Anemia as a Complication of Parvovirus B19 Infection in Renal Transplant Recipients

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Key words: *anemia; renal transplantation; B19 infection.*

Summary. *Background. The frequency of B19 infection in renal transplant donors and recipients was studied to determine the significance of active viral infection in the development of anemia.*

Material and Methods. Serum, plasma, and peripheral blood leukocyte samples of 47 renal transplant donors, 38 recipients with anemia (Group 1), and 25 without anemia (Group 2) after renal transplantation were evaluated for the presence of anti-B19 specific antibodies (ELISA) and B19 DNA (nPCR).

Results. Active persistent B19 infection after renal transplantation was detected in 12 of the 38 in the Group 1 (10 had reactivation and 2 primary infection), and none of the recipients in the Group 2 had it. Of the 12 recipients in the Group 1, 10 were seropositive and 2 seronegative before renal transplantation; 10 received the transplants from the seropositive and 2 from seronegative donors. rHuEPO therapy-resistant severe anemia was detected only in the recipients with active B19 infection after renal transplantation in the Group 1 (7/12). The logistic regression analysis revealed a significant relationship between active B19 infection and severe anemia (OR, 0.039; 95% CI, 0.006–0.257; P=0.001).

Conclusions. Active B19 infection was documented only in the anemic recipients and could be associated with the development of severe anemia after renal transplantation. This allows us to recommend concurrent screening for viral DNA in plasma and detection of anti-B19 IgM class antibodies. To find the association between B19 infection and the development of anemia, further investigations are necessary.

Introduction

Human parvovirus B19 (B19) was first discovered by Cossart et al. in the sera of healthy blood donors (1). The virus is ubiquitous, and the course of infection depends on the host's hematological status and immunologic response. A cellular receptor for B19 is globoside (blood group P antigen), which is expressed on erythroid progenitor cells (the site of virus replication), megakaryocytes, tissue cells of the heart, liver, lung, kidney, endothelium, aortic and gastrointestinal smooth muscle, and synovium (2, 3). The distribution of P antigen across tissues may explain the clinical manifestation of viral infection.

B19 encodes 3 major viral proteins: VP1 and VP2, the viral capsid proteins, and NS1, a nonstructural protein (4). The VP proteins contain the domains to which virus-neutralizing antibodies are directed (5). The appearance of antibodies to B19 is associated with the clearance of the virus from bloodstream; however, the high frequency of persistence of B19 DNA in the tissues of healthy persons under the presence of anti-B19 antibodies indicates that complete eradication of the virus from host body has not occurred (6, 7). In immunocompromised patients, such as renal transplant recipients, who are unable to mount a neutralizing antibody response, persistent viral infection may result in the chronic suppression of erythropoiesis with the development of chronic anemia or lead to B19-related recurrent anemia (8–12) and a renal allograft dysfunction; however, a causal relationship has not been definitively established yet (13, 14). The diagnosis of B19 infection is based on clinical data, morphological evaluation of peripheral blood and bone marrow specimens, and detection of specific antiviral antibodies and viral genomic sequences in peripheral blood leukocytes (PBL) and plasma DNA (15, 16).

Chronic anemia is a major problem in renal transplant patients. The treatment of anemic patients with high doses of intravenous immunoglobulin (IVIG) combined with the reduction of immunosuppression may result in the improvement of symptomatic infection (12), but not in B19 eradication (7). The frequency of B19 infection in renal transplant donors and recipients is underestimated due to the lack of routine clinical diagnostics for it,

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and anemia is often ascribed to immunosuppressive drugs.

The aim of our study was to investigate the frequency of B19 infection in renal transplant donors and patients before and after renal transplantation (RT) and to determine the significance of active viral infection in the development of anemia.

Material and Methods

Patients. A total of 47 renal transplant donors and their 63 recipients (29 men and 34 women; mean age, 49 years [SD, 6.7]) were enrolled in this study. The study was retrospective, and only recipients with complete clinical data were included underwent virological examination. The patients received renal transplants from deceased persons at the Transplantation Centre of Pauls Stradins Clinical University Hospital in Riga between January 2000 and December 2003. The mean follow-up was 35 months (SD, 7.8). The patients after RT were divided in 2 groups according to the hemoglobin (Hb) level: the Group 1 included 38 patients with anemia and Group 2 (control) included 25 patients without anemia during 3 months after RT and entire follow-up (Table 1). Anemia (Hb level, <13.5 g/dL for male and <12 g/dL, for women) was defined according to the National Kidney Foundation KDOQI Guidelines (The Clinical Practice Guidelines and Clinical Practice Recommendations for Anaemia in Chronic Kidney Disease, 2006). Moderate anemia was arbitrarily defined as an Hb level of 12–10 g/dL for males and 11–10 g/dL for females, and severe grade anemia, as an Hb level of <10 g/dL for both genders.

