

Case Report

## Severe Case of Peripheral Leukocytosis Initially Diagnosed as Myelodysplastic Syndrome/Myeloproliferative Neoplasm, Unclassifiable, but Possibly Prefibrotic Primary Myelofibrosis

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Leukocytosis is occasionally seen in patients with presumptive but undiagnosed myeloproliferative disorders (MPD). A 74-year-old woman was admitted to our hospital for tarry stools, anemia, and marked peripheral leukocytosis of  $1.4 \times 10^5/\mu\text{L}$ . Gastroenteroscopy revealed an acute gastric and duodenal mucosal lesion that was treated successfully via endoscopic hemoclippping. Bone marrow aspiration revealed marked megakaryocyte proliferation with atypia of naked nuclei and marrow hypercellularity (90% cellularity). A fluorescence *in situ* hybridization test could not detect the BCR-ABL fusion gene. Bone marrow aspiration later revealed further abnormalities of megakaryocytes. The patient died from cerebral bleeding. The present case fulfilled 2 of the 3 major criteria of primary myelofibrosis according to the World Health Organization 2008 classification: namely, megakaryocytic hyperplasia with hypercellular marrow and granulocytic hyperplasia. However, the megakaryocytic abnormality was not strictly compatible with the criteria. Instead, we considered prefibrotic primary myelofibrosis as a possibility, although myelodysplastic syndrome/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U) was technically the correct diagnosis. The present case shows that MPN diagnosis remains difficult and suggests that other cases of peripheral leukocytosis with diagnosed MDS/MPN-U might include similar findings.

**Key words:** prefibrotic primary myelofibrosis, leukocytosis, anemia, acute gastric mucosal lesion, multiple cerebral hemorrhages

**L**eukocytosis in excess of 50,000 cells/ $\mu\text{L}$  can be caused by acute leukemia, chronic myeloproliferative neoplasms (MPN) including chronic myeloid leukemia (CML), essential thrombocythemia (ET), primary myelofibrosis (PMF), or polycythemia vera

(PV) [1-4]. Other causes of leukocytosis include leukemoid reactions consequent to tuberculosis and other severe infections, adverse drug effects or, on rare occasion, granulocyte colony-stimulating factor (G-CSF)-producing tumors [5].

MPN diagnosis [6-10] occasionally proves to be

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difficult and has remained a matter of debate since William Dameshek first classified PV, ET, and PMF as pathogenetically related myeloproliferative disorders (MPD) in 1951 [11]. Leukocytosis is occasionally observed in patients with presumptive but undiagnosed MPN [12].

We report herein a case of a patient admitted with severe peripheral leukocytosis (140,000 cells/ $\mu\text{L}$ ); this case appeared to fulfill the criteria of prefibrotic PMF and could have been considered PMF, although myelodysplastic syndrome/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U) was technically the correct diagnosis.

### Case Presentation

A 74-year-old woman was referred to the office of a physician of internal medicine because of tarry stools in December, 2009. Complete blood count (CBC) revealed anemia and a markedly elevated white blood cell (WBC) count of  $1.4 \times 10^5/\mu\text{L}$ . The patient was referred to us for consultation and was admitted the following day to Himeji St. Mary hospital. Since October 2009, she had been using a Chinese medical agent synthesized primarily from aged garlic extract to improve her health, but stopped taking this supplement three days prior to her admission. She also had a history of hypertension and hyperlipidemia but no history of smoking. Her CBC results were almost normal in June, 2009, which was 6 months before her admission (WBC count, 8,900/ $\mu\text{L}$ ; red blood cell [RBC] count,  $4.24 \times 10^6/\mu\text{L}$ ; hemoglobin [Hb] level, 11.0 g/dL; and platelet [Plt] count,  $1.77 \times 10^5/\mu\text{L}$ ).

