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Progression of primary myelofibrosis to polycythemia vera
A case report

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Abstract

Rationale: This case report describes the progression of primary myelofibrosis (PMF) to polycythemia vera (PV), and discuss its potential mechanisms.

Patient concerns: The patient was admitted because of abdominal discomfort and enlarged spleen for 19 months.

Diagnosis: A case of PMF progressed to PV was retrospectively analyzed. There were 19 months between the diagnosis of PMF and PV. The JAK2 V617F mutation was positive before and after the diagnosis of PV; however, new chromosomal abnormalities were detected during the progression.

Interventions: For treatment of PMF, the danazol, calcitriol, and thalidomide were given. Then, the use of thalidomide and calcitriol was stopped, and hydroxyurea was started. For treatment of PV, interferon treatment was given, whereas hydroxyurea was continued.

Outcomes: After 30 months of the progression (at the recent follow-up), this patient had no obvious symptoms or thrombosis.

Lessons: PMF rarely progresses to PV, however, the progression will significantly improve the quality of life and prognosis.

Abbreviations: AML = cute myeloid leukemia, CK = creatine kinase, ET = essential thrombocythemia, Hb = hemoglobin, JAK = Janus kinases, LDH = lactate dehydrogenase, MF = myelofibrosis, MPN = myeloproliferative neoplasms, MPO = myeloperoxidase, PMF = primary myelofibrosis, PV = polycythemia vera.

Keywords: myeloproliferative neoplasms, polycythemia vera, primary myelofibrosis, progression

1. Introduction

Primary myelofibrosis (PMF), together with polycythemia vera (PV) and essential thrombocythemia (ET), are a kind of myeloproliferative neoplasms (MPN) caused by clonal proliferation of hematopoietic stem cells.[1] Patients with ET may slowly progress to PV, especially those carrying the Janus kinases (JAK)-2(V617F) mutation.[2,3] Furthermore, PV and ET may progress to secondary myelofibrosis (MF) (post-PV and post-ET myelofibrosis)[4,5] and subsequently progress to acute myeloid leukemia (AML).[6] However, the PMF to PV progression is rarely reported and the PMF-PV progression rate is extremely low, with zero case in 1000 cases of PMF patients.[7] Therefore, this report describes a rare case of the progression of PMF to PV and discuss its potential mechanisms.

2. Case report

Prior written and informed consent were obtained from this patient and the study was approved by the ethics review board of Qianfoshan Hospital Affiliated to Shandong University, P.R. China. The previously healthy 56-year-old female patient was admitted because of abdominal discomfort and enlarged spleen for 19 months. There were no constitutional symptoms or thrombosis. The size of the spleen was 48×138 mm by ultrasound. Routine blood test showed that hemoglobin (Hb) and hematocrit (Hct) was slightly below normal range (9.3 g/dL and 0.31, respectively). White blood cell count and platelet count were within normal range. Metarubricytes and metamyelocytes were visible in peripheral blood with poikilocytosis. Lactate dehydrogenase (LDH) was elevated (477 U/L). Reticulocyte count, serum ferritin, and bilirubin were within normal range. Bone marrow cytology showed reduced proliferation of all cell lines with poikilocytosis and red blood cell fragments. Bone marrow biopsy showed bone marrow hyperplasia was extremely active (90%) with increased myeloid erythroid ratio (Fig. 1A). Myeloid and erythroid at all stages could be seen, mainly as myelocytes or more immature cells. Immature granulocytes slightly increased. Megakaryocytes increased with scattered or cluster-like distribution. Megakaryocytes with small cell body and less karyolobism were commonly seen. Reticular fiber staining was strongly positive (+++) (Fig. 1B). Immunohisto-logical staining showed paired box protein (PAX5) was weak positive. CD20–, CD3, and CD5 was scattered positive. The myeloperoxidase (MPO) neutrophil cells, CD42B megakaryo-cytes, and CD34 endothelial cells were positive, and creatine
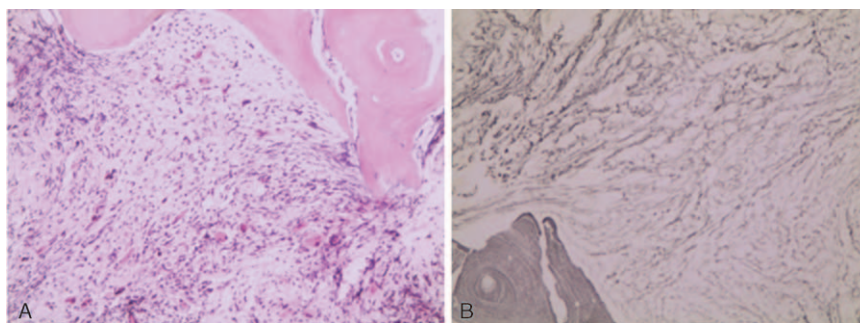
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Figure 1. Bone marrow biopsy showed extensive proliferation of fibroblasts (A) (Magnification: 10X) and Gomori reticulin staining was strongly positive (+++) (B) (Magnification: 10X), in accordance with the diagnosis of bone marrow fibrosis.

