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Clinical Characterization of Polycythemia Vera Associated with IgA Nephropathy in a Single Chinese Center

Wang Xia[1], Yang Nannan[2], Lu Chunyu[3], Xu Feng[1], Cheng Zhen[1], ZhangTi[1] and Wang Jinquan[1]*

[1]*Jinling Hospital, Nanjing University School of Medicine, Nanjing, 210016, PR China*
[2]*Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, 210004, PR China.*
[3]*Nanjing University of Chinese Medicine, Nanjing, 210004, PR China*

Abstract

Polycythemia vera (PV) is a myeloproliferative disorder which is characterized by excessive production of erythrocytes as well as myeloid and megakaryocytic proliferation. PV associated with IgA nephropathy (IgAN) has rarely been reported in the literature. The long-term renal prognosis of these patients is unknown. PV associated with IgAN mainly occurred in males and was often accompanied with hematuria and mild-to-moderate renal insufficiency. Long term prognosis was good for most patients, and few progressed relatively faster to ESRD has been observed in our study.

Keywords: IgA • Nephropathy • Polycythemia vera • Prognosis

Introduction

Polycythemia vera (PV) is a clonal stem cell disorder, characterized by increased erythrocyte production, and identified as a chronic myeloproliferative disorder [1]. PV is a rare disease with an incidence rate estimated in Europe and in the United States at approximately 1.9-2.3 new cases/100,000 persons per year. The incidence of PV is slightly higher in male than female, and is highest for males aged 70-79 years.

The incidence of PV combined with glomerulonephritis (GN) is quite low [2,3]. IgA nephropathy (IgAN), focal segmental glomerular sclerosis (FSGS), diffuse mesangial proliferative glomerulonephritis, Henoch-Schonlein purpura nephritis may be presented in PV patients. So far, only 23 cases of PV associated with IgAN have been reported, in which patients presented with proteinuria and hematuria with or without mild renal dysfunction [2]. Here, we retrospectively investigated the clinicopathological features and long-term prognosis of 7 cases of PV associated with IgAN.

Methodology

We reviewed the renal pathology archives at Jinling hospital, NanJing, from January 2003 to Febuary 2013, and 7 biopsy-proven IgAN combined with history of PV were enrolled in this study. The diagnoses of PV were established according to the criteria proposed by World Health Organization [4]. The diagnostic criteria of IgAN included IgA deposition or predominant IgA deposition in the glomerular mesangium as shown by immunofluorescence microscopy. Patients with Secondary IgAN were not included.

Each patient was subjected to detailed demographic information, and underwent clinical examination (including renal biopsy, the routin examination, biopsy of bone marrow biopsy and JAK2V617F).

***Address for Correspondence:** Wang Jinquan, Jinling Hospital, Nanjing University School of Medicine, Nanjing, 210016, PR China, Tel: +862580862005, Fax: +862580862005; E-mail: wangjq@medmail.com.cn*

Zhang Ti, Jinling Hospital, Nanjing University School of Medicine, Nanjing, 210016, PR China, Tel: +862580862005, Fax: +862580862005; E-mail: drteezhang@163.com

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Results

The study consisted of 7 men with a mean age of 49.1±18.8 years at the time of renal biopsy. Case 1 and 4 were diagnosed with PV and IgAN at the same time. Case 3, 5 and 6 were diagnosed with PV before the kidney damage. Case 2 and 7 were diagnosed with PV followed by IgAN. The history of hypertention was presented in case 2, 3, 5, 6, multiple lacunar infarction was presented in case 6, and splenomegaly was presented in case 2, 4, 5. When the patients were admitted to our hospital, their chief complaints were proteinuria and microscopic hematuria. Heavy proteinuria was found in case 1 and 2. All the patients except case 1 had microscopic hematuria. Mean serum creatinine levels were 1.17±0.36 mg/dl. Mean blood platelet levels were 332×109±78×109g/L, hemoglobin levels were 187±29 g/L and hematocrit levels were 0.563±0.087 on diagnosis of PV (Table 1). Histologically, all the

Table 1. Clinical data of patients with polycythemia vera associated with IgAN at renal biopsy.

