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Acute Myeloid Leukemia after Intensive Immunosuppressive Therapy in Aplastic Anemia

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A 10-year-old boy was admitted with complaints of fever, pallor, fatigue and skin bleeds of 10 days duration and diagnosed as very severe aplastic anemia. He was given intensive immunosuppressive therapy but showed no response to therapy. He later evolved into acute myeloid leukemia. The occurrence of AML is reviewed and possible pathogenesis is discussed.

Key words: *Aplastic anemia., Immunosuppressive therapy, Myeloid leukemia.*

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Manuscript received: September 6, 2004;
Initial review completed: February 3, 2005;
Revision accepted: May 3, 2005.

Acquired aplastic anemia is an uncommon but potentially life threatening hematological disease in children. The ideal treatment is HLA matched allogenic bone marrow transplant (BMT) but the high cost involved, non-availability of histocompatible sibling donor or age restrictions and nonavailability of expertise has limited its use. Intensive immunosuppressive therapy (IIST) comprising lymphoglobulin, cyclosporine A with or without steroids has achieved cure rates similar to that of BMT. IIST however is not without its side effects. The causes of concern include serum sickness, infections, increased risk of solid tumors and clonal hematological complications such as paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)(1).

We report first Indian pediatric case of aplastic anemia that evolved into AML after IIST.

Case Report

A 10-year-old boy was admitted with complaints of fever, pallor, fatigue and skin bleeds of 10 days duration. He had no other positive medical or family history of any

specific disease. On physical examination he had severe pallor and numerous skin bleeds. There was no hepatosplenomegaly or lymphadenopathy. Rest of the systemic examination was normal. Laboratory investigations showed severe anemia with hemoglobin (Hb) 1.8g/dL, white blood cell count 2500/mm^3 with absolute neutrophil count (ANC) of 75/mm^3 and platelet counts of 17000/mm^3. Blood smear examination revealed normocytic normochromic red cells. The reticulocyte count was 0.4%. Liver and kidney function tests were normal. Serology for HIV, HBsAg and HCV was negative. Bone marrow biopsy and aspiration examination showed severe hypocellular marrow showing mainly mature lymphocytes and plasma cells. Residual erythroid and myeloid series showed normal maturation. No megakaryocytes were seen. With these bone marrow findings and the ANC of 75/mm^3, platelet counts 17000/mm^3 and the reticulocyte count 0.4% the patient was diagnosed as very severe aplastic anemia. He received multiple blood and platelet transfusions, androgens and cyclosporin A (CSA). Therapy with antilymphocyte globulin could be instituted only 13 months after the diagnosis.

ATG (Pasteur marieux) was administered in a dose of 10 mg/kg for 5 consecutive days through a central venous catheter. CSA was given at a dose of 10 mg/kg. Oral prednisolone was given at a dose of 2mg/kg for 14 days for serum sickness prevention. Child was also put on oral fluconazole and ciprofloxacin prophylaxis in initial 2 weeks. CSA was continued for 6 months. The blood requirement minimally decreased but he continued to be transfusion dependent during follow-up.

Thirteen months after receiving lymphoglobulin he presented with high-grade fever and hepatosplenomegaly of 2 cm each and leukocyte counts of 43,700/mm^3. Peripheral smear revealed 19% myeloblasts. A bone marrow aspiration and biopsy done at this stage showed hypercellular marrow showing 69% blasts which showed cytoplasmic granules. Blasts were myelo-peroxidase and Sudan black B positive. Erythroid precursors were decreased and no megakaryocytes were seen. Based on these findings a diagnosis of acute myeloid leukemia (AML-M2) was made. Because of financial reasons and prognosis the family decided against further treatment.

Discussion

ATG is an effective treatment of aplastic anemia in most of the patients as the high cost, non-availability of histo-compatible sibling donor or age restrictions limit the use of BMT. Hematological response has been observed in 40-70% of patients in different series within one year of treatment(1).