At admission, her WBC count was 124,000/ $\mu\text{L}$ , comprising 2% promyelocytes, 5% myelocytes, 1% metamyelocytes, 83.5% polymorphonuclear neutrophils, 4% lymphocytes, 0% eosinophils, and 1.5% basophils. The following values were also recorded: RBC count,  $1.64 \times 10^6/\mu\text{L}$ ; Hb, 4.3 g/dL; mean corpuscular volume, 84.1 fL; mean corpuscular Hb, 26.2 pg; mean corpuscular Hb concentration, 31.2%; and Plt,  $1.46 \times 10^5/\mu\text{L}$ . Her serum lactate dehydrogenase (LDH) level was 299 IU/L (normal range, 105-210 IU/L). A physical examination revealed conjunctival anemia and a non-palpable spleen; moreover, no lymphadenopathy or skin eruptions were observed. Gastroenteroscopy revealed an acute gastric mucosal lesion (AGML) and an acute duodenal

mucosal lesion (ADML; Fig. 1). The patient received a blood transfusion, and her gastric ulcer was treated successfully by endoscopic hemocclipping.

Bone marrow (BM) aspiration stained according to the May-Grunwald-Giemsa (Fig. 2A) and hematoxylin-eosin protocols (Fig. 2B) revealed a nucleated cell count of  $611 \times 10^3/\mu\text{L}$  (normal range, 50-200  $\times 10^3/\mu\text{L}$ ), a megakaryocyte count of 712/ $\mu\text{L}$  (normal range, 50-150/ $\mu\text{L}$ ), and a myeloid to erythroid cell ratio of 9.5 (normal range, 1.5-3.3), indicating marked myeloid cell proliferation. However, there were no findings compatible with acute leukemia (Table 1). A silver-stained BM biopsy specimen revealed no BM fibrosis (Fig. 2C). The megakaryocytes displayed

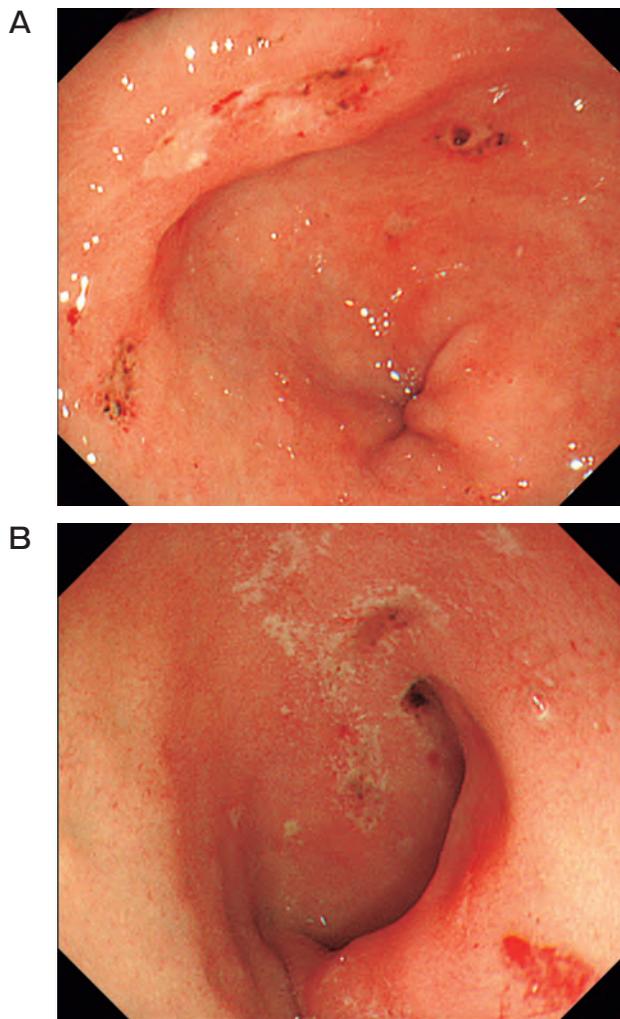
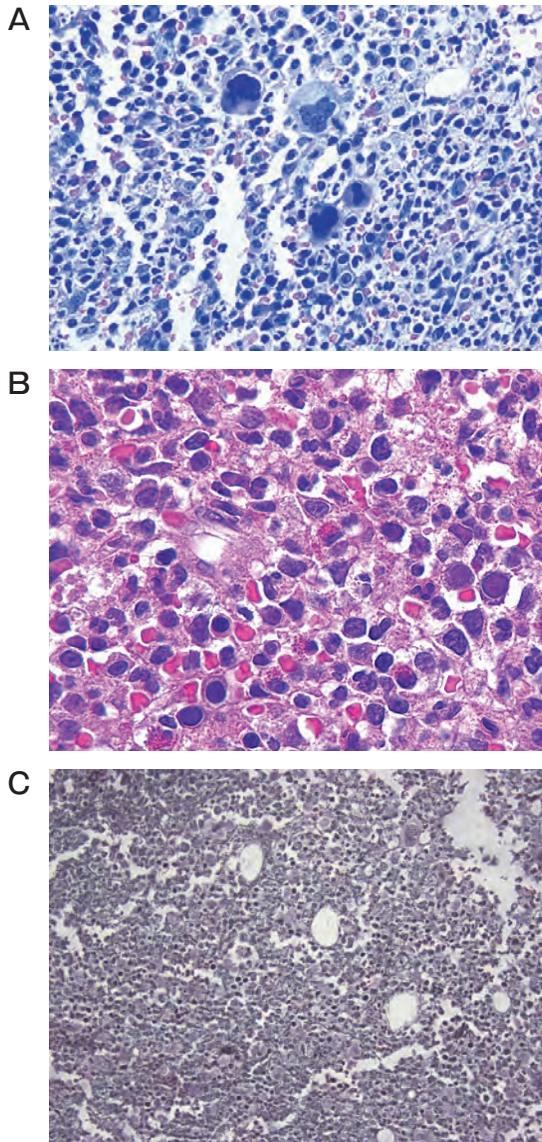


