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Pure Red Cell Aplasia After Kidney Transplantation: Parvovirus B19 Culprit or Coincidence?

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Background: Anemia is present even in long-term observation after kidney transplantation. Observational study results indicate the presence of chronic post-transplantation anemia in 1 in 3 recipients. An extreme form of erythroid line dysfunction is pure red cell aplasia (PRCA). It may be caused by immunosuppressive treatment *per se* or a side effect, opportunistic pathogen activation. Parvovirus B19 (PV B19) infection is quite likely the cause of refractory normocytic anemia in immunocompromised patients.

Case Report: In this case report we discuss biological and clinical features of this phenomenon and the treatment strategies, based on 2 PRCA cases in kidney transplant recipients. Additionally, a systematic review of published reports of PV B19 related PRCA in kidney recipients is presented.

Conclusions: PV replication should be ruled out in cases of persistent and/or refractory anemia after kidney transplantation. The established first-line treatment of PRCA is passive immunization. Taking into account cost effectiveness, a decrease in immunosuppression load is reasonable under careful control of allograft function.

MeSH Keywords: **Kidney Transplantation • Parvovirus B19, Human • Red-Cell Aplasia, Pure**

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Background

Pure red blood cell aplasia (PRCA) is characterized by inhibition of erythropoiesis with normal megakaryopoiesis and myelopoiesis. It causes refractory normocytic anemia with a low reticulocyte percentage. Anemia is often present in patients with chronic kidney disease and is a frequent symptom in the early period after kidney transplantation [1,2]. One of the predisposing factors for anemia after kidney transplantation is immunosuppression regimens. Every drug used after transplantation except steroids can potentially inhibit physiological bone marrow function. Nowadays, there are no feasible routine methods to monitor the individually required dose of immunosuppression agents. On the other hand, the inhibition of a recipient's humoral response provides an ideal environment for the activation of opportunistic pathogens. Patients after solid organ transplantation are at an increased risk of developing clinical signs of infection with different opportunistic viral pathogens: cytomegalovirus (CMV), parvovirus B19 (PV B19), human polyoma virus (BKV), human herpes virus 6 (HHV-6), and Epstein-Barr virus (EBV). These viruses may coexist with one another.

Biological feature

The pathogen inducing PRCA is human PV B19, which belongs to the genus Erythroparvovirus of the Parvoviridae family. PV B19 is the only PV that has been confirmed to be pathogenic to humans. It is a non-enveloped virus. Its single DNA strand reproduces 5 proteins: 2 capsid proteins (VP1 and VP2), the non-structural protein 1 (NS-1) and 2 small non-structural proteins of 7.5 and 11 kDa. Proteins produced by the virus cause significant changes in the cell cycle of erythroid progenitor cell (EPC) lines [3].

Role of NS-1 protein

NS-1 is a multifunctional protein: it regulates the activity of the viral protein p6 and the replication of the viral DNA, among other functions. At the same time, it inhibits the cell cycle in the G1 and G2 phases and initiates apoptosis in erythroid cell lines. It is also a transcription activator for various cellular and viral genes. In experimental models the order of events in which an NS-1 particle affects the regulation of the cell cycle has been determined [4].

It does so through an interaction between the PV B19 NS-1 protein and the E2F4 or E2F5 transcription factor. These proteins belong to the E2F family, which is composed of 8 proteins. Their role is to regulate the progress of the cell cycle, DNA replication, repair, and apoptosis. These proteins repress phase G0/G1 of the cell cycle. The virus causes these particles to shift from cytoplasm to the cellular nucleus, inducing

a permanent inhibition of phase G2. This maneuver compromises erythroid cell differentiation. At the same time, the virus activates transcription factors associated with phase G2 and DNA-repairing proteins, which increases viral transcription and replication [5]. Dysregulation of the remaining proteins from the E2F family, primarily E2F7 and E2F8, is also conducive to an increased replication of the virus, while effectively inhibiting host cell differentiation [6]. In experimental models in which caspase-3, caspase-6, and caspase-8 inhibitors were used, the process of apoptosis induction by the NS-1 particle was effectively inhibited [7].

