Case Report

Chronic parvovirus B19 infection-associated pure red cell anaemia in a kidney transplant recipient

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Key words: immunoglobulin; parvovirus B19; pure red cell anaemia; renal transplantation

Introduction

Transplant recipients are known to be susceptible to primary viral infections or to reactivation of a persistent virus. Most of the clinically relevant infections are caused by the herpes-viridae group (CMV, EBV, VZV, HSV I and II). Human parvovirus B19 was first discovered 1975 in human packed blood [1] and subsequently shown to cause fifth disease or erythema infectiosum in children [2]. The virus also causes aplastic crises in patients with underlying haemolytic anaemia [3-5].

Chronic parvovirus B19 infection can induce pure red cell anaemia in patients with congenital immunodeficiency, acquired immunodeficiency syndrome, and children with lymphoblastic leukaemia. Pure red cell anaemia due to chronic parvovirus B19 infection has rarely been described in organ transplant recipients: Nour et al. [6] reported on five paediatric liver and heart recipients, Ramage et al. [7] described the case of a liver transplant recipient and in a report on renal effects of immunoglobulin therapy Cantu et al. [8] mentioned a patient with parvovirus B19 infection after combined heart–kidney transplantation. Some of these patients with persistent parvovirus infection were treated successfully with high-dose intravenous immunoglobulin (HD-IVIG).

In this paper we report on a kidney transplant recipient developing parvovirus B19-induced pure red cell anaemia 6 months after transplantation and its successful treatment with intravenous immunoglobulin.

Case report

A 57-year-old female suffering from polycystic kidney disease received a first cadaveric kidney transplant in January 1994. The donor, who had died of subarachnoid haemorrhage, had received a liver transplant herself 4 years earlier for post-hepatitis liver cirrhosis, and had been treated with cyclosporin, azathioprine, and prednisolone after transplantation. Because of normal kidney function tests and urine analysis the liver transplant recipient was found suitable as kidney donor. At the time of transplantation both donor and recipient had negative tests for Hbs-Ag and anti HCV-antibodies and both were positive for CMV-IgG.

Post-transplant immunosuppressive regimen

Despite a triple immunosuppressive therapy (FK506), azathioprine, and prednisolone), the post-transplant course was complicated by four rejection episodes. In the early post-transplant period a biopsy verified mild vascular rejection was treated with a steroid pulse (dexamethasone 100 mg for 3 days). Nine weeks after transplantation, another vascular transplant rejection episode was reversed by a 14-day course of antithymocyte globulin (ATG, Fresenius, FRG). Two additional rejection episodes 13 and 27 weeks after transplantation were successfully treated with steroid pulse therapy. Thereafter the kidney graft functioned well and the serum creatinine remained stable at 1.8–2.0 mg/100 ml.

Anaemia

Six months after transplantation the patient developed transfusion-dependent normochromic, normocytic anaemia. Despite high-dose erythropoietin treatment (167 IE/kg s.c. twice per week up to 6 times per week), the patient required an average of two red cell packs every 2–3 weeks to maintain a haemoglobin greater than 7 g/100 ml (Figure 1). Iron depletion was excluded repeatedly. After extensive investigation, the diagnosis of pure red cell anaemia was finally...
established because of the concurrent occurrence of normochromic, normocytic anaemia, reticulocytopenia (1-3%), normal white blood count, and normal platelet numbers. In the bone marrow a massive reduction of erythropoiesis with rarefied erythropoietic precursors (3%) was found, but myelopoiesis and megakaryocytes were normal.

Azathioprine was discontinued because of its known myelosuppressive effects. When after 2 months the anaemic state remained unchanged, FK506 was switched to cyclosporin A, because it had been reported that chronic anaemia resolved after discontinuation of FK506 in a liver transplant recipient [9]; the authors suspected that the anaemia was induced by treatment with tacrolimus although the mechanisms leading to the suggested myelosuppressive effect of FK506 were unclear. After exclusion of other causes of pure red cell anaemia (Table 1) we focused on viruses in the differential diagnosis (e.g. CMV, parvovirus B19).

Viral infections

Cytomegalovirus

During the ATG course (9th post-transplant week), the patient developed a serologically proven cytomegalovirus (CMV) infection. In this highly immuno-

suppressed state a pre-emptive 14-day course of 10 mg/kg gancyclovir per day was given (Table 2). Subsequently the patient never lost the CMV-IgM antibodies. Between the 12th and the 50th post-transplant week, four courses of gancyclovir were given for episodes of CMV-associated disease (one episode of fever and myalgia, one episode of CMV infection triggered mild transplant rejection, two courses were given for severe anaemia, which initially was thought to be CMV related).

Parvovirus B19

Fifty weeks after transplantation, parvovirus B19-DNA was detectable by polymerase chain reaction (PCR) and specific IgM-antibodies were found in the patient’s serum. A bone marrow aspirate was also positive for parvovirus B19-DNA. Retrospective screening of deep frozen sera revealed an infection with parvovirus B19 already 5 months prior to transplantation, as indicated by specific IgM, that persisted thereafter (Table 2).