Fig. 1 Gastrointestinal scope showing an acute gastric mucosal lesion (A) and acute duodenal mucosal lesion (B).



**Fig. 2** **A**, Light microscopic findings of a bone marrow (BM) smear stained by May-Grunwald-Giemsa. Low-power field; **B**, HE. Bone marrow aspiration showed marked proliferation of myeloid cells. High-power field; **C**, Silver stain of BM biopsy specimen showing no fibrosis of BM. Low-power field.

atypia (Fig. 3A and B). A BM biopsy revealed marked marrow hypercellularity (90% cellularity). No obvious fibrosis was observed. Moreover, fluorescence *in situ* hybridization (FISH) did not indicate the presence of the BCR-ABL fusion gene. In addition, an elevated neutrophil alkaline phosphatase (NAP) score of 426 was observed (normal range, 188–367). The lack of

the BCR-ABL fusion gene and the elevated NAP score were inconsistent with the chronic phase of chronic myeloid leukemia, during which the NAP score would normally decrease. A cytogenetic analysis of 20 cells revealed a normal karyotype (46, XY) in 18 cells and a 46, XX, del (20) (q1?) in 2 cells. These findings did not support a diagnosis of PV or CML, and the presence of BM megakaryocytic hyperplasia and hypercellular marrow with granulocytic hyperplasia suggested prefibrotic PMF.

The Chinese drugs that the patient had used previously were synthesized mostly from aged garlic extract. A drug-induced lymphocyte stimulation test (DLST) was conducted because we suspected that these drugs might have induced the marked leukocytosis. Following the incubation, the numbers of lymphocytes treated with and without (control) the Chinese drug were 104 and 152 counts per minute, respectively, suggesting that the drug did not stimulate lymphocyte proliferation and presumably had not caused the leukocytosis.

Following admission, the patient's WBC count remained markedly high at 30,000–60,000/ $\mu\text{L}$ . Her serum G-CSF level was 19.5 pg/mL (normal, < 39 pg/mL), which excluded the possibility of a G-CSF-producing tumor. Chest and abdominal computed tomography (CT) revealed no abnormalities indicative of a severe infection, tumor, or bone metastasis. The splenic size was within the upper limit of the normal size range. The patient was discharged from the hospital on day 27 and received no specific treatment for her leukocytosis. Her final visit to our hospital was in February, 2010. On that date, the CBC revealed a WBC count of 58,000/ $\mu\text{L}$ , RBC count of  $4.15 \times 10^6/\mu\text{L}$ , Hb level of 10.9 g/dL, Plt count of  $1.04 \times 10^5/\mu\text{L}$ , and LDH level of 299 IU/L. The patient was followed-up at an outpatient clinic of the Himeji Red Cross hospital. The BM aspirations (Fig. 3C and E) and HE clots (Fig 3D, F) performed in February 2010 (Fig. 3C, D) and April 2011 (Fig. 3E, F) revealed megakaryocytic atypia. A BM aspiration revealed a nucleated cell count of  $1.72 \times 10^6/\mu\text{L}$  (normal range,  $50\text{--}200 \times 10^3/\mu\text{L}$ ), and a myeloid to erythroid cell ratio of 15.8 (normal range, 1.5–3.3) in February 2010 (Table 1). No JAK2 gene mutation was found, contrary to usual findings in PV. The MPL mutation (W515K/L) was not examined. The patient was prescribed a daily hydroxycarbamide dose