Role of 11-kDa protein

Based on *in vitro* culture observation, the 11-kDa protein is considered to induce apoptosis in EPC cells. It was demonstrated that this protein has a 100 times higher expression in the cytoplasm of infected cells than the NS-1 particle. The set of factors accelerating the programmed death of EPC also includes the small 7.5 kDa particle [8]. The metabolic pathways which increase apoptosis are the subject of research.

Tropism of PV B19 to erythroid cells

The mechanisms causing the tropism of the virus towards human erythroid cells have not been determined yet. It is well established that erythropoietin (Epo) is indispensable for normal erythrocyte synthesis [9]. However, Epo is indicated as one of the factors required for the creation of an appropriate micro-environment for the development of the virus in EPC lines. It has been demonstrated that the signal sent by an activated Epo/Epo receptor (EpoR) complex activates 3 kinase lines via Janus kinase 2 (Jak2): Signal transducer and activator of transcription 5A (STAT5A), extracellular signal-regulated kinases/mitogen-activated protein kinase (ERK/MAPK) and phosphatidylinositol 3-kinase (PI3K). Activated/phosphorylated STAT5 is the primary factor promoting erythropoiesis and ERK is important for the proliferation and survival of progenitor cells. Kinase coordination affects the EPC differentiation and proliferation pathway. Under experimental conditions, it has been demonstrated that STAT5 phosphorylation is critical to the creation of favorable conditions for PV B19 infection of EPC. In addition, a state of cellular hypoxia causes STAT5 phosphorylation to increase and ERK activity to decrease, which creates optimal conditions for viral replication [10–12].

By way of conclusion, it is worth mentioning that the search for effective methods of evaluating the level of immunosuppression focuses on the monitoring of intracellular signaling pathways. The determination of the phosphorylation level of signaling proteins in lymphocytes, such as nuclear factor of activated T-cells (NFAT), p38MAPK, extracellular signal-regulated

Table 1. Descriptive data of PRCA clinical course in presented kidney transplant recipients.

	Case 1	Case 2
Gender	Women	Men
Age	34	30
CKD aetiology	GN*	GN
PRA**	26%	0%
Mismatch	3	3
No KTx	2	1
Basic IS***	TAC/MMF/Cs	TAC/MMF/Cs
Actual IS	TAC/AZA/Cs	CsA/Cs
Time to first symptoms (months)	4	2
Time to recovery (months)	10	7
Time to post KTx current	120	30
Transfusions	12 units	6 units
PV B19 PCR	Positive	Negative
Parameters 1 month post Tx	Cr 1.0 mg/dl, HgB 12.0 g/dl	Cr 1.16 mg/dl, HgB 11.6 g/dl
Parameters et clinical manifestation	#Cr 1.2 mg/dl, ##HgB 7.2 g/dl	Cr 1.5 mg/dl, HgB 7.8 g/dl
Parameters et peak	Cr 2.0 mg/dl, HgB 4.9 g/dl	Cr 1.54 mg/dl, HgB 5.6 g/dl
Parameters et present	Cr 1.2 mg/dl, HgB 12.5 g/dl	Cr 1.2 mg/dl, HgB 8.3 g/dl

* GN – glomerulonephritis; ** PRA – panel reactive antibodies; *** Basic IS – primary immunosuppression regimen; # Cr – creatinine; ## Hgb – hemoglobin. TAC – tacrolimus; CsA – cyclosporin A; MMF – mycophenolate mofetil; Cs – corticosteroids; AZA – azathioprine.

kinases 1, and 2 (ERK1/2), among others, is the proposed direction in immunosuppression effect monitoring [13].

Clinical feature

Kidney transplant recipients are at an increased risk of developing clinical disease due to PV B19. The lack of full knowledge of PV B19 biology and cellular effects determines the manner of diagnosis and treatment of the clinical symptoms of PV B19 infection. Observations from experimental studies provide evidence for a commonly observed clinical fact, which is the lack of an adequate response of bone marrow to Epo administration. The probable mechanism of the lack of sufficient response to treatment may be associated with a high level of viral replication due to the EpoR signaling pathway. A decrease in the number of erythrocytes with consequence, which is cellular hypoxia, promotes PV B19 replication.