Initial immunosuppression in all patients included cyclosporine (CsA), mycophenolate mofetil (MMF), and prednisolone (P), but the patients who were considered to be at moderate and high immunological risk of acute rejection (AR) received also induction with IL-2R monoclonal antibodies (Basiliximab). Maintenance immunosuppression included CsA, MMF, and P. The treatment with oral CsA in microemulsion was initiated before surgery (10 mg/kg per day) to obtain therapeutic CsA blood levels and then was adjusted based on target through levels 150–250 ng/mL during the first 4 weeks and at 150–200 ng/mL thereafter. The CsA level was measured using an AxSym (Abbott) cyclosporine fluorescence polarization immunoassay. The maintenance dosage of orally administered MMF was 1.0–2.0 g per day. Methylprednisolone (MP) was administered at a dosage of 5.0 mg/kg per day on 3 consecutive days from the first day of RT. The administration of oral P was initiated at a dosage of 0.5 mg/kg per day on the first day after operation and reduced gradually to 5.0–10 mg per day. AR episodes were identified based on characteristic clinical features and were confirmed by percutaneous biopsy. The histological features were graded according to the Banff 97 classification. AR episodes were treated with intravenous MP at a dosage of 500 mg/day for 3 days. Steroid-resistant cases were treated with antithymocyte globulin (ATG) at a dosage of 4 mg/kg for 7–10 days. A delayed graft function was estimated based on serum creatinine concentration (>0.2 mmol/L).

The serum, PBL, and cell-free plasma samples were taken from the donors and all patients before and after RT. The EDTA-anti-coagulated peripheral blood, serum, and plasma samples were stored at –70°C.

This retrospective study was performed with the permission of Local Ethics Committee, and all the participants gave informed consent before the examination.

Detection of B19 Genomic Sequences by Nested Polymerase Chain Reaction. B19 DNA analysis was carried out in the samples from PBL to detect persistent viral infection and cell-free plasma to detect plasma viremia (PV). Total DNA was purified by proteinase K digestion overnight and extraction by a standard phenol-chloroform technique. To assure the quality of PBL DNA and to exclude a possible contamination of plasma by cellular DNA, a β-globin gene polymerase chain reaction was carried out. B19 genomic DNA was detected by a nested polymerase chain reaction (nPCR) assay that amplified the VP1 region as described before (10). PCR amplification was performed in the presence of 1 μg of PBL DNA and 10 μL of plasma DNA (corresponding to 100 μL of plasma). B19-negative DNA was used as a negative control, and DNA from the viremic serum (kindly provided by Prof. K. Hedman, Hartman Institute, Department of Virology, University of Helsinki) was used as a positive control. Water controls were included after every third sample in each experiment.

Detection of B19 anti-VP2 Specific Antibodies. Serum samples of donors as well as pre- and post-transplants from the patients were tested for B19-specific IgG and IgM class antibodies using a sandwich enzyme immunosorbent assay (ELISA) with a purified virus recombinant VP2 protein according to the manufacturer's protocol (Biotrin Ltd, Dublin, Ireland).

Negative B19 infection was defined as the absence of B19-specific markers; past infection, as the presence of IgG class specific antibodies only (IgG+) (although in some cases, latent persistent infection could not be excluded); latent persistent infection, as the presence of IgG class antibodies and viral genomic sequences in PBL DNA (IgG+ IgM– PBL+); active persistent infection (virus reactivation), as the presence of IgM and IgG class antibodies and viral sequences in PBL DNA and/or

plasma DNA (IgM+ IgG+ PV+, IgM+ IgG+ PBL+, IgM+ IgG+ PBL+ PV+, IgG+ PV+, and IgG+ PV+ PBL+); and primary (acute) infection, as the presence of anti-B19 specific IgM class antibodies with or without IgG class antibodies and/or viral genomic sequences in plasma DNA (IgM+ IgG– PV–, IgM+ PV+, IgM+ IgG+ PV–, IgM+ IgG+ PV+).

Statistical Analysis. Statistical differences in the prevalence of past infection, latent- and active persistent B19 infection before and after RT were assessed by using the MedCalc software for Windows, version 12.2.1, and the Fisher exact test. The logistic regression analysis was performed using the SPSS 16.0 for Windows software to assess the relationship between past infection, latent and active persistent B19 infection, and moderate and severe anemia after RT. A P value of <0.05 was considered statistically significant.

