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Schnitzler syndrome complicated by membranous nephropathy

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Key words

membranous nephropathy – Schnitzler syndrome – autoinflammatory syndrome

Abstract. Schnitzler syndrome is a rare clinical entity characterized by the association of chronic urticarial rash and monoclonal immunoglobulin M gammopathy. A 62-year-old male developed nephrotic syndrome with Schnitzler syndrome. A renal biopsy revealed mild thickening of the glomerular basement membrane with spikes and mild expansion of the mesangial matrix; prominent fine granular immunoglobulin G depositions were found along the capillary walls by immunofluorescence study and electron dense deposits were observed in the subepithelial spaces and in a part of mesangium by electron microscopically. The histological findings were compatible with secondary form of membranous nephropathy. To the best of our knowledge this is the first renal biopsy case of Schnitzler syndrome. With corticosteroid treatment chronic rash and proteinuria have disappeared, but immunoglobulin (IgM) paraprotein has been still present.

Introduction

Schnitzler syndrome (SS) is a rare clinical entity characterized by the association of chronic urticarial rash and monoclonal immunoglobulin (Ig) M gammopathy. Additional clinical findings include intermittent fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepato- or splenomegaly, leukocytosis, and elevated erythrocyte sedimentation rate [1]. This syndrome is a rare disorder and little known, so renal injury associated with SS has not been well studied. We describe a first case of membranous nephropathy (MN) developed in a patient of SS.

Case history

A 62-year-old male was referred to our hospital because of a 6-year-history of inter-

mittent urticaria with low-grade fever and recent leg edema. Two years before admission, his routine laboratory tests including urinalysis were normal. On examination, his blood pressure was 130/70 mmHg, pulse 60/min, temperature was 36.9 °C. He was not anemic and not icteric. The heart and lungs were normal, and lymph nodes were not palpable. A diffuse urticarial rash noted his trunk and hip, and mild peripheral edema was present. No neurological abnormalities were noted.

Urinary protein was 4 – 5 g/24 h and the urinary sediment showed 1 – 4 erythrocytes, 1 – 4 leukocytes per high-power field. The hematocrit was 47.5% (normal range (NR) 40.5 – 51.8), the hemoglobin concentration 16.6 g/dl (NR 13.5 – 17.6), the platelet count 248,000/mm³ (NR 151,000 – 325,000), leukocyte count 5,610/mm³ (NR 3,850 – 9,870). The serum urea nitrogen level was 18.4 mg/dl (NR 7.5 – 20.4), the creatinine 1.01 mg/dl (NR 0.75 – 1.34); estimated glomerular filtration rate (eGFR) 58.7 ml/min/1.73 m²; the uric acid 8.2 mg/dl (NR 2.5 – 6.9); the cholesterol 374 mg/dl (NR 128 – 219); the total protein 5.2 g/dl (NR 6.5 – 8.2); and albumin 2.5 g/dl (NR 4.4 – 5.7). Erythrocyte sedimentation rate was 41 mm/h (NR < 10). The C reactive protein level was 0.08 mg/dl (NR < 0.27); IgG 309 mg/dl (NR 870 – 1,700); IgA 116 mg/dl (NR 110 – 410); IgM 926 mg/dl (NR 34 – 220); and the ferritin 146 ng/ml (NR 26 – 240). Protein immunoelectrophoresis revealed an IgM κ -paraprotein in the serum. Bone marrow revealed a slight hypocellular one composed of all elements of hematopoietic three cell lines, with slight increase of small to medium sized lymphocytes. Macroglobulinemia suspected but not confirmed because of lack of diffuse or nodular proliferation of small lymphocytes.

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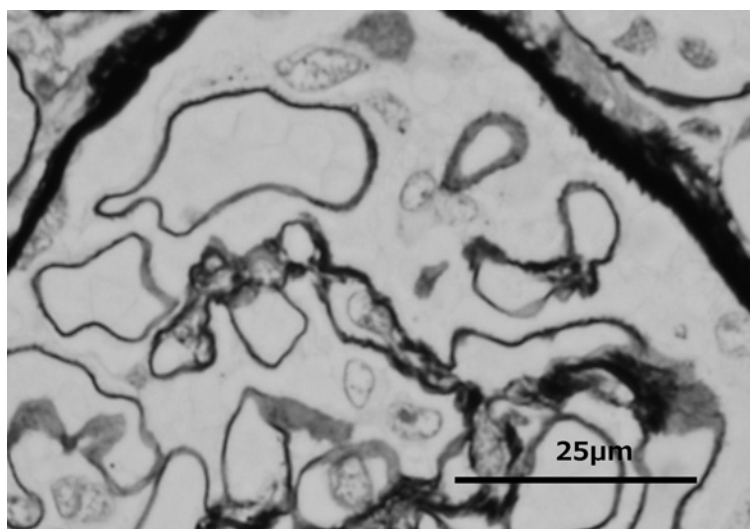


Figure 1. Light microscopy shows mild thickening of the glomerular basement membrane with spikes (PASM).

