

## Co-existence of Ig A nephropathy and polycythemia vera, case report

Kaynar K<sup>1</sup>, Özben O<sup>2</sup>, Karaduman MM<sup>2</sup>, Mungan S<sup>3</sup>, Güvercin B<sup>1</sup>

<sup>1</sup>Department of Nephrology

<sup>2</sup>Department of Internal Medicine

<sup>3</sup>Department of Pathology

Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

### Abstract

**Background:** Polycythemia vera (PV) is a chronic myeloproliferative disease. Kidney involvement in PV is not a clinical manifestation. However, rarely, especially untreated, uncontrolled forms of PV may complicate ischemic and proliferative glomerular diseases with fibrosis.

**Description of the case:** This paper reports a 53-year-old male patient treated for PV for two years. A gradual decrease in kidney function with proteinuria was observed. This is the first report of a controlled PV patient with a newly diagnosed advanced immunoglobulin A nephropathy (IgAN) entity from Türkiye.

**Conclusion:** In conclusion, repeat urinalysis in every patient should be performed for hematuria and proteinuria in order not to delay the diagnosis of kidney involvement. IgAN and PV's togetherness is rare, but the underlying mechanisms must be elucidated. HIPPOKRATIA 2025, 29 (1):35-38.

**Keywords:** Glomerulonephritis, immunoglobulin A nephropathy, hypertension, renal, polycythemia vera

**Corresponding author:** Prof. Dr. Kubra Kaynar, Karadeniz Teknik Üniversitesi, Tıp Fakültesi, Nefroloji Bilim Dalı, 61080 Trabzon, Turkey, tel: +905422415879, fax: +904623252270, e-mail: kkaynar@yahoo.com

### Introduction

The prevalence of immunoglobulin A nephropathy (IgAN) among patients with primary glomerulonephritis (GN) differs between the countries (45, 22, 11, and 25 % in China, Europe, USA, and Türkiye, respectively). It is even different in the distinct time periods within the same countries<sup>1,2</sup>. The genes that code Ig A are found on chromosome 14<sup>3</sup>. The major known factors for the genesis of IgAN are abnormal glycosylation patterns in the liver, abnormal IgA-producing plasma cells, the presence of galactose-deficient O-glycans in the hinge region of IgA1 (GD-IgA1), and genetic defects leading to nephritogenic IgA production by abnormal gastrointestinal tract-associated mucosal immune response<sup>4,5</sup>. Approximately 40 % of patients with IgAN end up with end-stage kidney disease (ESRD) in nearly 20 years<sup>5</sup>. Therefore, clinicians should be aware of IgAN, which is most common in all GN types and usually asymptomatic, by screening urine for microscopic hematuria<sup>5</sup>.

Polycythemia vera (PV), with an estimated incidence of 1.9/100000 per year, is an acquired and rare myeloproliferative neoplasm (MPN) that is caused by specific *JAK2* (Janus kinase 2) mutation in exons 14 or 12 resulting in erythrocytosis, thrombocytosis, hepatosplenomegaly, hypertension, erythromelalgia, leukocytosis, and thromboses<sup>6</sup>. The kidney diseases associated with MPN were reported as focal segmental glomerulosclerosis,

IgAN, nonIgA mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, ischemic glomerulopathies, and minimal change disease<sup>7,8</sup>. Fifteen published cases are reporting the development of IgAN in patients with PV<sup>8-13</sup> (Table 1). The literature also reported that erythrocytosis was observed in 3.5 % of patients with IgAN, and recovery of anemia was better in the post-transplantation period of patients with IgAN<sup>7</sup>. The mechanism underlying the togetherness of these two discrete entities (whether situations are present) is not evident.

Here, we present the first case of newly diagnosed but advanced IgAN treated for PV for two years from Türkiye.

