

Polycythemia vera associated with IgA nephropathy: A case report and literature review

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Abstract. A case of polycythemia vera (PV) associated with immunoglobulin A nephropathy (IgAN) in a 57-year-old man is described. The patient had a mild enlargement of the kidneys and elevated serum creatinine level, whereas the glomerular filtration rate was normal. Pathological observation under a light microscope showed mild mesangial hyperplasia. The urinary protein level was found to be positively correlated with changes in blood cell counts. After controlling blood pressure, anti-platelet, hydroxyurea treatment, the patient's proteinuria decreased and renal function remained in the normal range. PV associated with renal disease is rare and generally considered to be associated with hypervolemia or high-viscosity-induced renal hyperperfusion and hyperfiltration. This is a rare case of PV associated with IgAN without a high filtration rate. A review of the clinical features of PV associated with renal disease from previous literature was also conducted. The histological results of the cases varied and included IgAN, focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis.

Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) of unknown etiology that involves the clonal proliferation of erythrocytes. PV typically manifests as blood circulation disorder, hypertension and cerebral infarction. Its pathogenesis is unknown and may be associated with JAK2 mutation (1). The pathological lesions of PV are predominantly involved bone marrow, spleen and liver (2). PV associated with renal disease is clinically rare. Only 23 cases have been reported in the literature, and in the majority of these cases it was considered that PV-induced glomerular hyperperfusion and hyperfiltration were associated with the occurrence of nephropathy (3).

A rare case of PV associated with immunoglobulin (Ig) A nephropathy (IgAN) and an elevated serum creatinine (SCr) level but normal glomerular filtration rate is described in the present case report. In addition, the previous case reports of PV associated with renal disease are reviewed and the clinical features are summarized.

Case report

A 57-year-old Chinese man with a 6-year history of PV associated with protein- and hematuria was admitted to the Department of Nephrology of Navy General Hospital (Beijing, China) on November 21, 2011 with week-long symptom exacerbation. Six years prior to this, the Department of Hematology used a bone marrow aspiration to diagnose this patient with PV and observed significantly increased leukocyte, erythrocyte and platelet counts. The urinalysis performed at that time showed a 1,200 mg 24 h urine protein content (24-h UR) and 10-15 erythrocytes/high-power field (hp). The patient also displayed hypertension and hyperuricemia. The patient was treated with hydroxyurea (HU), regular phlebotomies (RPs) and interferon (IFN) therapy, and his leukocyte, erythrocyte and platelet counts returned to the normal range. The 24-h UR was 300-500 mg at follow-up. One week prior to admission, the patient complained of a sore throat. The patient's past medical history included an enlarged liver, widening of the portal vein and splenomegaly. The physical exam showed a blood pressure of 148/102 mmHg, facial flushing, conjunctival hyperemia and a dark red color on the forehead, tip of the nose, lips, thenar muscles and fingers. No throat congestion or edema was detected. The spleen was palpable below the rib ridge.

Serum analysis revealed a leukocyte count of $19.25 \times 10^9/L$, hemoglobin content of 207 g/l and platelet count of $735 \times 10^9/L$. The urea nitrogen and SCr levels were 14.89 and 1.22 mg/dl, respectively. The urine erythrocyte count was 8-10/hp, and the 24-h UR was 2,796 mg. The liver function, serum lipid profile, uric acid, electrolytes, glucose, IgM, IgA, IgG and complement 3 (C3) and C4 serum levels were normal. Coagulation and the levels of anti-streptolysin O and high-sensitivity C-reactive protein were also normal. Several antibodies, such as anti-myeloperoxidase, proteinase 3 (PR3), double-stranded DNA (dsDNA), nucleosome and Sjögren's syndrome type A (SS-A) and type B (SS-B) antibodies, tested negative and excluded an autoimmune disorder or systemic disease. The urine osmolality was 609.00 mOsm/kg. An ultrasonography

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revealed increased renal parenchymal echogenicity of both kidneys. The maximal dimensions of the right and left kidneys were determined to be 12.4 and 12.1 cm, respectively. A renal radioisotope test was conducted to measure the glomerular filtration rate (GFR) and was 41.2 ml/min in the left kidney and 51.9 ml/min in the right kidney. The total GFR was 93.3 ml/min.