Results

Clinical Presentation. The mean Hb level in the Groups 1 and 2 after RT was 10.03 g/dL (SD, 0.29) and 14.81 g/dL (SD, 1.93), respectively. Chronic persistent anemia and recurrent anemia were detected in 81.6% and 18.4% of recipients, respectively, from the Group 1 (Table 1). The duration of recurrent anemia ranged from 3 to 12 months after RT. All the recipients with anemia received intravenous human recombinant erythropoietin (rHuEPO) therapy (12 000 units once weekly). In the Group 1, 81.6% of recipients had moderate anemia (Hb level, 10.7 g/dL [SD, 1.67]) and 18.4% had severe posttransplant anemia (Hb level, 8.8 g/dL [SD, 1.12]). The recipients with severe anemia received rHuEPO therapy (mean dosage, 6000 IU per week subcutaneously) during a mean duration of 11.2 months (SD, 2.4) after RT. rHuEPO therapy failed to raise the Hb level in 1 recipient, while in 6 recipients, a short-term (within 1–2 months) positive effect was observed.

Table 1. Characteristics of the Study Population After Renal Transplantation

Characteristic	Group 1 (n=38)	Group 2 (n=25)
Anemia	38 (100)	0 (0)
Chronic persistent	31 (81.6)	0 (0)
Recurrent	7 (18.4)	0 (0)
3–6 months	4 (57.1)	0 (0)
6–9 months	2 (28.6)	0 (0)
9–12 months	1 (14.3)	0 (0)
Moderate anemia	31 (81.6)	0 (0)
Severe anemia	7 (18.4)	0 (0)
Induction therapy		
Basiliximab	23 (60.5)	21 (84)
Antithymocyte globulin	6 (15.8)	2 (8)
Biopsy-proven acute rejection	8 (21.1)	2 (8)
Chronic allograft dysfunction	13 (34.2)	4 (16)
6–12 months	3 (23.1)	1 (25)
12–24 months	7 (53.8)	1 (25)
>24 months	3 (23.1)	2 (50)
Transplant loss	5 (38.5)	0 (0)

Values are number (percentage).

There were no significant differences in the percentages of patients receiving the induction therapy with basiliximab or ATG comparing both the groups (P=0.054 and P=0.372, respectively) (Table 1). No significant difference was also detected in the frequency of biopsy-proven AR between patients in the Groups 1 and 2 (P=0.181) (Table 1). Chronic allograft dysfunction after RT was observed in 34.2% of recipients in the Group 1 and 16% of recipients in the Group 2 (P=0.119) (Table 1). Five recipients with anemia and chronic allograft dysfunction in the Group 1 lost allograft and were given chronic dialysis therapy again. None of the recipients with chronic allograft dysfunction in the Group 2 lost allograft (Table 1).

None of the recipients underwent bone marrow biopsy. The causes of anemia after RT, such as gastrointestinal bleeding, iron/vitamin B12 deficiency, hemolysis, and drug toxicity, were ruled out.

Prevalence of B19 Infection in Renal Transplant Donors. Serological and virological testing revealed that 83.0% of renal transplant donors had B19 infection: 68.1% had past infection, 10.6% had latent persistent infection, and 4.3% had active persistent infection. Of the 47 donors, no B19 infection was documented in 17.0% (Table 2).

Prevalence of B19 Infection in Patients Before Renal Transplantation. B19 infection before RT was detected in 55 (87.3%) of the 63 patients (Table 2). Past infection was documented in 28 of the 38 patients in the Group 1; latent persistent infection, in 4; active persistent infection, in 2; and no B19 infection was detected in 4 patients (Table 2). In the Group 2, of the 25 patients, 20 had past B19 infection, 1 patient had latent persistent infection, and none had active viral infection. No significant difference in the frequency of past infection and latent persistent infection between the Group 1 and the Group 2 was found (P=0.566 and P=0.367, respectively) (Table 2). Four patients of each group had no markers of B19 infection (P=0.526).