### Case report

A 53-year-old male patient was diagnosed with PV two years before based on the WHO 2016 diagnostic criteria<sup>8</sup> with a hemoglobin value of 20 g/dL, *BCR/ABL* (P210)-major negativity, V617F mutation positivity in *JAK2* gene, and low serum erythropoietin levels. He had a medical history of hypertension (follow-up period of 10 years), duodenal ulcer bleeding episode due to peginterferon alpha-2a (one year ago), and hypercholesterolemia (follow-up period of two years). He was treated with amlodipine (10 mg/d), doxazocin (8 mg/d), furosemide (120 mg/d), paroxetine (20 mg/d), sucralfate (1g/d), esomeprazole (40 mg/d), and aspirin (100 mg/d). He was

referred to the nephrology department to detect a gradual increase in serum creatinine levels from 1 to 3 mg/dL over two years (Figure 1). His main complaint was leg swelling. The blood pressure was 160/85 mm Hg, bilateral pitting pretibial edema was positive, and physical examination revealed anxiety mood and mild (second-degree) hypertensive retinopathy. Initial evaluations revealed proteinuria of 13.1 g/d, albuminuria of 9.3 g/d, creatinine clearance of 32.5 mL/min, and erythrocyturia of 80 /mL (normal <10) (Figure 2). Proteinuria and albuminuria were rechecked and found to be 8.8 and 6.35 g/d, respectively. Osteopenia was detected by bone mineral densitometry. Echocardiography detected left ventricular hypertrophy. Autoantibodies (antinuclear, anti-dsDNA, anti-Ro-52, anti-Ro/SSA, anti-centromere, anti-La/SSB, anti-Scl 70, anti-Smith, anti-glomerular basement membrane, and anti-neutrophil cytoplasmic antibodies) and hypocomplementemia were not detected. A kidney biopsy was performed.

Pathological examination shows that seven out of 14 glomeruli are globally sclerotic, diffuse, and severe mesangial matrix expansion, and cellular proliferations are observed in the remaining glomeruli. Lobulations are found in four glomeruli. Segmental sclerosis, fibrous crescent, and fibrin microthrombi are present in other glomeruli. Severe (95 %) interstitial fibrosis, patchy chronic inflammation, microcalcification, and subintimal vascular fibrosis are also observed. Immunofluorescence microscopy revealed dominant (+3) IgA deposition, moderate (+2) C3 and lambda, and mild (+1) IgG and kappa depositions (Figure 3). IgAN with a MEST-C score of M1E0S1T2-C1 was diagnosed. Prednisone (32 mg), dapagliflozin (10 mg), calcium (600 mg) - vitamin D (400 IU), ramipril (2.5 mg), and nebivolol (5 mg), and allopurinol (150 mg) were

added to previous treatments (Figure 1).