Table 1

Changes of hemoglobin, white blood cell count, platelet count, and treatment over time.

| Time	Hemoglobin	White blood cell count	Platelet count	Therapy
Diagnosis of PMF	9.3 g/dL	8.78×10^9/L	234×10^9/L	danazol (0.2 g bid), calcitriol (0.25 μg bid) thalidomide (75 mg qn)
At 15 months after diagnosis	14.6 g/dL	11.66×10^9/L	448×10^9/L	calcitriol (0.25 μg, bid), thalidomide (25 mg, qn) aspirin (0.1 g, qd)
At 17 months after diagnosis	16–18g/dL	5.58×10^9/L	172×10^9/L	hydroxyurea (0.5 g, qd)
At 19 months after diagnosis	18.2g/dL	6.21×10^9/L	194×10^9/L	hydroxyurea (0.5 g, qd) interferon (300MIU, 2/w)
At 30 months of the progression	14.3 g/dL	5.77×10^9/L	135×10^9/L	interferon (300 MIU, 2/w)

PMF = primary myelofibrosis.

kinase (CK) was negative. Chromosome analysis showed 46, XX; del (20) (q11) with positive JAK2 V617F mutation and negative bcr/abl fusion gene. Abdominal CT scan showed splenomegaly and multiple low-density lesions on lumbar and thoracic vertebrae. The immunofixation electrophoresis showed no monoclonal components of IgG, IgA, IgM, light chain κ, and λ. After excluding hemolytic anemia, plasma cell diseases and other diseases leading to anemia, the patient was diagnosed as myelofibrosis. For treatment, the danazol (0.2 g bid), calcitriol (0.25 μg bid), and thalidomide (75 mg qn) were given. The patient's Hb increased after 3 months of treatment (Table 1).

At 15 months after diagnosis, the patient underwent routine checkups. She did not have any clinical complaints. Routine blood tests showed higher white blood cell count (11.66×10^9/L), Hb (14.6g/dL) and platelet count (448×10^9/L). Chromosome analysis showed del (20) (q11) with positive JAK2 V617F mutation. The above indicated successful treatment; therefore,

the treatment was changed to calcitriol (0.25 μg, bid), thalidomide (25 mg, qn), and aspirin (0.1 g, qd) (Table 1).

At 17 months after diagnosis, the patient underwent routine checkups. She did not have any complaints. The marrow biopsy showed that compared with last biopsy, bone marrow hyperplasia was less active (70%) with obvious proliferation of fibrous tissues. The myeloid and erythroid ratio returned to normal levels, and immature granulocytes decreased. Reticular fiber staining was positive (++). The above results showed that the treatment was effective. The chromosomal analysis showed 42–46, XX; −10, −18, −19, −20, −22. However, the Hb increased to a level between 16 to 18 g/dL, and white blood cells and platelets were within normal range. Therefore, the use of thalidomide and calcitriol was stopped, and hydroxyurea (0.5 g, qd) was started (Table 1).

At 19 months after diagnosis, blood test showed Hb was 18.2 g/dL and Hct was 0.62 without immature blood cells or
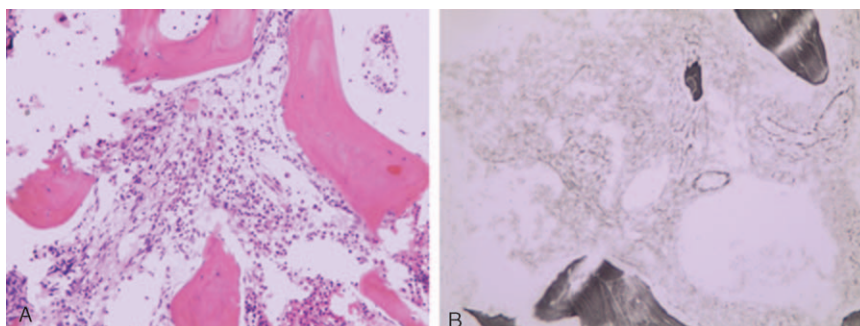
Figure 2. Bone marrow biopsy showed reduced proliferation of fibroblasts (A) (Magnification: 10X) and Gomori reticulin staining was weakly positive (+−) (B) (Magnification: 10X).

poikilocylosis, whereas the white blood cell count and platelet count were still within normal range. Epo level was 4.2 mIU/mL. Bone marrow biopsy showed bone marrow hyperplasia was active (80%) (Fig. 2A). Myeloid and erythroid ratio slightly decreased, mainly shown as erythroidhyperplasia. Myeloid, erythroid, and megakaryocytes were mainly matured cells, without hemosiderosis or fibrosis. The reticular fiber staining was weak positive (Fig. 2B). Abdominal ultrasound showed splenomegaly with the size of 56 × 153 mm. CT scan showed extensive bone destruction in thoracic vertebrae, lumbar vertebrae, and pelvis. The immunofixation electrophoresis and urine free light chain assay all showed negative. The chromosomal analysis showed 46, XX; del (20) (q11) /46, XX, with positive JAK2-V617F gene mutation. Other abnormal chromosomal clones mentioned above disappeared.

