloidosis, lacrimal apparatus, Sjogren syndrome

## 1. Introduction

Amyloidosis is a disease caused by the extracellular deposition of amyloid proteins that induces morphological and functional impairment in several organs; it is classified into primary, secondary, genetic, and hemodialytic.<sup>[1]</sup> Primary amyloidosis (amyloid light-chain [AL] amyloidosis) is associated with plasma cell diseases such as multiple myeloma, while secondary

amyloidosis (amyloid A [AA] amyloidosis) occurs as a result of tissue deposition of serum amyloid A, an acute-phase reaction substance, produced by the liver in response to elevation of inflammatory cytokines in infections or chronic inflammatory diseases, such as rheumatic diseases.<sup>[1]</sup> Although secondary amyloidosis has been associated with potential etiologic factors such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS), the association between Sjogren syndrome (SS) and amyloidosis is not well recognized.<sup>[1,2]</sup> Here, we report a case of primary SS co-occurring with localized amyloidosis of the lacrimal gland as its initial presentation.

## 2. Case presentation

Institutional review board approval was obtained from the Research and Ethical Review Board of the Pusan National University Hospital (IRB No.: 1804-009-064), and the patient has consented to the publication of the case report.

A 45-year-old woman visited our ophthalmology department because of a left eyelid mass existing for 2 years. A mass was palpated in the lateral aspect of the left upper eyelid, and ptosis was obvious because of the mass (Fig. 1). There was no macroglossia, and cervical lymph nodes were not palpable, but she complained of dry mouth and eyes that persisted for several months. She had no history of chronic disease, such as hypertension and diabetes mellitus, tuberculosis, or hepatitis B and C; or family history of amyloidosis or autoimmune diseases. Contrast-enhanced orbital magnetic resonance imaging revealed

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**Figure 1.** Gross appearance of both eyes before excisional biopsy. Opened eyes (A) and closed eyes (B).

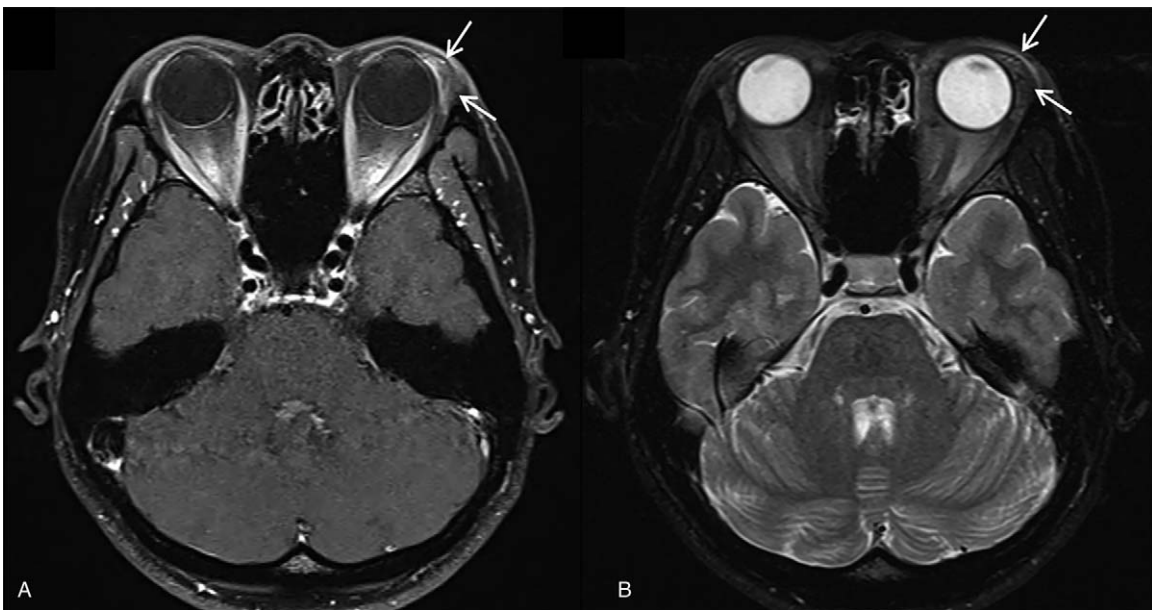
that the left upper eyelid mass was caused by a mild enlargement of the left lacrimal gland, showing moderately elevated signal on T2 image (Fig. 2). The mass was excised, and histopathologic examination revealed the deposition of amorphous eosinophilic substance in the lacrimal gland that demonstrated birefringence of apple-green color on Congo red staining, suggestive of amyloid (Fig. 3).

