Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Secondary renal amyloidosis due to primary Sjogren's syndrome: a case report

Shorsh A. Mohammed, PhD[a], Dana O. Karim, PhD[a,b], Saman S. Fakhralddin, PhD[a,c], Rawa Bapir, PhD[a,d,e], Tahani Shakr Hadi, PhD[a], Dlsoz M. Hussein, MSc[a], Dilan S. Hiwa, PhD[c], Hussein M. Hamasalih, MSc[a], Sabah J. Hasan, MSc[a], Fahmi H. Kakamad, PhD[a,c,d,*]

Introduction and importance: Amyloidosis is a rare disorder characterized by the deposition of abnormal proteins in extracellular tissues, resulting in the dysfunction of vital organs and, eventually, death. The occurrence of amyloidosis due to primary Sjogren's syndrome (pSS) is a rare finding. This study describes a rare case of pSS complicated by amyloid-associated amyloidosis.

Case presentation: A 35-year-old male was diagnosed with nephrotic syndrome and secondary amyloidosis caused by pSS. He had microscopic hematuria, a creatinine level of 6.59 mg/dl, and an elevated erythrocyte sedimentation rate of 107 mm/hrs. Furthermore, investigations of antinuclear antibodies, antimitochondrial antibodies, SSA, SSA native, and Ro-52 recombinant as well as rheumatoid factor showed positive results. After establishing the diagnosis of pSS through clinical, physical, and laboratory assessments, a renal biopsy was performed, which revealed the occurrence of secondary amyloidosis.

Clinical discussion: The risk of developing secondary amyloidosis depends on the extent of elevated serum amyloid levels as well as persistent subclinical inflammation. The definitive diagnosis of amyloidosis requires histological confirmation of amyloid fibril deposition in tissue.

Conclusion: Secondary renal amyloidosis is an unusual condition in patients with pSS. Still, it should be regarded in the differential diagnosis of patients with proteinuria and/or renal failure, and a renal biopsy should be performed.

Keywords: renal amyloidosis, renal biopsy, secondary amyloidosis, sjogren's syndrome

Introduction

Primary Sjogren's syndrome (pSS) is a chronic inflammatory autoimmune disorder characterized by lymphocytic infiltration of exocrine glands (Sicca syndrome), especially of the lacrimal and salivary glands, with polyclonal B-cell activation[1]. Various systemic manifestations may occur due to lymphocytic infiltration of different organ tissues, such as the lungs, central nervous system, liver, and kidneys. Most cases of pSS are in middle-aged women, usually in their fourth to sixth decades of life[2].

HIGHLIGHTS

- Amyloidosis is a rare disorder characterized by the deposition of abnormal proteins in extracellular tissues.
- Primary Sjogren's syndrome is an autoimmune disease of unknown etiology.
- Secondary amyloidosis as a complication of primary Sjogren syndrome is an unusual phenomenon.
- This study reports a rare case of secondary renal amyloidosis due to primary Sjogren's syndrome.

Amyloidosis is a rare disorder characterized by the deposition of abnormal proteins in extracellular tissues, resulting in the dysfunction of vital organs and, eventually, death[3]. Amyloid-associated protein (AA) amyloidosis is characterized by the deposition of serum amyloid A (SAA) fibrils in extracellular tissues, which is secondary to chronic inflammation[4]. The disease can be localized in 10–20% of patients, or it may affect several organs (80–90% of cases)[3]. The occurrence of amyloidosis in patients with pSS is a rare condition, and the correlation between the two conditions is not well understood[5]. Kidney involvement is a common manifestation in patients with systemic amyloidosis. The kidneys may be affected by lymphocytic infiltration, leading to interstitial nephritis. Rarely, cardiac and nervous system involvement may be seen[6].

The aim of this study is to describe a rare case of pSS, which was complicated by AA amyloidosis. The case has been written according to the Surgical Csse Report (SCARE) guidelines[7].