A renal biopsy was performed, after informed consent was obtained from the patient. The specimens were embedded in paraffin, sliced to 3-mm thickness and then stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), periodic acid silver methenamine (PASM) and Masson stains. Three pieces of renal tissue and a total of 16-20 glomeruli were then examined using light microscopy (LM). This analysis revealed 3 glomeruli with global sclerosis, and the remainder had mild diffuse hyperplasia of the mesangium and mesangial matrix. The glomerular capillaries were not dilated. No micro-thrombosis was observed. The renal tubular epithelial cells showed mild vacuolar degeneration. Frozen sections were stained for immunofluorescence (IF), and rabbit anti-human IgG, IgA, IgM, C3 and C1q were used for direct IF staining. IF showed 2-3 glomeruli with granular depositions of IgA (4+; Fig. 1) and IgM+ in the mesangium but negative results for IgG, C1q, C3 and fibronectin. These results generated a diagnosis of IgAN (Lee classification I-II) (4).

The patient was administered amlodipine besylate (5 mg), valsartan capsules (160 mg), an enteric-coated aspirin tablet (100 mg) and HU (0.5 g) daily. An outpatient follow-up was conducted once every 2 weeks. Multiple follow-up examinations yielded the following results: The 24-h UR was positively correlated with the red blood cell count, hemoglobin level, and white blood cell and platelet counts. In addition, the blood pressure of the patient was in the range of 120-140/70-95 mmHg.

Discussion

To the best of our knowledge, only 23 cases of PV associated with renal disease are reported in the current literature. Among these cases, 21 were diagnosed by renal biopsies. The average age of the patient at the time of the renal biopsy was 53.43 years. The male-to-female ratio was 1.63:1. The clinical manifestations included 14 cases (66.7%) of nephrotic syndrome (NS; 24-h UR ≥ 3.5 g/l), 6 cases (28.6%) of mild to moderate proteinuria (24-h UR < 3.5 g/l) and 1 case without information. Eight cases (38.1%) presented as hematuria positive, 12 cases (57.1%) were negative and 1 case was without information. Among those patients, there were 6 cases (28.6%) with normal renal function or mild renal insufficiency (defined as SCr ≤ 1.5 mg/dl in males and 1.2 mg/dl in females, GFR ≥ 70 ml/min), 8 patients (38.1%) with moderate renal insufficiency (SCr $\leq 1.5/1.2-2.8$ mg/dl, GFR 30-60 ml/min), 4 cases (19.0%) with severe renal insufficiency (SCr ≥ 2.8 mg/dl, GFR ≤ 30 ml/min) and 3 cases without information. Hypertension was observed in all cases. A hypertension crisis occurred in 1 case (5). With respect to patient follow-up, 5 cases (23.8%) progressed to end stage renal disease (ESRD) and required routine dialysis. The remaining patients (76.2%) continued to show mild proteinuria and renal insufficiency.

The histological results for these cases of PV associated with renal disease included 8 cases (38.1%) of IgAN (5-11), 10 cases (47.6%) of focal segmental glomerulosclerosis

(FSGS) (3,12-19), 2 cases (9.5%) of membranoproliferative glomerulonephritis (MPGN) (20,21) and 1 case (4.8%) of rapidly progressive glomerulonephritis (RPGN).