Table 1 Marrow differential cell count

Date		2009 Dec	2010 Feb	
Group	Cell type	Fraction	Fraction	Reference range (%)
Cells of myelopoiesis	Myeloblasts	3.0%	2.4%	0.2–2.9
	Promyelocytes	7.6%	1.5%	1.5–8.4
	Myelocytes	16.8%	32.5%	1.0–9.7
	Metamyelocytes	14.4%	32.5%	3.6–14.6
	Band cells	16.8%	8.5%	10.6–24.6
	Segmented neutrophils	26.2%	28.2%	8.5–33.2
	Eosinophils	2.6%	2.7%	1.2–5.3
	Basophils	1.6%	0.0%	0–0.8
	Total	89.0%	91.9%	50.4–70.5
	Cells of erythropoiesis	Proerythroblasts	0.2%	0.3%
Basophilic erythroblasts		1.2%	0.9%	0.8–6.7
Polychromatic erythroblasts		6.8%	3.2%	4.1–29.1
Orthochromatic erythroblast		1.2%	1.4%	0.1–5.7
Total		9.4%	5.8%	18.4–33.8
Other cell types	Megakaryocytes	0.4%	0.0%	0–0.1
	Plasma cells	0.2%	0.1%	0.2–1.7
	Lymphocytes	1.0%	1.9%	5.0–32.6
	Monocytes	0%	0.6%	0.7–6.0

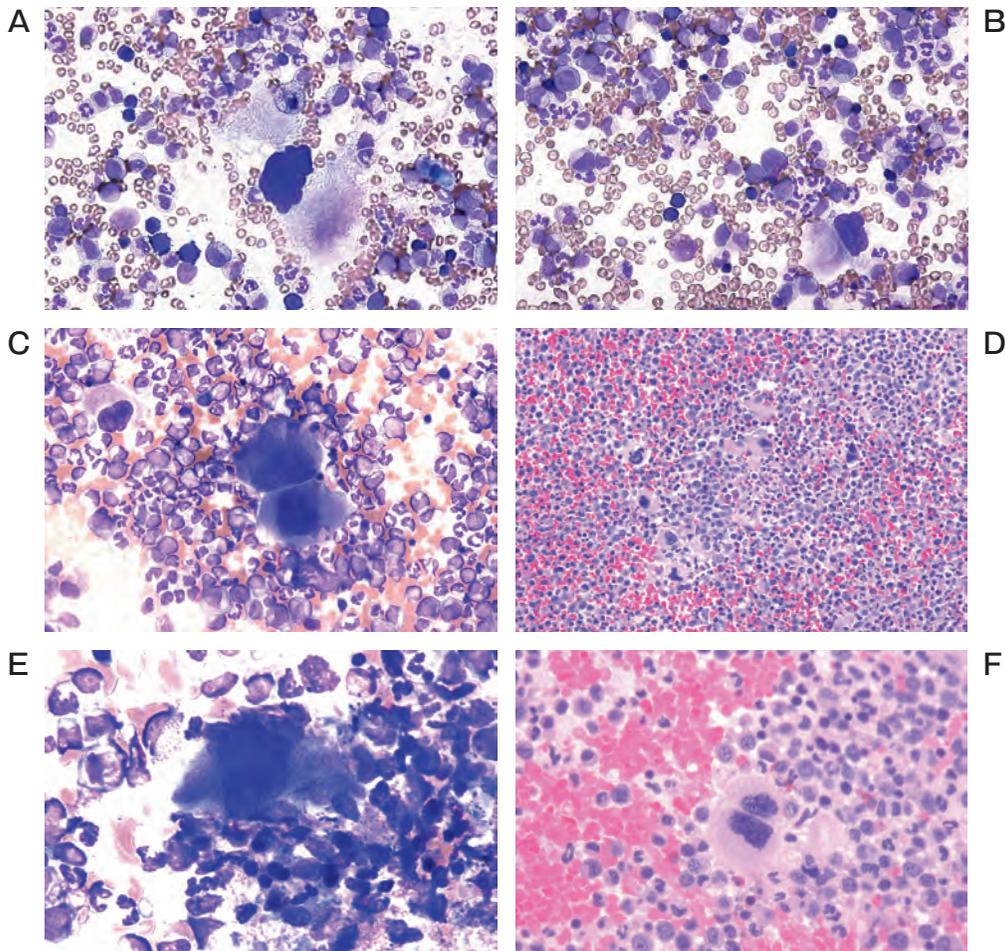
of 500 mg because her peripheral WBC count was recorded as  $> 100,000/\mu\text{L}$  in June, 2011. The WBC count subsequently increased to  $210,000/\mu\text{L}$  in August, 2011. The patient died the following day from multiple cerebral hemorrhages; this occurred precisely 1 year and 10 months after the first admission.