Of the 28 patients with past B19 infection before RT in the Group 1, 25 received allograft from the donors with past infection; 1 patient, from the donor with active persistent infection (IgM+ IgG+ PBL+); and 2 patients, from the donor without B19 infection (Table 2). All 4 patients with latent persistent infection received transplants from the donors with latent persistent infection. Two patients with active persistent infection (IgM+ IgG+ PV+) received transplants from the donors with latent persistent infection. Of the 4 patients without markers of B19 infection before RT, 1 received the transplant from the donor with active persistent viral infection, 1 from the donor with latent persistent

Table 2. Detection of B19 Infection in the Transplant Donors and Recipients Before and After Renal Transplantation

Group/Allograft	B19 Infection				
	Past Infection	Persistent Infection		Primary	Negative
		Latent	Active		
Donors (n=47)					
Donors	32 (68.1%)	5 (10.6%)	2 (4.3%)	0 (0%)	8 (17%)
Group 1 (n=38)					
Before RT	28 (73.7%)	4 (10.5%)	1 (2.6%)	1 (2.6%)	4 (10.5%)
Allograft	D+/R+ (26/28) D–/R+ (2/28)	D+/R+ (4/4)	D+/R+ (1/1)	D+/R+ (1/1)	D+/ R– (2/4) D–/R– (2/4)
After RT	20 (52.6%)	4 (10.5%)	10 (26.3%)	2 (5.3%)	2 (5.3%)
Group 2 (n=25)					
Before RT	20 (80%)	1 (4%)	0 (0%)	0 (0%)	4 (16%)
Allograft	D+/R+ (19/20, 95%) D–/R+ (1/20, 5%)	D–/R+ (1/1)	0 (0%)	0 (0%)	D–/R– (4/4)
After RT	20 (80%)	1 (4%)	0 (0%)	0 (0%)	4 (12%)

RT, renal transplantation.

infection, and 2 patients from the donors without B19 infection.

In the Group 2, of the 20 recipients with past infection before RT, 19 received transplants from the donors with past infection, and 1 from the donor without B19 infection; the only patient with latent persistent infection received the transplant from the B19 infection-negative donor. Four patients without B19 infection received transplants from B19 infection-negative donors (Table 2).

Frequency of Active B19 Infection in Recipients After Transplantation. Active B19 infection after RT was detected only in the recipients in the Group 1, and its frequency was significantly higher than before RT (31.6% and 5.3%, respectively; P=0.009) (Table 2). Primary B19 infection after RT was detected in 2 recipients, and active persistent infection (reactivation) was documented in 10 recipients. The characteristics of these 12 recipients and their donors are present in Table 3. In 2 recipients negative for B19 infection before RT (recipients 3 and 4), who received transplants from the donors with B19 infection, viral genomic sequence in plasma DNA and IgM class antibodies associated with primary viral infection were detected. All 10 recipients with active persistent B19 infection (reactivation) after RT had viral infection before RT (6 had past infection, 2 had latent persistent infection, and 2 persistent plasma viremia before and after RT), and 8 of them received transplants from the donors with B19 infection (Table 3). A possibility reinfection cannot be excluded in the recipient 5 with past infection before RT who received an allograft from the donor with active persistent B19 infection (Table 3). None

Table 3. Characteristics of Recipients With Active B19 Infection Before and After Renal Transplantation

Patient No.	Markers of B19 Infection												Hb, mean (SD), g/dL	AR	Transplant Dysfunction	Transplant Loss
	Transplant Donors				Patients Before RT				Patients After RT							
	Antibodies		Viral DNA		Antibodies		Viral DNA		Antibodies		Viral DNA					
	IgG	IgM	PBL	PL	IgG	IgM	PBL	PL	IgG	IgM	PBL	PL				
1	+	–	+	–	–	+	–	+	–	+	–	+	10.1 (0.34)	–	+	+
2	+	–	+	–	+	+	–	+	+	+	–	+	11.0 (1.01)	–	+	–
3	–	+	+	–	–	–	–	–	–	+	–	+	7.4 (1.61)	+	+	–
4	+	–	+	–	–	–	–	–	–	+	–	+	8.1 (0.24)	+	+	+
5	+	+	+	–	+	–	–	–	+	+	–	+	6.9 (1.69)	+	+	–
6	+	–	–	–	+	–	+	–	+	+	–	–	11.2 (0.12)	–	–	–
7	+	–	–	–	+	–	–	–	+	+	+	–	10.6 (1.39)	–	–	–
8	+	–	–	–	+	–	–	–	+	+	+	+	9.1 (2.04)	–	+	–
9	+	–	–	–	+	–	+	–	+	+	–	+	7.3 (2.15)	+	+	+
10	+	–	–	–	+	–	–	–	+	+	+	–	10.6 (1.13)	–	–	–
11	–	–	–	–	+	–	–	–	+	+	–	+	7.4 (0.24)	+	+	–
12	–	–	–	–	+	–	–	–	+	+	–	+	9.7 (1.31)	–	–	–

PBL, peripheral blood leukocytes; PL, blood plasma; AR, acute rejection; RT, renal transplantation; +, positive results; –, negative results.

of the 25 recipients in the Group 2 had active viral infection (Table 2).