[a]Smart Health Tower, Madam Mitterrand Street, Sulaimani, Kurdistan, Iraq, [b]Department of Clinical Hematology, Hiwa Hospital, Sulaimani, Kurdistan, Iraq, [c]College of Medicine, University of Sulaimani, Madam Mitterrand Street, Sulaimani, Kurdistan, Iraq, [d]Kscien Organization, Hamdi Str, Azadi Mall, Sulaimani, Kurdistan, Iraq and [e]Department of Urology, Sulaimani Surgical Teaching Hospital, Sulaimani, Kurdistan, Iraq

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Doctor City, Building 11, Apartment 50, Sulaimani 46000, Iraq. Tel: 00964 771 726 7454. E-mail: fahmi.hussein@univsul.edu.iq (F.H. Kakamad).

Annals of Medicine & Surgery (2023) 85:3035–3038

Received 29 March 2023; Accepted 15 April 2023

Published online 8 May 2023

http://dx.doi.org/10.1097/MS9.0000000000000721

Case presentation

Clinical presentation

A 35-year-old man presented with a 2-month history of generalized body swelling, dry cough, lack of appetite, nausea, vomiting, weakness, irritability, and gradually increasing fatigue. The case was neither diabetic nor hypertensive, and he had no history of chronic drug use or any known drug allergies. He had previously undergone an appendectomy. Clinical examination showed that the case had Raynaud's phenomenon, dry mouth, and chronic dry eyes, which had been present before the onset of systemic symptoms.

Diagnostic approach

The case was referred to a hematologist for additional evaluation and to exclude multiple myeloma. A bone marrow examination was conducted and showed normal cellular marrow with no evidence of neoplastic growth in the available material.

The laboratory test results revealed that hemoglobin levels were low, measuring 9.3 g/dl, with normocytic/normochromic red blood cells. There was no evidence of hemolysis. The patient's leukocyte count was elevated at 15.4×109/L, indicating leukocytosis, with 82% of leukocytes being neutrophils. In addition, the patient's platelet count was within the upper limit of the normal range. The erythrocyte sedimentation rate was 107 mm/hr, and the C-reactive protein level was 113 mg/l. Urine sediment examination revealed proteinuria and hematuria (14–16 per HPF). The urea level was 63 mg/dl, the creatinine level was 6.59 mg/dl, and the serum albumin level was 30 mg/dl. Investigations also revealed positive antinuclear antibodies, antimitochondrial antibodies AMA-M2 (M2), SSA native (60 kDa) (SSA) and Ro-52 recombinant (RO-52), and rheumatoid factor (RF) was (23 IU/ml). While each of the anti-glomerular basement membrane (Anti-GBM Ab), Anti-dsDNA antibody, Anti-c-ANCA antibody, Anti-p-ANCA antibody, anti-La/SSB antibodies, and anti-neutrophil cytoplasmic Ab-anti MPO were negative. Complement tests of C3 (1.72 g/l) and C4 (0.36 g/l) were normal. The immunoglobulin (IgA), (IgM), and (IgG) were normal. As immunoelectrophoresis results showed IgG kappa monoclonal gammopathy in serum, there were normal kappa (1.97 g/l) and lambda plasma light free chains (1.32 g/l)with a normal kappa/lambda ratio of 1.49. The serological test results for antihepatitis B and C were negative. The culture test did not show any infectious agents.

Abdominal ultrasonography revealed small-sized kidneys and enhanced parenchymal echogenicity. Additionally, an abdominal and pelvic ultrasonography revealed mild ascites, mild pericardial effusion, mild bilateral pleural effusion, and foci of pleural calcification. A whole-body low-dose computed tomography scan revealed no bone lesions. Echocardiography showed no significant findings. The diagnosis of pSS was made based on the clinical history, physical examination, and laboratory tests. The patient preferred that a labial gland biopsy be performed, but he could not tolerate it. The renal biopsy was performed, and a diagnosis of secondary renal AA amyloidosis was made.

Therapeutic intervention and follow-up

After 2 months of hemodialysis (every 3 days) without significant improvement, the patient began receiving monthly intravenous infusions of cyclophosphamide (500 mg) and rituximab (500 mg) on day zero and day 14, with close follow-up.