The first case of PV B19 infection in a patient after kidney transplantation was described in 1986 [14]. The virus causes hematological disorders such as severe refractory anemia, pancytopenia, and thrombotic microangiopathy. However, recent sources have indicated that PV B19 also infects non-erythroid lineage cells such as myocardial endothelial cells and liver tissue. Clinical scenarios for PV B19 infection range from asymptomatic to life-threatening multi-organ failure [15].

Table 2. Criteria for erythroid line cells to fulfill pure red cells aplasia diagnosis.

Peripheral blood	Bone marrow
Normocytic anemia	Erythroblasts <5%
Reticulocytes <0.1%	Giant pro-normoerythroblasts
	Normal megakariopoiesis
	Normal myelopoiesis

The diagnosis of the infection is based on positive PV B19 DNA polymerase chain reaction (PCR). The presence of specific IgM B19 class antibodies is less important in patients on immunosuppressive therapy.

In immunocompromised patients, the sensitivity of the serological method may be decreased due to impaired humoral response. In those patients, B19V PCR screening is recommended [16–18]. Refractory normocytic anemia with a low reticulocyte count resistant to Epo treatment is characteristic of PRCA. The diagnosis is confirmed by inhibited erythropoiesis and typical giant pro-erythroblasts with nuclear viral inclusions in bone marrow biopsy [19] (Table 1). In the 2 clinical pictures of PRCA in kidney transplant recipients, one shows PV B19 replication (Table 2).

Case Reports

Case 1

A 34-year-old female with chronic kidney disease due to chronic glomerulonephritis of unknown origin after her second kidney transplantation from a deceased donor in August 2008. Induction was not used. The function of the kidney graft was immediate. Creatinine concentration 1 month after surgery was 1.0 mg/dL, tacrolimus 15.3 ng/dL, and hemoglobin 12 g/dL. Four months after the transplantation, hemoglobin concentration decreased to 7.2 g/dL without symptoms of active bleeding. In the first management step, MMF (mycophenolate mofetil) dose was reduced to 1 g/24 hour. In the next 4 weeks, a further decrease in the hemoglobin level was observed (6.6 g/dL) with a deterioration of the kidney graft function and an increased creatinine level to 1.7 mg/dL. Persistent concomitant lower urinary tract infections were present at that time. Despite MMF withdrawal and Epo stimulating agent (ESA) supplementation in the next 4 months, no improvement was found. Due to clinical symptoms of anemia, the patient had to receive several blood transfusions. In April 2009, a bone marrow biopsy was performed because of refractory normocytic anemia. Bone marrow smears showed low reticulocyte percentage, inhibited erythropoiesis, and typical giant pro-erythroblasts with nuclear viral inclusions. Antibodies against epoetin were negative. PV B19 DNA PCR from whole blood was positive (10^5 copies). The bone marrow was not tested for viral replication. In the immunosuppression regimen a switch from tacrolimus to cyclosporine A was made. Normalization of red blood cell morphological parameters was achieved 4 months after conversion. Consecutive tests in blood for PV B19 replication within the next six months were negative.

Case 2

A 30-year-old patient with chronic kidney disease due to chronic glomerulonephritis of unknown origin received a kidney from a living donor (patient's father aged 55 years) in November 2015. Induction was not used. Triple immunosuppression regimen applied consisted of TAC/MMF/Cs. The function of the kidney graft was immediate. Allograft function 1 month after surgery was good, laboratory results showed creatinine 1.16 mg/dL, tacrolimus 17.5 ng/dL, and hemoglobin 11.8 g/dL. Two months after the transplantation the patient's hemoglobin concentration decreased to 7.8 g/dL without any bleeding symptoms and creatinine increased to 1.5 mg/dL. Signs of acute kidney graft rejection were excluded on biopsy. In the first management step, MMF dose was reduced. In the next 4 weeks, a further decrease in the hemoglobin level was noticed. The MMF dose was further decreased. Five months after kidney transplantation, there was no improvement in blood morphology parameters. A bone marrow biopsy was performed.

