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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Primary myelofibrosis with concurrent *CALR* and *MPL* mutations: A case report

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Abstract

BACKGROUND

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by recurrent mutations in the *JAK2*, *CALR*, and *MPL* genes. The *CALR* and *MPL* co-mutation is very rare. To our knowledge, no more than five cases have been reported. Here, we report a case of PMF in which a *CALR* and *MPL* co-mutation was detected by next-generation sequencing (NGS) technology, and a literature review was performed.

CASE SUMMARY

A 73-year-old woman was admitted to our hospital in 2018 due to abdominal distension. The patient had splenomegaly, lymphadenopathy, leukopenia, anemia, and immature granulocytes in peripheral blood. There were dacrocytes and atypical megakaryocytes in bone marrow, and megakaryocytic proliferation was very active, accompanied by reticulin fibrosis grade 2. By NGS analysis of the bone marrow sample, we detected mutations in *CALR*, *MPL*, and *PIK3RI*, while *JAK2 V617F* and *BCR-ABL* were negative. Therefore, the patient was diagnosed with PMF and received oral ruxolitinib. However, the spleen and hematologic responses were poor. We review the literature, analyze previous reports of the mutation sites in our patient and differences between our patient and other reported cases of co-mutated *CALR* and *MPL* genes, and discuss the reason why the *CALR* and *MPL* co-mutations are rare and possible mechanisms and their impact on the prognosis of patients.

CONCLUSION

CALR and *MPL* mutations can be concurrent in MPN, but they are rare. The use of NGS may help to identify more patients with co-mutated *CALR* and *MPL* genes. This will help to further explore the mechanism and its impact on these patients to develop appropriate treatment strategies.

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Core Tip: We report a rare case of primary myelofibrosis in which a *CALR* and *MPL* co-mutation was detected by next-generation sequencing technology. It demonstrated that *CALR* and *MPL* mutations can be concurrent in myeloproliferative neoplasm. We review the literature, analyze previous reports of the mutation sites in our patient and differences between our patient and other reported cases of co-mutated *CALR* and *MPL* genes, and discuss the reason why the *CALR* and *MPL* co-mutations are rare and possible mechanisms and their impact on the prognosis of patients.

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INTRODUCTION

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by recurrent mutations in the *JAK2*, *CALR*, and *MPL* genes. Although these mutations were initially reported to be mutually exclusive in MPN, several studies have reported the presence of *JAK2-CALR* or *JAK2-MPL* co-mutations in PMF patients^[1-4], and *CALR* and *MPL* co-mutation cases are still very rarely reported. With the increasingly wide application of next-generation sequencing (NGS) technology, rare myelofibrosis cases with co-mutated *CALR* and *MPL* genes are increasingly being detected. Here, we report a patient with PMF, in which co-mutated *CALR* and *MPL* genes were detected.

CASE PRESENTATION

Chief complaints

Abdominal distension for 2 mo.

History of present illness

A 73-year-old woman was admitted to Sir Run Run Shaw Hospital, Zhejiang University School of Medicine in 2018 due to abdominal distension for 2 mo, especially after eating with no complaints of abdominal pain, diarrhea, vomiting, or reduced anal exhaust and defecation.

History of past illness

The patient had a history of a left kidney cyst.

Personal and family history

She denied any other specific personal or family history of other diseases.

Physical examination

The patient's conjunctiva and skin were pale, and the sclera was not yellow. Slightly swollen lymph nodes could be felt in the neck and armpit. The abdomen looked a little distended and felt soft, with no tenderness; the spleen under the ribs could be felt, and the texture was slightly hard. The rest of the abdomen did not have any obvious masses. The bowels sounded normal.

Laboratory examinations

Peripheral blood tests demonstrated a leukocyte count of $2.9 \times 10^9/L$, platelet count of $126 \times 10^9/L$, and hemoglobin of 87 g/L, and a smear revealed immature granulocytes

of 4%. Liver function tests showed normal levels of transaminases, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, direct bilirubin, indirect bilirubin, serum creatinine, and potassium. Lactate dehydrogenase was 570 IU/L, and total cholesterol was 2.6 mmol/L.

Imaging examinations

An abdominal computed tomography scan showed that the spleen was enlarged and uniform (Figure 1), with a left kidney cyst. Abdominal ultrasound showed that the spleen was enlarged, with a thickness of 5.6 cm and a length of 16.1 cm.