Discussion

Amyloidosis is a primary or secondary disorder characterized by amyloid deposition in tissues. Amyloid is a heterogeneous, hyalinizing, and eosinophilic substance that represents a group of various proteins with fibrillar structure[1]. Amyloidosis is classified into a variety of categories based on the type of protein, such as light-chain, amyloid-associated protein, or familial[8]. Approximately 45% of all generalized amyloidosis are AA amyloidosis[9]. The onset of AA amyloidosis is frequently abrupt, and some of the causes include rheumatic diseases (rheumatoid and juvenile arthritis and ankylosing spondylitis), idiopathic diseases (Rosai-Dorfman disease, Crohn's disease, ulcerative colitis, and sarcoidosis), infectious diseases (tuberculosis and leprosy), inherited diseases (familial Mediterranean fever, tumor necrosis factor receptor-associated periodic fever syndrome), and malignant tumors (mesothelioma and Hodgkin's lymphoma)[9,10]. The magnitude and persistence of elevated AA amyloid levels, as well as continuous subclinical inflammation, are related to the possibility of developing AA amyloidosis[4]. In a study by Zaher *et al.*[11], one of the cases did not demonstrate a biological inflammatory syndrome, while a mild inflammatory syndrome was present in another one.

In patients with pSS, amyloidosis is rare[5], probably related to the low-level production of acute phase reactants during the course of the disease[1]. pSS is a rare type of systemic autoimmune disease, and its pathogenesis is generally mediated by B lymphocytes[11]. The T cells were formerly considered to be the key roles in the autoimmune process, whereas B cells were restricted to autoantibody production[12]. Activation of B cells results in hypergammaglobulinemia as well as the production of various autoantibodies. During pSS, elevated IgA levels are common, and these immunoglobulins can reveal rheumatoid factor activity. Therefore, circulating IgA-containing immune complexes are frequently found in patients with pSS and are significantly associated with abnormal salivary-gland biopsy[13]. As a result, B-cell depletion therapies are being developed for the management of pSS[14].

The presence of autoantibodies is one of the diagnostic criteria for the majority of autoimmune diseases. However, the detection of autoantibodies may overlap with the spectrum of other autoimmune diseases, and there are no specific autoantibodies that are unique to pSS[14]. Anti-Ro/SSA and anti-La/SSB are diagnostic markers for the disease, which are included in the classification criteria of the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR)[15]. However, up to 30–40% and 10–15% of patients with systemic lupus erythematosus, respectively, have these autoantibodies[16]. The most sensitive method for detecting autoimmune diseases is the detection of antinuclear antibodies, but they might also be related to other diseases, including malignancy and infectious diseases, or they may be found in the healthy population. Although many autoantigens are shared between SS and systemic lupus erythematosus, the inflammatory tropism at the glands in pSS may account for the differential pathogenic mechanism. Nevertheless, the molecular explanation for this phenomenon is still unknown. Although autoantibodies are important diagnostic tools for

autoimmune diseases, their diagnostic relevance may vary depending on the specific clinical context in which they are evaluated[14]. The current case's laboratory investigations revealed positive results for ANA, anti-Ro/SSA antibodies, anti-Ro-52 recombinant antibodies, RF, and AMA-M2 antibodies.

Amyloidosis symptoms depend on the distribution pattern and deposit quantity[9]. Amyloidosis may be suspected in patients exhibiting nonspecific symptoms such as weight loss, weakness, dizziness, or syncope. The involvement of specific organs may result in nephrotic syndrome, renal failure, congestive heart failure, conduction disturbances, or arrhythmias[8]. The most prevalent form of renal involvement is tubulointerstitial nephritis, which affects 60–75% of cases. Glomerular nephritis, a less common type of renal injury caused by immune complex deposition, occurs in 5–30% of cases and its underlying pathogenesis remains uncertain. On the other hand, polyclonal activation of B cells can cause cryoglobulinaemia and the development of membranoproliferative glomerulonephritis and systemic vasculitis[5,10]. AA amyloidosis is recognized by specific characteristics, such as green-yellow birefringence after Congo red staining[11]. Proteinuria is frequently the first clinical manifestation of generalized AA amyloidosis, and the severity of albuminuria is correlated with the prognosis of the disease[9].

