A Case with Sjogren's Syndrome and Behçet's Disease Developing Secondary Amyloidosis

Sjögren Sendromu ve Behçet Hastalığı Olan Bir Olguda Gelişen Sekonder Amiloidoz

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ABSTRACT Sjogren's syndrome (SS) is an autoimmune disease characterized by lymphocytic and plasma cell infiltration of lacrimal and salivary glands. Behçet's disease (BD) is a systemic disease characterized by recurrent orogenital apthous ulcerations and eye lesions like iridocyclitis. In this report, we describe a case that has both SS and BD associated with systemic AA type amyloidosis. The patient was a 70-year-old female who has been diagnosed with BD for twenty-two years and SS for ten years. She complained of nausea, vomiting, leg swelling and nocturia for the last few months. Duodenal biopsy was consistent with systemic AA type amyloidosis. Minor salivary gland biopsy demonstrated both systemic amyloidosis and autoimmune sialoadenitis. Both BD and SS can predispose amyloidosis deposition.

Key Words: Behcet syndrome; Sjogren's syndrome; amyloidosis

ÖZET Sjögren sendromu (SS) lakrimal bezler ve tükrük bezlerinde lenfositik ve plazma hücre infiltrasyonu ile karakterize olan otoimmün bir hastalıktır. Behçet hastalığı (BH) yineleyen orogenital aftöz ülserasyonlar ve iridosiklit gibi göz lezyonları ile karakterize olan sistemik bir hastalıktır. Bu raporda, sistemik AA tipi amiloidoza bağlı hem SS hem de BH olan bir olgu sunulmuştur. Hasta yirmi iki yıldır BH ve on yıldır SS olan 70 yaşında bir kadındır. Birkaç aydır devam eden bulantı, kusma, bacakta şişme ve noktüri yakınmaları ile başvuran olgunun duodenal biyopsisi sistemik AA tip amiloidozla uyumlu bulunmuştur. Minör tükürük bezlerinin biyopsisinde hem sistemik amiloidoz hem de otoimmün sialoadenit gösterilmiştir. Hem BH hem de SS, amiloidoz birikimine yatkınlık yaratabilir.

Anahtar Kelimeler: Behçet sendromu; Sjögren sendromu; amiloidoz

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Sjögren's syndrome (SS) is an autoimmune disease characterized by lymphocytic and plasma cell infiltration of lacrimal and salivary glands. The extraglandular tissues may also be affected.[1] BD was first described by Prof. Dr. Hulusi Behçet as the triple complex of oral and genital ulcers and uveitis with hypopyon formation.[2] Although SS may accompany several autoimmune diseases, association of SS with BD is rare.[3] Amyloidosis is a variety of protein folding diseases due to extracellular deposition of amyloidal fibrils. The peptide subunit of protein fibrils differs among subgroups of amyloidosis and is the basis for its classification, like AL

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amyloid referring to the immunoglobulin light chain-associated amyloid, and AA amyloid referring to the inflammation-associated amyloid. Amyloidosis can also be classified as either systemic or localized.[4] Systemic AA type amyloidosis may occur due to longstanding inflammation while systemic AL type amyloidosis may be due to the development of immunoglobulin light chain-producing lymphoproliferative disease.[2] Localized amyloidosis in primary SS has rarely been reported.[1,4-6] Amyloidosis in SS may sometimes be associated with lymphoproliferative diseases.[7,8] Prevalence of secondary amyloidosis in BD varies between 0.04 and 3%.[9,10]

In this report, we present a case of secondary amyloidosis with SS and BD and discuss the relationship between amyloidosis and the mentioned diseases.

CASE REPORT

A 70-year-old female patient was admitted to our hospital with nausea, vomiting, pretibial edema, and nocturia. She had been diagnosed with BD twenty-two years ago due to her recurrent oral aphteous lesions, genital ulcerations, erythema nodosum, uveitis and positive pathergy test and colchicine treatment had been initiated. Ten years ago, she was admitted to our hospital with complaints of dry mouth, dry eyes, and knee arthritis. SS-B antibody was positive while rheumatoid factor (RF) and antinuclear antibody (ANA) were negative in the serum. Schirmer's test was measured as ≤ 5 mm in 5 min for both eyes. Minor salivary gland biopsy was specific for SS. A treatment regime consisting of methotrexate 7.5 mg/week and hydroxychloroquine 200 mg/day was initiated.

