【 CASE REPORT 】

Accelerated Phase of Atypical Chronic Myeloid Leukemia with Severe Disseminated Intravascular Coagulation at Initial Presentation

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Abstract:
Patients with myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) are often asymptomatic and thus can remain undiagnosed until they become symptomatic due to progression to the accelerated phase (AP) or transformation to acute leukemia (leukemic transformation; LT). We herein report the case of a previously healthy 38-year-old man who had hyperleukocytosis with dysplastic myeloid precursor cells and severe disseminated intravascular coagulation. Hematopoietic recovery with features of atypical chronic myeloid leukemia (aCML) after induction chemotherapy was a diagnostic clue. Although rare, this case highlights the limitation of the diagnostic approach for aCML with AP or LT at the initial presentation.

Key words: atypical chronic myeloid leukemia, leukemic transformation, disseminated intravascular coagulation

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Introduction

Patients with a myeloproliferative neoplasm (MPN) or myelodysplastic syndrome / myeloproliferative neoplasm (MDS/MPN) generally have an asymptomatic clinical course, so some cases remain undiagnosed. However, although no distinct disease phases have been assigned to MDS/MPN, a proportion of patients experience evolution during the clinical course to an accelerated phase (AP) and subsequently develop acute leukemia, referred to as leukemic transformation (LT). Such patients may, therefore, initially present to a hospital with aggressive symptoms induced by AP or LT.

Atypical chronic myeloid leukemia (aCML) is a rare hematopoietic stem cell disorder categorized by the presence of MDS/MPN. Leukocytosis with left-shift and proliferation of highly dysplastic neutrophilic precursors in peripheral blood (PB) and bone marrow (BM) lacking a BCR-ABL1 translocation is a characteristic finding in aCML (1). A relatively high proportion of patients with aCML (30-40%) develop LT, resulting in a critical status with a poor outcome (2); therefore, allogeneic stem cell transplantation, with its potential to achieve a long-term survival, should be considered in the therapeutic management of aCML (3).

In practice, we diagnose aCML by its clinical course and morphologic features, with confirmation by differential diagnosis according to the latest WHO criteria (1). However, the optimal diagnostic approach for aCML with AP or LT at the initial presentation has not been clearly determined.

We herein report a case showing hyperleukocytosis with dysplastic myeloid precursor cells that was complicated with severe disseminated intravascular coagulation (DIC) at the initial presentation. We diagnosed aCML with AP retrospec-

Table.　Laboratory Analysis of Peripheral Blood on Admission.

Cell counts and differential		Blood chemistry		Coagulation	
WBC	12.59×10^4 /μL	TP	6.7 g/dL	PT	16 sec
stab	3 %	ALB	3.7 g/dL	APTT	29.8 sec
seg	48 %	AST	76 U/L	Fib	66 mg/dL
lym	4.5 %	ALT	50 U/L	AT3	68.9 %
mono	2.5 %	LDH	1,235 U/L	FDP	208.8 μg/mL
eos	1 %	ALP	178 U/L	D-dimer	93.54 μg/mL
baso	0 %	γ-GT	40 U/L	PIC	6.48 μg/mL
myeloblasts	7.5 %	CK	245 U/L	TAT	78.4 ng/mL
promyelo	12.5 %	T-bil	1.7 mg/dL		
myelo	6 %	BUN	21.9 mg/dL		
metamyelo	15 %	Cre	0.85 mg/dL		
RBC	149×10^4 /μL	UA	6 mg/dL		
Hb	5.3 g/dL	CRP	5.06 mg/dL		
MCV	102.7 fl				
PLT	1.5×10^4 /μL				

WBC: white blood cells, stab: stab cells, seg: segmented neutrophils, lym: lymphocytes, mono: monocytes, eos: eosinophils, baso: basophils, promyelo: promyelocytes, myelo: myelocytes, metamyelo: metamyelocytes, RBC: red blood cells, Hb: hemoglobin, MCV: mean cell volume, PLT: platelets, TP: total protein, ALB: albumin, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GT: gamma-glutamyl transferase, CK: creatinine kinase, T-bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, UA: uric acid, CRP: C-reactive protein, PT: prothrombin time, APTT: activated partial thromboplastin time, AT3: antithrombin III, FDP: fibrin degradation products, PIC: plasmin-alpha2-plasmin inhibitor complex, TAT: thrombin-antithrombin complex

tively according to the hematopoietic recovery features after induction chemotherapy. Although rare, this case highlights the limitation of the current diagnostic approach for aCML with AP or LT at the initial presentation.

Case Report

A 38-year-old man who had an unremarkable medical history and had never undergone annual medical checkups presented to a primary care doctor with a 1-month history of a fever, gingival bleeding, and cough. Hyperleukocytosis, anemia, and thrombocytopenia were detected, and he was referred to the hematology department for a detailed examination.

