**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 79035

**Manuscript Type:** CASE REPORT

**Minimal change disease caused by polycythemia vera: A case report**

Xu L *et al*. MCD caused by PV

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**Author contributions:** Xu L was responsible for writing the manuscript and data analysis; Lu LL helped with document retrieval; Gao JD was responsible for supervision; all authors agree with the final version of the manuscript.

**Supported by** the National Natural Science Foundation of China, No. 81874437 and 81904126; Science and Technology Commission of Shanghai Municipality, No. 20Y21901800.

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**Received:** August 24, 2022

**Revised:** September 27, 2022

**Accepted:** October 19, 2022

**Published online:** November 16, 2022

**Abstract**

BACKGROUND

Polycythemia vera (PV), often attributed to the JAK2 V617F mutation, is characterized by enhanced red blood cell counts in the peripheral blood. PV-associated renal disease is clinically rare; to date, there have been reports of other chronic kidney diseases related to PV, but no reports on PV-associated minimal change disease.

CASE SUMMARY

A 37-year-old man presented with proteinuria and high red blood cell count on January 4, 2021. The patient underwent bone marrow and renal biopsies, then was subsequently diagnosed with PV and minimal change in disease. Hydroxyurea was administered and proteinuria remission was achieved. The patient’s last visit was on April 14, 2022.

CONCLUSION

We inferred that there may be a causal relationship between PV and minimal change disease.

**Key Words:** Polycythemia vera; Minimal change disease; Proteinuria; Chronic kidney disease; JAK2 V617F mutation; Case report

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**Citation:** Xu L, Lu LL, Gao JD. Minimal change disease caused by polycythemia vera: A case report. *World J Clin Cases* 2022; 10(32): 11993-11999

**URL:** <https://www.wjgnet.com/2307-8960/full/v10/i32/11993.htm>

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i32.11993

**Core Tip:** Polycythemia vera (PV) is a myeloproliferative neoplasm that can influence the immune system and affect organs such as the kidneys. This is the first report of PV-associated minimal change disease. In our case, hydroxyurea administration was effective and proteinuria remission was achieved. Therefore, we infer there may be a causal relationship between PV and minimal change disease.

**INTRODUCTION**

Polycythemia vera (PV)[1], a myeloproliferative neoplasm (MPN), is the ultimate phenotype of the JAK2 V1617F mutation, and is characterized by erythrocytosis, leukocytosis, thrombocytosis, splenomegaly, and occasional myelofibrosis. PV-associated renal disease is rare. A literature review[2] referred to cases of PV-associated renal diseases, including immunoglobulin (Ig) A nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and rapidly progressive glomerulonephritis. However, to the best of our knowledge, there have been no reports of minimal changes in disease. Here, we report the case of our patient.

**CASE PRESENTATION**

***Chief complaints***

A 37-year-old man, a base station engineer, was admitted to the Shuguang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine, Department of Nephrology (Shanghai, China), on January 4, 2021. He complained of proteinuria for approximately one month.

***History of present illness***

During inpatient care, the patient presented with dizziness, slight weakness, no hematuria, no back pain, good appetite, sound sleep, and normal urine and stool.

***History of past illness***

The patient claimed no history of past illness*.*

***Personal and family history***

The patient claimed no personal or family history.

***Physical examination***

Physical examination revealed no abnormities, except for blood pressure, which was 153/106 mmHg

***Laboratory examinations***

On December 15, 2020, the patient underwent physical examination, and the report showed positive urine protein (++), blood routine: white blood cell count, 16.531 × 109/L; hemoglobin level, 229 g/L; red blood cell > 7.8 × 1012/L; and platelet count, 489 × 109/L. Biochemistry test: albumin 37 g/L, total albumin 60 g/L, blood uric acid 490 µmol/L, triglyceride 3.87 mmol/L, and blood creatinine 88 µmol/L.

On December 31, 2020, the 24-hour urine total protein quantitative was 5.08 g/24 h.

On January 7, 2021, routine blood tests showed white blood cells: 21.71 × 109/L; platelets, 431 × 109/L; red blood cells, 7.65 × 1012/L; and hemoglobin, 216.7 g/L.

