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Case Report

# Primary Myelofibrosis-Related Renal Disorders Treated with a Janus Kinase Inhibitor

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**Keywords**
Primary myelofibrosis · Janus Kinase Inhibitor · Extramedullary hematopoiesis · Interstitial nephritis · Chronic thrombotic microangiopathy

**Abstract**
Extramedullary hematopoiesis is widely known to occur in patients with primary myelofibrosis (PMF). Autopsy studies on individuals with PMF revealed that extramedullary hematopoiesis occurred in the kidneys in 35% of the cases, but there is little awareness regarding such lesions. A 63-year-old man was diagnosed with PMF based on a detailed examination of persistent high white blood cells. An examination of the patient's medical records revealed an increased white blood cell count, deterioration of kidney function, and urinary protein excretion developed simultaneously. Thus, a kidney biopsy was performed. Advanced lymphocyte invasion was recognized in the interstitial tissue, and the tubular structure was highly disrupted. Based on these findings, he was diagnosed with interstitial nephritis. However, because of the large

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number of cells with nuclear atypia in the stroma, additional immunohistochemical staining was also performed, such as glycophorin A, naphthol AS-D, myeloperoxidase, and CD42b. As a result, invasion of three lineages of immature cells, erythroblasts, megakaryocytes, and granulocytes, was identified. Renal dysfunction resulting from interstitial cellular infiltration due to extramedullary hematopoiesis was therefore diagnosed. Treatment with ruxolitinib was initiated after a renal biopsy and the rate of decline in renal function was slightly reduced. Although, in myeloproliferative disorders, proliferative glomerular lesions are widely considered to be renal disorders, there is little awareness regarding interstitial lesions. Extramedullary hematopoiesis of the kidney in PMF is not uncommon, but 40% of cases are reportedly misdiagnosed as interstitial nephritis. Because extramedullary hematopoiesis can be controlled by ruxolitinib, early detection is important.



## Introduction

Cancer incidence increases with age, and myeloproliferative disorders are no exception. Recently, glomerulopathy secondary to myeloproliferative disorders has been proposed [1]. The number of affected individuals is unknown but may be higher than expected. However, because of the rarity of the disease, its natural history is still unknown. In addition, little recognition is given to the fact that the disorder occurs outside the glomerulus. We experienced a case of primary myelofibrosis (PMF) treated with a JAK inhibitor and report it here.

## Case Presentation

A 63-year-old man was diagnosed with PMF with a JAK2 V617F gene mutation (Dynamic International Prognostic Scoring System Plus: intermediate-2-risk group) based on a detailed examination of persistent white blood cells (count >10,000/μL). An examination of the patient's medical records revealed an increased white blood cell count, deterioration of kidney function, and urinary protein excretion developed simultaneously (Fig. 1). Hence, a kidney biopsy was performed (Table 1). Advanced lymphocyte invasion was recognized in the interstitial tissue over 50% of the cortical area, and the tubular structure was highly disrupted (Fig. 2f). Mesangium cell proliferation and double contour of glomerular basement membrane were observed in some glomeruli, but endothelial cell proliferation and semilunar formation were absent (Fig. 2a–c). Immunofluorescence staining was positive for IgA and C3 in the mesangium region and negative for IgG (Fig. 2d). Furthermore, electron microscopy showed that endothelial cells were swollen and detached from the basement membrane, as well as foot process effacement of podocytes (Fig. 2e). There were also small amounts of granular deposits in the mesangium area. He had a 7-year history of diabetes but no findings of diabetic nephropathy such as basement membrane thickening or nodule formation. Based on these findings, the pathologist diagnosed the patient with interstitial nephritis as the primarily cause of kidney dysfunction. However, because of the large number of cells with nuclear atypia

in the stroma, we suspected renal extramedullary hematopoiesis. Thus, additional immunohistochemical staining was performed for glycophorin A, naphthol AS-D, myeloperoxidase, and CD42b (Fig. 3). As a result, invasion of three lineages of immature cells (erythroblasts, megakaryocytes, and granulocytes) was identified. Renal dysfunction resulting from interstitial cellular infiltration due to extramedullary hematopoiesis was therefore diagnosed. Treatment with ruxolitinib was initiated after a renal biopsy because he did not want an allogeneic stem transplantation. The patient's rate of change in eGFR yearly and urine protein levels improved slightly after ruxolitinib administration. Specifically, when compared before and after treatment (1.5 years), the annual change in eGFR decreased from –7.1 to –4.5 mL/min/1.73 $m^2$, and the urine protein from a mean of 4.6 ± 1.6 to 4.0 ± 1.6 g/g Cr.