The patient was referred to the rheumatology department for additional evaluation for amyloidosis. Peripheral blood test results were as follows: white blood cell  $5420/\text{mm}^3$  (polymorphonuclear leukocytes 49.7%, lymphocytes 40.0%), hemoglobin 14.1 (normal range, 12.5–15) g/dL, hematocrit 42.5% (normal range, 36–46) %, platelet count 184,000 (normal range, 140,000–400,000)/ $\text{mm}^3$ , erythrocyte sedimentation rate 6

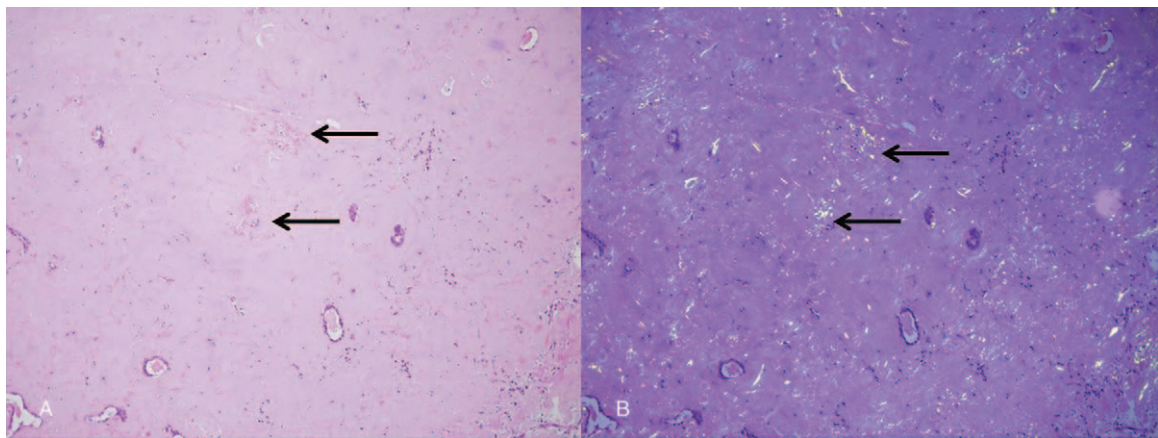
(normal range, 0–10) mm/h, and C-reactive protein 0.01 (normal range, 0–0.5) mg/dL. Serum biochemical testing showed no abnormal findings: blood urea nitrogen was 14.1 (normal range, 6–26) mg/dL, creatinine 0.8 (normal range, 0.4–1.2) mg/dL, aspartate aminotransferase 20 (normal range, 10–40) IU/L, alanine aminotransferase 16 (normal range, 6–40) IU/L, sodium 141.8 (normal range, 138–148) mmol/L, potassium 4.40 (normal range, 3.5–5.3) mmol/L, chlorine 102.9 (normal range, 100–110) mmol/L, total protein 7.3 g/dL (normal range, 6–8) g/dL, and albumin 4.5 (normal range, 3.3–5.2) g/dL. Urine testing was negative for protein, and the urine protein creatinine ratio was 115.14 (normal range, 0–150) mg/g. The patient was negative for HBsAg but positive for HBsAb, and both anti-HCVAb and HIV Ab were negative. Results of immunologic test were listed in Table 1. Antinuclear antibody, anti-Ro antibody, and anti-La antibody were positive. Serum and urine immunofixation and protein electrophoresis testing did not show a clonal immunoglobulin population. Serum  $\kappa$  and  $\lambda$  light chain levels were 17.68 (normal range, 3.3–19.4) mg/L and 23.19 (normal range, 5.7–26.3) mg/L, respectively.

