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BRIEF REPORT

Incidence and Impact of Parvovirus B19 Infection in Seronegative Solid Organ Transplant Recipients

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Routine monitoring of parvovirus B19 (B19V) the first 6 months posttransplantation was performed in 241 seronegative solid organ transplant (SOT) recipients. Incidence rates during the first month and the second to sixth months posttransplantation were 1.2 (95% confidence interval [CI], .33–3.2) and 0.21 (95% CI, .06–.57) per 100 recipients per month, respectively. Of the 6 SOT recipients with positive B19V polymerase chain reaction, 3 (50%) were admitted to hospital and 2 (33%) were treated with intravenous immunoglobulin. Thus, routine monitoring of B19V in seronegative SOT recipients may not be necessary. Targeted screening 1 month posttransplantation and screening upon clinical suspicion could be an alternative strategy.

Keywords. organ transplant; parvovirus B19, human; polymerase chain reaction; incidence.

In immunocompromised patients such as in solid organ transplant (SOT) recipients, parvovirus B19 (B19V) may cause persistent infection and pure red cell aplasia [1, 2]. However, fever is the most common clinical sign of B19V infection in SOT recipients, and anemia the most prevalent laboratory finding [3]. Positive anti-B19V immunoglobulin M (IgM), anti-B19V immunoglobulin G (IgG), and B19V polymerase chain reaction (PCR) are found in 75%, 39%, and 87% of SOT recipients who have symptomatic B19V infection, respectively [3]. Symptomatic B19V infection often occurs early posttransplantation. Seronegative SOT recipients who have a seropositive donor (D^+/R^-) are reported to have the highest risk, because of donor-derived infection and no preexisting immunity, whereas B19V-seronegative SOT recipients who have a seronegative donor (D^-/R^-) have the lowest risk [3, 4]. However, most of the knowledge about B19V in SOT recipients is from case reports and retrospective studies on SOT recipients who had persistent anemia [1, 3, 5–7]. Atypical presentation of B19V infection is common in SOT recipients, and B19V is a common cause of anemia; hence, regular monitoring for B19V has been suggested [1].

At present, there is no consensus or recommendation for routine monitoring of B19V-seronegative SOT recipients [1]. In this prospective study, we used a routine monitoring program to investigate virologic evidence of B19V infection in a large cohort of B19V-seronegative SOT recipients during the first 6 months posttransplantation to determine the incidence and clinical impact of B19V infection.

MATERIALS AND METHODS

This prospective cohort included all adult SOT recipients (heart, lung, kidney, liver, and simultaneous kidney-pancreas recipients) who underwent SOT at Copenhagen University Hospital, Rigshospitalet, between 1 January 2011 and 31 December 2017 (Supplementary Figure 1). Rigshospitalet is a highly specialized hospital with a center of knowledge for organ transplantation. All SOT recipients were included in the Management of Posttransplant Infections in Collaborating Hospitals (MATCH), which was launched in 2011 to monitor viral diseases in transplant recipients [8]. B19V-seronegative SOT recipients were included in a screening program consisting of monthly screening with B19V PCR during the first 6 months posttransplantation regardless of donor B19V IgG serostatus. Extra B19V PCRs could be requested upon clinical suspicion of B19V infection. If the PCR was positive, and the patient was treated for B19V infection, follow-up PCRs were requested on weeks 1, 2, 4, 8, 12, and 16 after the first positive PCR. If B19V infection was not suspected and no treatment was given, follow-up PCRs were requested on weeks 1, 2, 3, and 4. There were no planned PCRs after 6 months.

SOT recipients who were B19V seronegative at the time of transplantation were eligible for inclusion in the study. We excluded 30 B19V-seronegative SOT recipients with no B19V PCR in the first 6 months posttransplantation (Supplementary Figure 1).

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Clinical characteristics, serology, and virology data were extracted from the Centre of Excellence for Personalized Medicine of Infectious Complications in Immune Deficiency (PERSIMUNE) data warehouse [9]. Data were prospectively collected as part of the routine care of SOT recipients. Data from several national registries and clinical databases, including the national Danish Microbiology Database (MiBa), integrate into the PERSIMUNE data repository. MiBa contains all microbiological data including PCR and serology results from general practice and hospitals in Denmark since 2010 [10].