On January 11 and 15, the patient underwent bone marrow and renal biopsies, respectively, after providing informed consent. A bone marrow biopsy revealed dense bone and a small amount of bone marrow tissue. The ratio of hematopoietic cells to structural fat in the area available for observation was 85%:15%, and the grain-to-red ratio was approximately 4–5:1. Hematopoietic cells in all stages of the red line could be seen; megakaryocytes were 7–17 per high-power field, distributed in clusters, and the cell bodies were relatively large with more nuclear lobes.

On January 11, 2021, a bone marrow biopsy showed that PV was first considered, and further genetic examination was recommended to clarify the type. IHC2021-0042: CD34 (individual +), CD117 (individual +), CD15 (partial +), MPO (partial +), CD56 (-), CD138 (individual +), CD61 (discrete +), CD71 (part +), Kappa: Lambda (not restricted expression), and special stain results: mesh (-), Periodic Acid-Schiff stain (+/-), Prussian blue (-).

On January 13, 2021, karyotype analysis showed the following karyotype: 46,XY (Figure 1). Gene test: JAK2 V617F (+). The mutation ratio of JAK2 V617F was 86.60%.

On January 15, 2021, renal biopsy (renal puncture tissue) revealed four glomeruli. The morphology and structure of glomeruli were normal. Some glomeruli showed mild proliferation of mesangial cells and increased matrix. No glomerular sclerosis changes, crescents, or infiltration of inflammatory cells were observed. Protein casts were observed in individual tubules, and some renal tubules showed atrophy and unclear structure. No obvious abnormalities were observed in the renal interstitium or blood vessels. Diagnosis: Minimal change disease (MCD). Fluorescence staining: IgG (-), IgA (-), IgM (-), C3 (-), C4 (-), C1q (-), Fb (+/-). Special staining: PAS (+), silver staining (+), Masson’s trichrome (+), Congo red (-). IHC2021-0045: TGF B1 (-) (Figure 2).

***Imaging examinations***

Abdominal ultrasonography showed splenomegaly.

**FINAL DIAGNOSIS**

The patient was diagnosed with the following conditions: (1) MCD; (2) PV; and (3) hypertension.

**TREATMENT**

The patient was given hydroxyurea 0.5 g qd p.o. (total duration of administration: 3 mo), olmesartan 20 mg qd p.o. (till last vist) and has been receiving interferon biweekly since cessation of hydroxyurea.

**OUTCOME AND FOLLOW-UP**

On March 13, 2021, the patient visited the hospital for a second visit. Routine blood test results revealed the following findings: hemoglobin, 167 g/L; red blood cells: 5.34 × 1012/L; white blood cells: 5.5 × 109/L; and platelets, 170 × 109/L. On March 18, 2021, the patient’s 24 h proteinuria was 1.33 g/24 h. The patient is currently in good condition. Other laboratory data for each visit are shown in Table 1 and Figures 3-5.

**DISCUSSION**

MCD is a primary cause of idiopathic nephrotic syndrome (NS), which manifests as mass proteinuria, resulting in edema and depletion of intravascular volume[3]. MCD occurs much less frequently in adults than in children[3]. The pathological features of MCD include a lack of visible changes on light microscopy and depletion of foot processes on electron microscopy. Podocyte modifications and immune disorders synergize to change the integrity of the glomerular basement membrane (GBM), thereby determining proteinuria[3]. MCD is primarily associated with extra-glomerular diseases, including neoplastic processes and undesirable reactions to drugs.