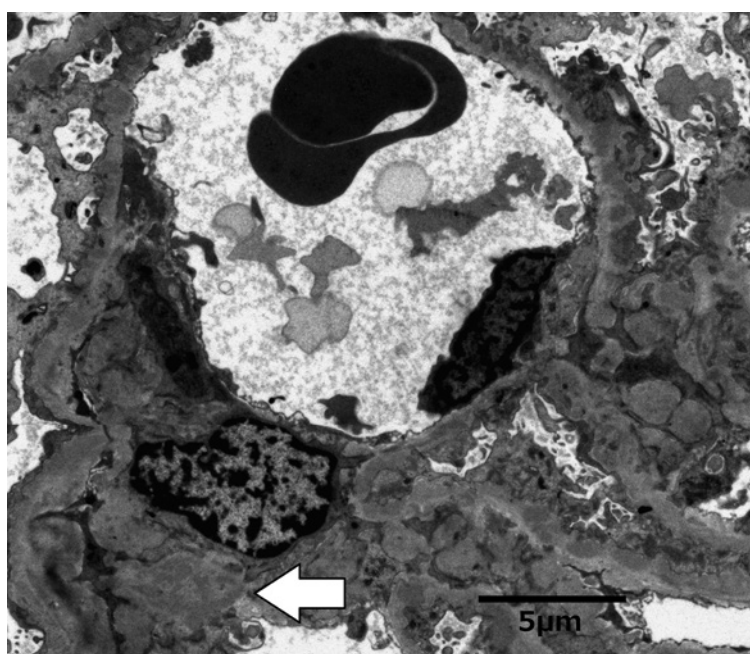


Figure 2. Electron microscopically many electron dense deposits on the epithelial aspect of glomerular basement membrane and a few in the mesangium (arrow) were observed.

Serum C3, C4 and total serum hemolytic activity were normal. Circulating immune complexes were negative. Anti-myeloperoxidase and anti-proteinase3-specific anti-neutrophil cytoplasmic antibodies were both negative. Rheumatoid factor, Antistreptolysin-O, Hepatitis B virus surface antigen, Hepatitis C virus antibody, human immunodeficiency virus antibody, antinuclear antibody and cryoglobulin

were all negative. All other laboratory tests were within normal limits. A chest X-ray and an electrocardiogram were normal. Renal ultrasound and computed tomography showed normal kidneys.

On the 2nd hospital day the renal biopsy was performed to investigate the cause of nephrotic syndrome. By light microscopy 18 glomeruli were found. It showed 1 globally sclerosed glomerulus, and the remaining 17 glomeruli had a normocellular appearance, mild thickening of the glomerular basement membrane with spikes and mild expansion of the mesangial matrix (Figure 1). The tubulointerstitium and vessels appeared normal. By immunofluorescent study prominent fine granular IgG depositions were found along the capillary walls. Stains for IgM, IgA and Congo red were negative. By IgG subclass analysis revealed positive IgG4 (2+), weakly positive IgG2 (1+) and IgG3 ($\pm$ 1+), and negative IgG1. Electron microscopically many electron dense deposits on the epithelial aspect of glomerular basement membrane and a few in the mesangium were observed (Figure 2). These findings led to the diagnosis of MN Stage II.

Cutaneous biopsy of urticarial lesion revealed perivascular infiltrates of lymphocytes in the superficial dermis. A total body bone scan showed abnormal increased activity in the right parietal bone (Figure 3A). Radiography and computed tomography of cranium showed a solitary sclerotic lesion in the same area (Figure 3B). There was no evidence of any other diseases (negative check-up for thoracoabdominal computed tomography, gastrointestinoscopy, and colonoscopy) or drug therapy usually associated with MN.