On an examination, he had a high fever, tachycardia, and hypoxemia. His palpebral conjunctivae were pale, and petechiae on the oral mucosa, ulcers at the tongue tip, swelling of the gingiva, and purpura on the lower legs were observed. Auscultation detected coarse crackles in both lungs, and no lymphadenopathy or hepatosplenomegaly was obvious on palpation. Laboratory tests showed hyperleukocytosis 12.59×10^4/μL, with 7.5% myeloblasts, 12.5% promyelocytes, 6% myelocytes, 15% metamyelocytes, and 51% neutrophils (Table). A PB smear showed highly dysplastic myeloid cells and hypersegmented neutrophils (Fig. 1A-C). The hemoglobin concentration was 5.3 g/dL, and the platelet count was 1.5×10^4/μL. An increased level of lactate dehydrogenase was detected, and coagulation tests showed hypofibrinogenemia with an abnormal increase of fibrin degradation products,

which was consistent with DIC (Table).

X-ray and computed tomography of the chest revealed multiple ground-glass opacities and interlobular septal thickening in both lungs (Fig. 2). Because no evidence of pulmonary infectious microorganisms, including bacterial and fungal disease, was detected, we assumed that these findings were consistent with pulmonary infiltration of leukocytes. BM aspiration showed severely hyperplastic marrow (with a myeloid/erythroid ratio of 38) with the proliferation of highly dysplastic and azurophilic granule-rich immature myeloid cells. Neither leukemic hiatus nor faggot cells were observed, and myeloblasts comprised 13% of nucleated marrow cells. There was no evidence of dysplastic megakaryocytic or erythroid cells. The abnormal cells were strongly positive for myeloperoxidase stain and negative for nonspecific esterase stain (Fig. 1D-G). A flow cytometric analysis showed that they were positive for CD13 and CD33 expression and negative for CD34 and HLA-DR. Common genetic abnormalities of leukemia, including a BCR-ABL1 transcript and translocation of the *RARa* or *PDGFR* gene, were not detected. A cytogenetic analysis revealed a normal karyotype (46, XY).

Although he lacked a history of a preceding episode of MPN or MDS/MPN, the presence of highly dysplastic myeloid precursors in the PB and BM along with the rapid progressive clinical course complicated by severe DIC prompted us to suspect aCML with AP. Induction therapy (cytarabine and idarubicin) was rapidly commenced, along with thrombomodulin-alpha to treat the DIC. On day 3 of
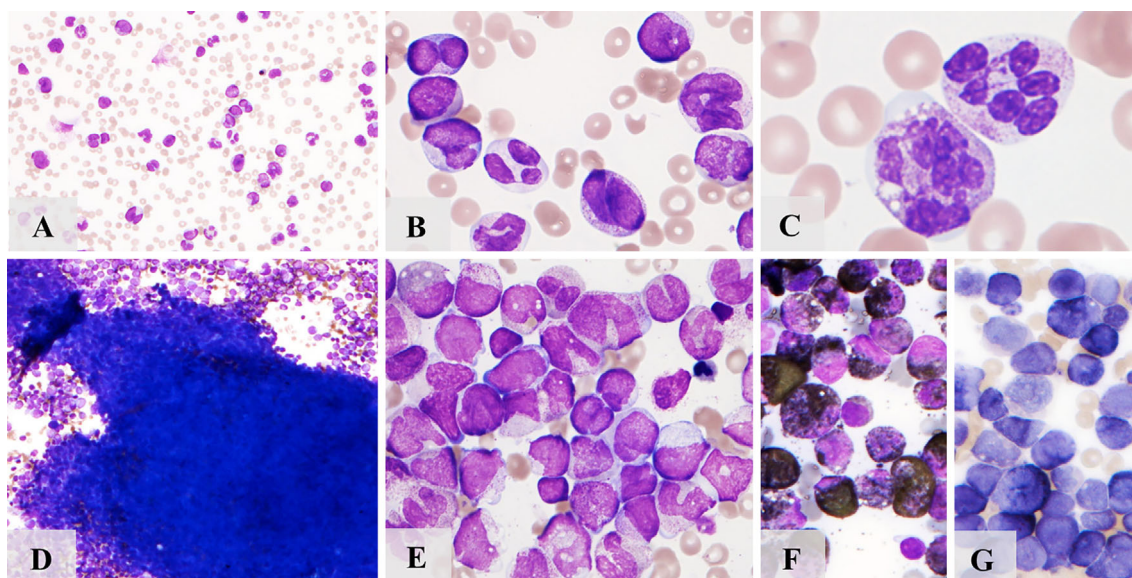
Figure 1. Images of May-Giemsa-stained peripheral blood and bone marrow smears on admission. The peripheral blood smear showed highly dysplastic myeloid cells (A, B) and hypersegmented neutrophils (C). Original magnification ×100 (A), ×750 (B), and ×1,000 (C). The bone marrow aspirate showed severely hyperplastic marrow with the proliferation of highly dysplastic and azurophilic granule-rich immature myeloid cells (D, E). These abnormal cells were strongly positive for myeloperoxidase stain (F) and negative for non-specific esterase stain (G). Original magnification ×40 (D), ×250 (E), and ×200 (F, G).
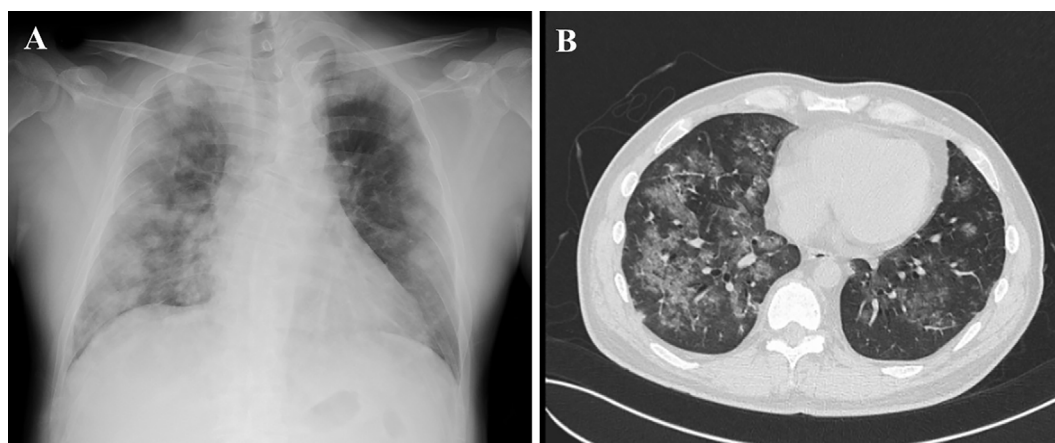

