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Successful High-Titer Immunoglobulin Therapy for Persistent Parvovirus B19 Infection in a Lymphoma Patient Treated with Rituximab-Combined Chemotherapy

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1. Introduction

Persistent parvovirus B19 infection is likely to develop in the absence of appropriate immune responses. Because this virus has a tropism for human erythroid progenitor cells and induces apoptosis in the infected cells, **persistent infection causes pure red cell aplasia (PRCA)** [1–3]. Rituximab is a chimeric monoclonal antibody against B-cell antigen (CD20) and currently is used to treat several B-cell lymphoproliferative diseases. **Although chemotherapy combined with rituximab results in excellent treatment of B-cell lymphoproliferative disease, this strategy seems to reduce humoral and cellular immunity** [5]. **Recent reports showed that persistent parvovirus B19 infection may occur after antibody-combined chemotherapy against lymphoma [6–8].**

How's it unique?
Although intra-venous immunoglobulin (IVIG) therapy is effective against the persistent infection, this treatment often fails to eradicate the virus [6, 7]. A similar result was reported for parvovirus B19-associated PRCA patients in an HIV-infected population [9, 10]. These patients also had impaired humoral immunity against parvo-virus B19. **IVIG therapy showed excellent effects against the anemia. However, a considerable number of patients relapsed after IVIG therapy because of incomplete eradication of the virus** [9, 10]. These reports show that IVIG therapy may be an imperfect treatment against persistent parvovirus B19 infection in immuno-compromised patients. **Here, we report that we succeeded in the early eradication of parvovirus B19 using high-titer immunoglobulin against the virus in a case of PRCA due to persistent parvovirus B19 infection.**

2. The Case

History
A **66-year-old woman** was admitted to our hospital for generalized weakness and fever. She was a **known case of Follicular Lymphoma, Stage III and was treated elsewhere with 6 cycles of 3 weekly R-CHOP chemotherapy** till March 2020 and had attained a complete response as per the imaging studies.

In May 2020, she **presented with fever and myalgia but no skin rash**. Although most of her symptoms improved within a week, she continued to complain of general fatigue.

Investigations
Her hemoglobin level fell from 10.5 to 6.1. **Reticulocyte count was undetectable with Total Leukocyte Count (TLC) being 800** and platelet count being 1.87 lakhs with 25 % neutrophilsand 62 % lymphocytes

Examination
On clinical examination, **pallor was seen with no palpable lymphadenopathy and no hepatosplenomegaly**.

Further Investigations
Her Serum B12, Folate, Iron, Ferritin and TIBC levels were within normal limits. CMV DNA was negative. Both direct and indirect Coombs tests were found to be negative. **There were no findings suggesting the presence of blood loss or hemolysis.**

Although serum immunoglobulin levels were normal in May 2020; IgG, IgA, and IgM were 485, 79, and 20 mg/dL, respectively. **A bone marrow examination revealed normocellular marrow with maturation arrest in the erythroid series and the presence of large pro-normoblasts** (Fig. A, B). **Hemophagocytosis was also observed** (Fig. C). However, there was no evidence for lymphoma infiltration even by flowcytometry and cytogenetic examination. Computed tomography failed to detect thymoma in her mediastinum. **These findings suggest that this patient suffered from PRCA due to parvovirus B19 infection.**

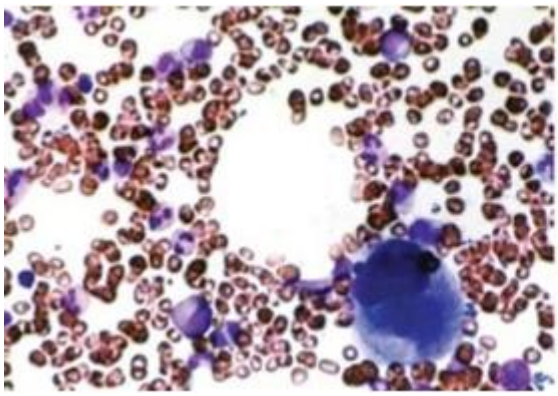

Figure A

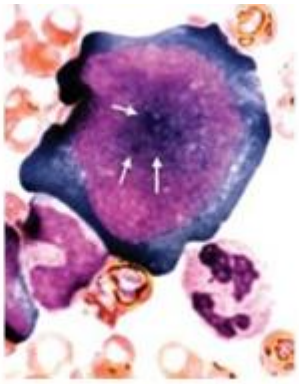

Figure B

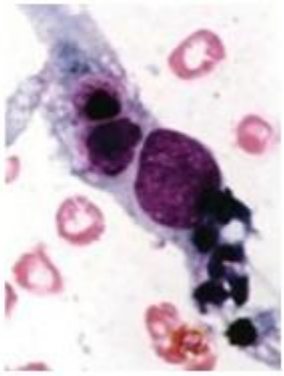

Figure C

Treatment

IVIG, whose titer against parvovirus B19 was above 10.0 on the ELISA index. **High-dose IVIG, 0.5g/kg/day, was given weekly for 2 weeks, with 4 units of erythrocyte concentrate.**

