

Transformation of aplastic anemia to acute myeloid leukemia in a Chinese adult after 16 years

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Abstract

Aplastic anemia (AA) is a potentially life-threatening failure of hemopoiesis defined as pancytopenia and an empty bone marrow. It is a more common disease in Asia than in the west with the annual incidence in china of 7.4 per million in contrasts to 2.34 per million in Europe and Israel (1 2). Clonal hematopoiesis has been related to AA, including paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) (3). The true incidence of acute leukemia after AA in China is not known but appears to be rare. Here, we report a case of aplastic anemia evolving into acute myeloid leukemia (AML) after 16 years.

CASE REPORT

A 56-year-old Chinese man presented with a 5-month history of pallor and fatigue in June 1992. He did not have a history of benzene exposure. On admission, he was pale, afebrile and petechiae, but he had no evidence of lymphadenopathy or organomegaly on physical examination. A blood count showed hemoglobin (Hb) 5.0 g/dl, platelet count (PLT) 42,000/μl, White blood cell count (WBC) 1,800/μl, differential count being neutrophils 37%, lymphocytes 57%, monocytes 4% and eosinophils 1%. Reticulocytes were 1.0% and Ham's test was negative. Bone marrow aspiration showed significant hypocellular marrow without morphological abnormalities in erythroid, myeloid and megakaryocytic lineages, and there was no elevation of myeloblast levels. A bone marrow biopsy revealed hypocellular fatty marrow. A diagnosis of aplastic anemia was made. He was treated with prednisone and androgens (oxymetholone), which led to slightly improvement in the peripheral blood cell count. In may 1993, therapy was begun to combine with Chinese herb, including Ginseng, Membranous Milkvetch Root, Chinese angelica, Chinese Dodder Seed, Hairy Antler for three years. His anemia improved and he no longer required transfusion therapy. His Hb remained between 8.0 g/dl and 10 g/dl, the PLT remained approximately 75,000/μl, and WBC remained a normal count. He did not receive immunosuppression therapy due to a poor economic condition. Then he stopped receiving treatment for another 12 years.

In September 2008, the patient returned with fatigue and fever. His complete blood count at this time revealed an elevated WBC 82,400/μl, Hb 9.5 g/dl, PLT 13,000/μl. Bone marrow studies confirmed the diagnosis of AML and flow cytometry revealed blasts with myeloid and monocytic markers. Chromosome analysis revealed the karyotype of 46, XY. After lowering WBC with hydroxyurea, induction therapy with daunorubicin (60mg/day for 3 days) and cytarabine (200mg/d for 7 days), but remission was not achieved. He died after a second course of chemotherapy due to intracranial hemorrhage.

DISCUSSION

The hallmark of AA is the empty bone marrow, and by all measures hematopoiesis is markedly reduced. AA is closely related to other bone marrow failure syndromes. MDS, PNH and AA are easily confused in the clinical classification of a patient with pancytopenia and a hypocellular bone marrow, and the may indeed share common pathophysiologic features. A clear distinction between AA and MDS must always be made, because the have different risk of developing with AML: 9% for patient with AA and 83% for those with MDS [4]. Typical AA is usually distinct from typical MDS with respect to dysplastic morphology and BM cellularity. Detection of chromosomal aberration provides definite evidence of MDS. However, AA is considered a clonal hematopoietec disorder, and some researchers have proposed the concept of hypoplastic MDS [35]. Thus, it may not be easy to differentiate MDS from AA. In our case, the

bone marrow biopsies were helpful in answering this question. And our patient presented gradually improvement in hematopoiesis after therapy. Moreover, he did not need transfusion for 12 years. All these aspects support the diagnosis of AA.

In the past, leukemia was an unusual complication of AA, estimated at less than 1% and sufficiently rare to have warranted case reports of its occurrence after androgen therapy, marrow transplantation; less than 2% of patients with AML have a history of AA [36]. The therapeutic outcome for AA has improved markedly with the introduction of immunosuppressive drugs including antithymocyte globulin, cyclosporine and hematopoietic growth factors [78]. But, at the same time, the risk of late clonal hematological complications has increased [910]. Whether this is treatment related or due to longer survival after immunotherapy displaying its malignant natural history is not clear. Our case epitomizes the concept of premalignant disorder of AA.

AA is considered to be a preleukemic disorder with clonal hematopoiesis and defective stem cells. The key question is the defect intrinsic or extrinsic to the stem cell. However, clonal does not necessarily mean leukemic or malignant; clonality may be the result of extrinsic selection rather than genetic mutation. As reported, some proportion of patients with a diagnosis of AA show evidence of clonal hematopoiesis on molecular analysis. Nevertheless, it is not known whether clonal hematopoiesis could have a prognostic value in AA.

CONCLUSION

This case raises further questions about biology of AA in leukemic transformation. Further studies into the biologic and molecular mechanisms involved in the development of leukemic clone arising from AA should be explored.

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