Successful Treatment of Acute Promyelocytic Leukemia Accompanied by Serious Subdural Hematoma

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Abstract

We present a 56-year-old woman with acute promyelocytic leukemia (APL) complicated with serious chronic subdural hematoma at presentation. She was treated with urgent hematoma evacuation and subsequent prompt chemotherapy, with administration of platelets and fresh frozen plasma. After six weeks, she achieved hematological complete remission. Thereafter she received three courses of conventional consolidation chemotherapy and achieved molecular remission. Even under conditions of severe coagulatory disturbance, aggressive therapeutic intervention including surgical procedures can save the life of a patient suffering from simultaneous APL and fatal subdural hematoma at presentation.

Key words: acute promyelocytic leukemia, disseminated intravascular coagulation, chronic subdural hematoma


Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myelogenous leukemia (AML), characterized by abnormal promyelocyte proliferation, the typical t(15;17) chromosomal translocation forming the PML-RARA chimeric gene, and significant coagulatory disturbance at presentation (1). The high susceptibility to all-trans retinoic acid (ATRA) contributes to the significantly high complete remission rate and prolonged long-term survival. The rate of early hemorrhagic death has been decreased after the introduction of ATRA to remission induction therapy; however, it is still the primary cause of remission induction failure. In particular, hemorrhage in the central nervous system (CNS) or lung becomes fatal when it occurs. Here, we report a case of APL with serious subdural hematoma at presentation. The patient was successfully treated by prompt initiation of chemotherapy and repeated urgent operations with thorough supportive care, including antibiotic administration, blood transfusion, and subdural hematoma drainage.

Case Report

A 56-year-old woman who had suffered from headache for five days presented at our emergency department in June 2011. She was slightly drowsy (Japan coma scale 1), but had no other apparent neurological deficits. There was no hemorrhagic symptom except for a small bruise on her right lower leg. On computed tomography (CT), left chronic subdural hematoma (CSH) with transtentorial cerebral herniation was detected (Fig. 1a). However, her laboratory data showed cytopenia with many leukemic cells (WBC 5,140/μL, blasts 29%, promyelocytes 64%, Hb 8.8 g/dL, and platelets 35,000/μL) and severe coagulatory disturbance (PT-INR 1.23, APTT 24.6 s, fibrinogen 97.0 mg/dL, antithrombin III 108%, FDP 15.4 μg/mL, and D-dimer 6.8 μg/mL). Therefore, a diagnosis of APL was made. No apparent findings of infection were detected. She was immediately admitted to our department. There was no history of any head injury or trauma. There was a past history of Graves’ disease, for which she received radioiodine therapy one year prior previously. Bone marrow examination revealed infiltration by abnormal hypergranular promyelocytes with multiple
Auer rods. Flow cytometry showed the typical expression pattern of APL, i.e., CD13⁺, CD33⁺, HLA-DR⁺, and no aberrant expression markers. PML-RARA fusion gene was detected by fluorescence in situ hybridization (FISH), and cytogenetic analysis revealed the karyotype of typical t(15;17)(q22;q12) with no aberrant abnormalities.

