Clinical Case Report

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Bleeding with negative coagulation screening test as initial presentation of chronic myelogenous leukemia managed by fresh frozen plasma

A case report

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Abstract

Introduction: Chronic myelogenous leukemia (CML), a clonal disorder of pluripotent stem cell, rarely presents with bleeding in chronic phase due to the function preservation of the platelets. Factor (F) XIII deficiency, an extremely rare hemorrhagic disease, can cause fatal bleeding, which has been previously described in autoimmune disorders and leukemias.

Patient concerns: A 38-year-old woman with a 20-day history of spontaneous subcutaneous hemorrhage visited our hospital, who presented with intracranial hemorrhage, hematuria, and delayed hematoma after a bone marrow puncture. Initial management included cytogenetics analysis, molecular analysis, and coagulation evaluation.

Diagnosis: Bone marrow puncture, cytogenetics, and molecular analysis indicated the diagnosis of CML. With the normal results of clotting screening tests and platelet counting, as well as the relief of bleeding after infusion of fresh frozen plasma (FFP), acquired rare bleeding disorder probably associated with factor XIII (FXIII) deficiency.

Interventions: Management with anti-hyperleukocytosis and chemotherapy, hydration, alkalization, diuresis, uric acid-lowering, molecular targeted drugs, and freshly frozen plasma transfusion therapy resolved the bleeding diathesis.

Outcomes: The patient survived from the initial bleeding, however, she died. Twenty six months later due to the progression of CML.

Lessons: CML can initially present as unusual bleeding, possibly related to FXIII defect. It is essential to screen coagulopathy including FXIII activity and to supplement plasma for CML patients who present initially as bleeding, which cannot be deciphered by the routine clotting screening test.

Abbreviations: ALL = acute lymphoblastic leukemia, AML = acute myelogenous leukemia, APTT = activated partial thromboplastin time, BCR = breakpoint cluster region, CBC = complete blood count, CML = chronic myelogenous leukemia, CT = computed tomography, ET = essential thrombocythemia, FFP = fresh frozen plasma, FDP = fibrinogen degradation product, FXIII = factor XIII, PT = partial thromboplastin time, TKI = tyrosine kinase inhibitor, TT = thromboplastin time, VWD = Von Willebrand Disease, VWF = von Willebrand factor.

Keywords: acquired rare hemorrhage, chronic myelogenous leukaemia, plasma transfusion therapy

1. Introduction

Chronic myelogenous leukemia (CML) is clinically manifested with increasing fatigue, lassitude, weight loss, night sweats, massive splenomegaly, and gout. Unlike acute leukemia, CML in chronic phase (CP) manifested with bleeding is unusual due to the generally preserved function of platelets.[1] The occurrence of bleeding in CML usually suggests disease progression, which is caused by abnormal quantity or quality of thrombocyte.[1] Though anecdotal, the reported CML in CP initially presenting with hematoma includes intramuscular hematoma,[2,3] mediastinal hematoma, and hemothroax,[4] spinal epidural hematoma,[5] cerebellar hemorrhage,[6] subdural hematoma,[7–9] and deep soft-tissue hematomas.[10] Except for blast cell infiltration,[7] acquired von Willebrand factor (VWF) deficiency[8] or speculated platelet dysfunction[10] associated with hyper-thrombocytosis, most reported cases show almost normal results of clotting screening tests, including PT, activated partial thromboplastin time (APTT), thromboplastin time (TT), and platelet counting.[2–10]

As a matter of fact, there are few rare defects which cannot be recognized by PT, APTT, and platelets counting in a hemorrhagic patient including VWF, factor XIII (FXIII), plasminogen activator inhibitor 1 (PAI-1), and platelet dysfunction in clinical practice.[11–13] Disease-associated FXIII deficiencies have been reported both in acute leukemia and solid tumors.[14,15] Moreover, bleeding caused by FXIII deficiency is generally

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The patient provided written informed consent that has been signed for publication of the case.