Pathological examination

Bone marrow aspiration revealed erythroid and megakaryocytic hyperplasia; dacrocytes were easily observed, and megakaryocytes had atypia (Figure 2). Bone marrow biopsy showed megakaryocytic proliferation and atypia, accompanied by reticulin fibrosis grade 2 (Figure 3).

Examination for gene mutations

The bone marrow samples were sequenced by NGS, which showed mutations in *CALR*, *MPL*, and *PIK3RI* (Table 1), while *JAK2 V617F* and *BCR-ABL* were negative.

FINAL DIAGNOSIS

The patient was ultimately diagnosed with PMF (International Prognostic Scoring System score = 3, high risk).

TREATMENT

The patient received oral ruxolitinib 15 mg twice per day.

OUTCOME AND FOLLOW-UP

Half a year later, the spleen response was poor, and the size of the spleen increased from 16.1 × 5.6 cm to 17.7 × 6.6 cm. Anemia was progressively aggravated in the meantime and developed to blood transfusion dependence, indicating that PMF with co-mutated *MPL* and *CALR* genes cannot benefit from ruxolitinib.

DISCUSSION

Most PMF patients carry *JAK2*, *MPL*, or *CALR* driver mutations^[5]. Mutations in *MPL* and *CALR* are drivers in the pathogenesis of MPNs, and mutant *CALR* can bind with *MPL* to activate the JAK-STAT signaling pathway. Previous studies have shown that *JAK2*, *MPL*, and *CALR* are mutually exclusively mutated in MPN patients^[6,7]. However, studies have also reported the presence of *JAK2-CALR* or *JAK2-MPL* co-mutations in PMF patients^[1-4], and cases of *CALR* and *MPL* co-mutations are still very rarely reported. Here, we report the case of a PMF patient with *CALR*-p.364fs and *MPL*-p.X636W mutations. The *CALR*-p.364fs mutation is usually detected in essential thrombocytosis (ET) and PMF patients, while the *MPL*-p.X636W mutation is not a common mutation and has only been reported in refractory anemia with ring sideroblast patients^[8,9]. Furthermore, we also detected a low-burden *PIK3RI* mutation in this case. The *PIK3RI* gene belongs to the Akt signaling pathway and plays a direct role in regulating cell survival, growth, and differentiation. Mutated *PIK3RI* can cause aberrant PI3K signaling, and the p.R228fs mutation site has already been reported in acute lymphocytic leukemia patients^[10,11]. To the best of our knowledge, this is the first report of a *CALR* and *MPL* double mutant PMF patient from East Asia.

Earlier research reports show that *CALR* and *MPL* mutations are mutually exclusive in MPN patients. This case demonstrated that *CALR* and *MPL* mutations can coexist in MPN patients. Three MPN cases with co-mutated *CALR* and *MPL* genes have already been reported since 2017^[12-14]. Partouche *et al*^[12] reported that a post-ET PMF patient carried type I *CALR* and *MPL* W515R mutations, with a variant allele frequency

Table 1 Gene mutation list in the primary myelofibrosis patient

Gene	VAF	HGVS	Exonic function
CALR	30.04%	NM_004343: c.1092_1143del (p.364fs)	Frameshift deletion
MPL	50.11%	NM_005373: c.1908A>G (p.X636W)	Nonsynonymous SNV
PIK3R1	3.18%	NM_00181523: c.683delG (p.R228fs)	Frameshift deletion

VAF: Variant allele frequency; HGVS: Human Genome Variation Society; SNV: Single nucleotide variant.

