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Original Article

Acute promyelocytic leukemia transformation in a patient with aplastic anemia: a case report with literature review

Xiaoning Wang[1], Tingting Yuan[2], Wenjuan Wang[1], Limei Chen[1], Huaiyu Wang[1], Yalin Liu[1]

[1]Department of Hematology, The First Affiliated Hospital of Xi'an Jiaotong University, Shaan Xi, P. R. China; [2]Department of Clinical Laboratory, Affiliated Hospital of Yulin, Traditional Chinese Medicine of Shaan Xi Province, P. R. China

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Abstract: Aplastic anemia (AA) is a hematological disorder presenting with pancytopenia in peripheral blood and hypocellularity in bone marrow. AA patients with immunosuppressive therapy and granulocyte colony-stimulating factor treatment have a risk of development of acute leukemia including acute myeloid leukemia (M0, M1, M2, M4, M5, M6) and acute lymphoblastic leukemia. However, AA with transformation to acute promyelocytic leukemia (APL) has never been reported. Here, we reported a patient initially diagnosed with AA. while 19 years later, PML/RAR αfusion gene were detected and the patient was eventually diagnosed as APL. The diagnosis and management of this interesting case are discussed.

Keywords: Aplastic anemia, acute promyelocytic leukemia, immunosuppressive therapy

Introduction

Aplastic anemia (AA) is a hematological disease characterized by low bone marrow hematopoietic function and decrease of whole blood cells caused by a variety of reasons. Immunosuppressive therapy (IST) including anti-thymocyte globulin (ATG) and cyclosporine A (CSA) is indicated for patients with severe AA who are >40 years old those <40 years and without an HLA-matched sibling donor and patients with non-severe AA [1]. It's well known that patients with IST have a higher risk of later clonal disorders such as myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and paroxysmal nocturnal hemoglobinuria and solid tumors [2, 3]. In this paper, we report a case of patient initially presented with AA and finally transformed to acute promyelocytic leukemia (APL) 19 years later. To our knowledge, it has never been reported previously.

Case report

A 20-year-old female was admitted to our hospital for fatigue and excessive menstrual blood in 1996. She had no other subjective symptoms, such as fever, coughing, night sweating, and weight loss. No hepatosplenomegaly or lymphadenopathy was noted. Her complete blood cell (CBC) count was hemoglobin (Hb) of 3.0 g/dL (normal range 13-17.5 g/dL), white blood cell (WBC) of 2,290/mL (normal range 3,500-9,500/mL), neutrophil of 0,980/mL (normal range 1,800-6,300/mL) and platelet of 19,000/mL (normal range 125,000-350,000/uL). Bone marrow aspirate and biopsy showed a markedly hypocellular marrow (**Figure 1**). Blood folic acid and vitamin B12 test were normal. Hepatitis C and B as well as HIV testing were negative and the autoimmune antibodies were negative. Coombs and Ham's tests were all negative. According to her symptoms and signs, CBC count, as well as hypoplasia of bone marrow, the diagnosis of AA was confirmed definitely. Since the patient took neither consideration about ATG nor sibling donor transplantation for economic reasons, CsA, androgens, levamisole, granulocyte colony-stimulating factor (G-CSF), hemopoietin and Interleukin-11 were initiated as the main treatment for her and she got hematologic improvement by these attempts.