## Discussion

We report a case of PMF-related glomerulopathy and interstitial damage. PMF-related interstitial nephropathy is caused by extramedullary hematopoiesis, but it is not well known, and there are few cases where it has been clearly demonstrated by immunohistochemistry. In addition, we treated this case with a JAK inhibitor. Although JAK inhibitors have been standardized as a treatment for PMF ineligible for stem cell transplantation, their effects on the kidney are not well known.

PMF is a disease which causes extensive fibrosis in bone marrow via an abnormality of hematopoietic stem cells. When it progresses, hemopoiesis is disrupted, and bleaching (approximately 20% in 10 years) occurs. PMF causes hepatosplenomegaly due to extramedullary hematopoiesis. In addition, various systemic symptoms, such as general malaise, night sweats, and bone pain, are thought to be due to cytokines. The average life span of PMF patients is about 6 years, and treatment is typically chemotherapy and bone marrow transplantation. In recent years, JAK2, CALR, and MPL have been identified as driver genes of PMF. In JAK2 V617F gene mutation-positive PMF, the use of a JAK inhibitor as cytoreductive therapy has been reported to improve splenomegaly and prolong overall survival.

PMF-associated renal injury can be divided into interstitial disorder and glomerular damage, and interstitial lesion mainly caused by extramedullary hematopoiesis. Extramedullary hematopoiesis in the kidney occurs in 35% of PMFs, fourth most common after liver, spleen, and lymph nodes [2]. The mechanism by which extramedullary hematopoiesis occurs is still unclear, but the redirected differentiation theory suggests that it occurs when tissue stem cells are induced to differentiate by some circulating substance [3]. Less is known about secondary extramedullary hematopoiesis in the kidney to PMF. Therefore, approximately 40% of extramedullary hematopoiesis cases involving the stroma have been misdiagnosed as interstitial nephritis [4]. This indicates that extramedullary hematopoiesis is challenging to judge by the morphology alone. This case report is considered to be unique as there are few reports that demonstrate the presence of extramedullary hematopoiesis in the kidney immunohistochemically.

In a literature review summarizing the clinical characteristics of glomerular disease with renal extramedullary hematopoiesis from 38 myeloproliferative neoplasms, who had

proteinuria, 61% of patients were in the nephrotic range, as in the present case [5]. The histological features of the glomeruli in PMF are characterized by endothelial damage caused by chronic thrombotic microangiopathy-like lesions and by the proliferation of mesangial cells [1, 4]. In immunofluorescence studies, IgG is consistently negative as in this case, but IgA, C1q, C3, kappa, and lambda are positive in some cases [5]. Electron microscopy reveals foot process effacement with the enlargement of the subendothelial space and duplication of the basement membrane with mesangial interposition [1]. Glomerular involvement is thought to be caused by growth factors associated with myelofibrosis, such as platelet-derived growth factor (PDGF) and transforming growth factor-β [5]. In the present case, the presence of diabetic nephropathy was an issue, but there were no findings to suggest this. Histological examination is also consistent, suggesting that advanced proteinuria with nephrotic levels is associated with PMF.

This case might be complicated by IgA nephropathy, based on immunofluorescence studies. However, as noted above, the histological examination could be explained by the findings of glomerulopathy caused by PMF alone.

Although allogeneic stem transplantation remains the mainstay of treatment for PMF, JAK inhibitors are recommended for patients at intermediate or higher risk, who are not candidates for transplantation. Ruxolitinib is an orally bioavailable, potent, and selective inhibitor of JAK1 and JAK2. The JAK2 V617F gene mutation occurs in more than 50% of PMF and essential thrombocythemia cases [6]. Ruxolitinib inhibits extramedullary hematopoiesis and improves debilitating symptoms resulting from disease-related systemic inflammation and excess metabolism.