From the findings such as chronic urticaria, osteo-condensation, monoclonal IgM κ -gammopathy without features of lymphoproliferative disease the diagnosis of SS was reached. He was treated with pulse intravenous methylprednisolone of 0.5 g for 3 days during the early phase of the disease, followed by an oral prednisolone regimen (40 mg/day). Two weeks after pulse intravenous methylprednisolone urticarial lesions improved. Six months later, when the prednisolone was reduced 15 mg daily, proteinuria disappeared. Prednisolone was slowly tapered off to 5 mg daily. The patient is currently asymptomatic after 48 months of fol-

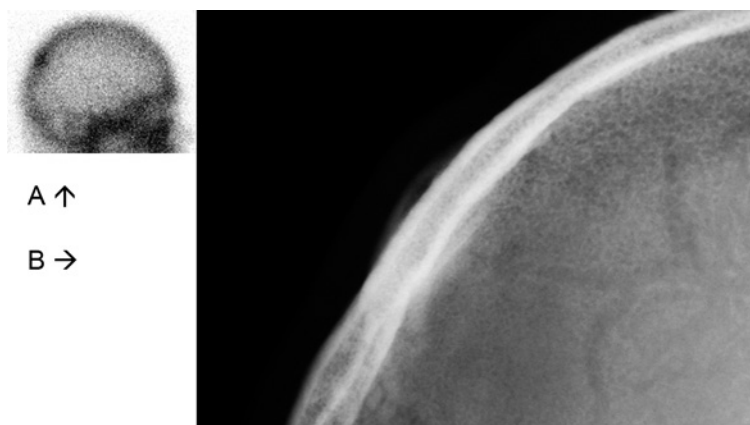


Figure 3. A total body scan showed abnormal increased activity (A) and radiography of cranium showed a solitary sclerotic lesion (B) in the right parietal bone.

low-up. IgM level were reduced with disappearance of clinical findings include chronic rash and proteinuria. His bone lesion has not been enlarged during his clinical course. After 3 years from his admission, bone marrow revealed no massive proliferation of plasma cells, but IgM paraprotein was still present.

Discussion

SS was first described by Schnitzler, a French dermatologist, in 1972 [1], and since then ~ 100 cases have been reported [2]. SS is a disabling disorder which affects multiple systems and which can be considered as one of the autoinflammatory syndromes [3, 4].

Chronic urticarial rash and monoclonal IgM are major criteria when a patient can be diagnosed with SS. Importantly, other causes must have been excluded [2]. Chronic urticarial rash and renal lesion sometimes appear together with such as hypocomplementemic urticarial vasculitis [5] and systemic lupus erythematosus [6]. On the other hand monoclonal gammopathies can present with various renal diseases. Especially, IgM paraproteinemia and renal lesion may be seen in Waldenström's macroglobulinemia (WM) and monoclonal gammopathy of undetermined significance [7]. In our case chronic and recurrent urticarial rash without pruritus was present, and no monoclonal plasma cells revealed in bone marrow. The absence of bone marrow infiltration is often cited as a distinguishing feature between SS and WM

[2]. Moreover, a cranial solitary sclerotic lesion, which is one of minor criteria for SS, was present, and that bone lesion did not enlarge for over 4 years. Clinical course of that lesion is different from plasmacytoma. SS has a benign clinical course in about 85% of cases, but SS does require long-term follow up due to the potential development of lymphoplasmacytic malignancies [2]. So in our case careful follow-up, including the relapse of nephrotic syndrome, will be needed.

Recently Westhoff et al. [8] described a patient with SS and impairment of renal function. But in that case glomerulonephritis was improbable, since serological findings were normal and there was no proteinuria. Our case showed nephrotic syndrome and histologically typical findings of MN, and Congo red staining was negative.

MN is the most important cause of the nephrotic syndrome in adult patients [9]. The association of MN with some autoinflammatory syndromes, such as adult Still's disease [10], Behçet's disease [11], familial Mediterranean fever [12], and hereditary angioedema [13], were reported. This case is the first biopsy-proven MN with SS. It must await further detailed case reports whether this association is of pure coincidence or etiologically related.

We detected non-monoclonal IgG deposits in the glomerular compartment although the paraprotein was of IgM origin. In lymphoplasmacytic neoplasma concurrent glomerular injury may be a direct result of the lymphoplasmacytic disorder through a paraprotein deposition process resulting in amyloid or monoclonal immunoglobulin deposition disease, or may be caused indirectly through immune-mediated mechanisms, as in the cases of membranous nephropathy and so forth [14]. In our case the latter mechanism may be related. A case was also reported of a patient with WM associated with amyloidosis and MN [15]. A number of studies have shown differing distribution patterns of glomerular IgG subclass deposits in patients with MN [16, 17, 18]. In our case, although IgG4 was predominant, IgG1 was absent; these findings were rather favorable for secondary MN. And the presence of mesangial electron dense deposits also suggests that our patient has a secondary form of MN.

To date the pathogenesis of SS remains unclear and treatment of SS is difficult. Corticosteroids decrease symptoms significantly in 39% of patients [2]. In our patient after the oral prednisolone with pulse intravenous methylprednisolone urticarial lesions and proteinuria disappeared. From the clinical and laboratory findings our patient might be relatively milder, as SS, than other reported cases.

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