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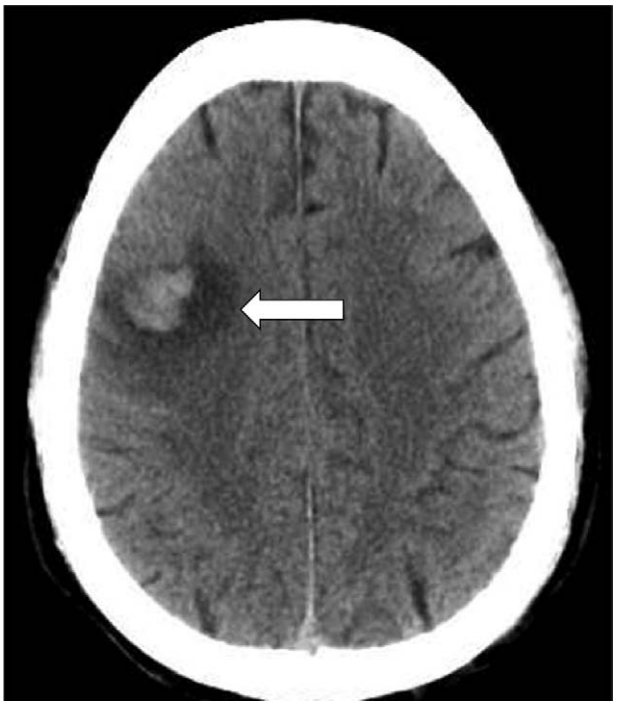

Figure 1. Computed tomography (CT) scan reported cerebral hemorrhage in the right parietal and frontal lobe (white arrow).

characterized by severe and delayed deep-tissue bleeding after trauma or operation.[12,13] In terms of FXIII deficiency, replacement therapy is feasible, as 2% to 5% FXIII plasma levels are sufficient to prevent severe bleeding. In addition, the long in vivo half-life (11–14 days) renders infrequent replacement.[13] fresh frozen plasma(FFP) is considered as a replacement choice for FXIII deficiency in case of no available factor concentrates.[12] In other word, FFP can relieve FXIII-associated bleeding quickly and persistently at a low dosage indicated that there was no inhibiting antibody or persistent consumption.

Here, in this case report, we described a woman with CML in CP initially presented with severe bleeding, which might be caused by FXIII deficiency and was later successfully treated with FFP transfusion.

2. Case presentation

In August 2013, a 38-year-old woman with multiple hematomas under the skin, hemorrhage in cerebrum, and hematuria was hospitalized for hyperleukocytosis. At admission, she suffered from progressive subcutaneous bleeding for 20 days with subsequent headache and hematuria, which had not been successfully managed with hemostatics. The initial complete blood counting (CBC) of local hospital indicated hyperleukocytosis, and the computed tomography (CT) scan suggested cerebral hemorrhage in the right parietal and frontal lobe (Fig. 1). Bone marrow puncture was performed in the local hospital and she was diagnosed as leukemia (data not provided). Unfortunately, a massive hematoma with tenderness occurred at the site of the puncture 1 day after bone marrow puncture.

At admission, physical examination revealed multiple hematomas in the mouth, abdomen, back, hips, thigh, and forearms. Moreover, the most substantial hematoma was around the left anterior superior iliac spine of puncture site, which was approximately 10×8 cm with tenderness. The CBC panel of the patient showed an elevated white blood count (WBC) of 454.84×10^9/L, with a significant left shift. The platelet count of the patient was 311×10^9/L, with hemoglobin level of 10.8 g/L. Urine examinations showed severe erythrocyturia of 2000 RBC/HP. Coagulation screening test revealed PT, APTT, TT, and fibrin at normal levels with slightly increased FDP and D-dimer (Table 1). Due to the severe tendency of hemorrhage, repeated bone marrow aspiration was delayed. Morphologic examination of the peripheral blood was suggestive of CML with increased cellularity and elevated percentages of the myeloid series at 2%, 20%, and 6% for promyelocyte, myelocyte, and metamyelocyte, respectively. The cytogenetics analysis proved the presence of the Philadelphia chromosome, 46, XY, t (9; 22) and the molecular analysis confirmed positive BCR-ABL fusion gene at a level of 6.18×10^5 copies/mL. Therefore, the patient was diagnosed with CML, and therapy started with hydroxyurea at a dosage of 1.0 g 3 times a day. Meanwhile, the patient was administered with intravenous hydration to ensure adequate urine flow and allopurinol to reduce serum uric acid levels. For the fatal hemorrhagic tendency and unavailable specific test, FFP was given empirically at a dosage of 5 mL/kg to correct coagulation and mannitol was administered to decrease intracranial pressure. The next day, the urine became clear and repeated urinary tests confirmed the cessation of hematuria. Three days later, the headache remitted and the patient was in a stable condition. Thus, the patient was discharged home on therapy with imatinib at the dosage of 400 mg per day, however, was lost follow-up.

In October 2015, the patient was re-hospitalized due to a worsening cough with fever and fatigue. At admission, the patient reported that the therapy was stopped by herself for 1 year and claimed no bleeding symptoms in the past 2 years. The physical examination showed anemic appearance and pulmonary rales. The chest radiography indicated severe pneumonia. CBC showed pancytopenia with a WBC count of 2×10^9/L, a platelets count of 65×10^9/L, and a hemoglobin level of 64 g/L. The bone marrow aspiration confirmed blast crisis with the morphologic features of acute myelomonocytic leukemia (AML-M4). TT results of the patient measured at 12.5 seconds with PT and APTT values of 11.5 and 36 seconds, respectively. The patient subsequently received antibiotic therapy with ceftazidime and supportive care of packed red blood cell transfusion. The pneumonia was under

Table 1

Laboratory evaluation and effect of substitution of FFP.