Figure 2. Images of chest X-ray and computed tomography. Chest X-ray showed multiple consolidation (A), and computed tomography of the chest revealed multiple ground-glass opacities and interlobular septal thickening (B) over both lungs.

chemotherapy, the patient suffered bilateral alveolar hemorrhaging requiring mechanical ventilation, and on day 10, cerebral hemorrhaging in the frontal lobe due to DIC exacerbated by tumor lysis syndrome (TLS) was noted. The DIC and lung abnormalities improved gradually with the leukocyte eradication, and complete hematological remission was obtained.

His general condition had not recovered enough to undergo allogeneic stem cell transplantation immediately. However, the leukocytes, mainly consisting of mature granulocytes with dysplasia not accompanied by an increase in myeloblasts and monocytes, gradually increased in number

to >1.5×10⁴/μL, at which point hydroxyurea (HU) at a dose of 500 mg/day was commenced to control the leukocytosis. BM aspiration 1 month after HU administration showed residual dysplastic myeloid cells with hypersegmented neutrophils, while the azurophilic granule-rich immature myeloid cells had almost disappeared (Fig. 3).

About three months later, the patient relapsed with an increase in myeloblasts in the BM, and he received re-induction therapy and subsequently underwent haplo-identical PB transplantation from a sibling donor. He remains relapse-free. Retrospective targeted next-generation sequencing of the BM cells obtained on admission revealed
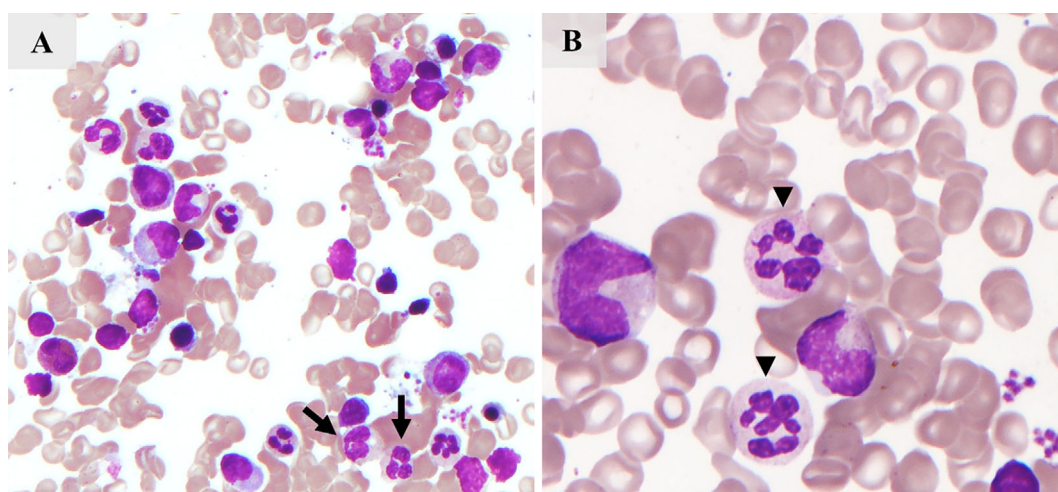
Figure 3. Images of a May-Giemsa-stained bone marrow smear after induction therapy and during HU administration. The bone marrow aspirate collected one month after HU administration showed residual dysplastic myeloid cells (A, arrows) with hypersegmented neutrophils (B, arrowheads). Original magnification ×200 (A) and ×400 (B).