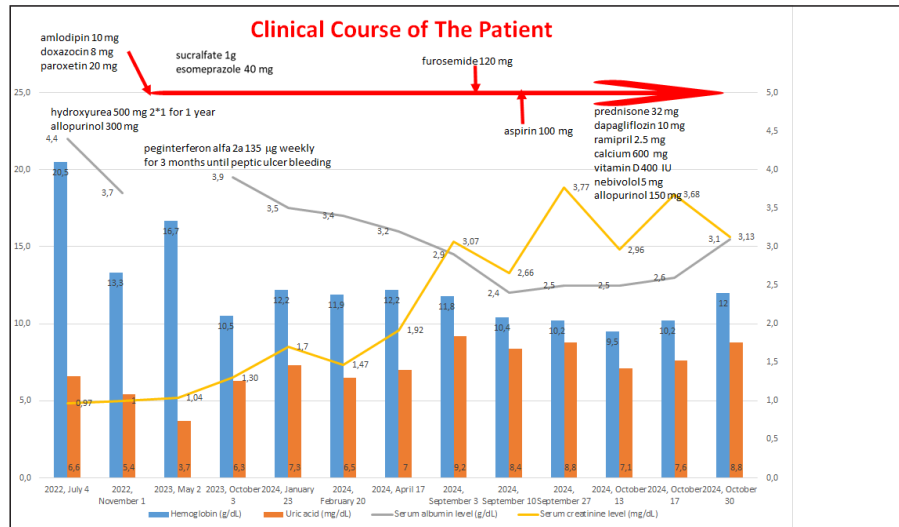
## Discussion

The co-existence of two sporadic diseases, IgAN and PV, has been reported in very few patients (15 out of 8 billion population) globally. Several growth factors, such as insulin-like growth factor (IGF)-1 and platelet-derived growth factor (PDGF), are highly expressed in peripheral mononuclear cells of patients with PV, causing mesangial cell proliferation and glomerular sclerosis in kidneys<sup>11</sup>. Several other cytokines causing endothelial damage, such as interferon-g, interleukin-6, transforming growth factor (TGF)- $\beta$ , and fibroblast growth factor, were also found in patients with MPN<sup>13</sup>. However, mesangial proliferative GN (MPGN) can be found in other forms of GN, such as minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), C3 and C4 glomerulopathies, monoclonal gammopathy deposition disease, lupus nephritis, and diabetic nephropathy) besides IgAN<sup>14</sup>. In addition, kidney diseases reported in patients with PV are known as FSGS, MCD, MPGN, and IgAN. The pathogenetic factors for kidney disease in patients with PV are hyperviscosity and complications such as endothelial damage, intrarenal hypertension, vascular thrombi, and glomerular capillary occlusion resulting in renal ischemia<sup>8</sup>. These mechanisms might be responsible for MPGN but can not clearly explain the defective galactosylation of polymeric IgA. In addition, a proliferation-inducing ligand (APRIL), mainly produced by dendritic cells, was reported to play a major role in the pathogenesis of the four-hit cascade leading to IgAN<sup>15</sup>. How APRIL formation ensues, and the cascade mechanisms that APRIL triggers in patients with PV have not yet been investigated. As a result, whether the pathogenetic pathways in the development of IgAN and PV share common mechanisms needs to be clarified.

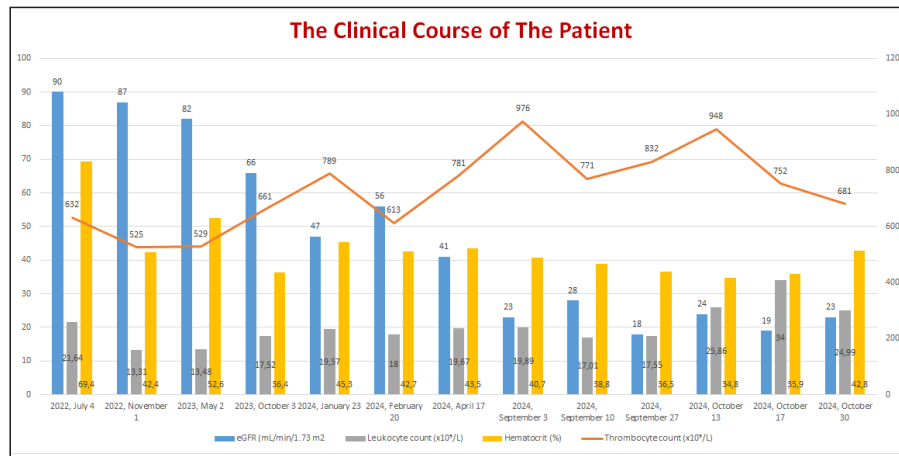
**Table 1:** Features of some reported patients with polycythemia vera associated with immunoglobulin A nephropathy.

Pt	Ref, year	Age/sex	PV duration	Kidney biopsy	Proteinuria SCr mg/dL	Clinical type	Therapy
1	#8, 2024	66 /M	Co-diagnosis	Ig AN	3.8 g/d SCr: 2.6	NS	Hydroxyurea telmisartan
2	#10, 2015	56/M	NR	Ig AN	7.8 g/d SCr: 1.3	NS	NR
3	#12, 2022	55/F	6 months	Ig AN	1.6 g/d SCr: 0.81	Nephritic syndrome	Hydroxyurea enalapril
4	#12, 2022	19 /M	1 year	Ig AN	0.52 g/d SCr: 0.71	Nephritic syndrome	Hydroxyurea Benazepril
5	#11, 2002	46/M	Co-diagnosis	Ig AN	9.1 g/d SCr: 2.7	NS	Hydroxyurea enalapril
6	#9, 2023	40/M	30 months	Ig AN	0.81g/d SCr: 1.17	Nephritic syndrome	Hydroxyurea Prednisone Levlunomide ARB Tripterygium wilfordii

Pt: patient, Ref: reference number, M: male, F: female, PV: polycythemia vera, NR: not reported, NS: nephrotic syndrome, SCr: serum creatinine, ARB: angiotensin receptor blocker.

