Asymptomatic sinusitis as an origin of infection-related glomerulonephritis manifesting steroid-resistant nephrotic syndrome

A case report

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Abstract

Rationale: Infection is a major trigger or pathogenic origin in a substantial proportion of glomerulonephritis (GN) patients, typically manifesting infection-related GN (IRGN). Various microorganisms, infection sites, and clinical and histopathological features are involved in IRGN. Once an infectious origin is identified and successfully eradicated, nephrotic syndrome or kidney dysfunction is spontaneously resolved. However, if patients are asymptomatic and the origin is undetermined, the diagnosis and treatment of GN is challenging. This case presentation reported on an IRGN case manifesting steroid-resistant nephrotic syndrome associated with asymptomatic sinusitis as a pathogenic origin.

Patient concerns: A 68-year-old male presented with severe kidney dysfunction and edema in both extremities.

Diagnosis: The patient was clinically diagnosed with hypocomplementemic nephrotic syndrome and kidney dysfunction and histopathologically with diffuse proliferative GN and a focal pattern of membranoproliferative GN. The findings suggested that idiopathic membranoproliferative glomerulonephritis type I was more likely than IRGN, given a critical lack of apparent infection.

Interventions: Combined intravenous methylprednisolone, oral prednisolone, and cyclosporin did not improve the patient’s condition. Thus, IRGN associated with inapparent infectious origin was suspected. Repeated thorough and careful examinations including CT scan showed sinusitis in his left maxillary sinus. Moreover, reanalysis of kidney specimen revealed positive nephritis-associated plasmin receptor in glomeruli, a typical finding for IRGN, supporting a pathogenic significance of his sinusitis. Medical treatment was initiated with 200 mg oral clarithromycin daily.

Outcomes: Oral clarithromycin gradually improved proteinuria and hypocomplementemia and resulted in nephrotic syndrome remission in parallel with opacification resolution of sinuses shown on CT.

Lessons: This case presentation showed that asymptomatic sinusitis is potentially a pathogenic IRGN origin. A gold standard therapy for idiopathic GN, corticosteroid could be damaging in uncontrolled or underdiagnosed infection. In asymptomatic patients, a thorough screening of infectious diseases, including sinusitis, together with a renal histological evaluation of glomerular nephritis-associated plasmin receptor deposition is also essential in treating a wide spectrum of GN.

Abbreviations: CKD = chronic kidney disease, CsA = cyclosporin A, ESKD = end-stage kidney disease, GN = glomerulonephritis, HSPN = Henoch-Schönlein purpura nephritis, IF = immunofluorescence, IRGN = infection-related glomerulonephritis, MPGN = membranoproliferative glomerulonephritis, NAPr = nephritis-associated plasmin receptor.

Keywords: asymptomatic infection, glomerulonephritis, nephrotic syndrome, sinusitis
1. Introduction

Chronic kidney disease (CKD), which eventually progresses to end-stage kidney disease, is a global health problem accounting for 10% to 15% of people.\(^1\)–\(^3\) CKD is a noncommunicable disease. However, in a substantial number of people with CKD, infectious disease has been recognized as a trigger or is a major reason for end-stage kidney disease.\(^4\)–\(^6\) Over the past few decades, infectious disease has been recognized as a trigger or pathogenic factor in a number of GN cases, typically infection-related GN (IRGN).\(^6\)–\(^8\) Over the past few decades, infectious disease has been recognized as a trigger or pathogenic factor in a number of GN cases, typically infection-related GN (IRGN).\(^6\)–\(^8\) Regardless of its microorganisms or infection sites. In IRGN, resolution of infection usually results in partial or complete recovery of kidney function and abnormal urinalysis, whereas immunosuppressive treatment is harmful in uncontrolled infection. Therefore, accurate diagnosis of apparent and inapparent infection is essential in treating all GN patients. However, diagnosis in asymptomatic patients is challenging as well as figuring out if asymptomatic infection is pathogenic in GN.

Here, a case of typical IRGN in an elderly, with a particular exception on asymptomatic sinusitis as a pathogenic source, is reported. Nephrotic syndrome accompanied by hypocomplementemia was resistant to corticosteroid and cyclosporin A (CsA) therapy. However, medical treatment for sinusitis improved GN considerably. Here, a case of typical IRGN in an elderly, with a particular exception on asymptomatic sinusitis as a pathogenic source, is reported. Nephrotic syndrome accompanied by hypocomplementemia was resistant to corticosteroid and cyclosporin A (CsA) therapy. However, medical treatment for sinusitis improved GN considerably.