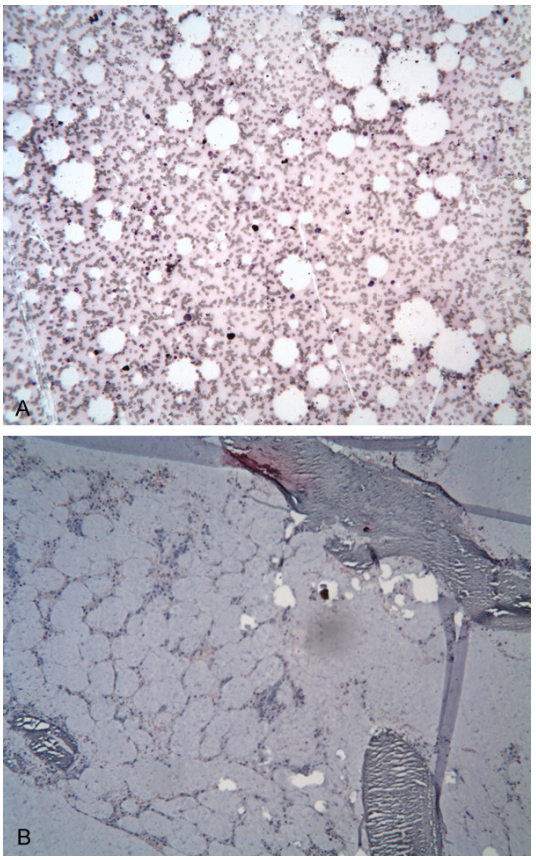

Figure 1. The composite pictures showed the pathological features of bone marrow of this patient. A. Bone marrow aspiration showed hypocellular marrow with failure of trilineage hematopoietic cells, HE × 1000. B. Bone marrow biopsy analysis, Giemsa × 1000.

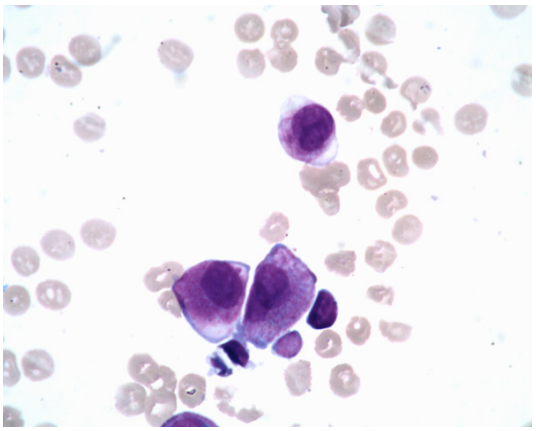

Figure 2. Ao's body in abnormal promyelocytic cells, HE × 4000.

Nineteen years later, she was transferred to intensive care unit department in our hospital due to hyperpyrexia and low blood pressure.

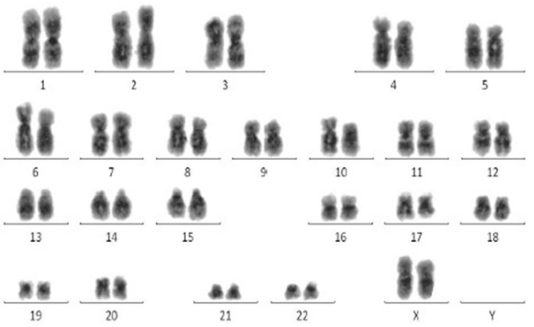

Figure 3. Bone marrow cytogenetics; Karyogram reveals translocation (15; 17).

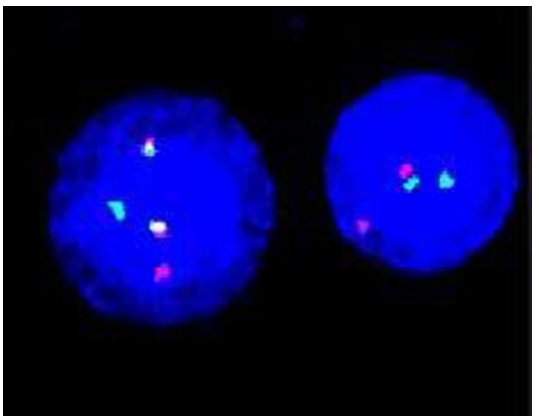

Figure 4. Detection results of PML/RAR α fusion gene by fluorescence in situ hybridization.

Physical examination found several scattered petechiae on her extremities and sternal tenderness without any superficial lymphadenopathy or hepatosplenomegaly. Her complete blood cell (CBC) count was hemoglobin (Hb) of 5.0 g/dL (normal range 13-17.5 g/dL), white blood cell (WBC) of 27.57/mL (normal range 3,500-9,500/mL), and platelet of 9,000/mL (normal range 125,000-350,000/mL). Bone marrow aspiration showed acute promyelocytic leukemia and Ao's body was easily seen in abnormal promyelocytic cells (**Figure 2**). Cytogenetic analysis revealed the presence of a t (15; 17) (q22; q21) in all examined metaphases. RT-PCR for PML/RARαtranscript was positive and fluorescence in situ hybridization (FISH) also confirmed the PML/RARαfusion gene (**Figures 3**, **4**). And Meropenem and Voriconazole were administrated, body temperature and white blood cells were decreased.