Patient	1	2	3	4	5	6	7
sex	M	M	M	M	M	M	M
Age at biopsy(y)	22	40	55	33	70	73	51
PV duration(m)	31	30	61	16	358	144	48
Renal disease duration(m)	31	32	50	16	83	108	216
Hypertension	No	Yes	Yes	No	Yes	Yes	No
Splenomegaly	No	Yes	No	Yes	Yes	No	No
Hemoglobin (g/L)	186	223	210	201	149	158	175
PLT (10^9/L)	250	256	333	439	410	306	341
WBC (10^9/L)	6.2	10.9	9.2	9.7	8.9	5.2	5.4
HCT	0.557	0.599	0.67	0.628	0.445	0.479	0.514
Proteinuria (g/24h)	11.76	9.63	2.1	1.25	2.06	0.73	0.25
Urinary microscopic hematuria (10000 cells/ml)	1	570	95	72	12	22	10
Serum albumin (g/L)	23.2	31.4	38.5	40.8	45.7	46.5	46
Serum creatinine (mg/dl)	1.09	1.05	1.91	0.75	1.19	1.28	0.95
eGFR (ml/min/1.73 m^2) at biopsy	98.89	84.04	37.95	130.77	65.35	59.3	90.99
bone marrow	+	+	+	+	+	+	+
JAK2V617F	-	-	+	+	ND	-	ND
BCR-ABL	-	-	-	-	ND	-	ND

Abbreviations: pv : Polycythemia Vera; M: Male; PLT: Platelet; WBC: White Blood Cell Count; HCT: Hematocrit

Table 2. The outcome of the 7 patients

Patient	1	2	3	4	5	6	7
Hemoglobin (g/L)	166	155	83	160	132	151	163
PLT (10^9/L)	222	224	557	554	724	314	322
HCT	0.505	0.47	0.495	0.491	0.407	0.439	0.48
Proteinuria (g/24h)	0.12	0.81	1.8	0.52	1.66	0.81	0.29
Urinary microscopic hematuria (10000 cells/ml)	1	4	127	2	32	16	3
Serum albumin (g/L)	47.7	40.9	54.2	49.1	43.1	43.3	43.7
Serum creatinine (mg/dl)	1.02	1.17	8.19	0.75	3.53	1.14	1.35
eGFR (ml/min/1.73 m^2)	95.31	73.53	6.3	130.77	17.08	68.41	58.98
Treatment	P+HU+ARB	P+TW+LEF+HU+ARB	TW+HU+ACEI	HU+IFN+ARB	TW+HU	IFN+ARB	TW+HU
Follow-up from biopsy (m)	31	30	48	14	82	48	144

Abbreviations: PLT: Platelet; HCT: Hematocrit; P: Prednisone; HU: Hydroxycarbamide; TW: Tripterygiumwilfordii; LEF: Leflunomide; ARB: Angiotensin Receptor Blocker; ACEI: Angiotensin-Converting Enzyme Inhibitor; IFN: Interferon; CR: Complete Remission; PRD: Persistent Renal Dysfunction; KT: Kidney Transplantation

patients performed bone marrow biopsy test, which revealed relative erythroid hyperplasia and atypical megakaryocyte proliferation consistent with a chronic myeloproliferative disorder. All cases performed the test of JAK2V617F and BCR-ABL. The mutant allele leading to a valine to phenylalanine substitution at amino acid 617 (V617F) of the JAK2 tyrosine kinase was found in case 3, and 4.

The renal biopsy showed mild mesangial proliferation in 5 patients, moderate/severe mesangial proliferation in 2 patients. Tubules were mildly atrophic and epithelial cells displayed degeneration or regeneration. Immunofluorescence microscopy revealed diffuse granular deposition of dominant IgA in mesangium with less amount of C3. Ultrastructurally, mesangial and paramesangial electron-dense deposits with the mesangial matrix widening were observed.