2. Case report

A 68-year-old Japanese man, with about a decade history of non-insulin-dependent type 2 diabetes mellitus, developed edema in lower and upper extremities 1 month prior to hospital admission. He did not report any recent fever, chills, night sweats, skin rashes, and macroscopic hematuria. Medical history also included hypertension and tobacco use. His regular medications were 2 mg trichlormethiazide, 10 mg amiodipine, and 125 mg irbesartan, respectively. On physical examination, the patient was afebrile, pulse rate was 77 beats/min, blood pressure was 154/89 mmHg, no murmurs or crackles were heard on his chest, and he had bilateral edema on both extremities. Laboratory findings included the following: gross hematuria and proteinuria with protein per gram of creatinine, 7.7; hemoglobin, 10.5 g/dL; white blood cell count, 5,790/mL; platelet count, 23.9 × 10⁹/mL; total serum protein, 4.7 g/dL; serum albumin, 2.3 g/dL; sodium, 144 mEq/L; potassium, 4.4 mEq/L; chloride, 114 mEq/L; hemoglobin A1c, 6.5%; and C3-dominant hypocomplementemia (Table 1). Pertinent antibodies associated with GN were negative (Table 1). Serum and urine electrophoresis and serum free light chain levels were unremarkable. Chest radiography showed no pulmonary congestion or pleural effusions and echocardiography no regurgitation or vegetations.

A kidney biopsy specimen showed 32 glomeruli, nine of which were globally sclerotic. Glomeruli showed diffuse proliferative and exudative GN with neutrophil infiltrates (Fig. 1A). Focal lobular accentuation and double contour of the capillary wall, typical of membranoproliferative GN (MPGN) type I (Fig. 1B), moderate to severe interstitial fibrosis, and arteriolar wall thickening in the inner layer were observed. Immunofluorescence (IF) microscopy showed granular mesangial and capillary wall deposits for IgG (1+) and C3 (2+) (Fig. 1C and D). IgA, IgM, C4, or C1q staining was not noted. Paramesangial dense deposits (Fig. 1E) were found on electron microscopy, but subepithelial deposits or humps were not evident. The histological findings suggested idiopathic MPGN because of a lack of apparent infection and typical humps on electron microscopy. Daily 500 mg intravenous methylprednisolone for 3 days followed by 50 mg oral prednisolone was started (Fig. 2). Given the poor response to steroids, oral CsA 75 mg per day was added on day 57, and the patient was discharged on day 67. The effect of the addition of CsA was limited, resulting in a slight increase in complement C3 and no improvement in proteinuria and serum albumin (Fig. 2). Thus, IRGN caused by a hidden infectious origin was reconsidered. After the repeated examinations and diagnostic tests including CT scan, mucosal thickening and fluid in the left maxillary paranasal sinus were detected (Fig. 3). The patient’s sinusitis remained asymptomatic even when diagnosed. Glomerular staining of nephritis-associated plasmin receptor (NAPr) was also evaluated, typically positive in IRGN.\(^11\)–\(^12\) Deposition of NAPr and related plasmin activity were observed in similar distributions in glomeruli (Fig. 4), suggesting that asymptomatic sinusitis contributed to the onset of GN. Thus, low-dose continuous administration of macrolide (clarithromycin 200 mg once daily) was started instead of a surgical treatment, after the patient’s comprehension of the disease and treatment options.

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Figure 1. Kidney biopsy findings. (A) Light microscopy (LM) showing diffuse proliferative and exudative glomerulonephritis with infiltrating neutrophils (periodic acid–Schiff; original magnification, ×400). (B) Membranoproliferative pattern showing lobular accentuation and basement membrane duplication was focally evident (periodic acid–methenamine silver; original magnification, ×400). (C, D) Immunofluorescence (IF) microscopy showed granular mesangial and capillary wall deposits for IgG (C) and C3 (D) (original magnification, ×400). (E) Electron microscopy showed paramesangial electron-dense deposits (original magnification, ×10,000).

Figure 2. Clinical course of the patient. Alb = serum albumin; C3 = complement C3; Cr = serum creatinine; mPSL= methylprednisolone; PSL = prednisolone. mPSL = methylprednisolone.
3. Discussion

In this case presentation, an elderly man developed GN presenting with nephrotic syndrome and C3-dominant hypocomplementemia that were corticosteroid and immunosuppressive treatment resistant. Oral clarithromycin for asymptomatic sinusitis gradually improved proteinemia in parallel with the increases in serum albumin and complement levels, resulting in nephrotic syndrome remission. Thorough analysis of this case revealed the pathogenic relationship between GN and sinusitis, even if asymptomatic. This report is the first to reveal asymptomatic sinusitis as a pathogenic origin of IRGN.

IRGN was earlier known to follow a streptococcal infection at the upper respiratory tract or soft tissues and was called postinfectious GN. Over the previous decades, this disease entity has been shifted particularly in terms of diversity of the causative microorganism and origin. In the present case, GN was associated with sinusitis and the typical histological findings for IRGN, showing diffuse proliferative GN with predominant C3 and IgG depositions on IF. The MPGN pattern focally seen in the patient’s histopathology was consistent with IRGN, given that 2% to 8% of IRGN patients develop MPGN. A case of MPGN following bilateral sinusitis is also reported, and immunosuppressive treatment provided little effect, leading to an

Figure 3. Sinus CT scan of the patient before and after treatment of sinusitis. The mucosal thickening and fluid were found in his left maxillary paranasal sinus (left, arrow), which was substantially improved after medical treatment of sinusitis (right, arrow). CT = computed tomography.