Eight cases of PV associated with IgAN have been reported in the literature (5-11). All 8 patients were male with an average age of 47.87 years. Six cases (75%) presented NS, and 1 case (12.5%) presented moderate proteinuria. Five cases (62.5%) were positive for uric erythrocytes, and 2 cases (25%) were negative. The numbers of cases of normal, moderate and severe renal dysfunction were 2 (25%), 4 (50%) and 1 (12.5%), respectively. All 8 patients presented with hypertension, including 1 case with a hypertension crisis that was diagnosed histopathologically as mesangial proliferative glomerulonephritis (MsPGN), global glomerulosclerosis and necrotizing arteritis (5). Two cases also presented with hyperuricemia (8,9) and 1 case with cerebral infarction (5). Pathological observations of the LM analyses revealed 5 cases (62.5%) of MsPGN, 1 case (12.5%) of sclerosing glomerulonephritis (SGN) (7) and 1 case that was initially diagnosed as MPGN following the initial renal biopsy but was determined to be crescentic glomerulonephritis (CGN) with a second biopsy, which was performed after the patient experienced a rapid deterioration in renal function (11). Five cases (62.5%) exhibited glomerular crescent formation. The IF analyses revealed IgA deposition in the mesangium and glomerular capillary walls in all cases. Three cases (37.5%) presented with IgA deposition only. The numbers of cases associated with depositions of C3, IgM or IgG were 5 (62.5%), 3 (37.5%), and 1 (12.5%), respectively. Electron microscopy (EM) was only performed in 2 of the 8 cases (5,8), and revealed electron-dense deposits in the mesangial region and platelets attached to the glomerular capillary wall. For treatment, 2 cases underwent steroid therapy, 2 cases received RP and 1 case received mycophenolate mofetil along with anti-hypertensive, anticoagulant, anti-platelet and bone marrow suppression therapies (HU, busulfan and ranimustine). The prognosis of the patients was evaluated during the follow-ups. One patient (12.5%) with pathological features of SGN and crescent formations had a poor prognosis and required hemodialysis because of ESRD (7). No prognosis was reported in 3 cases. In the remaining 3 cases (37.5%), proteinuria and renal function were effectively controlled (Table I).

Ten cases of PV associated with FSGS have been reported (3,12-19). The average age was 55.8 years with a male-to-female ratio of 0.67. Six cases (60%) presented NS, and 4 cases (40%) presented mild proteinuria. Three cases (30%) were positive for uric erythrocytes, and 6 cases (60%) were negative. The numbers of cases of normal or mild, moderate, or severe renal dysfunction were 3 (30%), 4 (40%) and 2 (20%), respectively. The pathological LM analyses confirmed the FSGS diagnosis in all cases. One patient also showed focal ischemic nephropathy (18). With the exception of 3 cases without available IF data, negative IF results were reported in 4 cases (40%), a combination of IgM, C3 and C1q depositions were observed in 2 cases (20%), and IgA deposition was observed in 1 case. EM results were reported in 3 of 10 cases, in which sclerosis, swelling segmental vacuolar formation of the podocyte foot processes, and electron-dense material in the mesangial area and partial effacement of the podocyte foot process were observed. With respect to treatment, 5 patients received RP, 7 patients received HU and 5 patients received steroid and immunosuppressive

