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Granulomatous interstitial nephritis associated with Primary Sjögren's syndrome

Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by lymphocytic and plasmacytic infiltration of the exocrine glands. Renal involvement in SS is not uncommon; however, clinically significant renal involvement is rare [1]. There are mainly two types of renal involvement in pSS: tubulointerstitial nephritis (TIN) and glomerulonephritis. TIN is the most common renal manifestation and generally has a relatively benign course [2].

Granulomatous interstitial nephritis (GIN) is a rare histopathological entity characterized by the presence of granulomas against a background of interstitial inflammation. It has been associated with drugs, sarcoidosis, infections, and certain rheumatic diseases such as granulomatosis with polyangiitis, and has also been reported to be idiopathic [3]. GIN is not a typical and commonly seen form of TIN in pSS. Herein, we report on a patient who was concurrently diagnosed with pSS and GIN and was treated successfully with rituximab (RTX).

Case presentation

A 42-year-old female patient was referred to our rheumatology clinic with a 3-month history of Raynaud phenomenon, fatigue, and progressive decline in renal functions. She had also been suffering from dry mouth and dry eyes for the past 2 years. Her past medical history included a 2-year history of mild hypertension; however, she was not taking regular medication and claimed that she seldom used amlodipine when her blood pressure was above 150/100 mm Hg. There was no history of nonsteroidal anti-inflammatory or any other drug use. On physical examination she had dry oral mucosa, Raynaud phenomenon in both hands and, +1 pretibial edema but otherwise the examination was unremarkable. Complete blood count showed: white blood cell count, 4.4 × 10.e^3/ul; hematocrit, 34.2%; hemoglobin, 10.3 g/dl, and platelet, 314× e^3/ul. Acute-phase reactants were increased; erythrocyte sedimentation rate was 94 mm/h; C reactive protein level was 14 mg/l (normal range: 0–6). Liver function test results were within normal range. Renal function tests showed a creatinine level of 2.03 mg/dl (0.3–1.2), which had been within normal limits 1 month earlier, blood urea nitrogen (BUN) level of 25 g/dl (7–25), normal levels of electrolytes, and an albumin level of 3.4 g/dl (3.4–5.0). Urinalysis revealed microscopic hematuria and proteinuria. There were no casts in the urinary microscopy examination and renal ultrasound was normal. Her 24-h urine protein excretion was 600 mg/day. Serologic test results for hepatitis B and C virus were negative. An ophthalmologic examination was normal except for bilaterally positive Schirmer test results (<5 mm/5 min). An antibody profile showed the presence of RF 30 (0–25), antinuclear antibody (1/320 speckled pattern), and anti-Ro/SSA and anti-La/SSB (with an immunoblotting method). She was negative for anti-double-stranded DNA, anti-nuclear cytoplasmic antibodies (ANCAs), antibodies to cyclic citrullinated peptide (anti-CCP), and cryoglobulins. Serum complement levels were normal. She had polyclonal hypergammaglobulinemia (IgG 3010 [range 751–1560] mg/dl) with mildly elevated IgA levels of 496 mg/dl (range: 82–453). Minor salivary gland biopsy demonstrated intensive lymphocytic infiltration graded as focus of 3.

The patient subsequently underwent a percutaneous renal biopsy, which revealed marked diffuse lymphoplasmocytic inflammatory cell infiltration in the renal parenchyma associated with well-formed, noncaseating, granuloma formations in the multifocal areas (**Fig. 1**). Few eosinophils were recognized within the inflammatory cell infiltrate. Giant cells were seen within in the granulomas. There was prominent acute tubular injury with severe tubulitis and destruction of the tubular basement membranes in focal areas. There was mild–moderate interstitial fibrosis. Special stains for acid-fast bacilli or fungi were negative. Moreover, 16 of 38 glomeruli were globally sclerotic. Immunoflourescence findings were normal. IgG4 immunohistochemical staining of the biopsy specimens was negative. Pulmonary function tests were normal, as were chest X-ray and high-resolution computed tomography of the lungs. Serum and 24-h urine calcium levels and serum angiotensin-converting enzyme (ACE) levels were

normal. A diagnosis of pSS and GIN was made. The patient was started on oral methylprednisolone 40 mg/day (0.5 mg/kg/day) along with hydroxychloroquine 200 mg/day, and vitamin D 800 IU plus calcium 1 g daily.