Figure 4. Histological staining for nephritis-associated plasmin receptor (NAPr) and plasmin activity. (A-D) Double immunofluorescent staining for NAPr (fluorescein isothiocyanate, green) and complement C3 (Alexa Fluor 594, red) with nuclear staining for DAPI (blue). NAPr (A) and C3 (B) were both positive in glomeruli, and their localization was essentially different in merged images (C and D). (E) Plasmin activity by in situ zymography was found in a similar distribution as NAPr staining in glomeruli. DAPI = 4, 6-diamidino-2-phenylindole, NAPr = nephritis-associated plasmin receptor.
unfavorable kidney outcome. Thus, in our case, added workups were repeated and CT scan showed asymptomatic sinusitis. The previous case series of IRGN or postinfectious GN included patients with unknown source of infection with and without sepsis.\(^1\) Thus, there would be much more GN cases with a hidden infectious origin than currently expected.

Positive glomerular NAPr staining and plasmin activity in this case support IRGN diagnosis. This finding led to the treatment of his sinusitis with medications preceding surgical treatment. This resulted in GN remission and determined the pathogenic significance of his sinusitis. NAPr is a nephritogenic protein that was originally isolated from group A streptococcus and shows high homology in nucleotide and amino acid sequences to streptococcal plasmin receptor.\(^2\) NAPr induces glomerular damages by trapping plasmin and maintaining its activity, and glomerular NAPr deposition and related plasmin activity are usually detected in classical postinfectious GN. However, these findings are increasingly reported irrespective of microorganisms or morphological types.\(^17\)–\(^20\) In such cases, infection resolution resulted in complete or incomplete remission of GN, similar to our case. If staining for NAPr and in situ zymography for plasmin activity on kidney biopsy tissues could be a key diagnostic tool in possible IRGN with unknown source of infection.

This case showed that asymptomatic sinusitis could be a pathophysiological IRGN cause. Several reports including non-English literatures have documented that symptomatic sinusitis treatment resulted in nephrotic syndrome remission in various types of GN such as membranous nephropathy\(^21\) and minimal change disease.\(^22\) Of interest is that the patient remained asymptomatic from the initial presentation until the sinusitis remission. Sinusitis is an inflammatory disease of the paranasal sinuses, annually affecting approximately 16% of the adult population.\(^23\) This condition typically causes cardinal symptoms including facial pain/pressure or nasal obstruction and decrease quality of life. The population is increasing, and acute/chronic/recurrent sinusitis is currently a healthcare burden.\(^23,24\) Previous epidemiologic studies included only symptomatic patients, and routine medical check-ups could not easily identify sinusitis especially when asymptomatic. Thus, the true incidence of sinusitis and sinusitis-associated GN may be much higher than reported.

The classical disease concept of postinfectious GN or IRGN has been increasingly expanded.\(^8\)–\(^10,16,23\) A relative disease of IRGN is IgA-dominant IRGN, alternatively called staphylococcus-associated GN, showing diffuse endocapillary proliferative and exudative GN with predominant IgA deposition.\(^26\)–\(^27\) We previously reported and overviewed post-staphylococcal infection Henoch-Schönlein purpura nephritis (HSPN), alternatively called staphylococcus-associated HSPN.\(^28\) This GN’s clinical and morphological characteristics are closely similar with those of IgA-dominant IRGN, rather than those of HSPN.\(^28\) Moreover, improvement of proteinuria or kidney function after controlling infection is not limited to GN but also to various glomerular diseases (eg, minimal change disease, membranous nephropathy, and proliferative GN with monoclonal IgG deposits),\(^19\)–\(^21,22\) indicating the pathogenic role of infection in a wider spectrum of glomerular diseases. “Infection-related glomerulopathy” may be adopted to characterize a broader domain of such diseases. This case presentation aimed to contribute in understanding the concept of a pathogenic role of infection and the need for screening in extensive glomerular diseases.

Therefore, an IRGN case associated with asymptomatic sinusitis manifesting nephritic syndrome and hypocomplementemia resistant to steroid with immunosuppressant was documented. Medical treatment of sinusitis resulted in nephrotic syndrome remission.

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**Author contributions**

S.N., S.M., T.S., H.S., K.S. participated in patient care, acquisition of data, and writing the manuscript. S.M. supervised and substantively revised the manuscript. T.O. contributed to IF staining for NAPr and and in situ zymography for plasmin activity on kidney biopsy tissues. T.O., K.H., Y.N., and S.U. participated in discussions and critical review of the manuscript.

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