An important unexplained complication in the clinical course of aplastic anemia is the development of late clonal hematologic diseases commonly AML or MDS often years after successful IIST. Frickhofen, *et al.*(2) and Kojima, *et al.*(3) showed 4.7 % (4/84) and 3/119 (2.5%) incidence respectively of AML/MDS in Pediatric aplastic anemia treated with ATG after a follow-up of 11 and 4 years respectively. In adults, the incidence varies from 2-9%(4-7). In a recent update of 619 patients, a 10-year cumulative risk for MDS or AML was 9.6% and 6.6% respectively. Prognosis of this secondary AML has universally been poor in those patients who opted for treatment(2,3).

The probability of developing a cytogenetic clone in one series was 40% (2/5 patients) in nonresponders, 6% (1/19) in partial responders, and 10% (3/30) in complete responders. Four MDS (2 had a deletion of chromosome 7 abnormality), 2

acute leukemias (1 with random deletions), and 1 PNH. The risk was greater in patients non-responding as compared with responders, but there was no difference between partial (10%) and complete responders (4%)(6). In another series 12 of 113 patients developed MDS between 9 and 81 months following diagnosis who had cytogenetic abnormalities at diagnosis of MDS: monosomy 7 (6 patients), monosomy7/trisomy 21 (1 patient), trisomy 11 (1 patient), del (11) (9?:14) (1 patient), add (9q) (1 patient), add 7 (q 32) (1 patient), and trisomy 9 (1 patient)(8).

Rosenfield found that single patient (2%) who evolved to acute leukemia never achieved transfusion independence(7), as was the case with our patient. It has been suggested that two or more courses of ATG may increase the risk of later clonal disorders(5,9).

Oligoblastic leukemia developed in one patient 15 months after initial presentation with aplastic bone marrow. Various malignancies seen included solid tumors (non-Hodgkin's lymphoma, hepatocellular carcinoma, squamous cell carcinoma of lung) occurred around 1-9 years following ATG therapy(4).

There is no evidence of premalignant cells early in the course of aplastic anemia, and the results of cytogenetic studies and more sensitive molecular assays for specific gene mutations have almost always been normal initially. Other observations have suggested that clones emerge because they are favored by certain extrinsic conditions. Patients may harbor clones with different PIG-A (phosphatidylinositolglycan-anchor) gene mutations a finding consistent with independent proliferation of genetically altered hematopoeitic stem cells under some selective pressure. Cells with the paroxysmal nocturnal hemoglobinuria phenotype have been detected in patients with lymphoma during treatment with an anti-T-cell monoclonal antibody that coincidentally recognized a PIG-A linked protein, suggesting that clones deficient in this type of protein expression may be normally present in the hematopoeitic stem cell compartment and expand if their proliferation is favored(10).

It may be that development of AML or MDS is potentiated by intensive immunosuppression used in the treatment of the disease. With improved survival of aplastic anemia, a higher incidence of these clonal diseases should be kept in mind.

Contributors: The patient was under the care of JC and RN who drafted the manuscript. SS was responsible for histopathological description and interpretation. All 3 analyzed the script critically.

Funding: None.

Competing interests: None.

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Ocular Manifestations of Behcet's Disease

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Behcet's disease is a systemic inflammatory vascular disorder characterized by recurrent oral and genital ulcers, eye lesion, arthritis and skin lesions. We report a case of Behcet's disease with ocular manifestation in an 8 year old boy.

Key words: *Behcet's disease, Ocular manifestation.*

Behcet's disease is a systemic inflammatory vascular disorder characterized by recurrent oral and genital ulcers, uveitis arthritis and skin lesions. It has a world-wide distribution with clustering among populations having a high prevalence of HLA-B5. There are only a few reports of Behcet's disease with ocular manifestation in children from India.

Case Report

An 8-year-old student from West Bengal presented with a history of fever, recurrent oral and genital ulcerations, skin pustules and joint swelling for 4 months. There was a history of bilateral parotid swelling at the onset of illness. He had been hospitalized elsewhere for 2 months for the above symptoms and had received antibiotics, IV Immunoglobulin, two blood transfusions, and was on nasogastric feeds.

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Manuscript received: February 4, 2005;
Initial review completed: March 23, 2005;
Revision accepted: June 3, 2005.