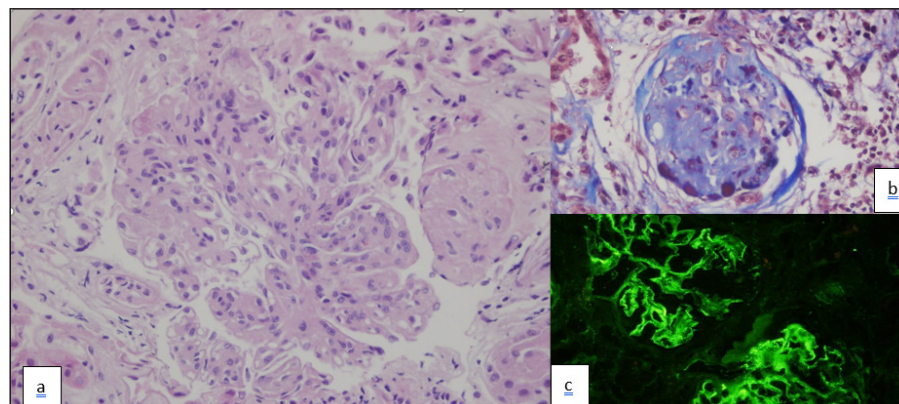


**Figure 1:** Composite image demonstrating the clinical course of the reported patient and treatment administered and hemoglobin, uric acid, serum albumin, and serum creatinine levels from July 2022 until October 2024.



**Figure 2:** Composite image demonstrating the clinical course of the reported patient and estimated glomerular filtration rate, leukocyte count, hematocrit, and thrombocyte count levels from July 2022 until October 2024.

eGFR: estimated glomerular filtration rate



**Figure 3:** Light microscopy findings showing A) mesangial matrix expansion and cellular proliferation with basal membrane thickening and glomerular lobulation (Hematoxylin and Eosin, ×400), B) glomerular fibrin microthrombi, mesangial matrix expansion, interstitial inflammation and fibrosis (Masson Trichrome stain, ×400), and C) mesangial granular IgA deposition (severity degree of +++)(immunofluorescence microscopy, ×400).

The secondary forms of IgAN occur in 9-25 % of cirrhotic patients, 30 % of patients with hepatitis B infection, 12% of patients with rheumatoid arthritis, and 24 % of patients with inflammatory bowel disease. Patients with ankylosing spondylitis, Sjogren's syndrome, dermatitis herpetiformis, psoriasis, cutaneous T-cell lymphoma, Hodgkin's disease, mucosa-associated lymphoid tissue, and extra-nodal T-cell lymphoma have also been reported to complicate secondary IgAN<sup>16</sup>. The mechanisms underlying the genesis of IgAN in these patients were considered mucosal inflammation, increased numbers of activity of IgA1-secreting cells, and decreased hepatic clearance of abnormal glycosylated IgA<sup>14</sup>. The exact answer to the question of why all patients with these morbidities do not develop IgAN remains unclear.

Recently, the specific treatment of both primary and secondary IgAN has evolved rapidly, encompassing immunologic (systemic glucocorticoids, mycophenolate mofetil, targeted therapies such as budesonide, avacopan, iptacopan, hydroxychloroquine) and nonimmunologic [renin-angiotensin-aldosterone (RAS) and sodium-glucose transporter-2 (SGLT-2) inhibitors, and endothelin (ET)-receptor antagonists] approaches<sup>17</sup>.

Typically, IgA, the most abundant immunoglobulin in the body with a short half-life of 4-6 days, constitutes 15 % of the total immunoglobulins in the circulation and is an inhibitor of autoimmune mechanisms. However, mucosal injury results in the activation of dendritic cells and, consequently, secretion of APRIL from these cells leads to Gd-IgA1 secretory plasma cell development. Mesangial deposition of circulatory Gd-IgA1 eventually causes RAS and ET activation, therefore, the inhibition of these activations is also significant for IgAN treatment. These therapies were also administered to our patient even though severe fibrotic damage was present.

Unfortunately, electron microscopy (EM) is not available in our center. It would have been better if we had evaluated the EM findings. However, the presence of mild (second-degree) hypertensive retinopathy, left ventricular hypertrophy, and subintimal vascular fibrosis together with glomerulosclerosis in kidney biopsy make us infer the diagnosis of benign hypertensive glomerulosclerosis, which might also increase the severity of proteinuria. In addition, the presence in at least one glomerulus of segmental sclerosis or adhesion (showing the presence of FSGS) is, according to the Oxford Classification study, correlated with a higher level of proteinuria at the time of biopsy and a more rapid loss of renal function, worse renal survival, independent of other histologic features. The presence of FSGS was reported as an adverse prognostic factor in IgAN<sup>18</sup>. Our patient had segmental sclerotic glomeruli, which means the togetherness of FSGS with IgAN and an increase in the severity of proteinuria. In conclusion, repeat urinalysis should be performed in every patient for hematuria and proteinuria not to delay the diagnosis of kidney involvement. IgAN and PV's togetherness is rare, but the underlying mechanisms need to be elucidated.