Histopathological examination confirmed the diagnosis of PRCA. Nucleic acid test for PV B19 in bone marrow was not performed. In terms of treatment, MMF was switched to everolimus, and pulses of methylprednisolone (total 1.5 g IV) were scheduled. Six months after kidney transplantation, the patient's creatinine concentration was 0.9 mg/dL with persistent hemoglobin concentration below 8 g/dL. Clinical symptoms of anemia were present, and transfusions were necessary. After another 2 months without improvement in the hemoglobin level, conversion from tacrolimus to cyclosporine A was made. As part of additional treatment, passive immunization with immunoglobulin (IVIG) was introduced. The patient received the dose of 30 g IV once a month for the next 3 months. Red blood cell parameters on blood count test were stable at the time (hemoglobin concentration 9.9–11.2 g/dL). Thirteen months after kidney transplantation there was a recurrence of anemia (hemoglobin concentration 8.3 g/dL). The concentration of everolimus in the blood was 6.4 ng/mL, cyclosporine A was 92.6 ng/mL, and creatinine was 1.32 mg/dL. Screening for opportunistic viral infections was negative in peripheral blood (CMV, BKV, and PV B19). The patient received another dose of IVIG of 30 g IV and everolimus was withdrawn. The immunosuppression regimen since that time has contained cyclosporine A and steroids. Normalization of blood morphology appeared after 2 months with no recurrence of anemia for at least 1.5 years and without deterioration of kidney graft function.

Discussion

Porignaux et al. examined 60 adult patients less than a year before and after kidney transplantation. Tests for PV B19 and other opportunistic viral infections were performed in plasma samples every 15 days during the first 3 months and every month from 4 to 12 months post kidney transplantation. The results rank PV B19 as one of the most prevalent opportunistic viral infections occurring during the first year (10% of patients), right behind CMV (13.3%) and EBV (11.7%) [20,21]. The clinical symptoms would be an effect of reactivation, reinfection, or primary infection. Capenko et al. studied the frequency of PV B19 infection in kidney transplant donors and recipients and determined the significance of an active viral infection in the occurrence of post-transplantation anemia. A group of kidney transplant donors, recipients with anemia (group 1) and without anemia (group 2) were evaluated for the presence of anti-B19V-specific antibodies (enzyme-linked immunosorbent assay) and PV B19 DNA (PCR) before and after transplantation. Active persistent B19V infection was detected in 12 patients from group 1 (10 patients had reactivation and 2 patients had primary infection) and none in group 2. Among those 12 recipients, 10 recipients received the transplants from seropositive donors and 2 recipients received transplants from seronegative donors. Logistic regression analysis revealed

a significant relationship between active B19V infection and severe anemia [22]. There was no evaluation of bone marrow aspirates or PRCA in this study. The role of donors' seropositivity still needs further investigation.

Xiao et al. investigated the incidence of B19V infection and risk of anemia and allograft damage in 114 patients at 1–18 months after kidney transplantation. The infection was diagnosed in 18.75% of recipients, which was a significantly higher rate compared to healthy controls. The infected versus non-infected patients presented a significantly higher incidence of anemia, urinary tract abnormalities, and lower eGFR (estimated glomerular filtration rate). There were 2 cases of PRCA confirmed by bone marrow biopsy with the deterioration of kidney graft function due to segmental mesangial cell proliferation in the transplanted kidney histology [23].

The identification of factors related to positive PV B19 PCR results may promote early detection of infection. Boeak et al. indicated deceased donor kidney transplantation, tacrolimus treatment, and decreased hemoglobin concentration as factors correlating significantly in multivariate analysis with PV B19 infection within the first-year after kidney transplantation [24]. Approximately 50 cases of PV B19 related PRCA in adult kidney recipients have been described in the literature to date [18,23,25–63], (see Table 3). PRCA was diagnosed from 4 days to 160 weeks after kidney transplantation, usually within the first year [25,59]. The standard protocol for immunosuppression nowadays consisting of tacrolimus and mycophenolate mofetil/sodium (MMF/MPA) and routine use of biological and fusion molecules (ATG, IL-2RI, belatacept) may contribute to an increase in the frequency of PV B19 active infections. The first case of PRCA after kidney transplantation was reported by Suzuki et al. in 1996 [26]. The authors postulated that tacrolimus as a factor causing deterioration in bone marrow function. PV B19 PCR was not tested, but after conversion of treatment from tacrolimus to cyclosporine A, recovery of erythropoiesis was observed. In the descriptions of pediatric cases after liver transplantation, tacrolimus was also pointed out as a reason for PRCA. Engelen et al. indicated MMF as a factor contributing to PV B19 infection (4 cases) [27]. Geetha et al. noticed positive effects by 7 MMF/MPA discontinuation on PRCA treatment [28]. However, in a report on the first case of PRCA in Mexico, MMF discontinuation did not bring any clinical improvement [29]. Similarly, in the 2 cases presented in this report, withdrawal of MMF did not affect the course of the disease.