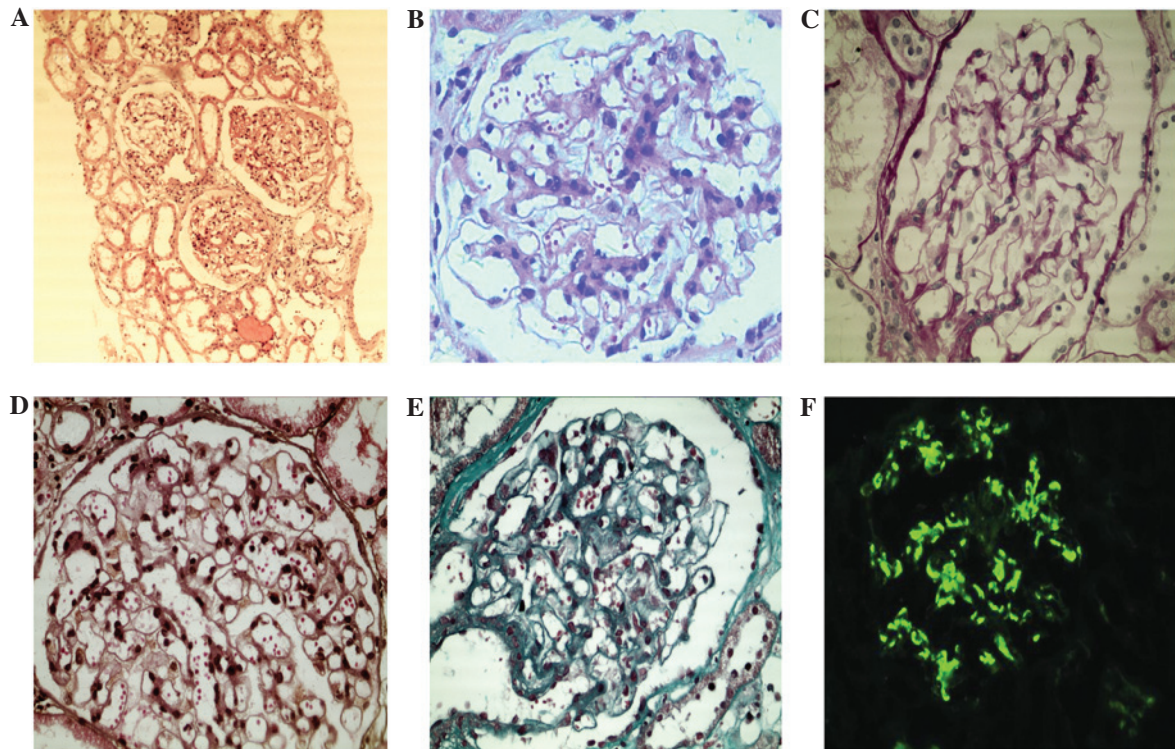


Figure 1. Light-microscopy and immunofluorescence microscopy of glomeruli. (A) H&E staining (magnification, x200); (B) H&E staining (magnification, x400); (C) PAS staining (magnification, x400); (D) PASM staining (magnification, x400); (E) Masson staining (magnification, x400). (A-E) Light-microscopy shows mild mesangial proliferation. (F) Immunofluorescence microscopy reveals intense granular IgA deposition in the mesangial area (magnification, x400). H&E, hematoxylin and eosin; PAS, periodic acid-Schiff; PASM, periodic acid silver methenamine; IgA, immunoglobulin A.

therapy. The prognosis of these patients was worse than that of the patients with IgAN. Four patients (40%) progressed to ESRD and required dialysis. In 6 patients (60%), proteinuria and renal function were effectively controlled (see Table II).

Three cases of PV associated with other pathological manifestations of renal disease have been reported.

Based on the literature, the possible pathogenesis of PV associated with renal disease may occur as follows. First, PV leads to increases in blood volume and viscosity, thus causing a passive expansion of the capillaries and intimal injury, which results in vascular microthrombi, glomerular capillary occlusion and a reduction in the GFR, thereby leading to tissue ischemia. If the ischemia persists without relief, it is likely to result in chronic renal damage. Second, PV is often associated with hypertension and hyperuricemia, which affect renal microcirculation. In addition, thrombocytosis and the abnormal activation of megakaryocytes might be critical factors for glomerular sclerosis. Cytokines and growth factors also play important roles. Au *et al* observed that increases in the number of megakaryocytes correlated with dysfunction and the overproduction of platelet-derived growth factor (PDGF) and transforming growth factor (TGF)- β in patients with PV (13). The degranulation of the platelet-induced sustained release of PDGF and other cytokines induces a rapid progression to crescentic glomerulonephritis and glomerulosclerosis. Nishi *et al* observed that in patients with PV associated with MPGN, platelets, macrophages and fibers could attach to the glomerular capillary wall and induce the upregulation of thrombomodulin in the capillaries and the PDGF receptor in mesangial cells (20). PDGF can subsequently stimulate the proliferation of glomerular mesangial cells and the