The first case in the Ooms *et al.* study was secondary renal AA amyloidosis in a patient with long-standing pSS who presented with acute renal failure and nephrotic syndrome. A renal biopsy demonstrated concurrent chronic interstitial nephritis and renal AA amyloidosis. Corticosteroid therapy led to the patient's partial remission of nephrotic syndrome and improvement in renal function[5,10]. The authors hypothesized that renal AA amyloidosis was caused by chronic interstitial nephritis itself, which has been associated with persistent disease activity. They believe that SS should be considered a predisposing condition for the development of renal AA amyloidosis. Thus, in SS patients who develop renal insufficiency or nephrotic proteinuria, a renal biopsy is required[5]. Although a positive diagnosis can be obtained in 100% of symptomatic cases with a kidney biopsy, its invasiveness and risk of bleeding have led to the recommendation of alternative, less invasive biopsy sites[17]. In cases where amyloidosis co-occurs with SS, the diagnosis of amyloidosis may be delayed by 1–25 years after the onset of SS-related inflammation. However, in some cases, both conditions may be diagnosed concurrently. This delay in amyloidosis diagnosis may be due to prior mild disease-related symptoms in some patients with SS[11].

Like C-reactive protein, SAA protein is largely synthesized by hepatocytes, although other cell types such as macrophages, smooth muscle cells, and endothelial cells can also generate it. The production of SAA is regulated by proinflammatory cytokines, particularly tumor necrosis factor (TNF) alpha, interleukin-1 (IL-1) beta, and IL-6. SAA expression is markedly reduced with hepatocyte-specific mutations in some transcriptional regulators. In healthy individuals, the median plasma concentration of SAA is 3 mg/l[4]. Results of abnormal echocardiograms, serum protein electrophoresis, or urine protein electrophoresis examinations may support a diagnosis of amyloidosis. However, a definite diagnosis requires histological confirmation of the amyloid fibril deposition[8]. The characteristic appearance of amyloid protein in tissue stained with Congo red is salmon pink, and under polarized light, it displays an apple-green birefringence[1]. In the current case, a renal biopsy was performed, and a diagnosis of AA amyloidosis was made. To detect and prevent end-stage renal disease, serum and urine analyses are required. Although AA amyloidosis is a recognized outcome of chronic inflammatory diseases, few studies have explored its natural history, prognostic markers, or effective treatments[10,17,18]. Renal failure and a low serum albumin level at diagnosis have been identified as the two main indicators of a poor prognosis. Sixty four patients with AA amyloidosis were studied by Gertz *et al.*, and they found that renal failure (serum creatinine value of >2 mg/dl) on presentation is strongly associated with a decreased survival time[17,19]. Other studies have confirmed that serum creatinine concentration is a significant predictor of survival rate in patients with AA amyloidosis[18,20]. The primary treatment goal for AA amyloidosis is to control the underlying inflammatory disease, reduce SAA levels, and limit further deposition of amyloid in the kidneys. Patients may also receive supportive care, including renal replacement therapy if necessary[21]. In the Yilmaz *et al.* series, it was not feasible to confirm the hypothesis that controlling the underlying inflammatory disease and reducing SAA levels could limit further amyloid deposition in the kidneys. This was due to several factors, including the advanced renal failure in most patients and the use of various treatment regimens with no available drug information to assess their impact on amyloidosis[9]. The current case was managed with an intravenous infusion of rituximab (500 mg) and cyclophosphamide (500 mg) with close follow-up.

In conclusion, AA amyloidosis is uncommon in patients with pSS and requires a biopsy for diagnosis. pSS is a type of systemic autoimmune disease where B lymphocytes play a significant role in the pathogenesis. The treatment for secondary amyloidosis is focused on reducing the inflammation associated with the underlying disease.

Ethics approval

Approval is not necessary for case report (till 3 cases in single report) in our locality. Written informed consent was obtained from the patient has given consent for possible publication of this case report.

Consent to participate

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Patient consent for publication

The patient gave consent for publication.

Sources of funding

None.

Author contribution

S.A.M.: was a major contributor to the conception of the study, as well as in the literature search for related studies, final approval of the manuscript; D.O.K.: the physician who managed the case, final approval of the manuscript; D.M.H. and F.H.K.: writing the

manuscript, literature review, final approval of the manuscript; S.S.F., R.B., and T.S.H.: were involved in the literature review, the design of the study, revision of the manuscript; D.S.H.: critical revision of the manuscript and final approval; H.M.H. and S.J. H.: confirm the authenticity of all the raw data, revision of the manuscript.

Conflicts of interest disclosure

The authors declare that they have no competing interests.

Research registration unique identifying number (UIN)

None.

