Acute Parvovirus B19 Infection Leading to Severe Aplastic Anemia in a Previously Healthy Adult Female

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Abstract Human Parvovirus B19 has been linked to a variety of diseases. One of the most common complications is transient aplastic crisis in patients with chronic hemolytic anemia. Very few case reports have implicated this virus as a putative etiology behind hepatitis and severe aplastic anemia in immuno competent individuals. We report a case of severe aplastic anemia in a previously healthy adult female due to acute parvovirus B19 infection. Laboratory examination showed pancytopenia in peripheral blood and severe hypoplastic bone marrow on biopsy. Serological analysis (ELISA) revealed acute Parvovirus B19 infection. In the face of unavailable HLA matched bone marrow donor, immuno-suppressive therapy was contemplated, but could not be given because of financial constraints. Pancytopenia persists till date, 4 months after the diagnosis, with the patient requiring repeated packed red cell and irradiated platelet transfusions. Thus, acute infection with this virus must be considered a cause of acquired aplastic anemia even in individuals without underlying disease.

Introduction

Most cases of parvovirus B19 infection are asymptomatic or present with flu like symptoms. However, it has also been implicated in a number of diseases. On one hand, in the immuno competent host, it causes Fifth disease in children and arthropathy in adults [1]; on the other hand, in the immuno compromised, it leads to pure red cell aplasia resulting in severe anemia requiring transfusions [2, 3]. In patients with chronic haemolytic anemia such as sickle cell anemia, acute infection with this virus results in transient aplastic crisis owing to reticulocytopenia in the background of short erythrocyte survival [4]. Cases of transient anemia with or without thrombocytopenia have been reported [5], as are rare cases of severe aplastic anaemia due to acute infection in individuals without underlying disease [6–11]. Here, we report a previously healthy adult female developing severe aplastic anemia due to serologically proven acute parvovirus B19 infection.

Case Report

A 34 year old female was apparently healthy until 2 weeks prior to presentation when she came to our OPD with gum bleeding, ecchymotic patches over both her legs, fever and curdy vaginal discharge. There was no previous or family history of any bleeding diathesis. But for the ecchymotic patches over her legs, her physical examination was unremarkable and there were no rashes, joint pains or hepatosplenomegaly. Her peripheral blood examination revealed Hb of 5.5 g/dl, reticulocytes 0.5%, WBC count $2 \times 10^9/L$ (neutrophils 40%, lymphocytes 58%, eosinophils 1% and basophils 1%), platelet count $20 \times 10^9/L$. Serum ferritin, vitamin B12, and folate levels, glucose 6

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phosphate dehydrogenase levels and osmotic fragility tests were all normal. Her renal and liver function tests were also normal. Bone marrow biopsy showed a cellularity of 10–15%, non hematopoietic to hematopoietic cell ratio of 10:1. The biopsy comprised predominantly of small lymphoid cells with sprinkling of plasma cells and macrophages. Hematopoietic cells were scarce and comprised of few cells of myeloid and erythroid series mostly in later stages of maturation. Megakaryocytes and giant pronormoblasts were not seen. These findings were consistent with a diagnosis of severe aplastic anemia (Fig. 1).

Further, to elucidate an etiologic agent behind the disease, we performed serological analysis for the following viruses: hepatitis A, B and C, cytomegalovirus, HIV, Epstein Barr virus, Rubella and Parvovirus B19. Parvovirus B19 IgM antibodies came out to be positive, whereas the IgG antibodies were negative. The IgM antibodies were

detected using ELISA (manufacturer Virion/Serion, negative control 0.060 units, standard serum control 0.727 units, and patient's serum value 1.623 units). Serology of all other viruses was negative. And there was no history of any previous drug intake or irradiation- therapeutic or accidental. We thus attributed this patient's aplastic anemia to acute parvovirus B19 infection.

In the face of unavailable HLA matched bone marrow donor, immunosuppressive therapy was contemplated but could not be given because of financial constraints. The patient was managed empirically for febrile neutropenia with broad spectrum antibiotics-piperacilin and tazobactam. Her vaginal discharge was due to candidiasis which was managed accordingly. Packed red cells and irradiated platelets had to be transfused in order to prevent any major bleeding. Peripheral blood examination was monitored regularly. Her pancytopenia improved marginally to a Hb of 6.5 g%, WBC count $-2.5 \times 10^9/L$, and platelet count $-46 \times 10^9/L$. On request she was discharged with advice of regular follow up. Over next couple of weeks, her pancytopenia worsened and she was admitted once again. Four months after the diagnosis, present peripheral blood examination reveals Hb of 5.0 g/dl, WBC count $2.6 \times 10^9/L$ (neutrophils 50%, lymphocytes 48%, eosinophils 1% and basophils 1%), platelet count $40 \times 10^9/L$. She is transfusion dependent.