### Conflict of interest

The authors declare no conflicts of interest.

### Acknowledgment

Written informed consent was obtained from the patient.

### References

- Cheung CK, Barratt J. IgA nephropathy: Clinical features and diagnosis. Available at: <https://www.uptodate.com/contents/iga-nephropathy-clinical-features-and-diagnosis>, date accessed: 14/11/2024.
- Gül CB, Küçük M, Öztürk S, Demir E, Eren N, Şumnu A, et al. Trends of primary glomerular disease in Turkey: TSN-GOLD registry report. *Int Urol Nephrol.* 2022; 54: 2285-2294.
- Al Hussain T, Hussein MH, Al Mana H, Akhtar M. Pathophysiology of IgA Nephropathy. *Adv Anat Pathol.* 2017; 24: 56-62.
- Patrapornpisut P, Avila-Casado C, Reich HN. IgA Nephropathy: Core Curriculum 2021. *Am J Kidney Dis.* 2021; 78: 429-441.
- Lee M, Suzuki H, Nihei Y, Matsuzaki K, Suzuki Y. Ethnicity and IgA nephropathy: worldwide differences in epidemiology, timing of diagnosis, clinical manifestations, management and prognosis. *Clin Kidney J.* 2023; 16: ii1-ii8.
- Tefferi A. Clinical manifestations and diagnosis of polycythemia vera. Available at: <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-polycythemia-vera>, date accessed: 20/12/2024.
- Aoun M, Jadoul M, Anders HJ. Erythrocytosis and CKD: A Review. *Am J Kidney Dis.* 2024; 84: 495-506.
- Rajasekar R, Nandakumar R, Singhvi SP, Mathew GG, Jayaprakash V, Mythili K. A case report and literature review of IgA nephropathy presenting as nephrotic syndrome in polycythemia vera. *CEN Case Rep.* 2024; 13: 495-498.
- Wang X, Yang N, Lu C, Xu F, Wang J. Clinical characterization of polycythemia vera associated with IgA nephropathy in a single Chinese center: A case series. *Medicine (Baltimore).* 2023; 102: e33493.
- Chen H, Zhang B, Li M, Hu R, Zhou C. Polycythemia vera associated with IgA nephropathy: A case report and literature review. *Exp Ther Med.* 2015; 10: 555-560.
- Chung J, Park PG, Song KI. IgA nephropathy in a patient with polycythemia vera. Clinical manifestation of chronic renal failure and heavy proteinuria. *Am J Nephrol.* 2002; 22: 397-401.
- Yang J, Yu X, Hu N, Su T. Clinical and Pathological Features of Renal Presentations in Polycythemia Vera. *Am J Med Sci.* 2022; 363: 33-41.
- Büttner-Herold M, Sticht C, Wiech T, Porubsky S. Renal disease associated with myeloproliferative neoplasms and myelodysplastic syndrome/myeloproliferative neoplasms. *Histopathology.* 2021; 78: 738-748.
- Bian Q, Anderson JC, Zhang XW, Huang ZQ, Ebefors K, Nyström J, et al. Mesangioproliferative Kidney Diseases and Platelet-Derived Growth Factor-Mediated AXL Phosphorylation. *Kidney Med.* 2021; 3: 1003-1013.e1.
- Cattran DC, Floege J, Coppo R. Evaluating Progression Risk in Patients With Immunoglobulin A Nephropathy. *Kidney Int Rep.* 2023; 8: 2515-2528.
- Saha MK, Julian BA, Novak J, Rizk DV. Secondary IgA nephropathy. *Kidney Int.* 2018; 94: 674-681.
- El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA Nephropathy: A Rapidly Evolving Field. *J Am Soc Nephrol.* 2024; 35: 103-116.
- Bellur SS, Lepeyre F, Vorobyeva O, Troyanov S, Cook HT, Roberts IS, et al. Evidence from the Oxford Classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy. *Kidney Int.* 2017; 91: 235-243.