Case Report

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Anemia with erythroid hyperplasia: An unusual presentation associated with parvovirus infection

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Abstract:

Most of the patients with parvovirus B19 infection manifest with anemia and erythroid hypoplasia in bone marrow when the immunity of host is not competent enough to kill the virus like in posttransplant patients on immunosuppressive drugs and immunodeficiency syndromes. Herein, we present a case of parvovirus infection in an immunocompetent patient presenting with anemia, showing erythroid hyperplasia with hemophagocytosis in bone marrow, and also discuss the pathogenesis with review of literature in such a rare presentation.

Keywords:

Anemia, erythroid hyperplasia, parvovirus B19

Introduction

Parvovirus is known to cause a wide spectrum of hematological diseases which include anemia, thrombocytopenia, neutropenia, dyserythropoiesis, bone marrow necrosis, and hemophagocytic lymphohistiocytosis (HLH).[1-4] The manifestation depends on the immunologic status and hematological status of host. Association of parvovirus with erythroid hypoplasia and immunosuppression (commonly in postrenal transplant patients) is a known phenomenon,[5] but it is very rare to encounter erythroid hyperplasia in acute parvovirus B19 infection in an immunocompetent host.

Case Report

A 69-year-old male patient presented with complaints of generalized weakness and bone pain. He was a known and untreated case of urothelial carcinoma, high grade of the urinary bladder. His previous reports revealed chronic anemia (hemoglobin varying from 6 to 7 g/dl), unresponsive to iron, vitamin B12 and folic acid and folic acid supplementation. He was admitted for further evaluation. Hemogram and peripheral smear findings revealed a normocytic normochromic anemia (Hb: 7.7 g/dl), mild leucopenia with a normal differential leukocyte count (total leucocyte count: 2.7 × 10^3/μl), and mild thrombocytopenia (platelets: 127 × 10^3/μl). No evidence of hemolysis or polychromasia was seen. Reticulocyte count was 0.7%. Iron profile showed normal serum iron levels (72.1 μg/dl [65–175]) with hyperferritinemia (>1500 ng/ml [23.9–336.2]). Vitamin B12 (404 pg/ml [180–914]) and folic acid (23.2 ng/ml [4–19.9]) were normal and mildly elevated respectively. All other routine biochemistry investigations (renal function test, liver function test, and lipid profile) were unremarkable. Serological tests for HIV, HbsAg, and hepatitis C virus were nonreactive.

Bone marrow aspiration and biopsy was performed to determine the cause of pancytopenia. Aspirate smears were

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hypercellular and revealed erythroid hyperplasia with a mixed pattern of maturation. Myelopoiesis and megakaryopoiesis was adequate. Also seen were large proerythroblasts, showing prominent intranuclear inclusions and cytoplasmic projections suggestive of viral cytopathic effect consistent with parvovirus [Figure 1]. In addition to this, there was an increase in macrophages showing hemophagocytosis [Figure 2]. Bone marrow biopsy also revealed similar inclusion-bearing large erythroblasts [Figure 3]. For confirmation, serum parvovirus IgM and IgG levels were ordered, which revealed a positive index value (IgM: 7.0 and IgG: 3.8, positive >1). Qualitative measurement of parvovirus B19 DNA levels also gave a positive result. Hence, a diagnosis of acute parvovirus infection with erythroid hyperplasia and hemophagocytosis was rendered.

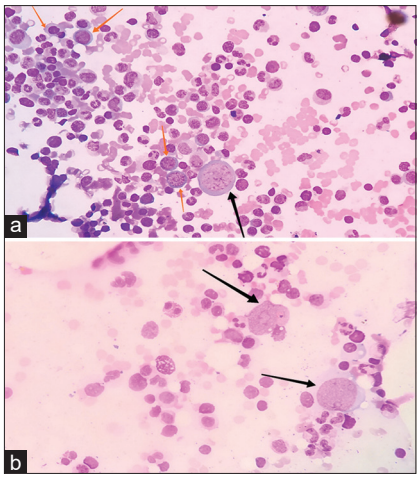

Figure 1: Low-power view of bone marrow aspirate showing (a) a large erythroblast with parvovirus inclusions (black arrow) and erythroid precursors (red arrow) (b) Another view highlighting the intranuclear inclusions (Leishman, ×100)