formation of extracellular matrix. TGF- β induces collagen and fibrinogen synthesis via mesangial cells, thus leading to mesangial sclerosis and podocyte apoptosis. These processes result in FSGS-like lesions. In addition, the medications used for PV treatment can cause renal impairment. Ravandi-Kashani *et al* reported that patients presented with thrombotic microangiopathy and RF following IFN therapy and subsequently required hemodialysis (23). Read *et al* observed that HU could induce dose-dependent minimal change nephrotic syndrome (MCNS) in Wistar rats. However, no similar results have been reported for humans (24).

The case reported in the present study is the ninth case of PV associated with IgAN. The patient was male, which is consistent with previous studies. More clinical evidence is required to conclude whether there are gender differences in the incidence of this disease. The protein- and hematuria were well controlled for >6 years with PV treatment. The patient's serum Ig and complement levels were normal. Both kidneys were relatively large and the SCr level was higher than normal, but GFR was within the normal range. The following points require consideration. i) The patient had no manifestations of tubular-interstitial damage, such as the increased output of nocturia and hypotonic urine, and it may be reasoned that the kidney damage caused by hypertensive renal arteriosclerosis and hyperuricemia was insufficient to explain the elevated SCr, and the glomerular lesions were the main diagnosis. ii) Renal hemodynamic changes could result in increased GFR in the early stage of diabetic nephropathy, and the GFR can gradually return to normal and then decrease to below normal in stage III. The patient might have experienced early stage hyperfiltration and hyperperfusion,

Table I. Selected features of patients with PV associated with IgAN.

Patient no.	Author (ref.), year	Age, years	Gender	PV duration	Renal biopsy LM; IF; EM	Pro; urinary RBC; Renal function	Clinical type	Symptoms	Therapy	Outcome Pro; SCr
1	Kim (6), 1994	56	M	NR	NR; IgAN; NR	7.8 g/day; Neg.; SCr 1.3 mg/dl	NS	HBP	NR	NR
2	Kasuno (5), 1997	35	M	5 years	MsPGN, NA, Cre; IgA, C3; EDD-GMA, PLT-CAP	4 g/day; 20-40/hp; CCr 34.2 ml/min, SCr 1.6 mg/dl	NS	HBP crisis	ACG, PSL	1.5 g/day; 1.2 mg/dl
3	Kasuno (5), 1997	51	M	SI	MsPGN, Cre; IgA, C3; NR	2.8 g/day; 30-40/hp; CCr 62.9 ml/min	GN	CI	BUS, RP	NR
4	Kwon (7), 1999	32	M	NR	SGN, Cre; IgA; NR	SCr 1 mg/dl	NS	HBP	NR	HD
5	Chung (8), 2002	46	M	SI	MsPGN; IgA, IgM, C3; EDD-GMA	9.14 g/day; 10-20/hp; GFR 34.09 ml/min, SCr 2.7 mg/dl	NS, CRF	HBP, HUA	HU, ACEI, CCB	2.7 g/day
6	Yaguchi (9), 2005	55	M	17 years	MsPGN, Cre; IgA, IgM, C3; NR	6.9 g/day; 664/ μ l; SCr 2.5 mg/dl	NS, CRF	HBP, HUA	PSL	3.4 g/day
7	Tian (10), 2011	55	M	NR	MsPGN, Cre; IgA, IgM, IgG, C3; NR	13.43 g/day; 202.3/ μ l SCr 1.15 mg/day	NS, CRF	HBP	MMF, ARB, CCB, RP	1.5 g/day; 56.5/ μ l, 0.9 mg/dl
8	Kanauchi (11), 1994	53	M	NR	MPGN ^a ; CGN; IgA; NR ^b	NR	RPGN	HBP	MCNU	NR

