Bone Marrow Necrosis and Pancytopenia Associated with Gram Negative Septicemia

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Bone marrow necrosis has been associated with hematological and non-hematological malignancies(1-3). Among the other causes, sepsis has been associated with bone marrow necrosis(4). From the review of literature it appears that sepsis causing bone marrow necrosis resulting in functional failure (pancytopenia) is extremely rare. Norgard et al.(2) in a careful examination of five hundred consecutive bone marrow biopsies from living patients, found incidental necrosis in one-third of them, but only in one case extensive necrosis was associated with pancytopenia, and two patients had extensive necrosis associated with Gram negative septicemia. We report here two pediatric patients with fulminant Gram negative septicemia presenting as pancytopenia associated with bone marrow necrosis.

Case Report

Case 1: A two-and-half-year male child presented with pallor, hepatosplenomegaly, mucocutaneous gangrene involving left ala of nose, left upper lip, nasolabial fold and an ulcer (6 x 10 cm) in right poplitical region. Blood culture grew Pseudomonas aeruginosa. Hemoglobin was 4.3 g/dl, total leucocyte count was 2x10^9/L (neutrophils 0.8x10^9/L), platelet count was 10x10^9/L, corrected reticulocyte count was less than 0.1%. Bone marrow aspiration did not contain any material and a trephine biopsy was done. It revealed depletion of hemopoietic elements without replacement by fat cells; the stroma was edematous with extensive areas of necrosis. He was treated with cephaloridin, carbenicillin, gentamicin and supportive therapy including blood transfusions. After twelve days of hospital stay, the infection resolved, hepatosplenomegaly regressed and the blood counts improved with a leucocyte count of 5x10^9/L (neutrophils 3x10^9/L), platelet count of 100x10^9/L, and reticulocyte count of 1%. At this stage, he was referred for skin grafting of the gangrenous area of the face.

Case 2: A three-and-half-year male child (diagnosed as thalassemia major at the age of seven months, receiving regular blood transfusion every 3-4 weeks for past three years) presented with fever, epistaxis and ulcer on inner side of lower lip. On examination, he was pale, toxic, had ulceration of the mucous membrane of mouth and hepatosplenomegaly. X-ray chest revealed right-sided bronchopneumonia. Blood culture grew Salmonella typhimurium. Hemoglobin was 5.2 g/dl, total leucocyte count was 1.6x10^9/L (neutrophils 0.2x10^9/L) and platelet count of 10x10^9/L. Bone marrow aspiration yielded

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dry tap. The bone marrow trephine section presented a pleomorphic picture with areas of hemorrhage, necrosis, amorphous eosinophilic material, sinusoidal dilatation and stromal edema (Fig. 1). There was marked reduction in the hemopoietic elements, but no increase in the fat cells. He was treated with gentamicin, cephloridin and amikacin, but with no response. His general condition continued to deteriorate. He developed septic arthritis of left ankle joint and multiple skin abscesses and died. Permission for autopsy was refused.

Discussion

In both cases there was no history of exposure to any drugs, chemicals or radiation prior to this illness. At presentation, both patients had pancytopenia, had Gram negative septicemia and morphological changes in the bone marrow indicating active bone marrow damage.

The chances that the bone marrow damage was caused by some factors other than the Gram negative septicemia appear less likely in view of the fact that the first case responded so dramatically to antibiotics. The blood counts returned to normal within days of instituting antibiotic therapy. A bone marrow injury from another cause would not be expected to respond so dramatically to antibiotics alone.

The second case, who had been on regular follow-up for the management of thalassemia, had maintained normal white cell and platelet counts until this present illness. He suddenly developed fever, bleeding and sepsis. Though an in-vitro culture report showed the organism (Salmonella typhimurium) to be sensitive to amikacin, the child did not respond. It could be that the extremely low granulocyte count was unable to handle the overwhelming infection, in spite of appropriate antibiotics. The bone marrow itself being, presumably, involved in the infective process, was not capable of turning out adequate granulocytes. In this situation granulocyte transfusions would have been desirable in breaking the vicious cycle. In neutropenic patients with documented Gram negative septicemia, granulocyte transfusions definitely have been shown to improve survival(5). Unfortunately, the facilities for granulocyte transfusions were not available with us.

The presentation and course of the sec-
ond patient was unlike that of an aplastic crisis. The aplastic crisis in chronic hemolytic anemia, including thalassemia is a self-limiting disorder caused by Parvovirus(6).

Moreover, in our patient there was pancytopenia. Salmonella typhimurium septicemia tends to occur more often in patients with reduced cellular immunity. There is some evidence that in thalassemia the cellular immunity is compromised(7). This may be related to the repeated blood transfusion therapy(8).

In both cases the bone marrow was hypocellular in terms of reduction of hemopoietic tissue but without compensatory increase infant cells. This abnormal architecture was accompanied by edema, necrosis, amorphous eosinophilic material and sinusoidal dilatation and congestion. In experimentally-induced hypoplasia using benzene or by immunological mechanisms, similar findings have been observed within hours of exposure to the offending agent by one of us(9). These changes have been interpreted as indicative of active bone marrow damage. In the two patients described here, it is possible that the fulminant Gram negative septicemia could via powerful endotoxins lead to similar marrow injury and functional bone marrow impairment. In support of this contention is that, in experimental animals, endotoxins have been shown to produce hemorrhage and necrosis of the bone marrow(10).

REFERENCES