MCD has been frequently associated with hematologic malignancies such as Hodgkin’s lymphoma[4], and this relationship indicates that MCD is a disease that results from lymphocyte dysfunction. The benefit of immunosuppressants and steroids also implies that the cause of MCD is immune dysregulation. The pathogenesis of PV-associated MCD is likely related to T cell dysfunction. The mechanism is speculated to be a T helper cell class 1 and 2 imbalance in MCD[5,6]. In brief, the main cause of MCD is immune disorders, particularly T cell dysfunction. These T lymphocytes can produce circulating lymphokines which are toxic to GBM, and thus alter their permeability to proteins. In 1974, Shalhoub postulated the existence of a circulating mediator produced by abnormal T-lymphocytes[7]. In our case, T-lymphocyte disorder also induced concurrent MCD with PV. Studies have shown that the immune system is thrown into enormous disruption by myeloproliferative neoplasms (MPNs)[8]. JAK2V617F mutation results in the overexpression of many cytokines and chemokines such as interleukins IL-2, IL-8, as reported in samples from both mice and patients[8,9]. Nephrotic-level proteinuria has been reported in cancer patients treated with IL-2[10]. Evidence indicates that IL-2 is associated with proteinuria[10]. Hermouet *et al*[11] were the first to report that serum IL-8 Levels were elevated in PV patients. Garin *et al*[12] speculated that circulating IL-8 may play a role in MCD.

Our patient’s business trip to Chernobyl 8 years ago lasted approximately 4 months. We suspected nuclear contamination, which would have affected the immune system.

Our question in this case was as follows: Was the occurrence of MCD with PV purely coincidental or was it etiologically linked, either by a common pathogenesis or could the MCD be secondary to the PV? We can see that proteinuria remission was positively associated with treatment with hydroxyurea, so it is reasonable to consider a causal relationship.

However, the exact mechanisms underlying the pathogenesis of MCD associated with PV remain unclear. In addition to immune dysregulation, kidney injury might also be attributed to hyperviscosity, abnormal function, and/or excessive neoplastic blood cell activation and growth factor production[13]. Increased blood viscosity and platelet hypersensitivity can induce microcirculatory disturbances, resulting in endothelial damage. Many cytokines and growth factors such as interferon-γ, IL-6, and platelet-derived growth factor, which have documented in patients with MPNs, can directly elicit endothelial damage. Growth factors can be generated locally by marginating platelets and cells of extramedullary hematopoiesis, accompanied by hyperviscosity, which exacerbates endothelial damage[13]. PV can not only result in thrombosis in the main blood vessels[14],but can also induce thrombotic microangiopathy[15]. Glomerular microvasculature is particularly vulnerable to injury due to thrombotic microangiopathy. Therefore, we posit that PV-induced hyperviscosity could be an important factor in the pathogenesis of MCD, except in immune disorders.

Nonetheless, two potential mechanisms, microcirculatory disturbances and immune disorders, may explain the development of MCD in PV patients.

**CONCLUSION**

Based on our findings, there may be a causal relationship between minimal change in disease and PV. However, this is a clinical inference rather than a critical appraisal of the differences between chance and causal relationships, which would require a study of extensive epidemiological data.

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**Footnotes**

**Informed consent statement:** Informed written consent was obtained from the patient for the publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** August 24, 2022