Her CSH critically required emergent surgical evacuation to save her life, despite the presence of severe coagulatory disturbance. After transfusion of adequate platelet concentrate (PC) and fresh frozen plasma (FFP), hematoma evacuation was performed without perioperative problems (Fig. 1b). Her consciousness level soon recovered. No definite hemorrhage from the surgical site was observed after the operation. Several hours after the operation, remission induction therapy for APL was started with a combination of ATRA (45 mg/m² daily until the day before the start of the first consolidation therapy), idarubicin (IDR, 12 mg/m² daily for 3 days), and cytarabine (Ara-C, 100 mg/m² daily for 5 days), according to APL97 protocol constructed by Japan Adult Leukemia Study Group (2), with some modifications. Her clinical course is shown in Fig. 2. Due to the risk of life-threatening infection, such as meningitis, sufficient antibiotics and antifungal agents were administered from the beginning of treatment. To control severe disseminated intravascular coagulation (DIC), transfusion of PC and FFP was performed repeatedly and recombinant thrombomodulin was administered. The initial clinical course was favorable with a rapid decrease of leukemic promyelocytes. No major regimen-related toxicities, such as APL differentiation syndrome, or another major hemorrhage were observed. On the 6th day, however, her consciousness level suddenly deteriorated, and CT scan showed resequestration of subdural hematoma and transtentorial cerebral herniation (Fig. 1c). At this point, her laboratory data was as follows: WBC 240/μL, blasts 1%, promyelocytes 46%, Hb 6.6 g/dL, platelets 80,000/μL, PT-INR 1.07, APTT 25.5 s, fibrinogen 146 mg/dL, FDP 16.9 μg/mL, and D-dimer 9.0 μg/mL. Platelet count and fibrinogen level were increased with normalization of PT. No other hemorrhagic symptoms emerged. Therefore, hematoma resequestration was considered to be caused by slight residual disturbance of hemostasis and coagulation within the surgical site, rather than by exacerbation of generalized hemorrhagic diathesis or deterioration of DIC. Reoperation was urgently performed without any problems. Considering her poor general condition, Ara-C administration was discontinued immediately before reoperation. From this time, continuous hematoma drainage was started and ATRA administration was continued via a nasogastric
tube. On the 12th day, she suffered sudden headache, and enlargement of the subdural hematoma was detected by CT scan, which was emergently evacuated again (the 3rd operation) without any problems. At this point, her laboratory data was as follows: WBC 170/μL, promyelocytes 2%, Hb 9.8 g/dL, platelets 71,000/μL, PT-INR 1.06, APTT 29.6 s, fibrinogen 431 mg/dL, FDP 19.1 μg/mL, and D-dimer 13.9 μg/mL. No other hemorrhagic symptoms emerged, and the situation was similar to that around the 2nd operation. After the 3rd operation, hematoma drainage was continued, and the amount of drainage was gradually decreased with no exacerbation of subdural hematoma (Fig. 1d). The drainage tube was removed on the 28th day, and subdural hematoma has not been detected since that time. Throughout the course of remission induction, no signs of meningitis emerged. To-
therapy of APL (6-8). In these cases, CNS bleeding occurred after the initiation of remission induction therapy, and emergent surgery was performed successfully under conditions of residual coagulopathy. On the other hand, in the present case CNS bleeding was detected simultaneously with the diagnosis of APL. There have been few reports on the successful treatment of APL and subdural hematoma co-existing simultaneously at presentation. Coagulopathy caused by untreated APL could be estimated to be substantially severe for considering surgical intervention; nevertheless we had to make a prompt decision regarding the treatment plan for the present patient at diagnosis. In the present case, immediate transfusion of platelet concentrate and fresh frozen plasma was done and emergent operation was performed only a few hours after admission. Chemotherapy was initiated a few hours after the operation. Although a total of three emergent operations were needed, they were performed promptly without major perioperative problems. Continuous antibiotic administration prevented surgical site infection and meningitis. This prompt and precise clinical decision making led to a successful outcome in this case.

As the existence of subdural hematoma can mean that circulating APL cells come into contact with cerebrospinal fluid, there is concern about CNS relapse of APL in the latter. Macheta et al. reported CNS relapse of APL in a patient with cerebral hemorrhage at diagnosis (9). In that case, all chemotherapy cycles consisted of ATRA and/or anthracyclines. It is poorly understood whether the existence of CSH at diagnosis raises the risk of CNS relapse of APL. However, the inclusion of cytarabine with systemic and intrathecal chemotherapy could reduce the probability of CNS relapse.

In the present case, APL developed after radioiodine treatment for Graves’ disease. However, therapy-related acute promyelocytic leukemia (t-APL) associated with radioiodine therapy is very rare (10). It has been reported that very low doses of radioiodine (usually 4-30 mCi) for the treatment or diagnosis of hyperthyroidism are not correlated with an increased incidence of acute leukemia (11). Therefore, it is improbable that this case could be considered as t-APL related to radioiodine therapy.

In conclusion, we present a successful clinical course of APL, simultaneously presenting with serious CSH. Active and prompt therapeutic intervention for both APL and CSH can lead to overcoming of the critical condition even under conditions of severe coagulopathy. The authors state that they have no Conflict of Interest (COI).

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