Guarantor

FHK.

Data availability statement

Not Applicable.

Provenance and peer review

Not commissioned, externally peer reviewed.

Acknowledgments

None to be declared.

References

[1] Rodrigues K, Neves FS, Stoeterau KBL, *et al*. Pulmonary amyloidosis in Sjögren's syndrome: a rare diagnosis for nodular lung lesions. Int J Rheumatic Dis 2009;12:358–60.
[2] Qin B, Wang J, Yang Z, *et al*. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis 2015;74:1983–9.
[3] Kinoshita Y, Ikeda T, Miyamura T, *et al*. Nodular pulmonary amyloidosis associated with Sjögren's syndrome. Intern Med 2022;61:877–81.
[4] Papa R, Lachmann HJ. Secondary, AA, amyloidosis. Rheumatic Dis Clin 2018;44:585–603.
[5] Ooms V, Decupere M, Lerut E, *et al*. Secondary renal amyloidosis due to long-standing tubulointerstitial nephritis in a patient with Sjögren syndrome. Am J Kidney Dis 2005;46:e75–80.
[6] Ayar Y, Ersoy A, Oksuz MF, *et al*. Clinical outcomes and survival in AA amyloidosis patients. Revista Brasileira de Reumatologia 2017;57: 535–44.
[7] Agha RA, Franchi T, Sohrabi C, *et al*. for the SCARE Grou. The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. Int J Surg 2020;84:226–30.
[8] Bowen K, Shah N, Lewin M. AL-amyloidosis presenting with negative Congo red staining in the setting of high clinical suspicion: a case report. Case Rep Nephrol 2012;2012:593460.
[9] Röcken C, Shakespeare A. Pathology, diagnosis and pathogenesis of AA amyloidosis. Virchows Arch 2002;440:111–22.
[10] Costa M, Greenfield H, Pereira R, *et al*. A rare case of renal AA amyloidosis secondary to Sjogren's syndrome. Eur J Case Rep Int Med 2019;6:001226.
[11] Zaher S, Nassar K, Razzouki I, *et al*. AA amyloidosis secondary to primary sjögren syndrome: can it be developed without chronic inflammation? Open J Rheumatol Autoimm Dis 2021;11:29–35.
[12] Cornec D, Devauchelle-Pensec V, Tobón GJ, *et al*. B cells in Sjögren's syndrome: from pathophysiology to diagnosis and treatment. J Autoimmun 2012;39:161–7.
[13] Basset C, Pers JO, Youinou P, *et al*. Practical usefulness of IgA-containing immune complex determination in the serum of patients with primary Sjögren's syndrome. Clin Exp Rheumatol 1997;15: 157–61.
[14] Vílchez-Oya F, Balastegui Martin H, García-Martínez E, *et al*. Not all autoantibodies are clinically relevant. Classic and novel autoantibodies in Sjögren's syndrome: a critical review. Front Immunol 2022;13:1003054.
[15] Vitali C. European Study Group on Classification Criteria for Sjogren's Syndrome. . Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
[16] Scofield RH, Farris AD, Horsfall AC, *et al*. Fine specificity of the autoimmune response to the Ro/SSA and La/SSB ribonucleoproteins. Arthritis Rheum 1999;42:199–209.
[17] Yilmaz M, Unsal A, Sokmen M, *et al*. Renal involvement in AA amyloidosis: clinical outcomes and survival. Kidney Blood Press Res 2013;37: 33–42.
[18] Tanaka F, Migita K, Honda S, *et al*. Clinical outcome and survival of secondary (AA) amyloidosis. Clin Exp Rheumatol 2003;21:343–6.
[19] Gertz MA, Kyle RA. Secondary Systemic Amyloidosis (AA): Response and Survival in 64 Patients. in Amyloid and Amyloidosis 1990: VIth International Symposium on Amyloidosis August 5–8, 1990, Oslo, Norway. Springer. 1991.
[20] Sasatomi Y, Kiyoshi Y, Uesugi N, *et al*. Prognosis of renal amyloidosis: a clinicopathological study using cluster analysis. Nephron 2001;87:42–9.
[21] Lachmann HJ, Goodman HJB, Gilbertson JA, *et al*. Natural history and outcome in systemic AA amyloidosis. New England J Med 2007;356: 2361–71.