Ruxolitinib is known to provide significant benefits for PMF patients by reducing spleen size and improving paraneoplastic symptoms, but its impact on renal function is not yet known. In one retrospective analysis, introducing ruxolitinib in 100 patients improved renal function [7]. Furthermore, renal improvement (>10%) was directly related to failure-free survival in this study (hazard ratio 1.4, 95% CI 1.1–2, $p = 0.02$) [7]. When other PMF patients were treated with JAK inhibitors, the urinary protein was improved, but complete remission was not achieved [8, 9]. We expected to change dramatically with ruxolitinib administration in this case. However, the improvement was marginal. One possible reason for this is that the patient was ruxolitinib resistant. In this case, the splenic index by ultrasound examination (product of length, thickness, and width) increased from 47.0 to 59.8 one year after starting treatment. It is also possible that the treatment intervention was simply too late because of the high degree of interstitial impairment. In order to prove these facts, we need to examine the histological findings after treatment, but we could not do so in this case.

In summary, we report a PMF case of renal extramedullary hematopoiesis associated with glomerular disease. Renal damage due to PMF is commonly associated with severe proteinuria due to secondary glomerular disease, but as shown by appropriate immunohistochemistry, renal dysfunction due to medullary damage is also possible. The natural history of PMF-related renal impairment is still poorly understood. Although this is a single case report, its natural history and the course of renal function after ruxolitinib administration may provide useful data for future treatment.

## Statement of Ethics

The research was conducted in ethical accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient and caregivers for the publication of this case report and any accompanying images.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

M.A., T.A., and M.A. were responsible for the clinical management of the patient and for preparing the draft version of this manuscript. T.E., T.H., and H.S. contributed to the review of the literature. All authors participated in the writing of the manuscript and read and approved the final version.

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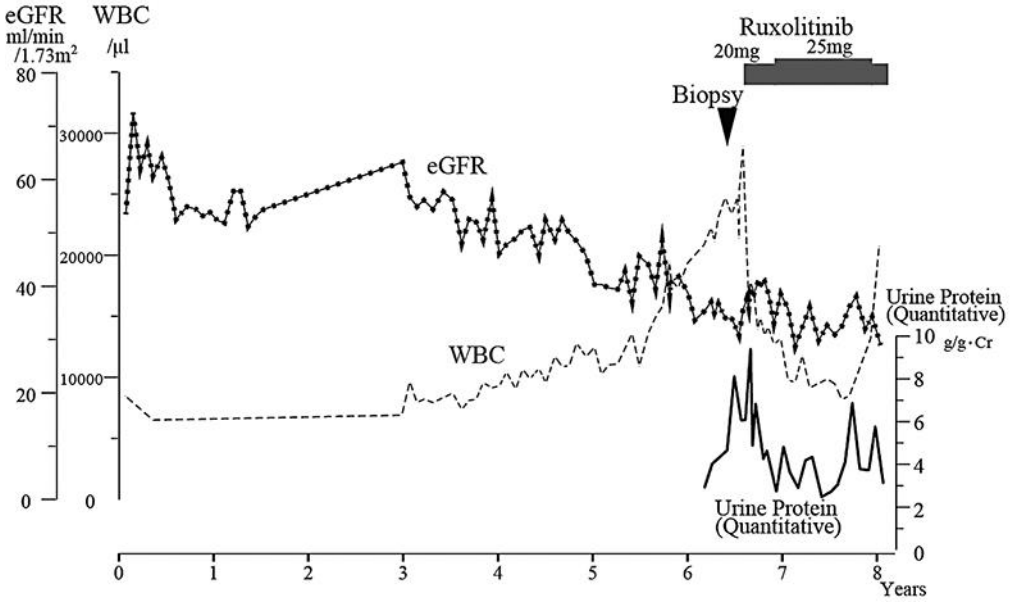


**Fig. 1.** Clinical course of case 1. Before renal biopsy, the patient's medical records revealed an increased white blood cell count, deterioration of kidney function, and urinary protein excretion developed simultaneously. The patient's rate of change in eGFR yearly and urine protein levels improved slightly after ruxolitinib administration. WBC, white blood cell.