A few months ago, she started to complain of nausea, vomiting, leg swelling, and nocturia. On physical examination, she had bilateral (+++) pretibial edema, arthralgia of both legs and myalgia. Laboratory findings were; hemoglobin concentration (Hb) 11.1 g/dL (12.2-18.3), blood urea nitrogen (BUN) 59 mg/dL (6-20 mg/dL), creatinine (Cr) 1.7 mg/dL (0.6-1.3 mg/dL), total protein (TP) concentration 6.1 g/dL (6.4-8.3 g/dL), albumin (Alb) 2.9 g/dL (3.4-5 g/dL), erythrocyte sedimentation rate (ESR) 78 mm/h(0-25), C-reactive protein (CRP) 7.6 mg/L (0-3 mg/L), and urinary protein excretion (UPE) 2.7 g/24 h. Microscopic urine analysis was normal. Anti SS-A and anti SS-B antibodies were positive with immune blotting test. ANA and RF were negative. Hypoalbuminemia was present on serum protein electrophoresis. [albumin 43,8 (55.1-65.2), alpha 1 globulin 5.8 (2.9-4.9), alpha 2 globulin 18.4 (7.1-11.8), beta 1 globulin 6.6 (4.7-7.6), beta 2 globulin 7.8 (3.1-6.7) and gamma globulin 17.6 (11.07-21.6)]. Venous Doppler ultrasound of lower extremity showed chronic thrombosis on right femoral vein, superficial femoral vein, and right small saphenous vein.

Duodenal biopsy and salivary gland biopsy were preferred to renal biopsy. Duodenal biopsy was consistent with systemic amyloidosis. Minor salivary gland biopsy demonstrated ≥1 foci of lymphoid aggregates per 4 mm^2 area consisting of at least 50 mononuclear inflammatory cells, predominantly of plasma cells around acini and ductuli (Figure 1). Lymphocytes were associated with acinar atrophy and fibrosis. Acellular, amorphous, eosinophilic substance was noticed to be deposited in the periductular and periacinar areas, as well as in the walls of blood vessels (Figure 2). When stained by gentian violet, the deposition was revealed to be amyloid. While the periductular, periacinar areas and the walls of blood vessels showed cytoplasmic staining for P component and amyloid A (Figure 3), the immunostains for the light chains of kappa and lambda were negative. The biopsy revealed autoimmune sialoadenitis and the diagnosis was consistent with reactive systemic (secondary) amyloidosis due to amyloid A deposits. She continued to take colchicine 1 mg/day, hydroxychloroquine 200 mg/day and metotrexate 7.5 mg/day. Angiotensin converting enzyme inhibitor (Ramipril 2.5 mg per day) was added to her treatment. Although the effects of currently available immunosuppressive drugs on the course of secondary amyloidosis are not known, azothiopurine 100 mg/day, methyl-prednisolone 8 mg/day were also prescribed. The disease course was somewhat mild and chronic renal failure did not develop during the 2 years of follow-up.

DISCUSSION

Sjogren's sydrome accompanies most autoimmune dirseases but association of Sjogren's sydrome and Behçet's disease is rare in the literature.[3,11,12] Systemic amyloidosis is a rare but major complication of BD. Amyloidosis in Behçet's disease is usually associated with renal failure and patients with amyloidosis have a five-year survival of 46%.[13] Male sex, prolonged disease duration, recurrent arthritis, multiple systemic involvement and peripheral vessel or pulmonary artery involvement were important predictors of amyloidosis.[9] Our patient also had vascular and arthritic involvement.

Amyloidosis in SS is quite rare and nodular amyloidosis is generally localized or limited to different organs.[1,4-6] Systemic amyloidosis in SS is rare.[14,15] Although the mechanism for amyloid development is not known in both diseases, chronic inflammatory process is suggested to trigger it.