At the 2-month follow-up her serum creatinine level had improved to 1.5 mg/dl. Steroid dosage was gradually tapered to 30 mg/day during the following 2 months. However, she had bilateral avascular necrosis of the femoral heads with an increase in serum creatinine levels to 2 mg/dl. The steroid dosage was further tapered 10 mg/day and RTX therapy (1 g 2 weeks apart) was introduced, followed by 1 g at the 6-month follow-up. After 6 months of RTX therapy, there was no need for steroid therapy and the patient's serum creatinine level was stabilized at 1.5 mg/dl. She was referred to an orthopedist for debilitating bilateral avascular necrosis of the femur heads. Additional RTX infusion was planned after the surgery.

Discussion

In this case report we have described a patient with GIN associated with pSS. To the best of our knowledge, the current case is the first detailed report showing the association between pSS and GIN in the literature. The patient meets the American College of Rheumatology classification criteria for pSS [4]. Kidney biopsy is generally not necessary to confirm the diagnosis of renal involvement in pSS; however, it is important to rule out other diseases such as vasculitis or IgG4-related disease [5].

TIN is usually associated with medications, infections, or autoimmune diseases such as systemic lupus erythematosus, pSS, or the syndrome of tubulo-interstitial nephritis and uveitis (TINU) [6]. GIN is a rare entity and shares common etiological factors with TIN; however, it is most commonly reported as a histological renal finding in patients with sarcoidosis [7]. It is well known that extrapulmonary sarcoidosis may present with isolated renal involvement as GIN [8]. Sarcoidosis must always be ruled out in patients presenting with GIN. Laboratory or radiological findings consistent with sarcoidosis are needed to diagnose isolated renal sarcoidosis, and other etiologies should be ruled out for a definite diagnosis [9]. The only consistent finding with sarcoidosis was noncaseating, granuloma formations in the biopsy of our patient. However, there are no well-defined criteria for the diagnosis of sarcoidosis. Therefore, sarcoidosis cannot be excluded in our patient.

The pathological features on renal biopsy generally may not help to determine the cause of GIN. The history of drug use should be questioned in all patients who present with GIN. TINU syndrome may show similar histopathological and clinical features with pSS [10]. However, our patient did not have a history of uveitis, and uveitis did not emerge during her follow-up. Infections were also excluded with appropriate laboratory, radiological, and pathological tests, since it was reported that GIN may be associated with some type of infections [11].

Even though some patients with GIN may eventually develop end-stage renal failure, GIN generally has a good prognosis. Therapy of GIN is determined by the underlying disease. Corticosteroids are the first-line treatment regardless of the etiologic factors, other than infections [3]. Since GIN is often associated with sarcoidosis, the data in the literature are often related to the treatment of GIN associated with sarcoidosis. Relapses of-

Abstract · Zusammenfassung

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Abstract

Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by lymphocytic and plasmacytic infiltration of the exocrine glands. Tubulointerstitial nephritis (TIN) is the most common type of renal involvement in pSS. However, clinically significant renal involvement is uncommon. Granulomatous interstitial nephritis (GIN) is a rare histopathological entity characterized by the presence of granulomas against a background of interstitial inflammation. GIN is not a typical and commonly seen form of TIN in pSS. Herein, we report on a patient who was concurrently diagnosed with pSS and GIN and was treated successfully with rituximab (RTX). pSS should be considered in the differential diagnosis of GIN, and RTX may be a good option in the treatment of this patient group.

Keywords

Sjögren's syndrome · Granulomatous interstitial nephritis · Rituximab · Sarcoidosis

Granulomatöse interstitielle Nephritis mit primärem Sjögren-Syndrom

Zusammenfassung

Das primäre Sjögren-Syndrom (pSS) ist eine Autoimmunkrankheit, die durch Lymphozyten- und Plasmazellinfiltration der exokrinen Drüsen gekennzeichnet ist. Als häufigste Form der Nierenbeteiligung ist die tubulointerstitielle Nephritis (TIN) zu nennen. Eine klinisch relevante Nierenbeteiligung ist dabei jedoch untypisch. Die granulomatöse interstitielle Nephritis (GIN) stellt eine seltene histopathologische Entität dar und zeichnet sich durch das Vorliegen von Granulomen vor dem Hintergrund einer interstitiellen Entzündung aus. Die GIN ist weder eine typische noch eine häufig zu beobachtende Form der TIN bei pSS. In dem vorliegenden Beitrag wird ein Fall beschrieben, in dem gleichzeitig die Diagnose eines pSS und einer GIN gestellt wurde und in dem eine Therapie mit Rituximab (RTX) erfolgreich war. Das pSS sollte also bei den Differenzialdiagnosen der GIN berücksichtigt werden, dabei kann RTX eine gute Option zur Behandlung dieser Patientengruppe darstellen.