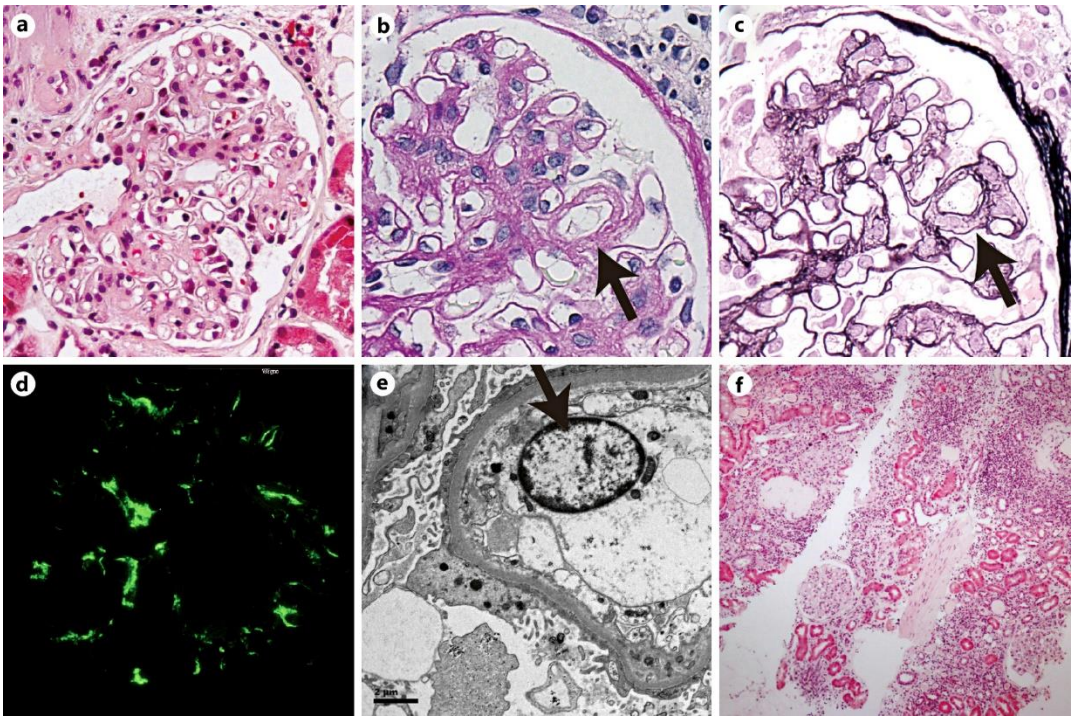


**Fig. 2.** **a** Light microscopy shows mesangial expansion and mild mesangial proliferation in almost all glomeruli. Hematoxylin-eosin stain. ×200. A double layer is formed at the capillary wall (arrow) without thickening as shown by periodic acid-Schiff staining (**b**), and periodic acid methenamine silver staining (**c**) (×400). **d** With immunofluorescence, IgA (×200) are deposited in a mesangial pattern. **e** Electron microscopy shows marked endothelial cell swelling (arrow) and podocyte foot process effacement (×5,000). **f** Advanced lymphocyte invasion is evident in interstitial tissue over 50% of the cortical area, and the tubular structure was highly disrupted. Hematoxylin-eosin stain. ×40.