Of the 13 recipients with delayed graft function in the Group 1, active B19 infection was observed in 8 recipients; 3 of them lost the allograft and were given chronic dialysis therapy again (Tables 1 and 3); however, the immunohistochemical analysis of transplants is required to confirm a relationship between B19 infection and chronic transplant dysfunction.

B19 Infection and Anemia of Different Grade. Moderate anemia after RT was documented in 31 of the 38 recipients. A total of 22 recipients had past infection, 2 had latent persistent infection, 5 had active persistent infection, and 2 recipients did not have any markers of B19 infection. The logistic regression analysis revealed no significant associations between past infection, latent persistent infection, and active persistent infection and moderate anemia.

rHuEPO therapy-resistant severe anemia after RT was observed in 7 of the 12 recipients with active B19 infection. Primary viral infection and active persistent infection was diagnosed in 2 and 5 of the 7 recipients, respectively. The logistic regression analysis revealed a significant relationship between active B19 infection and severe anemia (OR, 0.039; 95% CI, 0.006–0.257; P=0.001).

Discussion

Chronic anemia is one of the clinical manifestations of B19 infection in immunosuppressed individuals. The presence of anemia after renal transplantation is well-known; however, specific data on frequency and risk factors are scarce. The prevalence of B19 infection is difficult to estimate since the majority of reports are case reports rather than carefully monitored cohort studies. Furthermore, the interpretation of published data is difficult due to the selection of different criteria, different definitions of latent, persistent, and active infection, and various lengths of follow-up period.

The obtained results demonstrate that B19 seroprevalence in renal transplant donors and patients (83% and 84.1%, respectively) is similar to that in the overall population (40%–80%) (17, 18). The presence of IgG, but not IgM class, specific antibodies most likely represents past infection, although possibly latent persistent B19 infection in these individuals could not be excluded. The observation of B19 reactivation in 2 IgG-positive patients before RT who received the transplants from the virus-negative donors indicates that they had latent persistent B19 infection before RT despite the lack of a virus-specific sequence in PBL DNA.

Active persistent B19 infection was detected in 2 of the 47 donors and 1 of the 38 anemic patients before RT, but its significantly higher frequency was documented in the anemic patients after RT (12/38). The lack of IgG class antibodies in 3 of the 12 IgM-positive patients allows suggesting that they were functionally deficient or their quantity is insufficient for virus neutralization. One patient with the transplant dysfunction had active persistent infection during the overall follow-up period after RT despite the presence of IgG class antibodies that also could be due to the functional deficiency of these antibodies or their insufficient quantity for virus neutralization. Another patient with the transplant dysfunction accompanied by transplant loss had no IgG class antibodies and most likely had active persistent infection, since the presence of IgM class antibodies and plasma viremia were documented during the overall follow-up period after RT. However, the deregulation of the humoral immunity could not be excluded as well. These suggestions are consistent with the findings of other investigations (13, 19, 20).

In our study, severe anemia was diagnosed in 9 of the 38 recipients after RT who failed to respond to the repeated rHuEPO administration, and 7 of them had active persistent B19 infection. Similarly Egbuna et al. (21) have shown the presence of active B19 infection in 38% of recipients with erythropoietin-resistant severe anemia.

The detection of primary B19 infection in 2 recipients without the markers of B19 infection before RT, who received the transplants from the donors with latent persistent viral infection, shows a possible transmission of the virus via transplant, which could be a virus persistency site. Yango et al. reported donor-transmitted B19 infection in a renal transplant recipient (22).

In our study, active B19 infection was documented in 8 of the 17 recipients with chronic allograft dysfunction. These results are in accordance with those of Cavallo et al. (10), who reported that 36% of patients with active B19 infection had an elevated serum creatinine level after RT. In contrast, Ki et al. (23) did not find any relationship between allograft dysfunction and B19 infection.

Conclusions

Active B19 infection was documented only in the anemic recipients and could be associated with the development of severe anemia after renal transplantation. This allows us to recommend concurrent screening for viral DNA in plasma and detection of anti-B19 IgM class antibodies. To find the association between B19 infection and the development of anemia, further investigations are necessary.

Statement of Conflict of Interest

The authors state no conflict of interest.

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