Sicca sydrome can be due to amyloidal deposition in salivary gland and minor salivary gland biopsy is necessary for the definitive diagnosis of SS. Our patient had both SS shown by minor salivary gland biopsy and systemic AA type amyloidosis.

Secondary amyloidosis is usually treated by treating the underlying disease. The principal aim is to stop the production of serum amyloid A protein by controlling the underlying cause.[16]

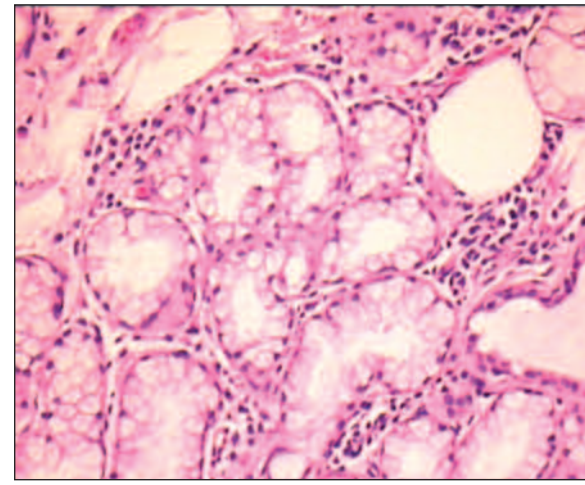

FIGURE 1: A focus of at least 50 mononuclear inflammatory cells, predominantly of plasma cells around the acini and ductuli (HE, x400).
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

Colchicine has been shown to be effective in prevention of amyloidosis in patients with familial Mediterranean fever (FMF), but has only been used sporadically for other types of secondary amyloidosis.[9] Eprodisate is a new drug for the treatment of secondary amyloidosis but it has not been approved by FDA yet.[17]

We presented a rare case with SS, BD and systemic AA type amyloidosis. In patients with Behçet's disease, systemic amyloidosis should be considered although it is rare. Coexistence of another inflammatory disease like Sjögren's syndrome may accelerate the development of amyloidosis.

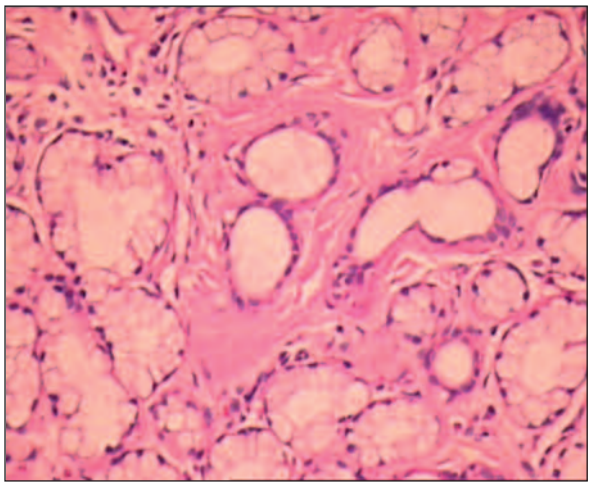

FIGURE 2: Acellular, amorphous, eosinophilic deposition in the periductular and periacinar areas (HE, x400).
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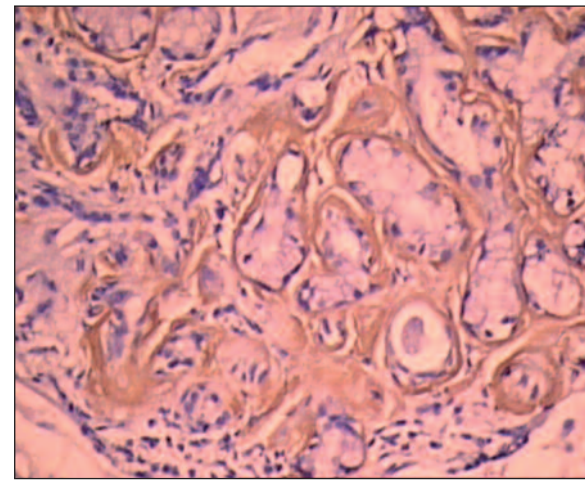

FIGURE 3: The periductular and periacinar areas showing cytoplasmic reactivity for amyloid A (Diaminobenzidine, x400).
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