## Discussion

For decades, the classification of BCR-ABL-negative MPN has remained a matter of debate. The World Health Organization (WHO) 2008 classification discriminated between ET, PMF, and PV [13–15]. Histopathology is the key component of such diagnoses and is defined by megakaryocyte proliferation atypia even in the absence of overt fibrosis; this technique also facilitates the differential diagnosis of MPN disorders and myelodysplastic syndromes [16].

In some percentage of PMF cases, fibrosis might exhibit a non-fibrotic cellular phase. This proliferation is clonal in nature [17, 18]. The present case fulfilled 2 of the 3 major criteria of PMF, specifically the presence of hypercellular marrow with

granulocytic hyperplasia; however, these findings did not meet the criteria of PV, CML, MDS, or other myeloid neoplasms and secondary causes of fibrosis were excluded. The present case exhibited abnormal megakaryocytic hyperplasia, but the findings were not strictly compatible with prefibrotic MF, which would include small- to large-sized megakaryocytes with an aberrant nuclear/cytoplasmic ratio, hyperchromatic, bulbous, or irregularly folded nuclei, dense clustering, an increased nucleo-cytoplasmic ratio, and the presence of cloudlike nuclei, hyperchromatic-dysplastic nuclei, paratrabeular megakaryocytes, or tight clusters [19, 20]. The present case fulfilled 2 of the 4 minor criteria required for diagnosis, specifically the presence of anemia and increased serum LDH. Anemia on admission might be influenced by alimentary tract bleeding; however, 3 months after admission, Hb was 10.9 g/dl, which can be considered to be anemic. Two minor criteria, namely splenomegaly and leukoerythroblastosis, were not observed. Based on these findings, we could not confirm a diagnosis of prefibrotic PMF. In addition, thrombocytopenia, which is usually present in PMF, was not observed in the



**Fig. 3** Megakaryocytes showed atypia. **A, B**, Megakaryocytes showed atypia of naked nuclei on admission in Dec 2009; **C, D**, The BM aspiration and HE clot in February 2010 showed atypia of megakaryocytes; **E, F**, The BM aspiration and HE clot in April 2011 showed atypia of megakaryocytes. **A, B, C, E, and F** are high-power fields. **D** is a low-power field.

present case. The patient was diagnosed with myelodysplastic syndrome/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U) [21]; however, the case could be made for a diagnosis of prefibrotic PMF.

The AGML, ADML, and gastric ulcer present at admission occurred when the patient had a peripheral WBC count of  $140,000/\mu\text{L}$ , and the fatal cerebral hemorrhages occurred when the WBC count was  $210,000/\mu\text{L}$ . Both of these conditions were assumed consequent to a bleeding tendency that is sometimes observed in patients with MPN. An elevated leukocyte count is correlated with an increased risk of total thrombosis and, in particular, an increased risk of arterial thrombosis [22]. If prefibrotic PMF cases could be diagnosed early among MDS/MPN-U cases,

it would help to reveal characteristics of relatively rare prefibrotic PMF.

Initially, our putative diagnosis was prefibrotic PMF, but the present case did not exhibit a megakaryocytic abnormality that would have been strictly compatible with prefibrotic PMF. The present case demonstrated that MPN diagnoses remain difficult and that several cases of severe peripheral leukocytosis and anemia [23], in which the patients died following diagnoses of MDS/MPN-U, might have included similar findings.

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