Minor salivary gland biopsy to confirm SS showed chronic inflammation accompanied by intralobular aggregation of plasma cells, and the focus score was 1 (Fig. 4). The Schirmer test was positive. Bone marrow biopsy to confirm primary amyloidosis demonstrated no notable findings (Fig. 5). Upper gastrointestinal endoscopy showed no notable findings other than atrophic changes of the gastric antral mucosa, and no significant abnormalities of the esophagus and duodenum were noted. Colonoscopy showed no notable findings. To evaluate for gastrointestinal amyloidosis, random biopsies were taken from the esophagus, stomach, duodenum, terminal ileum, ascending colon, transverse colon, descending colon, and rectum; biopsies showed no significant findings. Echocardiography revealed no signs of amyloid infiltration to the heart.

Amyloidosis was confirmed based on the excisional biopsy taken from the lacrimal gland mass, and SS was diagnosed



**Figure 2.** Orbital magnetic resonance imaging showed mild enlargement and subtle enhancement of left lacrimal gland on T1 (arrows in A) with intermediate signal intensity on T2 (arrows in B).



**Figure 3.** Excisional biopsy of the left lacrimal gland mass revealed amorphous eosinophilic material deposited in the lacrimal gland tissue, consistent with amyloid (arrows in A, hematoxylin and eosin stain, X100) and birefringence of amyloid deposits under a polarizing microscope (arrows in B, Congo red stain, X100).

according to the American–European consensus criteria for SS based on the oral and ocular symptoms, Schirmer test, salivary gland biopsy, and serum anti-Ro/anti-La antibodies. We excluded primary amyloidosis due to the absence of abnormal findings on bone marrow biopsy, immunofixation, and protein electrophoresis and diagnosed the patient with simultaneous primary SS and localized secondary amyloidosis of the lacrimal gland. Pilocarpine (10 mg/d) and hydroxychloroquine (200 mg/d) were initiated for the treatment of SS. Six months after the initial diagnosis, the patient reported no worsening of dry eyes and mouth and no masses suggestive of localized amyloidosis.

**3. Discussion**

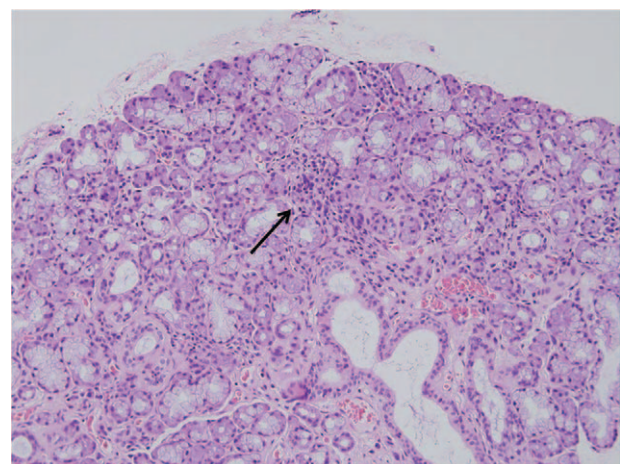
In this case report, excisional biopsy of a lacrimal gland tumor in a patient who presented to the hospital with a left eyelid mass confirmed amyloidosis, and SS was diagnosed during additional evaluation to determine the etiology of amyloidosis. Serum and urine immunofixation and protein electrophoresis to assess

amyloidosis did not show monoclonal bands, and  $\kappa$  and  $\lambda$  light-chain analysis and bone marrow biopsy also revealed no notable findings. Based on these findings, primary amyloidosis was clinically excluded. There were no signs of amyloid deposition in organs other than the lacrimal gland. Therefore, we confirmed the diagnosis of the patient, that is, simultaneous localized amyloidosis of the lacrimal gland and primary SS.