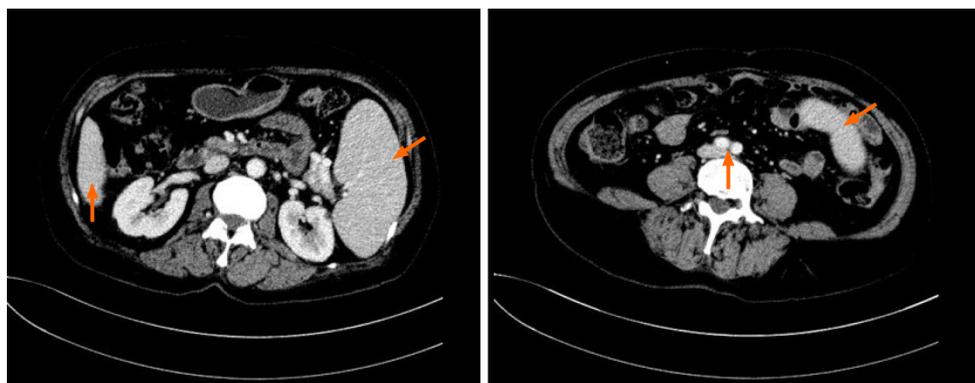


Figure 1 Computed tomography images showing splenomegaly. A and B: Abdominal computed tomography images showing that the inferior margin of the spleen was lower than that of the liver (A) and reached the level of abdominal aortic bifurcation (B).

(VAF) of 59.1% and 31.7%, respectively. Tashkandi *et al*^[13] reported a post-ET PMF patient carrying a *CALR* (p.L367Tfs*46) mutation at an allele frequency of 47% and two *MPL* (p.S505C and p.W515L) mutations at a lower allele frequency of 4%. Bernal *et al*^[14] detected a *CALR* (p.L367fs*48) mutation at an allele frequency of 30% and a *MPL* (p.Trip515L) mutation at an allele frequency of 11.75% in an ET patient. In contrast to these reported cases, we identified an uncommon mutation in *MPL* (p.X636W) in PMF patients, and its VAF was higher than that of the *CALR* mutation in our patient.

Patients with concurrent *CALR* and *MPL* mutations are truly rare in the clinic. In PMF patients, the frequency of *CALR* (20%-25%) and *MPL* (7%) gene mutations is low^[1,6,7]. Before 2017, there were no case reports about *CALR* and *MPL* co-mutations. Currently, a few MPN patients have been detected, which is inseparable from the progress of molecular testing technology. From previous cases, we can see that in MPN patients, a *MPL* mutation VAF is usually low^[2,3,15], and some uncommon mutations exist. Traditional Sanger sequencing may miss these mutations because of its test range and sensitivity^[7,13-15]. High-throughput sequencing may cover the full loci, and the detection VAF limit was lowered to 1%. Therefore, MPN patients with concurrent *CALR* and *MPL* mutations can be accurately detected.

The *MPL* mutation may have been a molecular event independent of the *CALR* deletion or a secondary event in the *CALR*-containing clone. Some researchers have proven that the *CALR* gene mutation is an early event during disease development, and *MPL* is a passenger event^[2,13]. It is speculated that the mutated *CALR* gene can trigger genome instability, which then causes mutations in the *MPL* gene^[13]. This is a possible explanation for why *CALR* and *MPL* can co-mutate. However, in our case, the *MPL* mutation was improbable as a secondary event because its VAF was more than 50%, indicating the possibility of a germline mutation. Some research has already proven that MPN patients can carry germline MPN mutations^[16-18]. The co-mutation mechanism is not clear and still needs more investigations.

Gene mutations can predict prognosis in PMF patients. *CALR* mutations indicate a good prognosis in ET and PMF patients^[19,20]. Compared to *JAK2* or triple-negative patients, *CALR* mutation-positive patients have a longer overall survival and low risk of thrombogenesis^[17,19,21]. Patients who harbor the *MPL* W515L/K mutation have a moderate prognosis and higher risk of thrombogenesis than *CALR* mutation-positive patients^[19]. The prognosis of patients with *MPL* and *CALR* co-mutations is still unknown due to the limited number of patients, but it seems that these patients have more aggressive progression based on our patient and other reported cases^[12,13]. Our