The National Committee on Health Research Ethics (H-170024315) and the Data Protection Agency (04433, RH-2016-47) approved the retrieval of the data.

Definitions

As part of the MATCH program [8], donor and recipient B19V serology were routinely performed at the time of transplantation. An unknown baseline serostatus could be due to either an inconclusive result or missing data, including missing data due to emergency transplant procedures.

All PCR data collected during the first 6 months posttransplantation were included. In the case of repeated positive PCRs, the date of the first positive PCR was considered as the target date to find hematologic variables.

B19V infection was defined by viral replication evidenced by at least 1 positive PCR result. Among patients with B19V infection, transient replication was defined as a single detectable viral load <10 000 copies/mL. Anemia was defined as hemoglobin value less than the lower limit of normal—that is, as ≤7.3 mmol/L for women and ≤8.3 mmol/L for men. Leukopenia was defined as a white blood cell count $\leq 3.5 \times 10^9$/L. Thrombocytopenia was defined as a platelet count $\leq 145 \times 10^9$/L. The cutoffs were defined in accordance with the reference intervals at the Department of Clinical Biochemistry, Rigshospitalet. Pancytopenia was defined as simultaneous presence of anemia, leukopenia, and thrombocytopenia.

B19V Serology and B19V PCR

B19V serology and PCR were performed at Department of Clinical Microbiology as part of routine clinical care. Serology was measured using the DiaSorin Liaison XL Biotrin Parvovirus B19 IgG and IgM (DiaSorin, Saluggia, Italy) or the Biotrin Parvovirus enzyme-linked immunosorbent assay IgG and IgM (Biotrin, Dublin, Ireland) assays.

B19V DNA was measured by quantitative real-time PCR in blood using the artus Parvo B19 LC PCR Kit (Qiagen, Hamburg, Germany) or the Parvovirus B19 R-GENE (Argen/bioMérieux, Lyon, France). The lower limit of detection of B19V PCR was 100 copies/mL.

Incidence of B19V Infection

For calculation of incidence rates, SOT recipients were followed from the date of transplantation to the first positive B19V PCR, retransplantation, death, or day 180 posttransplantation, whichever came first. Inclusion stopped on 31 December 2017 to allow 6 months of follow-up for all SOT recipients. Incidence rates were reported for the first month and the second to sixth months posttransplantation.

Statistical Analysis

Categorical data were reported as frequency (percentage), and continuous data were reported as median with interquartile range (IQR). Mann–Whitney *U* test and Fisher exact test were used as appropriate. The incidence rates of B19V infection were calculated as the number of recipients with a first B19V infection per person-months of follow-up. We calculated 95% confidence intervals (CIs) using Byar approximation to the Poisson distribution. Estimates of the cumulative incidence of B19V infection during the first 6 months posttransplantation were calculated using the Aalen–Johansen estimator with death as a competing risk.

In an explorative analysis, we conducted a matched case-control study. SOT recipients with positive B19V PCR were assumed as cases whereas controls were selected from PCR-negative SOT recipients (Supplementary Figure 1). Cases and controls were matched on type of transplantation, and days posttransplantation for the target PCR. We found hematology within ±7 days from the target PCR day and selected the result closest to the day the PCR was conducted. Wilcoxon signed-rank test and the Fisher exact test were used as appropriate.

The MatchIt package was used for the case-control study using the nearest neighbor matching method and 1:5 ratio. R software version 3.5.2 was used for statistical analyses, and a *P* value ≤ .05 was considered statistically significant.

RESULTS

During the study period, 1182 adults were transplanted; 241 (20%) were seronegative and had at least 1 available PCR during the first 6 months posttransplantation and were included in the analyses (Supplementary Figure 1). Clinical characteristics are shown in Table 1.

During 6 months of follow-up, 7 (2.9%) SOT recipients died, and there were no cases of retransplantation. Median follow-up was 173 days (range, 28–180 days) posttransplantation.