^aInitial biopsy; ^bbiopsy after 20 months of treatment. PV, polycythemia vera; LM, light microscopy; IF, immunofluorescence; EM, electron microscopy; IgAN, immunoglobulin A nephropathy; proteinuria; RBC, red blood cell count; SCr, serum creatinine; M, male; NR, not reported; SI, simultaneously; MsPGN, mesangioproliferative glomerulonephritis; NA, necrotizing arteritis; Cre, crescent formation; Ig, immunoglobulin; C3, complement 3; EDD, electron-dense deposits; GMA, glomerular mesangial area; PLT, platelets; CAP, capillary lumina; SGN, sclerosing glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; CGN, crescentic glomerulonephritis; Neg., negative; CCr, creatinine clearance; hp, high power field; NS, nephrotic syndrome; GN, glomerulonephritis; CRF, chronic renal failure; RPGN, rapidly progressive glomerulonephritis; HBP, hypertension; CI, cerebral infarction; HUA, hyperuricemia; ACG, anticoagulant; PSL, prednisolone; BUS, busulfan; RP, regular phlebotomies; HU, hydroxyurea; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; MMF, mycophenolate mofetil; ARB, angiotensin receptor blocker; MCNU, ranimustine; HSPGN, Henoch-Scholein purpura nephritis; HD, hemodialysis.

Table II. Selected features of patients with PV associated with FSGS.

Patient no.	Author (ref.), year	Age, years	Gender	PV duration	Renal biopsy LM; IF; EM	Pro; urinary RBC; Renal function	Clinical type	Symptoms	Therapy	Outcome Pro, SCr
1	Sharma (12), 1995	40	F	2 years	FSGS; NR; NR	2 g/day; Neg; SCr 2 mg/dl	GN, CRF	HBP	RP, MLS	0.24 g/day, 1.4 mg/dl
2	Au (13), 1999	28	M	20 years	FSGS; Neg.; GS	2.5 g/day; Neg; SCr 3.6 mg/dl	GN, CRF	HBP	HU, RP	PD
3	Au (13), 1999	41	F	14 years	FSGS; IgM, C3, C1q; NR	5.4 g/day; Neg; CCr 60 ml/min	NS	HBP	HU, RP	PD
4	Kosch (14), 2000	52	M	4 years	FSGS; Neg; EPE	4 g/day; Neg; SCr 1.1 mg/dl	NS	HBP	RP	0.4 g/day, NOR
5	Ulusoy (15), 2010	56	M	10 years	FSGS; Neg; NR	4-5.97 g/day; Neg; SCr 1.9 mg/dl	NS, CRF	HBP	RP, IFN, ACEI, PSL	1.26 g/day; 1.4 mg/dl
6	Okuyama (3), 2007	69	F	3 years	FSGS; IgM, C3, C1q, Fn; NR	8.3 g/day; Neg; SCr 1 mg/dl	NS, CRF	HBP	HU, PSL, MLS	2.1 g/day; 0.53 mg/dl
7	Martín (16), 2010	83	F	4 years	FSGS; NR; NR	4.2-8.4 g/day; 6,750/ μ l SCr 1.1-3.6 mg/dl	GN + NS CRF	NR	HU, PSL	HD
8	Iyoda (17), 2005	66	F	3 years	FSGS; NR; NR	9.6 g/day; NR; NR	NS, CRF	HBP	HU, PSL	HD
9	Cai (18), 2011	78	M	4 years	FSGS; ISCH KI; Neg; NR	2-3.5 g/day; +; SCr 2.11 mg/dl	GN + NS CRF	HBP	HU	1.72 g/d
10	Dai (19) 2008	45	F	SI	FSGS; IgA, IgM; EDD-GMA, EPE	eGFR 34.53 ml/min 0.714 g/day; ++; SCr 0.51 mg/dl	GN	HBP	HU, ARB, APD	0.228 g/day

