Parvovirus B19 Associated Pure Red Cell Aplasia Associated with R-CHOP Immunochemotherapy for Relapsed B-Cell Non-Hodgkin’s Lymphoma – An Indicator of A Poor Prognosis?

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Abstract

We describe the case of a patient who developed a severe and symptomatic Parvovirus B19 associated anemia during R-CHOP-14 chemoimmunotherapy of a secondary high-grade Non-Hodgkin’s lymphoma. While lymphoma responded to the initial therapy with R-CHOP plus consolidation radiation therapy, the anemia was interpreted as pure red cell aplasia and responded to treatment with intravenous immunoglobulins. However, both diseases failed to respond to salvage therapies when they recurred simultaneously 4 months after the completion of primary therapy.

The occurrence of Parvovirus-B19 associated pure red cell aplasia during the chemoimmunotherapy of a Non-Hodgkin’s lymphoma must be recognized and treated early in knowledge of the potentially adverse consequences associated with this rare viral reactivation syndrome. In the absence of feasible immunization strategies or antiviral drugs, it remains however unclear, whether this knowledge, and the implementation of currently available therapeutic resources will suffice to improve the treatment results of relapsed pure red cell aplasia in the setting of relapsed lymphoma. While remains unclear, whether the occurrence of Parvovirus-B19 associated pure red cell aplasia during the initial chemoimmunotherapy of B-cell NHL can be regarded as a sign of adverse prognosis and poor outcome, the combination of these two inter-related haematological disorders is undoubtedly associated with increased patient morbidity and, more likely than not, with decreased treatment efficacy.

Keywords: Parvovirus B19; Pure red cell aplasia; R-CHOP; Immunochemotherapy; Non-Hodgkin’s lymphoma; Anemia; Prognosis

Introduction

Parvovirus B19 is a small non-enveloped single stranded DNA virus, which is characterized by its tropism for erythroid progenitor cells [1]. Rituximab is a chimeric monoclonal antibody against CD20 that depletes not only malignant B-cells but also normal B-cells thus impairing humoral and cellular immunity. Treatment with rituximab – with or without concomitant chemotherapy - can increase the risk of bacterial, viral and other infections; another important mechanism for the development of clinically significant infectious diseases after rituximab therapy is reactivation of viral infections such as cytomegalovirus (CMV), Epstein-Barr-virus (EBV) or Parvovirus B19.

Parvovirus B-19 reactivations with the subsequent development of pure red cell aplasia have been described in many different settings of compromised immunity:

- as late complication of immunsupression and graft-versus-host disease after allogeneic bone marrow transplantation [2]
- as complication of different immunsuppressive regimens utilized after renal transplantation to prevent graft rejection [3,4]
- as complication of immunsuppressive regimens utilized to prevent graft rejection after transplantation of other solid organs [5]
- as specific complication of the immunological deficiencies observed in patients with human immunodeficiency virus (HIV) infections [6]
- as event occurring secondary to the antibody-mediated depletion of CD-20-positive lymphoid cells after primary rituximab therapy [7]
- as event occurring secondary to the immunsuppression associated with CHOP-chemotherapy in combination with antibody-mediated depletion of CD-20-positive lymphoid cells after rituximab (i.e. after R-CHOP) [8]
- recently, as an event occurring in the context of rituximab maintenance therapy in follicular lymphoma [9]

The association of refractory lymphoma-relapse in combination to an equally refractory relapse of Parvo-Virus-associated B-19 reactivation has not been published, as to our knowledge.

Case History

We present the case of a 67-year-old man with a prior history of liposarcoma (in remission for ten years) who developed a secondary
high-grade, diffuse large B-cell Non-Hodgkin’s lymphoma (NHL) only one month after the diagnosis of a marginal-zone B-cell Non-Hodgkin’s lymphoma (MZL) was made.

The diagnosis of diffuse large B-cell NHL with bulky abdominal stage II was made in January 2008. The International Prognostic Index (IPI) was intermediate-high based on three risk-factors (age > 60 years, ECOG 2, elevated Lactate Dehydrogenase (LDH)). Histology of a transcutaneous needle aspirate of the bulk tumor was consistent with a secondary high-grade lymphoma after a marginal zone NHL diagnosed during laparoscopy one month earlier.

From January to April 2008, the patient received five cycles of standard-dose R-CHOP-12 immunochemotherapy (consisting of Rituximab 375 mg/m², Cyclophosphamide 750 mg/m², Doxorubicin 50 mg/m², Vincristin 1,4 mg/m², all d1 i.v. and Prednisolone 50 mg/m² d1-5 p.o.) resulting in a very good partial remission of his NHL with a residual tumor in the area of the bulk that was marginally FDG-avid on PET-CT-examination in April 2008; radiation therapy of the residual bulk was given at the dose of 46 Gray and completed in June 2008.