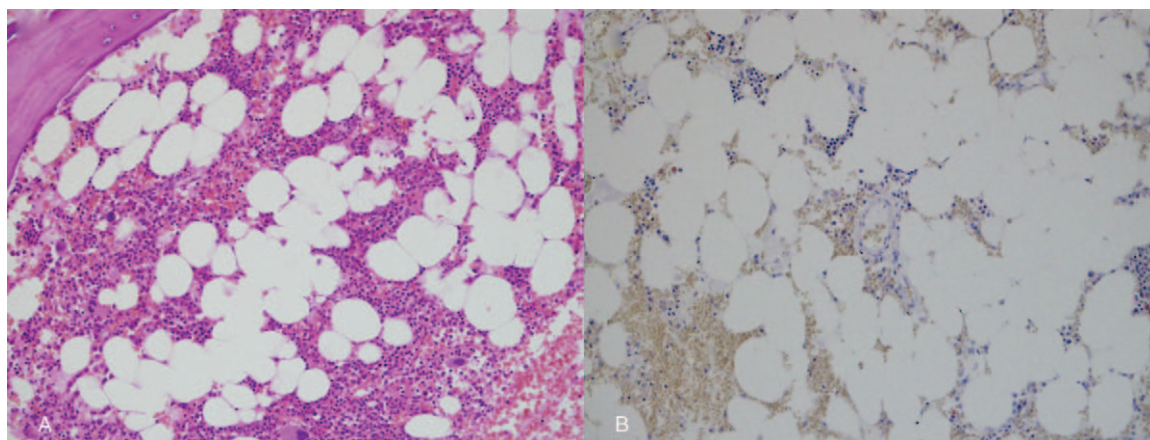
In general, amyloid A accumulation caused by chronic inflammation primarily occurs in secondary amyloidosis with chronic rheumatic diseases such as RA or AS.<sup>[3]</sup> For SS, 1 case of amyloid A deposition has been reported, but other cases of AL amyloidosis caused by polyclonal gammopathy as a result of B cell activation were also reported:<sup>[2,4]</sup> this may have been a result of polyclonal hypergammaglobulinemia of SS.<sup>[2]</sup> Although we could not accurately identify the type of amyloidosis in the current patient through immunohistochemical assessment of the lacrimal gland tumor, we diagnosed the patient with secondary amyloidosis (AA amyloidosis) based on the serum and urine immunofixation, protein electrophoresis, and bone marrow biopsy results.

In previous cases, localized amyloidosis with SS has been reported to affect the skin, lungs, tongue, mammary glands, and

<b>Table 1</b>	
<b>Results of immunologic tests.</b>	
<b>Test</b>	<b>Result</b>
Antinuclear antibody	1:640 positive
Anti-Ro antibody, U/mL	200.0 (normal range, <15)
Anti-La antibody, U/mL	36.9 (normal range, <15)
Anti-double-stranded DNA antibody	Negative
Anti-Sm antibody	Negative
Antiribonucleoprotein antibody	Negative
Rheumatoid factors	Negative
Anticyclic citrullinated peptide antibody	Negative
Antineutrophil cytoplasmic antibody	Negative
C3, mg/dL	82.7 mg/dL (normal range, 90–180)
C4, mg/dL	23.1 (normal range, 10–40)
IgG, mg/dL	1274.0 (normal range, 700–1600)
IgG subclass	
IgG1, mg/dL	10,700 (normal range, 4,050–10,110)
IgG2, mg/dL	2,200 (normal range, 1,690–7,860)
IgG3, mg/dL	102 (normal range, 110–850)
IgG4, mg/dL	420 (normal range, 30–2010)
IgA, mg/dL	305.4 (normal range, 70–400)
IgM, mg/dL	44.9 (normal range, 40–230)
$\beta$ 2 microglobulin, ug/mL	2.55 (normal range, 0.81–2.19)



**Figure 4.** Minor salivary gland biopsy revealed chronic inflammation with small intralobular aggregates of plasma cells; focus score was 1 (arrow, hematoxylin and eosin stain, X200).