Before admission, case 3, 5 and 6 were diagnosed with PV in other hospitals, and case 3 and 5 received hydroxycarbamide, case 6 received interferon after diagnosed. Case 3 and 6 received ACEI/ARBs at the same time. After admission to Jinling hospital and diagnosed with IgAN by renal biopsy, case 2, 3, 5 and 7 received Tripterygium wilfordii, case 1 and 2 were also received prednisone. Case 1 and 4 received hydroxycarbamide. During the follow-up, case 2 and 7 were diagnosed with PV and received hydroxycarbamide. After follow-up of 56.7±44.0 months (ranging from 14 to 144months), mean blood platelet levels were 416×109 ± 194×109g/L, hemoglobin levels were 144 ± 29 g/L and hematocrit levels were 0.470 ±0.03. The urine protein was 0.85± 0.64 g/24h compared with 3.97±4.68 g/24h at the time of biopsy. Case 3, 5 and 7 showed persistent renal dysfunction and case 3 progressed to ESRD and had hemodialysis for 5 years before renal transplantation (Table 2).

Discussion

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) of unknown etiology that involves the clonal proliferation of erythrocytes. IgAN is recognized as the most common glomerulonephritis worldwide, and it can be combined with other diseases. PV associated with renal disease is clinically rare. To the best of our knowledge, only 11 cases of PV associated with IgAN have been reported in the literature [2, 5-11]. The twelvepatients were ten males and one females with a mean age of 45.1±12.6 years. Seven cases (58.3%) presented NS, 3 case (25%) presented moderate proteinuria. Nine cases (75%) were positive for uric erythrocytes, and 2 cases (16.7%) were negative. Hypertention and nephrotic syndrome-range proteinuria (58.3%) were most common clinical presentation reported in the literature. With respect to patient follow-up, 1 cases (8.3%) progressed to ESRD and required routine dialysis. In the remaining 3 cases (25%), proteinuria were complete remission. In our study, 4(57%) cases were presented with hypertension, 2cases (29%) were presented with nephrotic syndrome-range proteinuria and 5 cases (71%) were presented with proteinuria. The renal insufficiency was common presentation reported in the literature. The renal outcome in our study was followed up 56.7±44.0 months. Case 3 reached ESRD, whose renal histological biopsy showed 38.4% global and 7.6% segmental glomerular sclerosis. The Proteinuria was completely remitted in case 1 and 7, proteinuria and renal dysfunctions were effectively controlled in case 2, 4 and 5, and proteinuria remained stable in case 6. During the follow-up period, there were significant differences in hemoglobin levels and hematocrit leves.

Hypertension and thrombotic complications are commonly found, which accelerate the progression of PV in patients with IgAN. Cytokines and growth factors, such as platelet-derived growth factor (PDGF) and TGF-β, also play important roles in the pathogenesis in renal disease associated with PV. PDGF is the most potent stimulus of mesangial cell proliferation, and it also induces extracellular matrix produced by mesangial cells [12,13]. TGF-β induces mesangial sclerosis by enhancing the synthesis of collagen and fibronectin of mesangial cells, and has pro-apoptotic podocyte effects, which may promote podocyte depletion and the FSGS lesions seen in most cases [14-16]. Based on the present literatures, the possible pathogenesis of PV associated with renal disease include changing blood volume and viscosity which resulted in mesangial hypercellularity and matrix proliferation, vascular microthrombi, interstitium ischemia, and more rapid progression of renal failure. However, according to the literature, the coexistence of the two diseases might be simply coincidental and no causative relationship is presented.

There are some limitations in our study which related to its retrospective nature and small size. We were unable to assess the incidence of PV associated with IgAN or determine the serum levels of growth factors. This study will hopefully demonstrate the clinicopathological features and long term prognosis.

Conclusion

The clinical characteristics of PV associated with IgAN were common in males. Nephrotic-range proteinuria and renal insufficiency as well as histologically changes (variable degrees of mesangial proliferation and segmental sclerosis) were always found in these patients. The long term prognosis is good for most patients.

Disclosure

The author reports no conflicts of interest in this work.

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