Positive PCR Posttransplantation

In total, 1301 B19V PCRs were performed with a median of 6 (IQR, 5–6) PCRs per SOT recipient. Six (2.5%) SOT recipients had at least 1 positive PCR during the first 6 months posttransplantation and were diagnosed with B19V infection, 3 of the 6 (50%) within the first month posttransplantation. Five of 6 (83%) were kidney transplant recipients, and 1 (17%) was a lung transplant recipient. All 6 (100%) had a seropositive donor.

Table 1. Characteristics of Solid Organ Transplantation Recipients Who Were Parvovirus B19 (B19V) Seronegative Prior to Transplantation With at Least 1 Available B19V Polymerase Chain Reaction Result Posttransplantation

Characteristic	At Least 1 Positive B19V PCR Result (n = 6)	No Positive B19V PCR Result (n = 235)	Total (N = 241)	*P* Value
Age, y, median (IQR)	52 (35–55)	51 (39–59)	51 (39–59)	.84
Male sex, No. (%)	4 (67)	130 (55)	134 (56)	.70
Transplanted organ, No. (%)				
Heart	0 (0.0)	19 (8.1)	19 (7.9)	.91
Liver	0 (0.0)	37 (16)	37 (15)	
Lung	1 (17)	40 (17)	41 (17)	
Kidney	5 (83)	136 (58)	141 (59)	
Simultaneous pancreas-kidney	0 (0.0)	3 (1.3)	3 (1.2)	
Donor/recipient B19V IgG status at baseline, No. (%)				
D^-/R^-	0 (0.0)	42 (18)	42 (17)	.48
D^+/R^-	6 (100.0)	156 (66)	162 (67)	
Unknown/R^-	0 (0.0)	37 (16)	37 (15)	

Abbreviations: B19V, parvovirus B19; IgG, immunoglobulin G; IQR, interquartile range; PCR, polymerase chain reaction.

Incidence Rates of B19V Infection

The incidence rate of the B19V infection in B19V-seronegative SOT recipients during the first 6 months posttransplantation was 2.5 per 100 recipients per 6 months (95% CI, 1.1–5.2).

The incidence rates for the first month and for the second to sixth months posttransplantation were 1.2 (95% CI, .33–3.2), and 0.21 (95% CI, .06–.57) per 100 recipients per month, respectively.

The cumulative incidence of B19V infection in seronegative SOT recipients in the first 6 months posttransplantation was 2.5% (95% CI, .52–4.5) (Figure 1).

Four of the 6 (67%) SOT recipients with B19V infection had persistent B19V viremia up to 6 months posttransplantation while 2 (33%) only had transient replication (Supplementary Figure 2). Three of the 4 (75%) SOT recipients with persistent infection had positive IgG during follow-ups (Supplementary Figure 2).

Implications of B19V Infection

All 6 SOT recipients with B19V infection had anemia, 2 (33%) had simultaneous anemia and leukopenia, and there were no cases of pancytopenia. Furthermore, 3 (50%) with persistent

