**Case Report**

**IgA nephropathy associated with polycythaemia vera: accelerated course**

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**Key words:** crescentic glomerulonephritis; IgA nephropathy; platelet aggregation; polycythaemia vera

**Introduction**

Although cases of erythrocytosis with concomitant glomerulonephritis (GN) have occasionally been reported, there are few reports regarding polycythaemia vera. Polycythaemia vera is a myeloproliferative disorder resulting from clonal expansion of a transformed haematopoietic stem cell associated with prominent overproduction of erythrocytes, and to a lesser extent expansion of granulocytic and megakaryocytic elements. Previous reports presented three cases of polycythaemia vera associated with diffuse mesangiproliferative GN [1], and one case associated with Henoch–Schönlein purpura nephritis [2]. None of these cases was examined by immunofluorescence (IF) or electron-microscopy (EM). We report on two patients with concomitant polycythaemia vera and immunoglobulin-A nephropathy (IgA-N) with simultaneous aggravation of proteinuria and erythrocytosis. Renal biopsy specimens of both patients showed active crescentic GN with mesangial proliferation accompanied by mesangial predominant depositions of IgA. EM revealed aggregated platelet adhesion to the capillary walls of the glomeruli. The possible pathogenesis for the simultaneous aggravation is discussed.

**Case report**

Patient 1, a 35-year-old Japanese male, was referred to our hospital in June 1994 because of a hypertensive crisis (224/140 mmHg) with headache, visual disturbance, and dark urine. He had been normotensive until March 1994 when he developed an upper respiratory infection. His past history included recurrent gout attacks and urolithiasis from the age of 27 years, along with mild proteinuria and haematuria and mild polycythaemia 5 years before admission, blood values were haematocrit (Htc) 52%, white blood cell count 13 000/mL, red blood cell (RBC) count 5 600 000/mL, and platelet count 434 000/mL. There was no family history of hypertension; however, his father also had gout.

On admission, the patient was afebrile, but the skin on his face had a reddish hue. There was considerable eczema around the nose, cheeks, and forehead. The optic fundi showed retinal haemorrhage compatible with stage III hypertension and stage II arteriolosclerotic retinopathy by Scheie’s classification. Cardiac auscultation revealed accentuated second and fourth heart sounds. There was neither splenomegaly nor abdominal bruil. Both lower extremities had pruritus and the ankles were swollen with tenderness.

Patient 2, a 51-year-old male with a prior history of polycythaemia vera was referred to our department in September 1983 for the evaluation of intense proteinuria and haematuria. He had a 10-year history of bilateral pruritic legs and a 6-year history of a floating sensation with some episodes of fainting and dysbasia. At 47 he was hospitalized with cerebral infarction, and polycythaemia vera with mild proteinuria was simultaneously diagnosed. However, the treatment with busulfan and phlebotomy did not start until the next year when he began to complain of headaches, nausea, vomiting, and right facial palsy. He had been normotensive and among his relatives, only his father had moderately high blood pressure.

On admission, he presented with a reddish face, injected conjunctivae, and moderate hepatosplenomegaly. Neurological signs and the findings on head CT scan were consistent with cranial nerves VIII and IX damage due to cerebral infarction. Repeated and frequent blood pressure measurements were within normal limits.

Urinalysis in both cases demonstrated intense proteinuria (patient 1, 4.0 g/day; patient 2, 2.8 g/day) and haematuria (20–40 RBCs, 30–40 RBCs per high-power field in the sediments respectively) with numerous RBC casts. Creatinine clearance was moderately decreased.

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IgA nephropathy with polycythaemia vera

(34.2 ml/min; 62.9 ml/min respectively). Blood chemistry revealed increased serum uric acid (11.1 mg/dl; 9.2 mg/dl respectively), and serum creatinine was elevated in patient 1 (1.6 mg/dl) and normal in patient 2 (1.0 mg/dl). Cortisol, catecholamine, thyroid and parathyroid hormone levels were within the normal range. High plasma renin activity (PRA) (4.5 ng/ml/h) was noted in patient 1. Antineutrophil cytoplasmic autoantibodies (ANCA) were negative in patient 1.