3. Result

Remarkable reticulocytosis was observed by the time of the second IVIG administration. Her hemoglobin concentrate reached 10 g/dL by June 25th **without any transfusion**. As a serum PCR test for parvovirus B19 was still positive, she received 0.1 g/kg/day IVIG every other week. By July 25th, viral DNA in her serum was undetectable by PCR analysis. At that time, serum IgG, IgA, and IgM levels were 669, 85, and 24 mg/dL, respectively, which indicated that her immunoglobulin levels were below lower normal limits. In September 2020, bone marrow examination revealed normal erythropoiesis and the absence of large pronormoblasts (Fig. D, E). **IVIG therapy was stopped because quantitative PCR analysis showed a remarkable decrease in viral DNA in marrow mononuclear cells at 1000 copies/mg DNA. Two months later, her hemoglobin level stabilized at 11–12 g/dL, and serum viral DNA remained negative.**

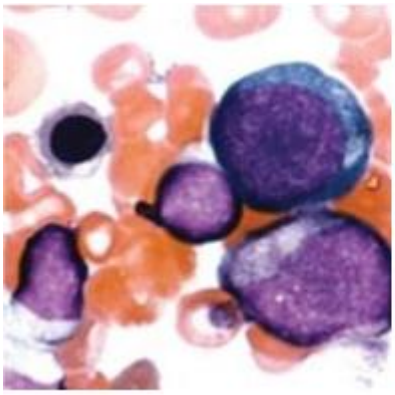

Figure D

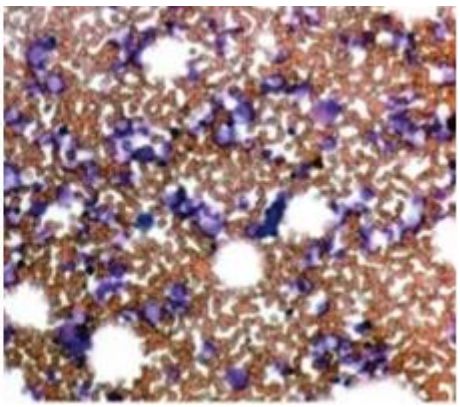

Figure E

Erythropoiesis was recovered (D), and most proerythroblasts became normal after therapy (E).

Follow-up

Although IgM antibody against parvovirus B19 remained negative during the clinical course, IgG antibody against the virus was positive in May 2021, with an ELISA index of 10.33. **A recent examination showed that her lymphoma has maintained a complete response for 2 years without anemia**.

4. Discussion

PRCA is characterized by severe anemia and selective deficiency of erythropoiesis in an otherwise normal bone marrow. This disorder is associated with thymoma lymphoproliferative disorders, autoimmune diseases, certain drugs, and infectious diseases [3]. In determining the course of PRCA in our case, the patient's history indicated an infectious etiology. **In addition, the appearance of giant pro-normoblasts and hemophagocytosis in her bone marrow directed our attention toward parvovirus B19**. Lymphoma was unlikely to contribute because the patient was in remission. She had also previously taken no medication or dietary supplements. Decreasing levels of serum immunoglobulins implied that her humoral immunity was impaired after rituximab- combined chemotherapy. Secondary humoral immune response to recall antigens is significantly decreased after rituximab therapy in lymphoma patients [5].

Although our patient had been previously infected with parvovirus B19, **we believe that she was re-infected and failed to eradicate the virus due to the insufficient immune response after rituximab-combined chemotherapy**. **The impairment of her humoral immune**

response permitted the viral expansion, resulting in chronic parvovirus B19 infection. Recent reports suggest that rituximab therapy is effective against immunologically mediated PRCA, especially for chronic lymphocytic leukemia patients [11–13], where auto-antibodies or T-granular lymphocytes inhibit erythropoiesis [3, 11–13]. Rituximab likely depletes auto-antibody-producing cells and reconstitutes the function of T-granular lymphocytes by reducing abnormal B cells [3,11–13]. However, the etiology of our PRCA case was different. **Parvovirus B19 infection is critical for immunocompromised patients. Persistent infection can also develop in patients treated with rituximab and immunosuppressive drugs.** For this reason, in a previous study prophylactic IVIG was administrated to a patient treated with rituximab for PRCA [11]. **IVIG therapy, which is effective against persistent parvovirus B19 infection in immunocompromised patients, often fails to eradicate the virus** [6,7,9,10]. Our patient succeeded in viral eradication before complete reconstruction of her immune system, indicating that neutralizing antibodies were sufficiently administrated and inactivated the virus. Neutralizing antibody against parvovirus B19 is recognized as an IgG against viral capsid protein, VP1 and VP2 [1,2]. Although antibody titer measured by ELISA can account for total IgG attached to viral capsid proteins, a considerable fraction may have the ability to neutralize parvovirus B19. Administration of high-titer immunoglobulin against parvovirus B19 is advantageous in eradicating the virus. A sufficient amount of neutralizing antibody can inactivate most of the virus in vivo and protect patients from viral expansion and pure red cell aplasia. It is important to consider parvovirus B19 infection as a possible cause of progressive anemia in B-cell lymphoma patients treated with rituximab-combined chemotherapy because patient immune response is impaired after this combined therapy. We propose that the use of high- titer immunoglobulin against parvo-virus B19 is appropriate for an eradication of the virus in such patients before complete reconstitution of the immune system.

Abbreviations

IVIG - intra-venous immunoglobulin, **PRCA** - pure red cell aplasia, **TLC** - Total Leukocyte Count,
CMV – Cytomegalovirus, **ELISA** – Enzyme Linked Immunosorbent Assay

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