DNMT3A and *NPM1* mutations, but no *FLT3-ITD, JAK2, CALR, MPL, SETBP1, ETNK1*, and *CSF3R* mutations or any other characteristics of hematological malignancies were detected.

Discussion

We encountered a case of hyperleukocytosis with severe DIC at the initial presentation that was subsequently diagnosed as aCML with AP. Because persistent MPN-relevant clinical signs, including marked hepatosplenomegaly and hyperplastic marrow with inconspicuous leukemic hiatus, are assumed for a diagnosis of MDS/MPN, the change in disease phase is difficult to define without a preceding diagnosis of MDS/MPN. Furthermore, leukemic cells infrequently retain the potential to differentiate into mature neutrophils with a dysplastic change, as represented by acute myeloid leukemia (AML) with t(8;21) (4, 5). Thus, at the initial presentation, aCML with AP or LT cannot be completely distinguished morphologically from AML with extensive maturation because that also resembles left-shifted leukocytosis with dysgranulopoiesis.

Detailed cytogenetic and somatic mutational information can be helpful for the diagnosis of MPN or MDS/MPN with AP or LT. Even if CML in the blastic phase is found at the initial presentation, it is typically diagnosed by the presence of a BCR-ABL1 translocation in neutrophils. In addition, the *CSF3R* mutation is specific for chronic neutrophilic leukemia (CNL) and detected in more than 90% of cases (6). Driver mutations of MPN, such as in *JAK2, CALR*, or *MPL*, also imply the pre-existence of polycythemia vera or essential thrombocythemia, although the *JAK2* mutation is not always detected in AML clones transformed from MPN (7). However, aCML shows a heterogeneous mutational landscape without recurrent and specific genetic mutations (8-11). *RAS, ASXL1,* and *TET2* mutations are seen in

8-30%, 23-66%, and 16-41% of patients with aCML, respectively (9, 12, 13), but such mutations are also frequently seen in MDS and other types of MDS/MPN, such as chronic myelomonocytic leukemia (CMML). Recent studies report that the *SETBP1* and *ETNK1* mutations are predominant in aCML (12, 14), so screening for these mutations would be useful for confirming the diagnosis despite their low frequency.

The assessment of hematopoietic recovery after induction chemotherapy can confer a clinical hint for retrospectively establishing a diagnosis of aCML with AP or LT at the initial presentation. MPN or MDS/MPN are clonal hematopoietic stem cell disorders; therefore, when induction chemotherapy successfully leads to the eradication of leukemic clones, distinctive features of hematopoietic recovery derived from pre-existing MPN or MDS/MPN clones can be observed. In the present case, we first needed to exclude temporary dysplastic changes due to HU, and then continuous HU administration was needed in order to control the number of residual dysplastic myeloid cells, with no increase in myeloblasts or monocytes in the BM, even after hematological remission was obtained. This finding supports the pre-existence of MDS/MPN, especially of the aCML type rather than the CNL or CMML type. The *NPM1* mutation detected in the present case may have been associated with progression to AP, as it is frequently detected in AML and related to leukemogenesis (15, 16).

Tumor lysis of a high number of azurophilic granule-rich myeloid precursors after chemotherapy may have induced severe DIC and subsequent hemorrhaging events associated with leukostasis in the present case. To avoid fatal events, leukapheresis and other supportive management approaches for DIC and TLS should be considered for the initial management of aCML with AP or LT (17).

In conclusion, identifying aCML with AP or LT at the initial presentation is not clear-cut, as there can be morpho-

logical confusion, and there are no established specific genetic abnormalities of aCML. Hematopoietic recovery with features of aCML after induction chemotherapy may confer a diagnostic clue as in the present case. Novel approaches for identifying aCML with AP or LT at the initial presentation are warranted to help expedite the implementation of appropriate therapeutic strategies.

Informed consent was obtained from the patient for the publication of this case report.

Author's disclosure of potential Conflicts of Interest (COI).
Kensuke Kojima: Honoraria, Janssen Pharmaceuticals. Shinya Kimura: Honoraria, Bristol-Myers Squibb, Novartis, Pfizer and Otsuka Pharmaceuticals.

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