CASE REPORT

Subdural Hemorrhage in a Child with Acute Promyelocytic Leukemia Presenting as Subtle Headache

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Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) and is rare in children (< 10% of childhood AML). It tends to bleed with disseminated intravascular coagulation (DIC) and intracranial hemorrhage complication is often fatal. We report a 12-year-old child with APL who suffered a subdural hemorrhage and initially presented with a subtle headache mistaken as the side effect of all-trans-retinoic acid (ATRA). Blood component therapy and a pediatric dosage of ATRA (25 mg/m^2/day) combined with idarubicin as induction chemotherapy were administered in the first week, but the bleeding diathesis persisted and DIC profiles showed no improvement. The patient then developed photophobia, neck stiffness, and constant headache. Evidence of increased intracranial pressure (IICP) and persistent bleeding from previous venous puncture sites were also noticed clinically. DIC and life-threatening IICP were beyond control until the ATRA dosage was increased to adult levels (45 mg/m^2/day). This case suggests that the ATRA dosage for pediatric APL patients must be modified according to clinical condition. Emergency brain imaging should be considered in APL patients with signs of IICP to distinguish intracranial lesions from ATRA complications. [*J Chin Med Assoc* 2005;68(9):437–440]

Key Words: acute promyelocytic leukemia, all-trans-retinoic acid, disseminated intravascular coagulation, subdural hemorrhage

Introduction

The predominant symptom in patients with acute promyelocytic leukemia (APL) is bleeding diathesis (> 85%) with laboratory findings of disseminated intravascular coagulation (DIC). The high morbidity and mortality come from hemorrhagic complications.[1–3] Past studies have revealed that fatal intracranial hemorrhage (40%) is the leading cause of death from cytotoxic chemotherapy, and that the complete remission rate in APL patients is low,[4] although current treatment that combines all-trans-retinoic acid (ATRA) and conventional chemotherapy has much improved the prognosis.

ATRA is known to have more frequent adverse effects in pediatric patients. Thus, the optimal dosage suggested in most pediatric series is 25 mg/m^2/day.[5] However, this dosage is not always adequate. We report a pediatric case of APL with life-threatening subdural hemorrhage (SDH) secondary to DIC who responded poorly to ATRA until an adult dosage of 45 mg/m^2/day was administered.

Case Report

A 12-year-old boy without a significant medical history was referred to our hospital in December 2003 with

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easy fatigability, decreased appetite, and easy bruising in all 4 limbs for 2 weeks. Initial laboratory data obtained at a local hospital included leukocyte count (1,420/mm^3), hemoglobin (7.5 g/dL), platelet count (8,000/μL), and differential white blood cell (WBC) counts (myeloblasts, 6%; myelocytes, 5%; promyelocytes, 7%).

On admission, the patient complained of general weakness and mild headache for 2 days, without vomiting. Physical examination showed stable vital signs and some ecchymoses over the face, trunk and limbs. There was a large hematoma over the right forearm. Neither hepatosplenomegaly nor lymphadenopathy were noted. Bone marrow examination revealed more than 70% hypergranular promyelocytes. Cytogenetic study showed 46,XY,der (15)t(15;17)(q22;q11.2) 45,XY,-11,t(15;17)(q22; q11.2). He was diagnosed as having APL. Laboratory tests showed a prolonged prothrombin time (PT; 16 seconds) and activated partial thromboplastin time (aPTT; 47 seconds), the presence of D-dimer, a fibrinogen concentration of 92 mg/dL, and a concentration of fibrin degradation products of 160 μg/mL, all of which were compatible with DIC.

Platelets, fresh frozen plasma and cryoprecipitate were infused, but bleeding from the venous puncture sites persisted. Intravenous fluid hydration and diuretics were given. ATRA was given orally twice daily at 25 mg/m^2/day. Intravenous idarubicin 9 mg/m^2 for 3 consecutive days and intrathecal (IT) chemotherapy with methotrexate were prescribed on the day of admission according to the Taiwan Pediatric Oncology Group protocol TPOG APL 2001. During IT chemotherapy, the patient complained of mild but tolerable neck pain while keeping in the knee-chest position. The cerebrospinal fluid was clear in appearance and cytology revealed 1 WBC/high-power-field (HPF) and 860 red blood cells/HPF; traumatic tapping was considered at that time. The neck pain disappeared after IT chemotherapy and the clinician did not check the eye fundus to rule out increased intracranial pressure (IICP).

On the day after IT chemotherapy, the patient complained of constant headache. Physical examination revealed neck stiffness. Tracing his history, the patient remembered that his head was hit against the wall 1 week prior to this admission when he fought with a classmate. However, there were no specific symptoms initially. Brain computed tomography (CT) was arranged on suspicion of an intracranial lesion and disclosed left frontotemporoparietal SDH (Figure 1A). Subsequently, photophobia developed and elevation of blood pressure and decreased heart rate were noted, compatible with IICP. New ecchymoses were found over the trunk and limbs. Bleeding from the insertion site of the neck central venous catheter also persisted.

Conservative medical therapy was suggested by the neurosurgeon instead of surgical decompression because of the obvious bleeding tendency. In addition to vigorous blood component transfusion, the dosage of ATRA was adjusted to 45 mg/m^2/day 1 week later because of the prolonged PT and aPTT. Mannitol was given to reduce intracranial pressure. Fortunately, after 2 weeks of strengthened therapy, DIC was controlled with gradual normalization of DIC profiles and cessation of bleeding. The headache and photophobia also subsided.

Bone marrow examination revealed partial remission in the third week and complete remission in the seventh week after a second course of idarubicin. Follow-up brain CT demonstrated obvious improvement of SDH (Figure 1B and 1C). At the time of writing, the patient was on maintenance therapy and well without complications.