PV, polycythemia vera; FSGS, focal segment glomerulonephritis; LM, light microscopy; IF, immunofluorescence; EM, electron microscopy; RBC, red blood cell count; Pro, proteinuria; SCr, serum creatinine; F, female; M, male; NR, not reported; Neg, negative; GS, glomerulosclerosis; C3, complement 3; Ig, immunoglobulin; Fn, fibronectin; ISCH KI, ischemic kidney injury; EDD, electron-dense deposits; GMA, glomerular mesangial area; EPE, epithelial podocyte effacement; CCr, creatinine clearance; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; CRF, chronic renal failure; NS, nephrotic syndrome; HBP, hypertension; CI, cerebral infarction; RP, regular phlebotomies; MLS, myelosuppressive; HU, hydroxyurea; IFN, interferon; ACEI, angiotensin-converting enzyme inhibitor; PSL, prednisolone; ARB, angiotensin receptor blocker; APD, antiplatelet drug; PD, peritoneal dialysis; NOR, normal.

followed by a reduction in the GFR to the normal range when the disease progressed to the elevated SCr stage. However, diabetic nephropathy is a glomerulosclerosis caused by the thickening of the glomerular capillary basement membrane and mesangial dilation, and IF mainly showed an IgG deposit. For this patient, only a mild diffuse hyperplasia of the mesangial cells and matrix was observed, and the pathological manifestation was mild, which was inconsistent with the elevated SCr and significantly different from renal damage caused by hyperfiltration in diabetic nephropathy. iii) No micro-thrombosis or platelet aggregation was observed in the renal tissues, and the coagulation tests did not show a high-coagulation or high-viscosity state. Therefore, renal hemodynamic changes were believed to play a major role in this patient. iv) Makdassy *et al* studied the pathogenesis of IgAN in 322 patients and observed its association with other diseases in 57.8% of cases, among which it was associated with hematopathy in 3.7%, and generally associated with PV (25). The main mechanism might be the increased formation of IgA immune complex and reduced clearance. The patient experienced a sore throat 1 week prior to hospitalization; therefore, the cause of the IgAN may be questioned. Possibly, the IgAN was combined with the 6-year PV diagnosis, or the IgAN was induced by the excessive activation of B cells and their differentiation toward IgA-producing plasma cells due to the recent immune regulation dysfunction of the palatine tonsils. We are certain that PDGF is associated with IgAN activity, which stimulates mesangial cell proliferation and is involved in the formation and development of IgAN nephropathy. In patients with PV, PDGF expression increases and significantly promotes the progress of IgAN. v) Finally, in some patients with secondary IgAN, IgAN could be improved or alleviated following the elimination of the cause. For the patient of the present study, the 24-h UR was positively correlated with the blood cell counts, which was consistent with this characteristic.

Currently, whether renal disease is a complication or comorbidity of PV remains unclear. More clinical evidence is required to confirm a causal relationship.

The comparison of the two main pathological types of PV combined with renal disease showed the following characteristics: i) IgAN mainly occurred in males. There was no detectable gender difference in the FSGS incidence and the age of onset for FSGS was older than for IgAN. ii) NS was the predominant clinical manifestation of both IgAN and FSGS, IgAN was often accompanied with hematuria and mild-to-moderate renal insufficiency. FSGS progressed relatively faster.

In summary, the present study reports a rare clinical case of IgAN in a patient with PV. Although PV associated with renal disease is rarely observed in clinical practice, there are a variety of pathological types, which should be considered by clinicians during the diagnosis and treatment of PV. More clinical studies are necessary to further characterize the clinical and histopathological features and incidence of this disease to develop the most appropriate treatment strategies.

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