Parvovirus B19 infection associated with severe chronic aplastic anaemia—a case report

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Abstract Aplastic anaemia (AA), the paradigm of bone marrow failure syndromes, is most simply defined as peripheral blood cytopenia and a hypocellular bone marrow. Parvovirus B19 (B19V) which is the best characterized amongst the four different parvoviruses infecting humans has a variety of clinical manifestations depending upon the clinical and hematological status of the host. We report a case of parvovirus B19-associated chronic aplastic anaemia in a 34-year-old female patient who presented with gum bleeding and ecchymotic patches over both legs and curdy vaginal discharge. She had pancytopenia on peripheral blood film examination and was subjected to bone marrow biopsy as the marrow aspirate showed peripheral blood only hence was not conclusive. Bone marrow biopsy was reported as AA, severe grade. The serological analysis performed later on revealed parvovirus B19 infection. Acute infection with B19V should be considered as a cause of acquired aplastic anaemia in individuals where other etiological factors are not elucidated.

Keywords Parvovirus · Aplastic anaemia · Bone marrow

Aplastic anaemia (AA), the paradigm of bone marrow failure syndromes, is most simply defined as peripheral blood cytopenia and a hypocellular bone marrow. Various factors, such as viral infections, drugs, organic compounds, and radiation, have been implicated as precipitating factors for AA. Among viruses, hepatitis viruses are most commonly encountered followed by Epstein–Barr virus, human immune deficiency virus (HIV), and parvovirus B19 (B19V).

B19V which is the best characterized amongst the four different parvoviruses infecting humans has a variety of clinical manifestations depending upon the clinical and hematological status of the host [1]. In persons with underlying hemolytic disorders or increased erythropoiesis or both, it can lead to a transient aplastic crisis. It is not known to induce aplastic anaemia. A case reported as pancytopenia on peripheral blood film examination was subjected to bone marrow biopsy. Bone marrow biopsy was reported as aplastic anaemia, severe grade. The serological analysis performed later on revealed parvovirus B19 infection. Acute infection with B19V should be considered as a cause of acquired aplastic anaemia in individuals where other etiological factors are not elucidated.

Case report

A 34-year-old female presented in the emergency of the clinical hematology laboratory with gum bleeding and ecchymotic patches over both legs and curdy vaginal discharge. She was reported as pancytopenic with Hb 5.5 g/dl, reticulocyte count 0.5%, TLC $2 \times 10^9/\mu\text{l}$, and platelet count was $20 \times 10^9/\mu\text{l}$; differential leucocyte count showed neutrophils, lymphocytes, monocytes, eosinophils, and basophils to be 33%, 56%, 9%, 1%, and 1%,

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respectively. Her clinical history was sought, and it was found that she was apparently well until 2 weeks prior to presentation. There was no family history of any bleeding disorder, and her obstetric history was uneventful. There were no rashes, joint pains, or hepatosplenomegaly. The patient was investigated for hemolytic disorders and deficiency diseases. Serum ferritin, vitamin B12, folate levels, glucose 6 phosphate dehydrogenase levels, and osmotic fragility tests were normal. Renal and liver function tests were normal. High-performance liquid chromatography revealed normal peaks of HbF, HbA, and HbA₂. No other abnormal windows (HbS, HbC, and HbD) or abnormal peaks were observed. Bone marrow biopsy was performed as the bone marrow aspiration smears revealed blood only and were inconclusive. The bone marrow biopsy showed a cellularity of 10–15% with the ratio of nonhematopoietic to hematopoietic cells as 10:1 (Fig. 1). The biopsy comprised predominantly of small lymphoid cells with sprinkling of plasma cells and lymphocytes. Mast cells and eosinophils were conspicuously absent. Hematopoietic cells were scarce and comprised of few cells of myeloid and erythroid series mostly in later stages of maturation. Megakaryocytes and giant cells were not seen. No fibrosis was evident (Fig. 2). Immunohistochemistry was done using CD3, CD20, and CD34. In the lymphoid cells, CD3 and CD20 were positive showing bilineage differentiation. There was no expression of CD34. Immunohistochemistry for parvovirus was not done due to nonavailability. The case was reported as severe aplastic anaemia.

Serological analysis was performed for hepatitis A, B, and C viruses; cytomegalovirus; HIV; Epstein–Barr virus; rubella; and parvovirus B19 to elucidate any viral etiology for aplastic anaemia. ELISA performed in the microbiology department at the National Center for Diseases Control revealed high titer of IgM antibodies against parvovirus,

Fig. 1 Marrow biopsy showing cellularity of 10–15% (H & E, 100×)

Fig. 2 Biopsy comprising predominantly of small lymphoid cells with sprinkling of plasma cells and lymphocytes (H & E, 400×)

whereas the IgG antibodies were negative (manufacturer Virion/Serion; negative control 0.060 units, standard serum control 0.727 units, patient's serum value 1.623 units). Serology for all other viruses was negative. There was no history of any previous drug intake, irradiation (therapeutic or accidental), and transfusion of blood or blood products. The aplastic anaemia was thus attributed to acute parvovirus B19 virus infection. Packed red cells and irradiated platelets were transfused as bone marrow replacement and immunosuppressive therapy could not be contemplated due to financial constraints. She was followed up with hemograms in the special hematology department. Her pancytopenia showed a marginal improvement (Hb 6.5 g/dl, TLC $2.5 \times 10^9/\mu\text{l}$, and absolute platelet count $46 \times 10^9/\mu\text{l}$). She was admitted again when her pancytopenia worsened.