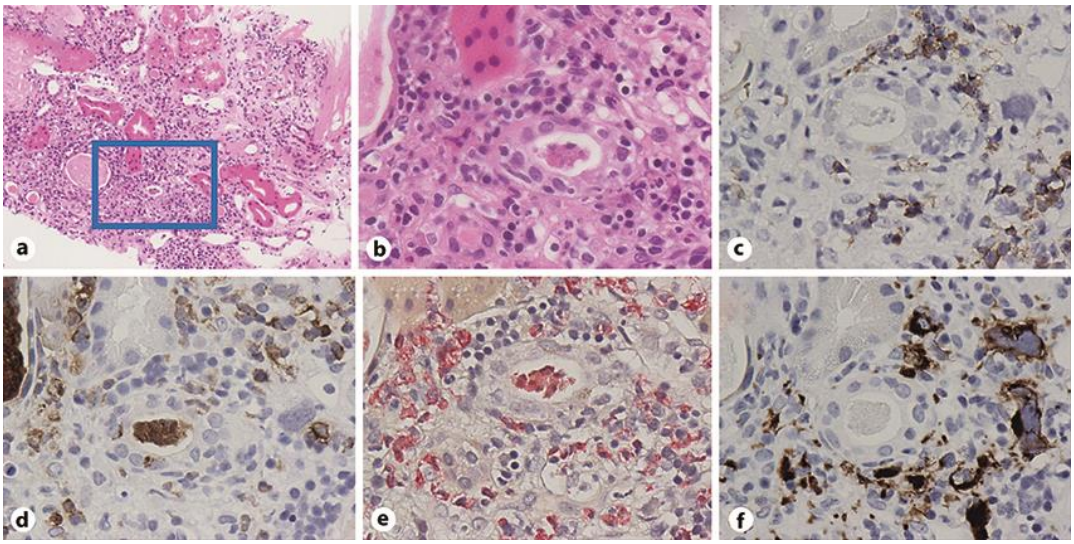


**Fig. 3.** Extramedullary hematopoiesis. There are three lineages of immature cells: erythroblasts, granulocytes, and megakaryocytes. **a**, **b** Hematoxylin-eosin stain. **c–f** Immunohistochemistry. **c** Glycophorin A (specific marker of erythroid cells). **d** Myeloperoxidase (granulocytic lineage marker, especially neutrophilic and eosinophilic types). **e** Naphthol AS-D chloroacetate (especially myeloid and mast cells). **f** CD42b (marker of megakaryocytes and platelet). **a** ×40; **b–f** ×400.

**Table 1.** Laboratory findings on admission

| | | Unit | | | Unit |
|---|---|---|---|---|---|
| WBC | 25,070 | /μL | BUN | 24.3 | mg/dL |
| Blast | 3 | % | Cr | 1.81 | mg/dL |
| Promyelo | 0 | % | Na | 138.2 | mEq/L |
| Myelo | 3 | % | K | 4.7 | mEq/L |
| Metamyel | 2 | % | Cl | 103 | mEq/L |
| Stab | 3 | % | CRP | 0.78 | mg/dL |
| Seg | 66 | % | ANA | <40 | |
| Eosino | 6 | % | PR3-ANCA | <1.0 | U/mL |
| Baso | 4 | % | MPO-ANCA | <1.0 | U/mL |
| Lym | 7 | % | Rheumatoid factor | 18.1 | IU/mL |
| Mono | 6 | % | IgG | 1,593 | mg/dL |
| Hb | 13.8 | g/dL | IgA | 697 | mg/dL |
| Plt | 56 | $10^4$/μL | IgM | 121 | mg/dL |
| PT-INR | 1.32 | | CH50 | 38.7 | CH50/mL |
| APTT | 39.5 | s | C3 | 122 | mg/dL |
| TP | 7.3 | g/dL | C4 | 25 | mg/dL |
| Alb | 3.3 | g/dL | Serum immunofixation electrophoresis | | M protein (–) |
| T-Bil | 0.44 | g/dL | Uric protein | 5.5 | g/1 g Cre |
| GOT | 37 | IU/L | Uric blood | 1~4 | /HPF |
| GPT | 21 | IU/L | Epithelial cells | 5~9 | /HPF |
| LDH | 1,045 | IU/L | Granular cast | 11~30 | /WF |
| T.Chol | 113 | mg/dL | Waxy cast | 1~10 | /WF |
| TG | 297 | mg/dL | Urine NAG | 47.1 | IU/L |
| HbA1C | 8.8 | % | | | |

HPF, high-power field; WF, whole field; NAG:N-acetyl-β-D-glucosaminidase.