Discussion

The use of ATRA to treat APL, especially in combination with chemotherapy, in patients with coagulopathy has improved the survival rate.[6–8] The major side effect of ATRA is retinoic acid syndrome, which includes fever, leukocytosis, dyspnea, weight gain and pleural effusion. Another complication is pseudotumor cerebri, a syndrome of IICP that can produce headache, vomiting, blurred vision, and papilledema. This complication is reportedly more common in pediatric patients than adults.[9–11] As ATRA has more side effects in children, the AML-BFM study group suggested that 25 mg/m^2/day was a rational pediatric dosage.[5] However, our patient responded poorly to this dosage. On the contrary, his coagulopathy improved and clinical bleeding was controlled by increasing the ATRA dosage to an adult level of 45 mg/m^2/day.

Another concern is to recognize IICP secondary to SDH, which might mimic the manifestation of pseudotumor cerebri associated with ATRA. This patient had a clinical picture of DIC with persistent bleeding in the first week, and the initial manifestation of his SDH was persistent headache, which was difficult to differentiate from the side effect of ATRA. However, neck stiffness became evident later and emergency brain CT confirmed the diagnosis of SDH. Therefore, when subtle headache occurs in a child with APL and DIC, the differential diagnosis of intracranial

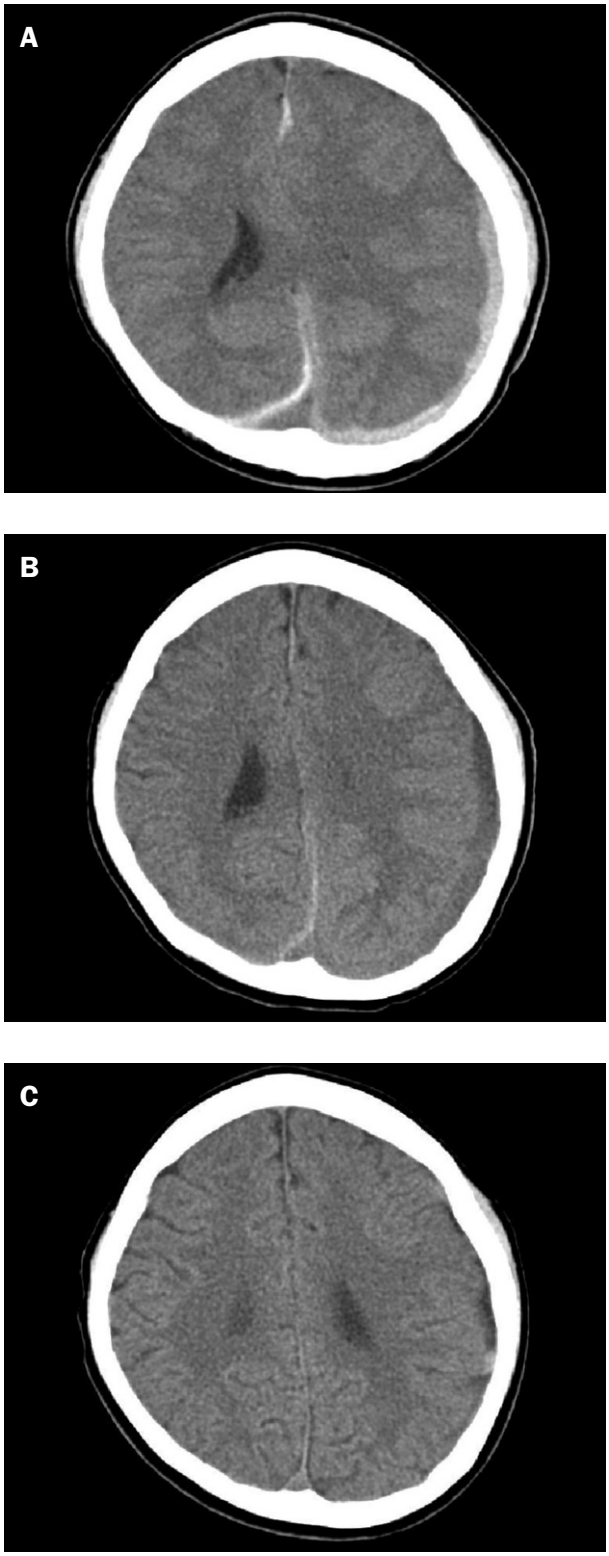

Figure 1. (A) Axial computed tomography (CT) of the brain reveals acute subdural hemorrhage (SDH) over the left fronto-temporoparietal region with slight mass effect. (B) After 2 weeks, CT scan reveals left temporoparietal subdural effusion with increased thickness but decreased density. (C) After a further 1 month, axial CT of the brain reveals nearly no subdural effusion.

hemorrhage should be taken into consideration. The authors would like to remind every pediatrician caring for hematology patients to be aware that minor previous trauma may cause an immense intracranial hemorrhage in APL patients with coagulopathy.

We found that laboratory data including PT and aPTT and clinical bleeding signs improved dramatically by increasing the ATRA dosage from 25 to 45 mg/m^2/day. Therefore, we suggest modifying the ATRA dosage for children with APL according to clinical condition. In some situations, an adult dosage of 45 mg/m^2/day is appropriate, especially for patients who have received ATRA 25 mg/m^2/day for more than 3 days without improvement in PT and aPTT. However, further study of the pharmacodynamic differences of ATRA between adult and pediatric patients, including serum levels of ATRA and drug interactions, is warranted.

In conclusion, the combination of an adult dose of ATRA 45 mg/m^2/day and chemotherapy with idarubicin can be prescribed for pediatric APL patients with severe DIC and bleeding complications including SDH. Emergency brain CT is indicated for APL patients with IICP signs to distinguish intracranial hemorrhage from complications of ATRA.

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