Discussion

Aplastic anemia is a disease of bone marrow failure characterised by pancytopenia with marrow hypocellularity. In most cases a specific cause usually cannot be elucidated and the disease is labelled as being of idiopathic origin. The etiologies that have been implicated in the rest include drugs, irradiation and preceding viral infections as non-A, non-B, non-C hepatitis, Epstein Barr virus, cytomegalovirus, HIV and rubella. Rare cases of severe aplastic anaemia due to acute Parvovirus B19 infection in individuals without underlying disease have been reported [6–11]. An Indian study has documented the presence of Parvovirus B19 IgM and viral DNA in 40.7 and 37% of aplastic anaemia patients, respectively, thereby showing an association of parvovirus infection with aplastic anaemia [12]. Here we have described a previously healthy adult female who presented with vaginal candidiasis, febrile neutropenia and bleeding tendency. Though she had no features like arthralgia or exanthema, serology (ELISA for IgM antibodies) confirmed acute infection with Parvovirus B19. Polymerase chain reaction for detection of viral DNA was not done because the appearance of IgM antibodies is heralded by disappearance of viremia. More so, even if viremia is documented, it only points towards a more recent infection.

Fig. 1 **a** Bone marrow trephine biopsy showing bone trabeculae (vertical arrow) and the maximum cellularity seen (horizontal arrow); hematoxylin-eosin, $\times 200$, **b** Marked diminution of hematopoietic cells observed. Megakaryocytes and giant pronormoblasts not observed. Predominance of non hematopoietic cells seen -fat cells(F), stromal cells(horizontal arrows) and infiltrate of lymphoid cells (vertical arrows); hematoxylin-eosin, $\times 400$

Epidemiologically, infection with parvovirus B19 is global as inferred by widespread presence of IgG antibodies in sera of individuals from US, Europe and Asia [13]. Half of 15 year old adolescents have parvovirus specific IgG antibodies [14]. Infection continues at a lower rate throughout life thereafter. Our patient was possibly exposed to this virus for the first time when she developed severe aplastic anemia.

The only known host cell of parvovirus B19 is human erythroid progenitor cell [13]. This tropism is because of Globoside (erythrocyte P antigen) that acts as receptor for the virus [15]. Other than erythroid progenitors, globoside is also present on placenta, fetal myocardium, some megakaryocytes and endothelial cells. The non structural protein (NS1) is responsible for G₁ arrest and apoptosis of erythroid progenitors while viral DNA can itself induce G₂ arrest in these cells [16]. Other cells such as megakaryocytes may be lysed by restricted expression of viral proteins in the absence of viral propagation [17]. This explains the inconsequential transient reticulocytopenia with or without thrombocytopenia seen in normal individuals, and the aplastic crisis seen in patients with hemolytic anemia, who have shortened erythrocyte survival. More so, the giant pronormoblasts seen in immunocompromised patients who develop pure red cell aplasia are also because of the direct cytopathic effects of this virus in the face of deficient humoral immunity [13]. These were not seen in our patient.

The pathogenesis of severe aplastic anemia caused by parvovirus B19 remains to be elucidated. As stated before, proteins of parvovirus B19 are expressed even in marrow cells other than erythroid progenitors where viral propagation takes place. Direct cytotoxicity by these viral proteins causes destruction of marrow elements. But how vast majority of normal individuals clear the virus and do not develop aplastic anemia, and only a few manifest it remains unclear. The most plausible explanation would be some autoimmune mechanism that leads to destruction of marrow cells expressing viral proteins. There are case reports in literature which show remission of pancytopenia and marrow aplasia with immunosuppressive therapy [6–8]. These provide strong evidence in favour of this thought. However, some other case reports show no or minimal improvement with immunosuppression but successful remission with HLA matched bone marrow transplantation [9–11]. Hence it may be argued that different, yet unclear mechanisms of marrow destruction operate in different patients. The success of bone marrow transplantation can be explained by the observation that normal cellular immunity is necessary for humoral response against B19 virus [18]. Restoration of cellular immunity following the transplant remits marrow aplasia and terminates B19 viremia.

HLA matched bone marrow transplantation is the treatment of choice for parvovirus B19 induced severe aplastic anemia. Immunosuppressive therapy is costly, and delays bone marrow transplant [13]. However, in our country, financial restrictions pose a huge hindrance to optimal patient care. Supportive and symptomatic treatment is all we can offer to a vast majority of patients requiring bone marrow transplant for any indication.

In conclusion, this report, and the few previous ones suggest that parvovirus B19 can have significant marrow aplastic effects even in immunocompetent individuals. So, it must be considered as one of the differential diagnosis in patients of acquired aplastic anemia. Further research to decipher the exact pathogenesis of this disease process is needed, as it might open up novel therapeutic possibilities for better patient management.

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