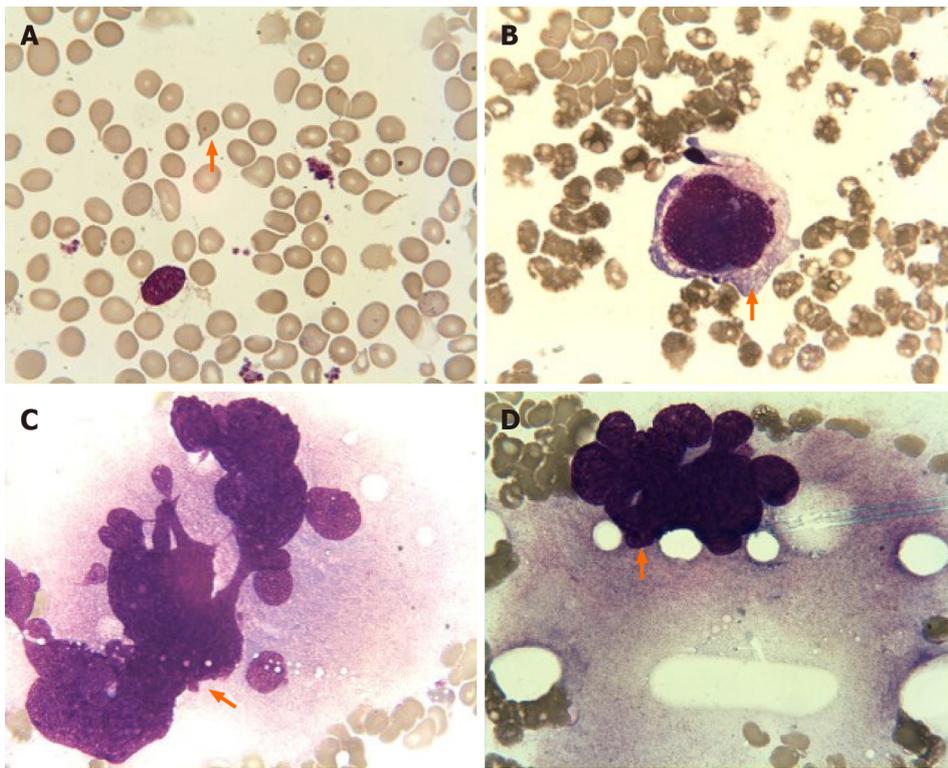


Figure 2 Bone marrow aspiration findings. A: Dacrocytes were easily observed; B-D: Images showing the presence of megakaryocyte atypia, including abnormal nuclear-cytoplasmic ratios, malformed nucleus (B), abnormal chromatin clumping with hyperchromatic nucleus (C), and extensive lobulation of the nucleus (D).

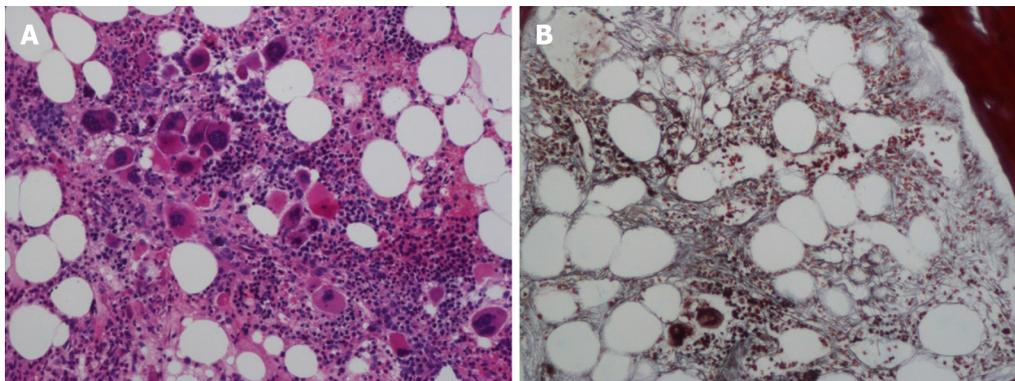


Figure 3 Bone marrow biopsy findings. A: Hematoxylin and eosin staining showed megakaryocytic proliferation and clustered distribution (magnification, 200 ×); B: Gomori staining showed diffuse and dense increase in reticulin fibres (magnification, 200 ×).

patient's disease progression was rapid. In Partouche's and Tashkandi's patients, the *CALR* mutation was a pre-existing clone in the ET stage, and the *MPL* mutation was acquired when the disease developed into PMF. Disease acceleration may be associated with *MPL*-mutated clones. Because of the lack of patients with coexisting mutations, further investigations in large cohorts are needed to better quantify the presence and clinical significance.

CONCLUSION

In conclusion, we have described a rare case of PMF with concurrent *CALR* and *MPL* mutations. This demonstrates that *CALR* and *MPL* mutations are not mutually exclusive in MPN. The use of NGS may help to identify more patients with *CALR* and *MPL* co-mutations. This will help to further explore the mechanism and its impact on these patients to develop appropriate treatment strategies.

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