In retrospect, it seems unlikely that cytomegalovirus caused the selective myelosuppression, because the rather sudden onset of the anaemia took place 18 weeks after the diagnosis of CMV reactivation, and the treatment with gancyclovir showed no improvement of the erythrocyte count. Furthermore, onset of anaemia was chronologically related to detection of B19 viraemia and increased reactivity of B19 IgM.

All specific parvovirus B19 antibodies were investigated, applying a commercially available enzyme-linked immunosorbent assay (EIA) (IDÉIA® Parvovirus B19 IgG and IgM; Dako, Denmark).

Treatment

Fifty-nine weeks after transplantation the patient was admitted to the hospital for high-dose immunoglobulin therapy. Clinical and laboratory findings on admission are shown in Table 3. An immunoglobulin course (planned for 10 days) was started at a dosage of 0.4 g/kg/day as a 3% solution over 12 h i.v. (Immunglobulin i.v. Biochemie®, Biochemie, Austria; identical to Sandoglobulin®, Switzerland). Since the patient developed acute renal failure under HD-IVIG, the therapy was stopped after day 4. Maximum serum creatinine rose to 3.9 mg/100 ml on the third day after therapy. Discontinuation of the Ig infusions led to restoration of renal function to pretreatment creatinine values within 12 days.

Values for haemoglobin rose from 7.2 g/100 ml to 10.2 mg/100 ml within 14 days. Erythropoietin therapy could be discontinued after the successful HD-IVIG course and no further transfusions were required. Full remission could be sustained subsequently without further immunoglobulin treatment. The patient’s kidney function remained stable throughout the observation period (28 weeks), as did haemoglobin values, which are currently within the normal range. Parvovirus B19-DNA, which was detected in the
mission of the virus occurs via the respiratory route.

Table 2. Virological studies in chronology to transplant rejection and antiviral treatment

<table>
<thead>
<tr>
<th>Week</th>
<th>Additional therapy</th>
<th>Remarks</th>
<th>Parvovirus</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgG (EIA)</td>
<td>IgM (EIA)</td>
</tr>
<tr>
<td>-48</td>
<td></td>
<td></td>
<td>(n.r.)</td>
<td>(n.r.)</td>
</tr>
<tr>
<td>-40</td>
<td></td>
<td></td>
<td>(n.r.)</td>
<td>(n.r.)</td>
</tr>
<tr>
<td>-30</td>
<td></td>
<td></td>
<td>(n.r.)</td>
<td>(n.r.)</td>
</tr>
<tr>
<td>-22</td>
<td></td>
<td></td>
<td>(n.r.)</td>
<td>(w.r.)</td>
</tr>
<tr>
<td>-13</td>
<td></td>
<td></td>
<td>(n.r.)</td>
<td>(r.)</td>
</tr>
<tr>
<td>-4</td>
<td></td>
<td></td>
<td>(n.r.)</td>
<td>(r.)</td>
</tr>
<tr>
<td>Transplantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SP</td>
<td></td>
<td>(n.r.)</td>
<td>(w.r.)</td>
</tr>
<tr>
<td>9</td>
<td>ATG, gancyclovir</td>
<td></td>
<td>(n.r.)</td>
<td>(w.r.)</td>
</tr>
<tr>
<td>13</td>
<td>SP</td>
<td></td>
<td>(n.r.)</td>
<td>(w.r.)</td>
</tr>
<tr>
<td>27</td>
<td>SP, gancyclovir</td>
<td></td>
<td>(n.r.)</td>
<td>(w.r.)</td>
</tr>
<tr>
<td>31</td>
<td>Gancyclovir</td>
<td></td>
<td>(n.r.)</td>
<td>(r.)</td>
</tr>
<tr>
<td>39</td>
<td>Gancyclovir</td>
<td></td>
<td>(n.r.)</td>
<td>(r.)</td>
</tr>
<tr>
<td>50</td>
<td>Gancyclovir</td>
<td></td>
<td>n.r.</td>
<td>r.</td>
</tr>
<tr>
<td>52</td>
<td></td>
<td></td>
<td>n.r.</td>
<td>r.</td>
</tr>
<tr>
<td>55</td>
<td></td>
<td></td>
<td>n.r.</td>
<td>r.</td>
</tr>
<tr>
<td>59</td>
<td>HD-IVIG</td>
<td></td>
<td>n.r.</td>
<td>r.</td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td>w.r.</td>
<td>r.</td>
</tr>
<tr>
<td>61</td>
<td></td>
<td></td>
<td>n.r.</td>
<td>r.</td>
</tr>
<tr>
<td>69</td>
<td></td>
<td></td>
<td>n.r.</td>
<td>r.</td>
</tr>
<tr>
<td>82</td>
<td></td>
<td></td>
<td>r.</td>
<td>r.</td>
</tr>
</tbody>
</table>

SP, steriod pulse; ATG, antithymocyte globulin; BM, bone marrow; CFR, complement fixation reaction; PCR, polymerase chain reaction; CMV, cytomegalovirus; HD-IVIG, high-dose intravenous immunoglobulin; EIA, enzyme-linked immunosorbent assay; IB, immunoblot; n.r., not reactive; w.r. weakly reactive; r, reactive. Retrospective virological studies are in parentheses.

