Progressive bicytopenia due to persistent parvovirus B19 infection after immunochemotherapy with fludarabine/cyclophosphamide and rituximab for relapsed B cell lymphoma

Human parvovirus B 19 is known as a virus causing erythema infectiosum, arthropathy, transient aplastic crisis and intrauterin fetal death.[1] Healthy hosts are able to clear the virus within weeks after infection.[2] There are a few reports available in the literature regarding immunocompromised renal transplant recipients with persistent infection without seroconversion.[3] Herein, we describe a 56-year old woman with a relapse of grade II follicular lymphoma who received a combined immunochemotherapy of rituximab, fludarabine and cyclophosphamide and subsequently developed a persistent parvovirus B19 infection. In the absence of serum immunoglobulin antibodies, PCR analysis of peripheral blood and bone marrow aspirate were positive for parvovirus B19. Treatment with IVIG treatment resulted in normalization of peripheral blood counts within 7 weeks.

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Case report

Our patient, a 56-year old woman, had been diagnosed with grade II follicular lymphoma in October 2002. Staging revealed a stage II with involvement of mesenterial and abdominal lymph nodes. We initiated a chemotherapy according to the CHOP regimen (6 cycles), which was followed by a partial response. Two years later, the patient presented to our outpatient clinic with progressing disease and treatment with rituximab, fludarabine and cyclophosphamide (R-FC) was started. She again attained a partial remission after 3 cycles and in this situation we decided to pause chemotherapy after completion of 6 cycles. Peripheral blood cell counts have fully recovered within 2 to 3 weeks.

Three months later, the patient was re-admitted to our institution because of progressive anemia. She reported that she has experienced a episode of fever a few weeks prior to admission to hospital which was accompanied by a maculopapulous exanthema. These symptoms have resolved spontaneously without further intervention. Laboratory analysis showed immunoglobulin levels, lymphocytes and B-cell subtypes within the normal values; however, a slight lowering of the subclasses IgM and IgG4 as well as of the CD4/CD8 ratio with 0.6 were observed. During the next weeks, the need for RBC transfusions increased to 2-3 units every 10 days and, in addition, a severe leukocytopenia (<1.000/µl) as well as an elevated lactatdehydrogenase (LDH) were observed.

Differential diagnosis of relapsed follicular lymphoma disease was excluded by CT scan and bone marrow biopsy which revealed no evidence for lymphoma infiltration, but a moderate hypocellularity with no specific abnormalities. A chemotherapeutic effect was also excluded because a full regeneration of the peripheral blood counts up to 3 months after completion of treatment has been documented by the patients´ family doctor.

On this clinical situation - combination of pancytopenia, recurrent fever and moderately elevated lactic dehydrogenase, indicating ineffective hematopoiesis and apoptotic events - a viral infection was supposed. Measurement of serum immunoglobulin IgG and IgM antibodies were negative, but positive plasma polymerase chain reaction (PCR) analysis of peripheral blood and bone marrow aspirate were present for parvovirus B19. Retrospectively, all patients´ peripheral blood samples and bone marrow trephine biopsy were positive for PVB19 genomes by means of PCR and/or ISH (Figure 1) during the fever episode three months after completion of chemotherapy. Therefore, intravenous treatment with unspecific immunoglobulin (IVIG) at 0.5 g/kg/day every 3 weeks was initiated.[4] A few days later, peripheral blood counts increased and finally normalized 7 weeks after onset of IVIG application (Figure 2). Six months after termination of IVIG infusions B-cell subtypes were in the

Figure 1. Detection of PVB19 genomes in hemopoietic cells of bone marrow trephine biopsy by *in situ* hybridization (original magnification x63). On conventional histology neither giant pronormoblasts nor so called Lantern cells were seen (*not shown*).

Figure 2. Peripheral blood counts before and after IVIG substitution, arrows indicate the start of unspecific intravenous immunoglobulin application.

normal range, but despite IVIG treatment no complete virus eradication has been achieved (positive PCR in peripheral blood samples for parvovirus B19).

In summary, despite absence of overt bone marrow signs of pure red cell aplasia suggesting parvovirus B19 infection, e.g. occurrence of giant proerythroblasts with eosinophilic intranuclear inclusions and hemophagocytosis as well as negative IgG and IgM parvovirus B19 antibodies, it is important to consider that (I) parvovirus B19 infection is a possible cause of progressive anemia and (II) of leukocytopenia in B-cell lymphoma patients[5] especially when treated with rituximab-combined chemotherapy. (III) Rituxmab plus fludarabine/ cyclophosphamide induced a prolonged immunosuppression without decreased quantitative immunoglobulin. (IV) Application of unspecific high-titer immunoglobulin may enable normalisation of peripheral blood counts even without complete eradication of parvovirus B19 in such patients. Another promising approach may be the establishment of functional B cell memory against the virus capsid protein VP2 in patients with persistent infection.[6]

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References

1. Isa A, Kasprowicz V, Norbeck O, Loughry A, Jeffery K, Broliden K et al. Prolonged activation of virus-specific CD8+T cells after acute B19 infection. PLoS Med 2005; 2:e343.
2. Lindblom A, Isa A, Norbeck O, Wolf S, Johansson B, Broliden K et al. Slow clearance of human parvovirus B19 viremia following acute infection. Clin Infect Dis 2005; 41:1201-3.
3. Kumar J, Shaver MJ, Abul-Ezz S. Long-term remission of recurrent parvovirus-B associated anemia in a renal transplant recipient induced by treatment with immunoglobulin and positive seroconversion. Transpl Infect Dis 2005; 7:30-3.
4. Isobe Y, Sugimoto K, Shiraki Y, Nishitani M, Koike K, Oshimi K. Successful high-titer immunoglobulin therapy for persistent parvovirus B19 infection in a lymphoma patient treated with rituximab-combined chemotherapy. Am J Hematol 2004; 77:370-3.
5. Heegaard ED, Brown KE. Human parvovirus B19. Clin Microbiol Rev 2002; 15:485-505.
6. Corcoran A, Crowley B, Dewhurst C, Pizer BL, Doyle S. Establishment of functional B cell memory against parvovirus B19 capsid proteins may be associated with resolution of persistent infection. J Med Virol 2006; 78:125-8.