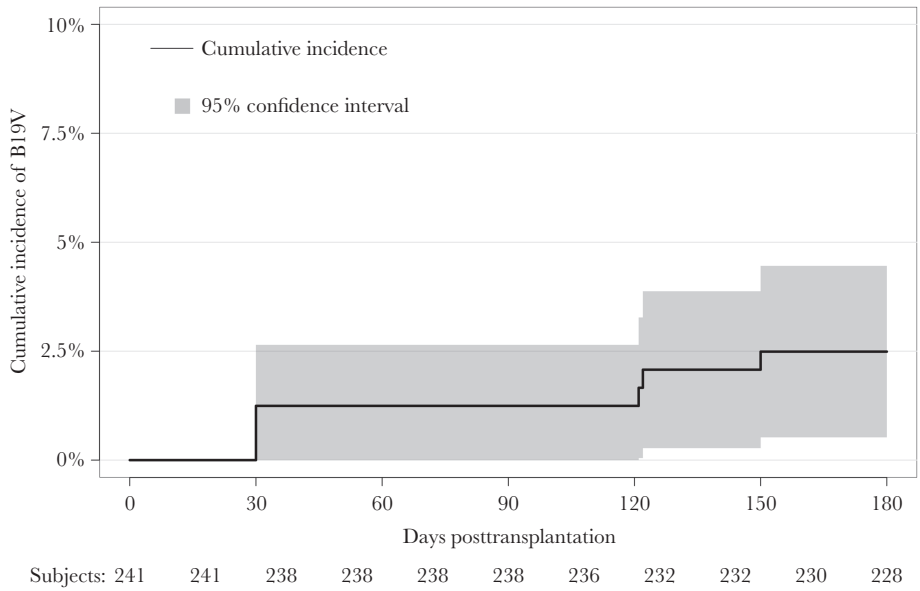

Figure 1. Cumulative incidence of parvovirus B19 (B19V) infection during the first 6 months posttransplantation in B19V-seronegative solid organ transplant (SOT) recipients. Six seronegative SOT recipients experienced B19V infection and 7 died. There were no cases of retransplantation. The gray area around the black line shows the 95% confidence interval for the cumulative incidence.

viremia were admitted to hospital and 2 (33%) received intravenous immunoglobulin (IVIG) therapy. To compare clinical characteristics in SOT recipients with positive B19V PCR with SOT recipients without positive PCR, we performed a case-control study including the 6 cases and 30 matched controls (Supplementary Table 2). There were no significant differences in hematologic variables between cases and controls (Supplementary Table 2).

DISCUSSION

In this study, we determined the incidence rate and impact of B19V infection in B19V-seronegative SOT recipients who underwent systematic monitoring of B19V with PCR monthly during the initial 6 months posttransplantation.

To our knowledge, this is the first study to use routine monitoring of B19V in seronegative SOT recipients. The incidence rate of B19V infection during the first 6 months posttransplantation in SOT recipients who were seronegative prior to transplantation was low and treatment was required in only a few SOT recipients. Comparable results were reported in a previous study that included both seronegative and seropositive SOT recipients [11]. We found 2 patients with persistent viremia who needed both hospital admission and IVIG treatment, 1 patient with persistent viremia who was admitted but for whom no IVIG treatment was prescribed, 1 patient with persistent viremia who was not admitted, and 2 patients with transient replication. Thus, the main burden of B19V infection was found in SOT recipients who had persistent infection and were detected 1 month posttransplantation.

In our cohort, approximately 83% of B19V-infected SOT recipients were kidney transplant recipients. It has been shown that B19V has a tropism to the kidney tissue [4], and B19V infection is more prevalent among kidney transplant recipients than in other SOT recipients, which may explain this finding [2, 3, 12].

Defining the time interval from transplantation to the first episode of B19V infection may help clinicians when considering differential diagnoses in SOT recipients with anemia. Half of the B19V-infected SOT recipients had their first detectable PCR at day 30 and the other half had a first positive PCR after day 120 posttransplantation of whom 2 had only transient replication. Similar results were found in 2 previous studies of SOT recipients [3, 13].

Although all SOT recipients with positive B19V PCR had anemia, we found no significant difference in hematology between seronegative SOT recipients with and without B19V infection, perhaps due to the low number of patients. Furthermore, kidney transplant recipients were the main group of SOT recipients with B19V infection in our cohort, and anemia is present in about 90% of kidney transplant recipients in the early posttransplant period [14].

A major strength of our study was the prospective systematic approach for monitoring of B19V infection in B19V-seronegative SOT recipients. In addition, data on B19V infection were extracted from the MiBa, which has been completed since 2010. However, B19V infection is uncommon, and we did not have enough power to determine risk factors of B19V infection in seronegative SOT recipients. Furthermore, we did not have access to the dosage and trough levels of immunosuppressive agents.

In conclusion, the incidence of B19V infection during the first 6 months posttransplantation in SOT recipients who were seronegative prior to transplantation was low. All B19V-infected SOT recipients had anemia, but few SOT recipients required hospital admissions and IVIG treatment. Thus, routine monitoring of B19V PCR in seronegative SOT recipients may not be necessary. A targeted screening 1 month posttransplantation combined with screening upon clinical suspicion could be an alternative strategy.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. O. R., C. E., S. S. S., M. P., F. G., A. R., J. R., J. L., and S. D. N. designed the study. All authors collected the data. O. R., C. E., and S. D. N. performed the statistical analyses with advice from J. R., and N. K. managed laboratory tests. O. R., J. L., A. R., and S. D. N. wrote the manuscript. All authors read and approved the final version of the manuscript.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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