Table 3. Clinical and laboratory findings on hospital admission 59 weeks after transplantation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Medication</th>
<th>Renal function</th>
<th>Blood count</th>
<th>Blood transfusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhaustion on light exercise</td>
<td>Cyclosporin A (2.3 mg/kg per day), prednisolone (10 mg/day), sucralfat (1 g x 3), erythropoetin (167 IE/kg s.c. 4 times per week)</td>
<td>Stable, serum creatinine 1.84 mg/100 ml, MCHC 34.1 g/100 ml; reticuloocyte count 3%; WBC 9.6 G/l; platelets 265 G/l</td>
<td>Hb 7.2 g/100 ml (MCV 89.4 fl, MCH 30.5 pg, MCHC 34.1 g/100 ml); reticuloocyte count 3%; WBC 9.6 G/l; platelets 265 G/l</td>
<td>22 (in 28 weeks)</td>
</tr>
</tbody>
</table>

patient serum before treatment, was not detectable immediately after immunoglobulin therapy, but recurred shortly thereafter.

Discussion

In this report we describe a patient with parvovirus B19 infection acquired under haemodialysis, persisting after renal transplantation initially without clinical symptoms. However, after extensive immunosuppression due to repeated rejections, parvovirus B19-associated pure red cell anaemia became apparent.

Parvovirus B19 infection usually occurs between the ages of 5 and 15 years, with a yearly peak in spring and leading to life-long immunity. Specific IgG can be found in high frequency in the normal population, about 40–70% of adults possess antibodies. The transmission of the virus occurs via the respiratory route.
tion can be explained by the altered immunological potential during the uremic state. Post-transplantation, the use of cyclosporin A and FK506 might have contributed to the lack of detectable antibody production.

Since, however, the serological constellation of persisting positive IgM and negative IgG antibodies is unusual after any kind of infection, we also tested the patient's sera by immunoblots for IgG (Biotrin®, Parvovirus B19 Immunoblot, Biotrin International, Ireland), a test which is more sensitive to detect very low amounts of antibodies. By this method IgG was clearly demonstrable in all IgM-positive sera (Table 2). In IgM-negative patient sera, testing for IgG by immunoblot revealed only very weak reactivity, which is questionable because of the limited experience with this assay. From these data it remains unclear whether the infection was due to primary exposure, reinfection, or reactivation, which is, however, of little relevance for the case presented here.

Six months after transplantation a transfusion-dependent anaemia occurred. It is possible that the high cumulative dose of immunosuppressive agents was a key factor for the infection to become symptomatic. The occurrence of anaemia coincided with DNA detectability by PCR and an increase of IgM antibodies, a constellation which persisted over the whole period of transfusion dependency, i.e. until the start of HD-IVIG therapy. The success of the immunoglobulin therapy was reflected by the improvement of the clinical course (no further transfusions were required) and was accompanied by the negative testing of B19 DNA (week 60).

Two weeks after immunoglobulin therapy, the initial serological constellation (positive B19-DNA testing by PCR, positive IgM, negative IgG by ELISA) recurred, in the absence of clinical symptoms. An accessible explanation for this lasting clinical remission might be seen in the withdrawal of erythropoietin therapy. Parvoviruses uniformly require actively proliferating host cells (erythroid precursors) for replication [11]. Our patient was treated with very high doses of erythropoietin (up to 167IE/kg six times per week). Since erythropoietin enhances the number of proliferating CFU-E considerably, it is possible that viral replication was promoted by this therapy. After the effective course of HD-IVIG the patient was without erythropoietin therapy, which may have reduced the viral load, thereby allowing her own immune system to balance the infection.

The beneficial effect of HD-IVIG on B19-associated pure red cell anaemia has been described in several case reports [6,7,15,17,18], but has never been investigated in a large-scale clinical trial. In addition, the mechanism of its action remains unclear. The most likely explanation for the efficiency of the treatment is that immunoglobulin preparations contain specific neutralizing antibodies, possibly leading to a reduction of the viral load. The charge of Immunoglobulin i.v. Biochemi® we used had a titre of specific IgG of 1:800 and could thus be sufficient to neutralize the viral activity.

Finally, we draw the attention of the reader to the unusual constellation that a liver-transplant recipient, after several years of immunosuppression, happened to become the donor of a renal graft.

From this case, the following conclusions can be drawn. In a transplant recipient persistent parvovirus B19 infection should be considered in the differential diagnosis of any type of anaemia. HD-IVIG is a useful therapeutic agent in this condition. Renal function must be monitored, however, during the administration of HD-IVIG. In patients with pre-existing renal disease further functional impairment can occur, although this was transient in our case.

References


Received for publication: 2.1.1996
Accepted in revised form: 31.1.1996