Upon review of the literature, the established first-line management of PRCA seems to be passive immunization. Due to the case-by-case nature of the available data, no consensus exists about the dose and intervals between immunoglobulin administrations.

In a clinical review of the treatment of PRCA of various origins, the suggested effective dose of IVIG was 2 g/kg/session. The number of globulin administrations was dependent on the clinical course of the disease and viral activity: 3–4 sessions were most commonly used [30]. In case-by-case reports, the IVIG dose in kidney recipients was established at 0.4 g/kg/session. Immunoglobulins administration seems to be a rational direction for symptomatic treatment in terms of pathophysiology. However, it is important to note the results of an economic analysis of the aforementioned cited observation, which showed that in 70% of cases the use of IVIG did not meet the criteria for considering PV B19 as the cause of PRCA [31]. In the 2 cases presented in this article both patients were converted from tacrolimus to cyclosporine A. In the first case, this maneuver was enough to recover the function of erythroid line. In the second case, 4 doses of IVIG (0.4 g/kg/session) were additionally given, which resulted in complete remission.

The reduction of the immunosuppression dose is as a second-line treatment variant. Lower immunosuppression regiment had been realized mostly by a decreased dose of the antimetabolite drug, with reluctant effect. In the minority of reviewed cases, the switch from tacrolimus to cyclosporine A was reported. All of the patients (6 cases) after conversion reported a successful recovery. The decrease of immunosuppression dose seems to be quite easy and effective, nevertheless it has the drawback of a higher risk of acute rejection in the context of early onset of the disease after transplantation. The general recommendation, one can surmise from published PRCA in kidney transplantation cases, is that modalities of PRCA treatment depend on the severity of clinical symptoms of impaired bone marrow function.

In our first case, there was a clearance of virus in follow-up PCR evaluation and normal bone marrow function after 16 weeks. In the second case, we observed 1 episode of recurrence of anemia without viral replication. Normalization of red blood cell parameters occurred 8 weeks after the initiation of a step down in immunosuppression protocol with a stable function to date. If we assume the lack of viral DNA replication to be the criterion for treatment efficacy, it has been reported to occur at various points in time, from 2 weeks to 20 weeks following therapeutic intervention [32,33]. A return of normal erythropoiesis was usually observed 2–4 weeks from the start of treatment. Published data shows that PV B19-related anemia may recur despite this treatment. PV B19 DNA may also remain positive despite the resolution of the symptoms of anemia. Gosset et al. described 2 cases of kidney recipients with PB19V infection with 9 and 7 B19V-related anemia recurrences, respectively. These patients were given IVIG as secondary prophylaxis every 3 months [34].

Table 3. PV B19-related pure red cell aplasia in adult kidney transplant recipients. Order by year of transplantation, if not given by year of publication. Search performed by PubMed website [18,23,25,38–60].