She was then transferred to hematology department for the treatment of APL. CBC count

showed leukocyte count reduced to 1,220/mL with 77.14% neutrophils, hemoglobin of 6.9 g/dL, and a platelet count of 5,700/mL. APTT 47 s (28 s-43.5 s), PT 16.3 s (11s-14 s), FIB 4.42 g/L (2 g/L-4 g/L), D-dimer 47.7 mg/L (0-1 mg/L), FDP 123 mg/L (0-5 mg/L), BUN 24.37 mmol/L (2.8 mmol/L-7.2 mmol/L), CREA 398 μmol/L (35-71 μmol/L). ATRA 30 mg/d and reduced dose of ATO (5 mg/d) were also administered and sustained CRRT was carried out. The WBC was gradually increased, renal function improved and now the patient was continuously treated in our department.

Discussion

AA is characterized by hypocellular bone marrow and pancytopenia. It is thought to be an aberrant immune response involving the T-cell mediated destruction of hematopoietic stem cells. Due to the immune suppress therapy (IST) and allogeneic stem cell transplantation, the survival of AA improved, but more and more late complications of clonal evolutions have been observed, such as MDS, AML and paroxysmal nocturnal hemoglobinuria (PNH). Previous studies have shown that sMDS/sAML develops in 15% to 20% of patients with aplastic anemia after IST and is associated with a very poor prognosis [4]. AA transformation to AML including M0, M1, M2, M4, M5 and M6 had already be reported. To our knowledge, this is the first report that one patient with AA transformed to APL ultimately.

It was still unclear that why AA can transform to MDS/AML. The risk of AA progression to MDS/AML factors may include IST treatment, the elderly, sustained G-CSF treatment and shortened telomere length [5]. RA Brodsky et al. [6] has reported that a primary insult to hematopoietic progenitor cells could lead to several abnormal cell clones, eventually one clone could dominated, with the others still present but below the level of detection. In AA, a bone marrow insult may primary trigger an autoimmune attack on the hematopoietic progenitor compartment, perhaps by exposing cryptic epitops or through molecular mimicry, and other damaged progenitor cells may expand and ultimately result in AML after the prolongation of survival of AA by IST. Tetsuichi Yoshizato et al. [7] has reported that clonal hematopoiesis was prevalent in aplastic anemia. Some mutations were related to clinical outcomes. Mutations in PIGA and BCOR and BCORL1 correlated with a better response to immunosuppressive therapy and longer and a higher rate of overall and progression-free survival; mutations in a subgroup of genes that included DNMT3A and ASXL1 were associated with worse outcomes and more easily evolution to clonal diseases. It could be easily seen that ATG combined with CsA could induce a clonal disease, but it was not clear CsA used alone could accelerate developing clonal disease. In this paper, the patient don't received ATG therapy and just used CsA as IST. It indicated that not only ATG but also CsA as IST could induce clonal disease in AA patients.

Whether G-CSF promotes the conversion of AA patients to MDS/AML is still conversial. Tichelli A et al. [8] reported a prospective random controlled clinical trial, the results showed there was no significance differences of long-term clonal disease between AA patients with G-CSF treatment and AA patients without G-CSF treatments. However, Socie G et al. [9] reported that 840 patients who received a first-line IST with (43%) or without (57%) G-CSF. The incidences of MDS/AML in patients who did or did not receive G-CSF were 10.9% and 5.8%, respectively. A significantly higher hazard (1.9) of MDS/AML was associated with use of G-CSF. Relapse of aplastic anemia was not associated with a worse outcome in patients who did not receive G-CSF as first therapy, whereas relapse was associated with a significantly worse outcome in those patients who received G-CSF. These results emphasize the necessity of the current European randomized trial comparing IST with or without G-CSF and to alert physicians that adding G-CSF to IST is currently not standard treatment for SAA. In this patient, continuously use G-CSF treatment may promote conversion to APL, and it still needs a larger sample of a prospective randomized controlled study to determine whether application of G-CSF promote the AA conversion to AML.

In conclusion, we described a rare case of APL after IST and G-CSF treatment for AA. It is also important to explore the potential mechanism and predisposing factors which increases the risk of this disease. For AA patients, the strategies may extended the time of evolution to clonal disease or the incidence of clonal evolution were as follows: priority selection of BMT or IST treatment to achieve the basic cure, reducing

the time of using G-CSF and long-term follow-up.

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Huaiyu Wang and Yalin Liu Department of Hematology, The First Affiliated Hospital of Xi'an Jiaotong University, Shaan Xi, P. R. China. Tel: +86-18991232608; E-mail: whymed@126.com (HYW); xykcls@163.com (YLL)

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