Schlüsselwörter

Sjögren-Syndrom · Granulomatöse interstitielle Nephritis · Rituximab · Sarkoidose

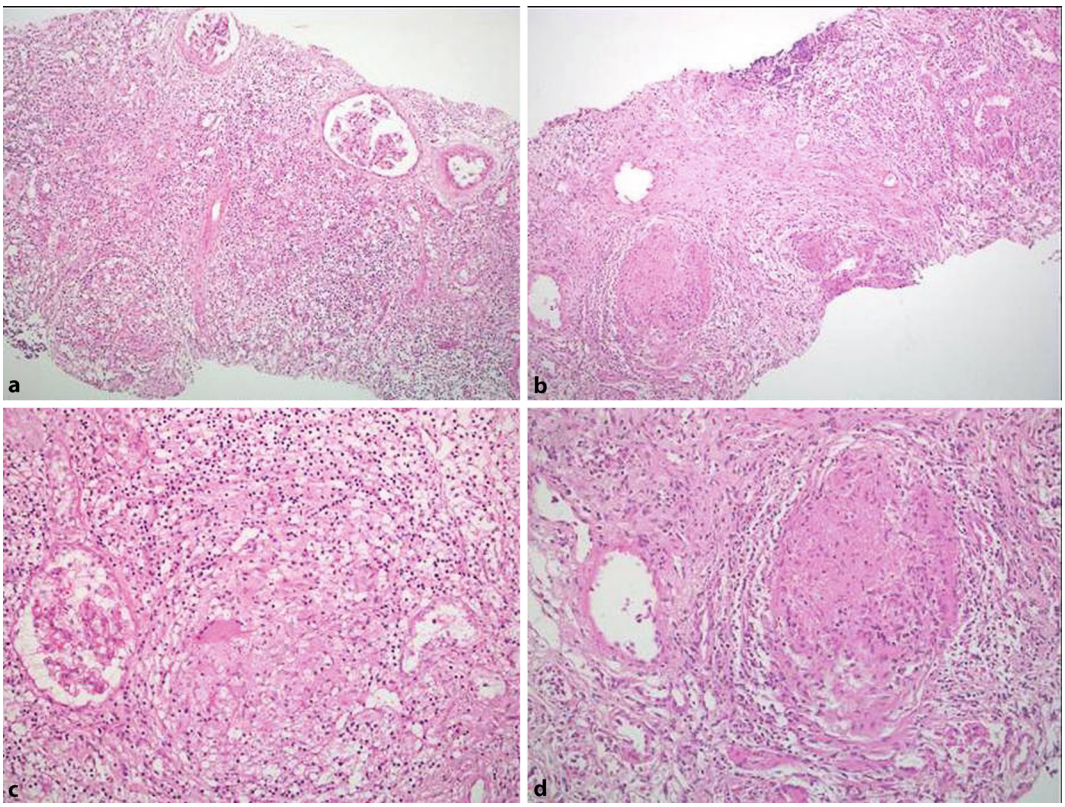

Fig. 1 ◄ Renal biopsy, microscopic findings. **a**, **b** Well-formed granulomas against a background of marked lymphoplasmocytic inflammation in the interstitium, H&E ×100. **c**, **d** Epithelioid, noncaseating granulomas with foreign-body-type giant cells, H&E ×200

ten occur in GIN when steroid dosage is tapered or discontinued [12]. Mycophenolate mofetil or tumor necrosis factor-alpha inhibitors were reported to be useful in cases of steroid-resistant or steroid-dependent GIN [13, 14]. In this case we observed a good clinical and laboratory response to RTX. RTX is known to be a promising treatment option for severe pSS with extraglandular manifestations, such as glomerulonephritis or vasculitis [15].

Conclusion

In conclusion, pSS should be considered in the differential diagnosis of GIN. RTX may be a good option in the treatment of this group of patients.

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Compliance with ethical guidelines

Conflict of interest. B. Bitik, İ.I. Gonul, S. Haznedaroglu, B. Goker, and A. Tufan declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors. Consent was obtained from all patients identifiable from images or other information within the manuscript. In the case of underage patients, consent was obtained from a parent or legal guardian.

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