As shown in Table 1, both patients showed marked elevation of Htc with poikilocytosis, target cells, metamyelocytes, and myelocytes. $^{51}$Cr-labelled autologous red cell measurement disclosed elevated RBC mass despite depressed serum erythropoietin (Epo) and normal arterial oxygen saturation in both cases. Bone marrow aspirations demonstrated hypercellularity and normal cell maturation with an increased number of megakaryocytes and myeloids. Philadelphia chromosomes were negative. Erythrocyte stem cell assay in patient 2 disclosed the Epo independence of endogenous erythroid colonies. Platelet aggregability in patient 2 was also decreased.

Both renal biopsy specimens showed moderate mesangio proliferative lesions with mesangial IgA (Figure 1a) and C3 deposition. IgA was the predominant immunoglobulin detected in the IF study. In patient 1, six of 17 (35%) glomeruli showed global sclerosis and another seven showed cellular or fibrocellular crescent formation (Figure 1b). Necrotizing arteritis with occlusion of the small arteries was sporadically observed. EM revealed platelets with and without granules, in addition to mesangial electron dense deposits, attached to the capillary walls along with microthrombi (Figure 2). In patient 2, two of 11 (18%) glomeruli were globally sclerosed and showed fibrous crescent formation. There were no necrotizing arterial lesions detected in this case. Scattered atrophic tubules with fibrosis and moderate cellular infiltrations were observed.

Treatment with manidipine, methyldopa and phlebotomy normalized the PRA in patient 1. Anticoagulant therapy with 20 000 units of heparin daily revealed increased serum uric acid (11.1 mg/dl; 9.2 mg/dl respectively), and serum creatinine was elevated in patient 1 (1.6 mg/dl) and normal in patient 2 (1.0 mg/dl). Cortisol, catecholamine, thyroid and parathyroid hormone levels were within the normal range. High plasma renin activity (PRA) (4.5 ng/ml/h) was noted in patient 1. Antineutrophil cytoplasmic autoantibodies (ANCA) were negative in patient 1.

Discussion

Two patients with rapidly progressive type IgA-N with concomitant polycythaemia vera were reported. In these patients, the diagnoses of polycythaemia vera were based on clinical manifestations, physical findings, and laboratory results including the increased numbers of three blood cell lineages. Both patients had depressed serum immunoreactive Epo levels, which is accordant with the earlier report of Cotes et al. [3]. Furthermore, in patient 2, early erythroid progenitors from the bone marrow produced endogenous erythroid bursts in the absence of Epo, which is a typical finding of polycythaemia vera [4].

Only two reports of polycythaemia vera with concomitant renal parenchymal disease have been published [1,2], whereas erythrocytosis with accompanying renal disease has been reported more often. First, Plomley et al. [1] reported six patients with polycythaemia vera and proteinuria. It is interesting that half of the cases showed mesangio proliferative GN accompanied by hypertension as in our patient. However, the diagnosis of IgA-N was not clearly established, since there were no data from IF studies. Second was a combination of polycythaemia vera and Henoch–Scho¨nlein purpura [2] which showed crescentic GN. The histological findings of necrotizing crescentic GN resembled that of our patients who had no signs of Henoch–Scho¨nlein purpura. They specu-

Table 1. Hematological findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell (/mm$^3$)</td>
<td>15 400</td>
<td>17 800</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>66800000</td>
<td>76600000</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>21.6</td>
<td>20.6</td>
</tr>
<tr>
<td>Platelet (/mm$^3$)</td>
<td>62.8</td>
<td>60.0</td>
</tr>
<tr>
<td>Reticulocyte (%)</td>
<td>421000</td>
<td>11500000</td>
</tr>
<tr>
<td>Red cell mass (normal range 28 ± 3 ml/kg body-weight)</td>
<td>20.8</td>
<td>ND</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>35*</td>
<td>45.5</td>
</tr>
<tr>
<td>Leukocyte alkaline phosphatase activity</td>
<td>96.5</td>
<td>96.0</td>
</tr>
<tr>
<td>Serum $B_{12}$ (normal range, 200–1000 pg/ml)</td>
<td>88%, 228</td>
<td>96%, 414</td>
</tr>
<tr>
<td>Serum erythropoietin (normal range 14.7–31.0 mIU/ml)</td>
<td>438</td>
<td>1382</td>
</tr>
<tr>
<td>Erythrocyte stem cell assay</td>
<td>ND</td>
<td>61.7%$^a$</td>
</tr>
<tr>
<td>Platelet function</td>
<td>ND</td>
<td>Disturbed$^c$</td>
</tr>
</tbody>
</table>