	PT (9.4–12.5S)	APTT (25.4–38.4S)	Fib (2–4 g/L)	FDP (0–5 μg/mL)	DD (0–0.5 μg/mL)	FFP, mL	UOB
D1	11.8	35	2.52	8.3	2.5	350	P
D2	12	32.6	2.62	5.7	2.38	375	N
D3	NT	NT	NT	NT	NT	-	NT

APTT = activated partial thromboplastin time, FFP = fresh frozen plasma, N = negative, NT = not test, P = positive, PT = partial thromboplastin time, UOB = urine occult blood.

control with remission of the cough, fever, and fatigue 1 week later. Afterwards, the patient discharged from the hospital and passed away 2 weeks later.

3. Discussion and conclusion

CML rarely present initially as hemorrhage in CP for the adequate thrombocyte and coagulation function for hemostasis. Symptoms of bleeding usually indicate disease progression in the case of the progression of qualitative or quantitative thrombocytic abnormalities.[1,10] In a few cases, bleeding in CML in CP after diagnosis can be caused by metastasis of leukemic cells,[7] interferon-γ (IFN-γ) induced inhibitor of clotting factors[16] or tyrosine kinase inhibitor (TKI) agents triggered platelet dysfunction.[17]

In the past 6 decades, there are only 8 reports of CML in CP presented initially as hematomas in deep soft-tissue, mediastinum, cerebellum, epidural, or subdural regions, including the present case report.[2–5,8–10] These patients failed to show any proof of metastasis or receive therapy with TKI or IFN-γ. In contrast to the external bleeding associated with platelet defects, coagulation factor defects result in delayed, deep bleeding, such as, into muscles or joints, deep soft-tissue, and mucocutaneous bleeding.[12] Thus, the hematoma in these patients (including ours) indicates coagulation factor defects. However, only 2 cases show abnormal coagulation screening tests including PT, APTT, TT, and platelet counting, one presented as initiative subdural hematoma with prolonged APTT caused by hyper-thrombocytosis associated deficiency of VWF,[8] and the other one manifested as spontaneous deep soft-tissue hematoma with prolonged bleeding time (BT) associated to speculated hyper-thrombocytosis related dysfunction of platelets.[10]

In the current opinion, there are few disorders that could not be detected by PT, APTT, TT, and platelets count in bleeding patients without history. These disorders mainly include qualitative platelet defects, VWD, factor XIII deficiency, and PAI-1 deficiency.[11] Although hyper-thrombocytosis can induce acquired VWF deficiency and platelets dysfunction in the above-mention 2 reports, platelet numbers of the other reported and our patients were only slightly elevated, which theoretically should not be able to cause platelet dysfunction or acquired VWD. In addition, FFP quickly ceased the bleeding in our patient before improvement of CBC, indicating that the defect was due to the deficiency of a plasma factor rather than platelet abnormality or hyperleukocytosis. On the other hand, the verified delayed bleeding between after 24 hours of operation in our patient is the peculiarity of FXIII deficiencies.[11–13] Acquired deficiency of FXIII has been proved in cancer patients, including acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL).[14,15] In spite of the reported inhibition of PAI-1 caused by elastase released from neutrophils in essential thrombocythemia (ET) and CML,[18] the markers of hyperfibrinolysis, FDP, and D-D, was slightly elevated, with normal level of fibrin in our patient (Table 1).

Nevertheless, we missed the chance to do a specific test on FXIII. Anyhow, we could cautiously, speculate that the critical bleeding in our patient may be caused by FXIII deficiency. In consideration the absence of bleeding even after the blast crisis, the deficiency of FXIII in our patient may be related to the leukemic cells at the onset. The rapid remission after FFP supplement before leukocyte reduction may be associated with the long half-phase of FXIII.

To sum up, acquired FXIII deficiency may be involved in CML bleeding, which may serve as the primary mechanism in some cases. When facing a bleeding patient with normal coagulation screening test, the doctors should consider specific examination on FXIII instantly, which is not only limited to CML.

In conclusion, we report a rare case of incipient CML presented with fatal hemorrhage possibly caused by the acquired deficiency of FXIII. The mechanism and influence on disease presentation and prognosis of FXIII deficiency in CML require further investigation.

Author contributions

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