Discussion

The usual bone marrow findings in acute parvovirus infections are marked erythroid hypoplasia and occasional giant proerythroblasts bearing intranuclear inclusions. It is the most likely cause of refractory anemia in immunocompromised patients like postrenal transplant patients.[5] The most striking feature in our case is acute parvovirus infection in an immunocompetent host with erythroid hyperplasia in the bone marrow, which is a very unusual finding. It is a well-known phenomenon that anemia triggers erythropoietin (EpO) production from kidney which stimulates erythropoiesis from the stem cells in bone marrow, provided nutrients such as iron and Vitamin B12 required for synthesis of red blood cells are present in optimal amounts. Iron deficiency causes ineffective erythroid maturation, which, in return, stimulates more EpO secretion and the cycle continues. This creates an EpO-rich microenvironment which favors the replication of parvovirus via extracellular signal regulate kinase (ERK) activity suppression and STAT 5 phosphorylation.[5] This decreases the proliferation and survival of progenitor cells in erythroid series. Secondly, cellular hypoxia due to decrease in the number of erythrocytes further promotes parvovirus B19 replication.[5] In such a stage, even supplementation with iron or Vitamin B12 may not be able to increase the hemoglobin levels because of a high viral load rendering erythropoiesis ineffective. As a result, there is erythroid hyperplasia with a prominence of early erythroblasts, like in our case. In a healthy immunocompetent host, B19 infection causes a self-limiting infection characterized by subclinical erythroid hypoplasia which resolves spontaneously with time.[6] In this case, there is a possibility of a transient phase of immunosuppression during and after the development of urothelial carcinoma which favored parvovirus transmission. On obtaining a suitable microenvironment, the virus started to replicate and show its effect. Erythroid

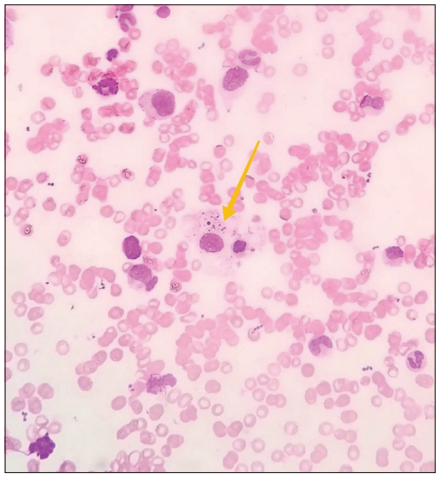

Figure 2: High-power view showing a macrophage phagocytosing a lymphocyte (yellow arrow) (Leishman × 400)

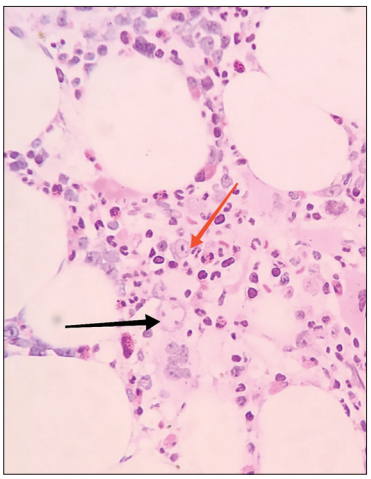

Figure 3: High-power view of bone marrow biopsy showing parvovirus inclusions in a giant proerythroblast (black arrow) and erythroid precursors (red arrow) (H and E × 400)

hyperplasia in immunocompromised hosts has also been observed with a likely explanation that failure

to produce effective IgG neutralizing antibodies leads to persistent infection through viral tolerance that allows erythroid development of infected cells past the pronormoblast stage.[7] Start a new paragraph beginning from HLH is a syndrome which requires fulfillment of at least five out of the following eight criteria based on the 2004 HLH guidelines:[8] fever; splenomegaly; pancytopenia/bicytopenia; hyperferritinemia (>500 ng/ml); hypertriglyceridemia (≥265 mg/100 ml); hypofibrinogenemia (≤150 mg/100 ml); high-soluble interleukin-2 receptor levels (>2400 U/ml); and hemophagocytosis in bone marrow, spleen, or lymph node. The present case showed hemophagocytosis in bone marrow with hyperferritenemia. Further evaluation could not be done due to patient's refusal because of financial constraints. Hence, a definite diagnosis of HLH could not be given. HLH in such cases is of secondary type. It is stated that the viral protein causes prolonged activation of immune system leading to uncontrolled proliferation and activation of lymphocytes and histiocytes releasing a plethora of cytokines which causes hemophagocytosis throughout the reticuloendothelial system. Parvovirus B19-associated HLH is characterized by a benign clinical course and better prognosis than other viral-associated HLH and may recover spontaneously.[9] The hemoglobin levels and leukocyte counts in our patient returned to normal (Hb: 12.5 g/dl and total leukocyte count: $4.3 \times 10^3/\mu l$) without any treatment, after 1 month of follow-up.

To conclude, it can be said that chronic anemia not responding to therapy (iron, vitamin B12, and EpO) and associated with a low reticulocyte count should raise a suspicion of parvovirus infection. Serological detection of antibodies (parvovirus B19 IgM and IgG) along with DNA testing in such cases can help in early diagnosis, thereby avoiding bone marrow examination, which is an invasive procedure.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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