Based on the above results, a diagnosis of PV was made. The red blood cell apheresis, interferon treatment was given, whereas hydroxyurea was continued (Table 1). After 17 days, Hb decreased to normal level, bone marrow biopsy, and bone marrow cytology remained and abdominal ultrasound showed spleen size of 48 × 167 mm. The patient is receiving maintenance therapy (interferon 300MIU, 2/w) and in constant follow up (Table 1). After 30 months of the progression (at the recent follow-up), this patient had no obvious symptoms or thrombosis.

3. Discussion

PMF has the most heterogeneous clinical presentations, including anemia, splenomegaly, leukocytosis or leukopenia, thrombocytosis or thrombocytopenia, and constitutional symptoms.[7] In this report, at diagnosis of anemia, reticulocytes, and bilirubin levels were within normal range. And, there was no evidence of red blood cell destruction. Thus, the diagnosis of hemolytic anemia was ruled out. Concerning PMF prognostication, the IPSS[8] (International Prognostid Scoring System) model at diagnosis and the DIPSS[9] (Dynamic IPSS) anytime during the course of the disease define survival of patients with PMF. The estimated median survival time for PMF is 6 years, ranging from a few months to many years.[8–12] In this study, at the diagnosis of PMF, the Hb of this patient was 9.3 g/dL without constitutional symptoms or other risk factors. Therefore, this patient was stratified as intermediate-2 risk and the estimated median survival time was 48 months.

The only treatment that is currently capable of prolonging survival of PMF patients or can cure PMF is allogeneic stem cell transplant (ASCT). However, the transplant-related death rate is more than 50% after ASCT, regardless of the intensity of conditioning regimens used.[13] There are several palliative therapies for DIPSS-plus low or intermediate-1 risk patients,[14] including management of anemia, splenomegaly, bone pain, and other constitutional symptoms. In recent years, the new drug JAK inhibitor is used for PMF treatment; however, its effect is limited to relief of symptoms and reduction of spleen size.[15–18] In this report, we recommended the treatment of JAK inhibitor and bone marrow transplant. However, the patient could not afford the JAK inhibitor and worried the high rate of transplant-related death. Finally, she chose the treatment method of low-dose immunomodulatory agent with thalidomide, danazol and calcitriol. The PMF-PV progression occurred at 19 months after diagnosis.

According to the diagnostic criteria by the World Health Organization (WHO), patients with Hb >18.5 g/dL in males or >16.5 g/dL in females and JAK2V617F mutations can be diagnosed as PV.[19] The British Committee for Standards in Haematology (BCSH) guidelines suggest that patients with Hct >52% in males or >48% in females and JAK2 mutation can be diagnosed as PV.[20–22] Barbui et al[23] proposed the concept of masked PV. The cases with JAK2V617F mutation and Hb level <18.5 g/dL in males (range 16.0–18.4) or <16.5 g/dL in females (range 15.0–16.4) should be diagnosed as masked PV. In comparison with PV, the overall survival of masked PV patients is shorter. In this report, the Hb in the patient was 9.3 g/dL, which was not within the range for masked PV suggested by Barbui et al.[23] Thus, masked PV was excluded at the first diagnosis of PMF.

The symptoms of PV patients are relatively mild. The main high risk symptoms for PV are thrombosis, secondary MF, and AML. Post-PV MF occurs at a rate of 10% to 20% after 15 to 20 years of follow up.[5] The reverse transformation from PV to PMF was described elsewhere.[24–27] However, these cases were reported when gene and chromosome detections were not available. In recent years, Paul et al[28] reported one case without chromosome abnormalities. In this case, patient showed anemia, splenomegaly, negative bcr/abl fusion gene, and fibrosis in bone marrow biopsy, therefore, the patient was diagnosed as PMF. However, clonal progression and new detected chromosome abnormalities occurred and Hb increased, which was in accordance with the diagnosis of PV. We also observed that some chromosome abnormalities (such as −10, −18, −19, −20, −22) appeared shortly and then disappeared. Whether these chromosome abnormalities are related with the progression of PMF to PV still needs further investigation.

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