**First decision:** September 23, 2022

**Article in press:** October 19, 2022

**Specialty type:** Hematology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

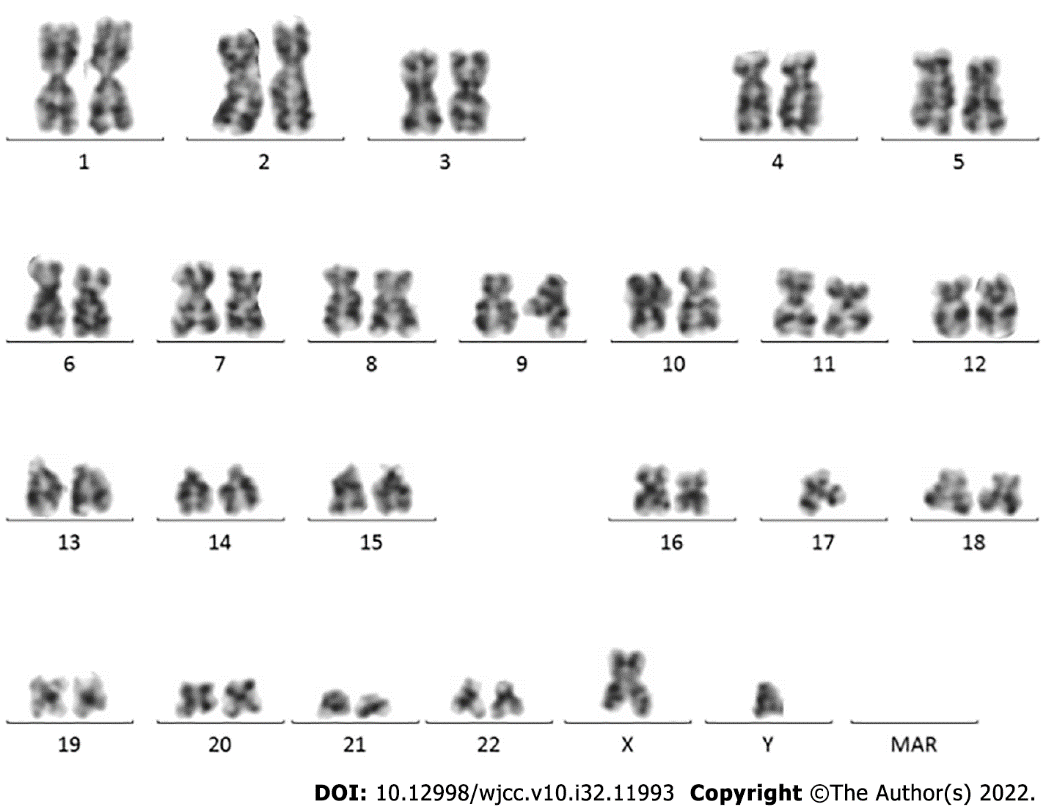
Grade C (Good): C, C

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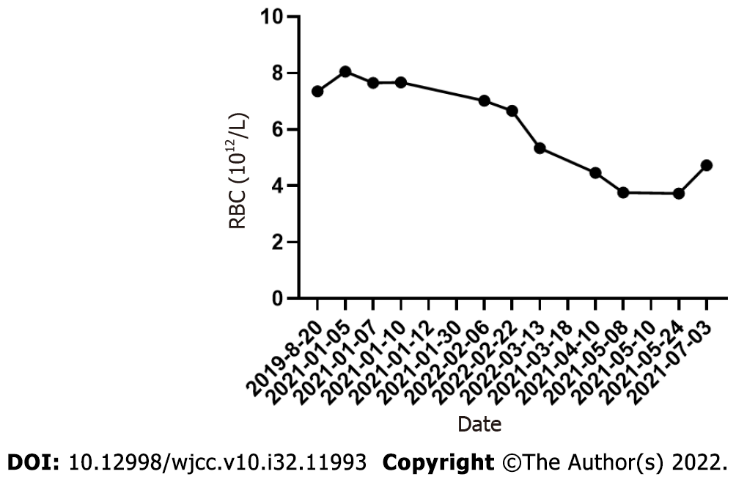
**Figure Legends**



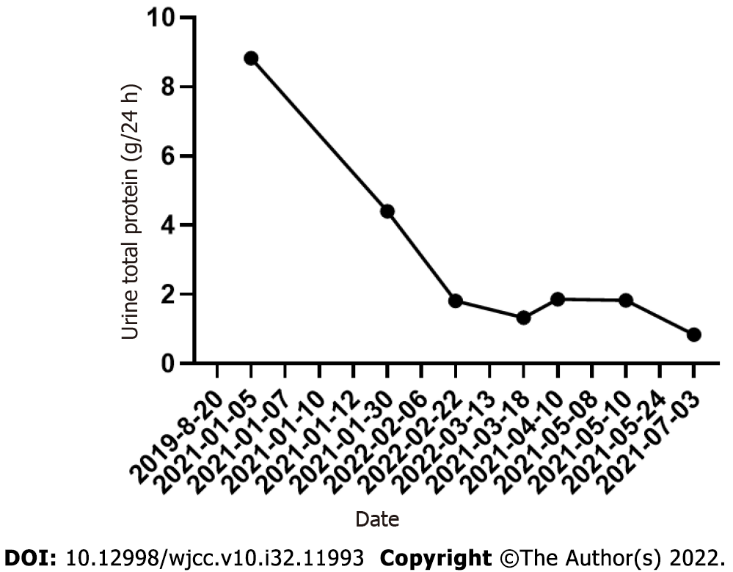
**Figure 1 Karyotype analysis results.**