Discussion

Parvovirus was discovered in 1974 during evaluation of assays for hepatitis B surface antigen using panel of serum samples. Sample 19 in the panel gave an anomalous result, a false positive in the relatively insensitive counterimmunoelectrophoresis assay, and when the precipitin line was excised, electron microscopy showed the presence of 23-nm particles resembling parvoviruses. Parvovirus B19 has a variety of clinical manifestations depending upon the hematological and immunological status of the patient. Infection is more common in late winter, spring, and early summer months. It usually spreads by respiratory route of transmission, but can be transmitted through blood and blood products. These are very heat resistant and resist inactivation by detergents–solvents also. In the normal immunocompetent children, B19V causes erythema infectiosum and in women, it

can cause an acute symptomatic arthropathy [2, 3]. In persons with underlying hemolytic disorders or increased erythropoiesis or both, it can lead to temporary failure of red cell formation and transient aplastic crises (TAC) [4]. In the immunocompromised host, persistent B19V infection manifests as pure red cell aplasia and chronic anaemia [5].

Humans are the only known hosts of B19V [6]. This can propagate effectively only in the erythroid progenitor cells. Erythroid specificity of the virus is partly due to the tissue destruction of the virus' cellular receptor globoside also known as blood group P antigen. P antigen is found on erythroid progenitors, erythroblasts, and megakaryocytes. It is also present on endothelial cells thereby causing vasculitis of the rash in fifth disease. In human erythroid cells derived from the bone marrow, susceptibility to parvovirus increases with differentiation; the pluripotent stem cell appears to be spared, and the main targets are the erythroid progenitors and CD36-positive erythroblasts [7]. Infection with B19V is cytotoxic [8], and the infected cultures are characterized by the presence of giant pronormoblasts 2–32 µm in diameter with cytoplasmic vacuolization, immature chromatin, and large eosinophilic inclusion bodies. In healthy volunteers B19V infection leads to an acute self-limited (6–8 days) cessation of red blood cell production with a corresponding decline in hemoglobin level [9]. In a patient with a high red cell turnover related to hemolysis, blood loss, or other causes, this temporary failure of erythropoiesis can precipitate an aplastic crisis [10, 11]. TAC is characterized by reticulocytopenia, absent erythroid precursors in the bone marrow, and worsening of anaemia. TAC is usually associated with underlying hemolytic disorders like hereditary spherocytosis, thalassemia, red cell enzymopathies, and autoimmune hemolytic anaemia. TAC and B19V infection in hematologically normal individuals are associated with changes in the other blood lineages, varying degrees of neutropenia, and thrombocytopenia [12]. Transient pancytopenia after parvovirus infection is rare [13]. B19V does not appear to be the cause of true (chronic) aplastic anaemia as per literature available [14].

Aplastic anaemia is a clinical syndrome manifested as deficiency of red cell, neutrophils, monocytes, and platelets in blood and fatty replacement of the bone marrow with a near total absence of hematopoietic precursor cells. The percentage of CD34+ cells especially the more primitive subset of (CD34+33 or CD34+38) are markedly reduced (almost 40-fold) in aplastic anaemia [15]. Most cases occur without a precipitating cause and result from autoreactive T lymphocytes that suppress or destroy primitive hematopoietic cells [16]. It can be hereditary or acquired due to drugs, specific viral infections as an idiosyncratic reaction, or autoimmune response [17]. The

viruses implicated in the pathogenesis of aplastic anaemia are Epstein–barr virus; non-A, non-B, non-C, non-D, non-E, and non-G hepatitis viruses; and the immune deficiency virus. Patients with TAC are often viremic at the time of presentation, and diagnosis is made by detection of B19V DNA in the serum by PCR. Once infected, an individual will produce IgM antibodies specific to B19V, 7–10 days after infection. These antibodies usually remain detectable for 2–3 months after infection. Approximately 10–12 days after infection, IgG antibodies specific for B19V are produced. These antibodies remain in the body for years and are thought to confer immunity literature that says that immunocompetent individuals who have evidence of current or recent infection may lack detectable levels of B19 DNA in their blood when tested by PCR. Hence it was suggested that PCR should not be used to detect B19V acute infection in immunocompetent persons. As immunocompromised persons are unable to mount an immune response to parvovirus, diagnosis is made by detecting parvovirus DNA by PCR [18].

Detection can also be made by immunohistochemical staining of marrow sections. A monoclonal antibody against VP1 and VP2 capsid proteins is a rapid and sensitive method to establish the diagnosis of parvovirus B19 infection in formalin-fixed tissues. Immunohistochemistry has been of particular help in cases with sparse inclusions and in cases of hydrops fetalis in which there is advanced cytolysis, and it has shown good correlation with morphologic, immunohistochemical, in situ hybridization, and polymerase chain reaction findings [19].

In conclusion we suggest that besides TAC, parvovirus B19 infection can cause severe aplastic anaemia in the immunocompetent without any underlying hemolytic diseases. It should be considered as a differential diagnosis in the etiology of aplastic anaemia even though the pathogenesis is unclear. Further research to elucidate the various mechanisms may open up novel strategies for better therapeutic management of these patients.

Conflict of interest The authors declare that they have no conflict of interest.

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