During this immunochemotherapy, the patient developed an increasingly severe and increasingly symptomatic anemia WHO I-II (with e.g. first-onset atrial fibrillation in early April 2008) as shown in table 1:

The anemia remained unexplained initially, puzzling the clinicians for the first four weeks; endoscopic examinations (gastroscopy, colonoscopy) showed no abnormalities, there were no signs of treatment- or lymphoma-associated hemolysis (LDH was within normal range after 2 cycles of R-CHOP, Haptoglobin was persistently elevated, a Vitamin B12 or Folate deficiency could be ruled out). After transfusion of a total of 12 units of red packed red blood cells (PRBC+s) further examinations were performed. The clue to the diagnosis of Parvovirus B19 associated pure red cell aplasia was a reticulocyte count of zero in April 2008 - reticulocytopenic anemia being the hallmark finding in immune compromised patients with parvovirus B19 infection [1].

Bone marrow aspiration showed no evidence of infiltration by lymphoma cells, but a depletion of erythroid precursor cells, reduced granulopoesis, and proliferating megacaryopoesis (Figure 1). Positive polymerase chain reaction (PCR) for parvovirus B19 DNA in the patient’s serum confirmed the diagnosis.

As treatment of this virus-induced haematological complication the patient received unspecific intravenous immunoglobulin IgIV from April through June 2008, which contained neutralizing antibodies to Parvovirus B19 [10] at a dosage of 0.1 g/kg. In accordance with published observations in a similar setting [11], a clinical response to IVIG was observed with reticulocytosis and increased haemoglobin concentrations; in contrast to the cited publications, however, a marginally and transiently to salvage chemotherapy of the lymphoma a relapse of symptomatic anemia. This time, the patient responded only marginally and transiently to salvage chemotherapy of the lymphoma as well as to the re-introduction of the IVIG therapy. The treatment therefore changed to mere supportive measures in December 2008; the patient succumbed to refractory lymphoma progression associated with a refractory parvovirus B19-associated red cell aplasia in February of 2009.

### Table 1: Development of Hemoglobin values during Parvovirus-B19-Reactivation.

<table>
<thead>
<tr>
<th>Datum</th>
<th>Hb g/dl</th>
<th>Transfusion requirement</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>02.01.08</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.01.08</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.01.08</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.02.08</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>03.03.08</td>
<td>8</td>
<td>2 units of packed-red-blood cells</td>
<td>Therapy: 14 doses of 15 gm IVIV</td>
</tr>
<tr>
<td>14.03.08</td>
<td>8</td>
<td>2 units of packed-red-blood cells</td>
<td>Beginning 23.04. end 25.06.08</td>
</tr>
<tr>
<td>25.03.08</td>
<td>8</td>
<td>2 units of packed-red-blood cells</td>
<td>PR of pure red cell aplasia</td>
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<tr>
<td>06.04.08</td>
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<td>2 units of packed-red-blood cells</td>
<td>PR of the NHL</td>
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<tr>
<td>13.04.08</td>
<td>8</td>
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<td>Lymphoma relapse</td>
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<td>20.10.08</td>
<td>10</td>
<td></td>
<td>Relapse pf pure red cell aplasia</td>
</tr>
<tr>
<td>28.10.08</td>
<td>8</td>
<td>2 units of packed-red-blood cells</td>
<td>Therapy: 12 doses of 15 gm IVIV</td>
</tr>
<tr>
<td>18.11.08</td>
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<td>2 units of packed-red-blood cells</td>
<td>Beginning 18.10. end 30.11.08</td>
</tr>
<tr>
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<td>2 units of packed-red-blood cells</td>
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</tr>
<tr>
<td>28.11.08</td>
<td>8</td>
<td>2 units of packed-red-blood cells</td>
<td></td>
</tr>
<tr>
<td>30.11.08</td>
<td>8</td>
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<td>Refractory lymphoma</td>
</tr>
<tr>
<td>03.12.08</td>
<td>7</td>
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<td>Refractory pure red cell aplasia</td>
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<td>20.12.08</td>
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<td>06.02.09</td>
<td>9</td>
<td>2 units of packed-red-blood cells</td>
<td></td>
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### Discussion

Many infectious complications have been associated with rituximab therapy or R-CHOP immunotherapy. The spectrum includes classic opportunistic infections such as pneumocystis jiroveci pneumonia [12], severe viral infections such as fulminant hepatitis.
after the completion of primary therapy. The following conclusions and
to salvage therapies when the recurred simultaneously four months
and treatment with IVIG, respectively), both diseases failed to respond
Parvovirus B19 associated pure red cell aplasia during R-CHOP-14
[2,4,14].
coping with parvovirus B19 infection, several observations point to an
humoral immunity is thought to be the most important factor in
associated with the diagnosis of non-Hodgkin’s lymphoma and its
Not only the impairment of B-cell activity, but also T-cell depletion
parvovirus B19 infection in immune compromised patients [1].
have been published [6]. However, there are currently no strategies
available to prevent reactivation or infection with Parvovirus B19 in
patients receiving Rituximab-based immunosuppressive combination
therapies – and prediction of successful treatment with IVIG in these
patients is notoriously difficult and depends primarily on an adequate
control of the underlying hematolocial malignancy [7-9].