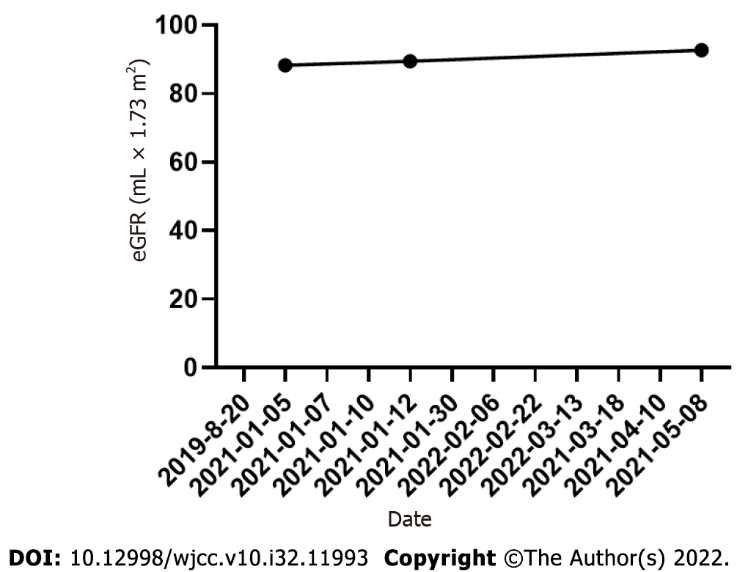
**Figure 2 Renal biopsy results.**



**Figure 3 Red blood cell counts at each visit.** RBC: Red blood cell.



**Figure 4 Urine total protein at each visit.**



**Figure 5 Estimated glomerular filtration rate at each visit.** eGFR: Estimated glomerular filtration rate.

**Table 1 Laboratory data according to each visit based on timeline**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Date** | **WBC (10**9**/L)** | **HB (g/L)** | **RBC (10**12**/L)** | **PLT (10**9**/L)** | **Hematocrits** | **UTP (g/24 h)** | **eGFR (mL × 1.73 m**2**)** |
| 2019-08-20 | 12.7 | 205 | 7.35 | 474 | 0.636 | - | - |
| 2021-01-05 | 16.57 | 226.1 | 8.05 | 435 | 0.665 | 8.83 | 88.33 |
| 2021-01-07 | 21.71 | 216.7 | 7.65 | 431 | 0.664 | - | - |
| 2021-01-10 | 15.77 | 218 | 7.67 | 500 | 0.659 | - | - |
| 2021-01-12 | - | - | - | - | - | - | 89.47 |
| 2021-01-30 | - | - | - | - | - | 4.4 | - |
| 2022-02-06 | 2.79 | 211 | 7.02 | 168 | 0.63 | - | - |
| 2022-02-22 | 3.97 | 203 | 6.66 | 161 | 0.591 | 1.81 | - |
| 2022-03-13 | 5.51 | 167 | 5.34 | 170 | 0.475 | - | - |
| 2021-03-18 | - | - | - | - | - | 1.33 | - |
| 2021-04-10 | 4 | 141 | 4.46 | 263 | 0.408 | 1.86 | - |
| 2021-05-08 | 4.53 | 125 | 3.76 | 337 | 0.362 |  | 92.69 |
| 2021-05-10 | - | - | - | - | - | 1.83 | - |
| 2021-05-24 | 6.3 | 128 | 3.73 | 450 | 0.369 | - | - |
| 2021-07-03 | 6.5 | 156 | 4.73 | 525 | 0.452 | 0.84 | - |

WBC: White blood cell; HB, hemoglobin; RBC: Red blood cell; PLT: Platelet; UTP: Urine total protein; eGFR: estimated glomerular filtration rate.



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