**Figure 5.** Bone marrow biopsy showed no amyloid deposits (A, hematoxylin and eosin stain, X200) and no birefringence of amyloid deposits under a polarizing microscope (B, Congo red stain, X200).

parotid gland:<sup>[2,5–7]</sup> systemic amyloidosis with SS is rarely reported than localized amyloidosis.<sup>[2,8,9]</sup> Among cases of localized amyloidosis in SS, the skin and lungs were the most common organs involved.<sup>[2]</sup> While cutaneous amyloidosis is generally painless, pulmonary amyloidosis in SS can cause dyspnea, cough, pleuritic chest pain, and even hemoptysis.<sup>[2]</sup> In addition, 25% of patients with localized nodular skin amyloidosis were reported to have SS.<sup>[10]</sup> Because the onset of localized nodular skin amyloidosis may precede SS, it would be beneficial to screen for the presence of SS when a patient has this type of amyloidosis.<sup>[5]</sup> Otherwise, to our knowledge, this is the first case in which amyloidosis with SS occurred in the lacrimal gland, but not in other more common sites such as skin and lung. Thus, our case suggests that coexistent SS should be considered when amyloidosis develops in the lacrimal gland or salivary gland, the major organs involved in SS.

For treatment of amyloidosis associated with SS, steroid therapy or surgical excision can be performed for amyloidosis affecting the skin or lungs when the lesions can be excised. For amyloidosis accompanied by lymphoma or systemic amyloidosis, general antineoplastic treatment involving cyclophosphamide is commonly used, and there are reported cases in which amyloidosis naturally regressed.<sup>[2]</sup> In our case, amyloidosis was not identified on bone marrow, gastrointestinal, cardiac, and immunoglobulin assessments; thus, we only excised the localized lesion. The patient is still on follow-up without recurrence or worsening of amyloidosis symptoms. The patient has received hydroxychloroquine and pilocarpine for the treatment of SS, and no therapy for amyloidosis.

In most cases in which amyloidosis accompanies SS, amyloidosis is diagnosed 1–25 years after the onset of SS,<sup>[2]</sup> but there are some cases in which SS and amyloidosis have been diagnosed simultaneously.<sup>[6,9]</sup> Considering the pathogenesis of the disease, amyloidosis is speculated to occur only after inflammation develops over the course of SS; hence, the reason that the 2 diseases were discovered simultaneously may be that SS developed first, but the patient was unaware of SS due to a lack of symptoms or mild symptoms, and was subsequently diagnosed with both amyloidosis and SS upon clinical presentation. The present case represents an additional report of the simultaneous diagnosis of SS and localized amyloidosis of the lacrimal gland.

#### 4. Conclusion

In conclusion, an excision biopsy of a lacrimal gland tumor discovered in a patient initially presenting with a left eyelid mass revealed localized amyloidosis of the lacrimal gland, and subsequent careful workup led to the additional diagnosis of SS. This is a rare case of amyloidosis, localized to the lacrimal gland, which was accompanied by SS. Thus, despite its rarity, physicians should be aware of the potential coexistence of secondary amyloidosis, even in the localized form, in patients with SS.

#### Author contributions

**Conceptualization:** Seong-Min Kweon, Jung Hee Koh, Han-Na Lee, Eunsung Kim, Ho-Jin Shin, Seung-Geun Lee.

**Data curation:** Jung Hee Koh, Han-Na Lee, Eunsung Kim.

**Funding acquisition:** Seung-Geun Lee.

**Investigation:** Seong-Min Kweon, Seung-Geun Lee.

**Methodology:** Seong-Min Kweon, Seung-Geun Lee.

**Software:** Seung-Geun Lee.

**Supervision:** Min Wook So, Ho-Jin Shin, Hee Young Choi.

**Validation:** Min Wook So, Ho-Jin Shin, Hee Young Choi, Seung-Geun Lee.

**Visualization:** Hee Young Choi.

**Writing – original draft:** Seong-Min Kweon, Seung-Geun Lee.

**Writing – review & editing:** Seung-Geun Lee.

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