$^a$Datum measured after emergency phlebotomy of 250 ml of blood. $^b$Growth rate of endogenous erythroid colonies in the absence of erythropoietin is expressed as a percentage of the growth rate in the presence of erythropoietin. $^c$Maximal aggregation by collagen was 54% and aggregation by adrenaline (5 mM) was absent in aggregometer. ND, not done.
Fig. 1. Immunohistology and light-microscopy of the glomeruli in patient 1. (a) Immunofluorescence microscopy revealed intense granular IgA deposition with cytosolic IgA-positive lymphocyte in the mesangial area. (b) Light-microscopy shows marked mesangial proliferation and fibrocellular crescent formation (H&E, × 380).

Fig. 2. Electron-microscopy in patient 1. Electron-dense deposits in the mesangial area (large arrow) and platelets in the capillary lumina are seen. Some of these platelets (small arrows) demonstrate characteristic granules, aggregate together, with elongated pseudo-legs. Another (large arrowhead) is attached to the capillary wall. Around these platelets, fibrin-like materials (small arrowhead) form in contact with the endothelium. (× 4000).
lated that ANCA may have led to an exacerbation of the GN; however, they did not test ANCA in their patient’s serum. We confirm the absence of ANCA in patient 1.

It is well known that thrombotic episodes are common in patients with polycythaemia vera, and therefore it is important to speculate on the relationship between the microthrombosis and the exacerbation of the GN in our cases. In patient 1, the malignant hypertension was associated with the exacerbation of GN. Indeed, polycythaemia vera itself is known to be a cause of hypertension; however, the severe hypertension observed in patient 1 is unusual [5]. It was notable that his severe hypertension became controllable after the aggressive treatment of the glomerular lesion. Although patient 2 was normotensive after hospitalization, intermittent hypertension cannot be excluded, because ambulatory blood pressure monitoring was not available. In addition, he showed signs of cerebral infarction before the exacerbation of GN. It is likely that severe circulatory disturbances, with or without hypertension, were closely related to the progressive course of GN in polycythaemia vera.

Recent reports have shown that several cytokines and growth factors play a role in the progression of GN. Nakamura et al. demonstrated abnormally upregulated mRNA expression of platelet-derived growth factor (PDGF) B-chain [6] and insulin-like growth factor-1 (IGF-1) [7] in peripheral blood mononuclear cells (PBMC) from patients with IgA-N. In addition, a positive correlation was found between mRNA levels of PDGF B-chain or IGF-1 and urinary protein excretion or the histopathological findings. IGF-1 is also considered to be a candidate factor for the exacerbation of polycythaemia vera. Under complete medium-free conditions, Correa et al. [8] reported that the proliferation of circulating burst-forming unit-erythroid from polycythaemia vera patients was significantly increased by IGF-1, but not by Epo compared with those from normal controls. They concluded that endogenous bursts and colony formation characteristics in polycythaemia vera were not due to the hypersensitivitiy of erythroid progenitors to Epo, but to IGF-1. These reports indicate that in addition to severe circulatory disturbances, some cytokines, especially IGF-1, might exacerbate IgA-N with polycythaemia vera.

In this report, we present EM findings showing aggregated platelets adhering to the capillary walls in the renal specimen from patient one, which is sometimes observed in active IgA-N [9]. The sudden transformation of IgA-N from mild to active crescentic type in these cases is highly suspected to be due to the increased number of platelets and leukocytes, including monocytes, and slow blood flow caused by high viscosity [10]. These factors contribute to activate platelets and/or inflammatory cells. Degranulating platelets may promote proliferation of glomerular cells possibly via PDGF and other cytokines. Further release of PDGF from intrinsic glomerular cells sustains the proliferation [11] and glomerular monocyte/macrophage infiltration, which may contribute to the progression to glomerulosclerosis. Furthermore, IGF-1 is characteristically secreted from PBMC in active IgA-N, and stimulates IGF-1-hypersensitive erythroid progenitors to expand extraordinarily. This excessive haematopoiesis accelerates the polycythaemia state, which further induces greater glomerular injury resulting in a vicious cycle. Simultaneous amelioration of both IgA-N and polycythaemia vera in patient 1 indicates that prompt and strict treatment to block these vicious circles in addition to appropriate treatment of high blood pressure may be beneficial in patients with this combination of diseases.

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