Case no.	Age	Gender	IS	Treatment	Onset (weeks)	References
1990–2000						
1	34	M	nd	IVIg	nd	25
2	62	M	TAC	IVIg	56	18
3	47	F	CsA/Cs	IVIg	2	38
4	48	M	ATG/CsA/Cs	IVIg	2	39
5	57	F	ATG/Tac/AZA/Cs	IVIg/ESA	24	40
6	62	M	CsA/AZA/Cs	IVIg	6	41
7	38	M	CsA/AZA/CS	IVIg	4	41
8	43	F	ATG/Tac/MMF/Cs	IVIg	4	41
9	37	M	TAC/MMF/Cs	IVIg	4	42
10	61	M	ATG/TAC/AZA/Cs	IVIg	4	43
11	26	F	TAC/AZA/Cs	IVIg/S	3	44
12	46	M	TAC/MMF/Cs	IVIg	40	45
13	40	F	TAC/MMF/Cs	IVIg	4	45
14	43	F	ATG/Tac/MMF/Cs	DEC/IVIg	52	25
15	21	M	nd	IVIg	6	25
16	39	M	CsA/MMF/Cs	IVIg	2	46
2001–2018						
17	39	F	nd	DEC/IVIg	6	25
18	26	M	nd	IVIg/DEC	5	25
19	40	M	TAC/AZA/Cs	IVIg/S	16	47
20	39	M	TAC/AZA/Cs	IVIg/DEC	6	48
21	50	F	Tac/MMF/Cs	IVIg/DEC/S	4	48
22	65	M	Tac/MMF/Cs	DEC/	5	49
23	39	M	BAS/MMF/SRL/Cs	IVIg/DEC	9	50
24	34	M	TAC/MMF/Cs	IVIg	4	51
25	55	F	nd	DEC/IVIg	4	25
26	49	M	Tac/MMF/Cs	DEC/IVIg	nd	52
27	20	F	TAC/MMF/Cs	S	4	53
28	22	F	CsA/MMF/Cs	S	4	29
29	39	F	TAC/MMF/Cs	DEC/IVIg	40	54
30	28	F	TAC/MMF/Cs	DEC/IVIg	8	55
31	34	F	TAC/MMF/Cs	S	12	Own case
32	30	F	nd	IVIg	4	56

Table 3 continued. PV B19-related pure red cell aplasia in adult kidney transplant recipients. Order by year of transplantation, if not given by year of publication. Search performed by PubMed website [18,23,25,38–60].

Case no.	Age	Gender	IS	Treatment	Onset (weeks)	References
33	42	F	TAC/AZA/Cs	IVIg	158	57
34	30	M	ATG/TAC/MMF/Cs	IVIg	12	29
35	35	M	BAS/TAC/MMF/Cs	DEC/S/IVIg	6	23
36	nd	M	TAC/MMF/Cs	DEC/IVIg	7	23
37	40	F	TAC/MMF/Cs	S	36	59
38	30	M	TAC/MMF/Cs	S	8	59
39	35	F	TAC/MMF/Cs	S	160	59
40	18	M	TAC/MMF/Cs	DEC/IVIg	4	60
41	65	M	TAC/MMF/Cs	IVIg	8	21
42	44	F	BAS/TAC/MMF/Cs	IVIg/DEC	7	61
43	30	M	BAS/TAC/MMF/Cs	IVIg/DEC	11	61
44	58	M	BAS/TAC/MMF/Cs	IVIg/DEC	8	61
45	30	M	TAC/MMF/Cs	DEC/S/IVIg	8	Own case
46	28	F	TAC/MMF/Cs	IVIg	4	62
47	32	M	TAC/MMF/Cs	IVIg	9	62
48	49	M	ATG/CsA/MMF/Cs	IVIg/DEC	8	63

IS – initial immunosuppression regimen; onset – time to clinical symptoms of PV infection; DEC – decreased immunosuppression; IVIg – immunoglobulin; S – switch TAC to CsA.

Conclusions

PRCA may appear during immunosuppressive treatment irrespective of the kind of protocol and the transplanted organ [28–38]. We still do not know the answer for several important clinical questions. Could certain drugs or interactions between drugs be the reason for an increased activity of PV B19? What level of immunological response is sufficient to control the infection after kidney transplantation? In light of studies published by researchers who are monitoring immunosuppression adequacy in patients after kidney transplantation

through the measurement of intracellular cytokine activity, it seems that clinical observation is the current mainstay in everyday practice. A decrease in immunosuppression load is reasonable under careful control of rejection symptoms. Modalities used in immunosuppression regimen in PV B19 related PRCA should depend on the patient's pre-transplantation history.

Conflicts of interest

None.

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