Unfortunately, clinical trials with human recombinant parvovirus
B19 vaccine had to be terminated due to vaccine-associated adverse
events.

Treatment with IGIV is the standard treatment to control
parvovirus B19 infection in immune compromised patients [1].
Not only the impairment of B-cell activity, but also T-cell depletion
associated with the diagnosis of non-Hodgkin’s lymphoma and its
immunocemotherapy lead to parvovirus B19 reactivation. Although
humoral immunity is thought to be the most important factor in
coping with parvovirus B19 infection, several observations point to an
important role of the cellular response system in clearing the infection
[2,4,14].

We describe the case of a patient with B-NHL who developed
Parvovirus B19 associated pure red cell aplasia during R-CHOP-14
therapy. While the lymphoma and the pure red cell aplasia responded
to the initial therapy (R-CHOP plus consolidation radiation therapy
and treatment with IVIG, respectively), both diseases failed to respond
to salvage therapies when the recurred simultaneously four months
after the completion of primary therapy. The following conclusions and
observations may be drawn from this case:

1. The case illustrates the difficulty to deal with a clinically
significant viral reactivation in the absence of an efficient, specific
antiviral medication. Clearly, the complex immunosupressed
state of this patient caused by the lymphoma and its therapy are
only partially corrected by the use of IVIG.

2. It remains unclear, whether the occurrence of Parvovirus-B19
associated pure red cell aplasia during the R-CHOP-
chemoimmunotherapy may be indicative of a more-than-
average degree of immune incompetence associated with a
particularly aggressive (and immunologically autoaggressive)
lymphoma per se - or with a particular sensitivity of the
individual patient to the immunosuppressive effects of
R-CHOP-therapy. So far, no methods or guidelines have been
published with regards to the prediction of this haematological
complication or to the characterization of parameters that may
help to identify patients at particular risk for the development
of Parvovirus-B19 associated pure red cell aplasia.

3. It is clear, however, that the onset of Parvovirus-B19 associated
pure red cell aplasia during the chemoimmunotherapy of a
Non-Hodgkin’s lymphoma heralds a disadvantageous course of
treatment with a potentially significant deterioration of
prognosis.

Individual features or mediators of this adverse prognostic effect
could include:

- reduced efficacy of the chemotherapy by lack of oxygen carries
and thus lower-than-normal generation of oxygen radicals
- reduced efficacy of additional consolidation radiotherapy by
lack of oxygen carries (and thus lower-than-normal generation of
oxygen radicals)
- reduction of chemotherapy dosage and increase of
chemotherapy intervals due to secondary complications of
anemia such as atrial fibrillation, depression and general
physical deterioration and inactivity
- reduced tolerance of crucial chemotherapy agents such as
anthracyclins as a consequence of general deconditioning,
reduced coronary oxygenation and cardiac arrhythmias
- increased susceptibility to secondary infections by other
microbial agents during the phase of Parvo-Virus-B-19
reactivation
- negative effects of multiple blood transfusions (in this case 30
PRBC’s in less than six months) with a significant iatrogenic
iron load (possibly contributing to a pre-existing altered
cardiac state)
- negative effects of multiple transfusions of intravenous
immunoglobulins such as allergic reactions and increased need
for antiallergic pre-medication with further in desired side
effects (steroids, antihistamines etc)

Summary

The occurrence of Parvovirus-B19 associated pure red cell aplasia
during the chemoimmunotherapy of a Non-Hodgkin’s lymphoma
must be recognized and treated early in full knowledge of the
potentially adverse complications and consequences associated with
this rare, but clinically significant viral reactivation syndrome. In
the absence of feasible immunization strategies or antiviral drugs, it
remains unclear, whether the implementation of currently available
therapeutic resources will improve the treatment results of relapsed
pure red cell aplasia in the setting of relapsed lymphoma. While it
remains unclear, whether the occurrence of Parvovirus-B19 associated
pure red cell aplasia during the initial chemoimmunotherapy of B-cell
NHL ca be regarded as a sign of adverse prognosis and poor outcome,
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