Aplastic anemia (AA) is defined as a peripheral blood pancytopenia with a hypocellular bone marrow. AA is considered an autoimmune disease with active destruction of blood-forming cells by lymphocytes. Most cases of the disease can be pathophysiologically characterized as T-cell-mediated organ-specific destruction of bone marrow hematopoietic cells, with a strong association between AA and antigen HLA-DR2. The etiology in secondary AA is represented by exposure to radiation, drugs and chemicals, viruses (Epstein Barr, hepatitis virus, parvovirus, human immunodeficiency virus), immune diseases (eosinophilic fasciitis, thymoma), paroxysmal nocturnal hemoglobinuria (PNH) and the rest of cases are idiopathic AA. The pathophysiologic pathways leading to AA are damage to DNA inducing apoptosis by cytotoxic chemotherapy, irradiation, chemical or physical agents; marrow failure caused by medical drugs (chloramphenicol, antiepileptics, gold salts, antithyroid drugs), complex immune reactions leading to bone marrow failure induced by viruses. The pathogenic mechanism of idiopathic AA is still unknown. The clinical picture includes an anemia-related syndrome, fever and hemorrhage. In tropical areas the differential diagnosis should include infectious disease, such as bacterial sepsis, leptospirosis, viral hemorrhagic fevers and visceral leishmaniasis. AA is a rare complication of dengue hemorrhagic fever, and its pathophysiology is still poorly understood. We report a rare case of AA induced by dengue virus infection.

**CASE**

An 8-year-old girl presented with complaints of fever, myalgia and petechiae. She had no history of drug abuse and contact with possible toxic agents. Laboratory tests at admission showed a hemoglobin of 12.5 g/dL with a hematocrit of 0.37; a white cell count of 4×10^9/L (lymphocyte 74% and polymorphs were 23%), platelets were 19×10^9/L (normal, 150-450). The hemoglobin showed a rising trend and reached a maximum of 15 g/dL with a hematocrit of 0.46. Dengue serology (Panbio, Brisbane, Australia) for IgM and IgG was positive at day 7 of illness. She was managed with fluid therapy and platelet transfusion. She recovered from fever and stayed well for 2 weeks, but her thrombocytopenia persisted. She started to have fever again 4 weeks later. Investigations showed pancytopenia (Hb 4.1 g/dL, total lymphocyte count with absolute neutrophil count of 0.25×10^9/L, absolute lymphocyte count of 1.9×10^9/L, platelets were 11×10^9/L and reticulocyte count of 0.1%). There was no family history of similar complaints. On physical examination she was pale without lymphadenopathy or organomegaly. A repeated complete blood count showed persistent pancytopenia and hypoplastic anemia was considered. Bone marrow aspiration showed severe hypopcellularity, an increased number of fat cells, residual...
lymphocytosis, plasma cells, and stromal elements. Bone marrow biopsy revealed a cellularity of 5% to 10% which confirmed the diagnosis of severe AA. Vitamin B12 and folic acid levels were normal. Serology for viral hepatitis A, C, HIV and cytomegalovirus were negative. Flow cytometry (CD55 and CD59) and chromosome breakage studies were negative for paroxysmal nocturnal hemoglobinuria (PNH) and Fanconi anemia. A possible diagnosis of dengue virus-induced AA was made. The child received packed cell and platelet transfusions multiple times. No spontaneous marrow recovery happened until 3 months and she was treated with rabbit antithymocyte immunoglobulin (Thymoglobulin) 3.75 mg/kg IV daily for 5 days followed by oral cyclosporine 10 mg/kg, later dose adjusted to a target trough level of 150-200 ng/mL. She became platelet and packed cell transfusion independent 2 months and 6 months later respectively (Figure 1).

DISCUSSION

Only a few cases are reported of AA due to dengue fever. Albuquerque et al. and Pallotta et al. have described similar cases from Latin America. In our case dengue was confirmed by serology, which was positive for both IgG and IgM antibodies. The patient was admitted with hemorrhagic manifestations and had recovery, but thrombocytopenia persisted and she later developed pancytopenia. Other possible causes like megaloblastic anemia and myelodysplasia were excluded on bone marrow examination. PNH workup was negative. After exclusion of other possible etiologies for AA, the final diagnosis was dengue virus-induced AA in our case.

Dengue fever virus is endemic and causes hemorrhagic fever in India. In year 2010, a total of 27,196 cases and 104 deaths were reported in India. Delhi had the highest, 6240 cases with 8 deaths. Dengue virus and other arboviruses can be associated with bone marrow failure. It is known that dengue subtype DEN-4 can reproduce in progenitor cells from the bone marrow. Neutropenia and thrombocytopenia are common in dengue infection, and the bone marrow is markedly hypocellular with abnormal megakaryopoiesis. The seventh day after viral infection an abnormal vacuolization of lymphocytes appears. Reticulocytopenia, lymphocytopenia, thrombocytopenia and granulocytopenia appear in this order. The patient described above had systemic symptoms, an increase in hematocrit, thrombocytopenia, and hemorrhagic manifestation of abnormalities of capillary permeability, which characterize dengue hemorrhagic fever (DHF). DHF usually appears during the second episode of dengue infection in 95% of cases. Our patient had no such previous history of dengue.

The association between viral infection and different forms of bone marrow failure can be caused by viral-induced inhibition of multiplication of hematopoietic cells. In the acute phase of infection and viremia, viral replication in the bone marrow leads to pancytopenia. The pathophysiology of dengue-induced AA is poorly understood. It is believed that cellular destruction is a direct consequence of both peripheral destruction induced by immune complexes and direct viral injury to bone marrow.

HLA-compatible stem cell donor is treatment of choice in AA. Unfortunately our patient did not have any matched sibling donor so antithymocyte immunoglobulin (ATG) was offered as alternative therapy. As seen in previous cases our patient also responded to ATG and cyclosporine. In summary, dengue virus infection can induce AA. Though it is a rare complication it must be identified early specially in endemic areas. Immunosuppressive therapy can lead to complete remission.

Figure 1. Weekly hemoglobin (Hb), absolute neutrophil count (ANC) and platelet values from the onset of dengue fever and at onset of aplastic anemia and after therapy with anti-thymoglobulin (ATG). Arrows show blood transfusion (BT) and platelet transfusion (PLT).
REFERENCES