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Is antibody-mediated rejection in kidney transplant recipients a risk factor for developing cytomegalovirus or BK virus infection? Results from a case-control study

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ABSTRACT

Background: Data are scarce on cytomegalovirus (CMV) and BK virus (BKV) infection after antibody-mediated rejection (ABMR).
Objectives: We hypothesized that the immunological response in patients with ABMR or the immune modulation associated with its treatment could predispose to CMV and BKV infection. Our objective was to investigate this hypothesis.
Study design: We conducted a single-center, matched case-control study (1:2 ratio) to analyze CMV and BKV replication during the first year after the ABMR diagnosis in kidney transplant recipients. Adult recipients with a histopathological diagnosis of ABMR between 2007–2015 were included as cases. Controls were kidney recipients who underwent transplantation immediately before and after the index case.
Results: Fifty-eight patients diagnosed with ABMR (33 chronic active ABMR and 25 acute ABMR), with their matched controls (116) were included. Forty-four cases received treatment for ABMR, including plasmapheresis (41), immunoglobulins (40), and rituximab (31). Within 1 year after ABMR, cases showed CMV replication more often than controls (9/58, 15.5% vs 7/116, 6%, OR = 4.21, CI 1.10–16.16, p = 0.04). Over the study period, CMV PCR determinations were requested more frequently in cases than controls (46/58, 79.3% vs 63/116, 54.3%, OR = 4.58, CI 1.92–10.9, p = 0.001). On multivariate analysis adjusted for CMV PCR determinations, retransplantation, antithymocyte globulin treatment and methylprednisolone treatment for acute rejection, CMV replication remained more common in cases than in controls (OR = 2.41, CI 0.49–11.73, p = 0.28). There were no differences in BKV replication in either urine or blood.
Conclusions: ABMR may be a risk factor for CMV but not for BKV replication in kidney transplant recipients.

1. Background

Cytomegalovirus (CMV) and BK virus (BKV) are the main viral infectious complications in kidney transplant recipients (KTR). The main risk factor for developing CMV disease is the absence of pre-existing CMV immunity, as occurs in CMV seropositive donor, seronegative recipient (D+/R-) transplantation. [1] Use of antithymocyte globulin (ATG) is also a risk factor for CMV disease [1]. In addition, the presence of T-cell mediated rejection (TCMR) has been considered a risk factor for CMV disease [2,3]. The immune response to CMV infection includes humoral, cellular, innate, and adaptive immune responses [4]. Hypogammaglobulinemia is reported to increase the risk of CMV infection during the first year after solid organ transplantation (SOT) [5], and low anti-CMV immunoglobulin titers are a risk factor for CMV disease [4,6]. These findings suggest that the humoral response has an important role in CMV infection.

BKV causes BKV-associated nephropathy (BKVAN) in 1%–10% of KTR. [7–10] Several factors have been found to increase the risk of BKV

Abbreviations: ABMR, antibody-mediated rejection; ATG, antithymocyte globulin; CMV, cytomegalovirus; BKV, BK virus; BKVAN, BK virus-associated nephropathy; IQR, interquartile range; KTR, kidney transplant recipients; OR, odds ratio; SOT, solid organ transplantation; TCMR, T-cell mediated rejection

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reactivation, such as donor BKV seropositivity plus recipient BKV seronegativity [10] and ATG administration. [11] However, the overall degree of immunosuppression is thought to be the most important factor [11]. As occurs in CMV infection, TCMR has shown an association with BKVAN [7–9]. The BKV specific T cell response is critical for controlling this infection and specific antibody responses likely play an important role in neutralizing the circulating virus [11].

Antibody-mediated rejection (ABMR) is the principal cause of graft failure in KTR. Around half the cases of acute rejection and half the late graft failures are attributed to ABMR. [12–14] The presence of donor-specific antibodies reorganizes the CD16+ lymphocyte compartment [15]. CD16 + γδ T cells can produce high levels of interferon gamma when recognizing IgG-opsonized CMV particles [16]. This cooperation between γδ T cells and the humoral response is a mechanism to control CMV reactivation. On the other hand, treatment of ABMR is directed toward elimination of pathogenic antibodies by plasmapheresis, by their inactivation with intravenous immunoglobulin, and by decreasing their production with rituximab. The role of immune system activation in the development of viral infection in ABMR patients, driven by pre-existing or de novo formation of donor-specific antibodies or their treatment, has not been well established.

2. Objective

We hypothesized that the immunological response in patients with ABMR or the immune modulation associated with its treatment could predispose to CMV and BKV infection in KTR. The aim of the present study was to investigate this hypothesis.

3. Materials and methods

3.1. Patients and setting

We performed a retrospective study in a tertiary referral hospital in Barcelona (Spain), where around 120 renal transplantations are performed every year. Inclusion criteria: Adults (> 18 years old) receiving a renal transplant after the year 2000 and with a histopathological diagnosis of ABMR in the period of January 2007 up to June 2015. Recipients of a transplant before the year 2000 were excluded due to an absence of electronic records.

3.2. Study design

We performed a matched case-control study (1:2 ratio). Two control KTR were included for each case with ABMR. Controls were KTR who underwent transplantation immediately before and after the index case, with grafts from a different donor. Inclusion criteria for controls was survival and maintenance of immunosuppressive treatment for at least one year after the diagnosis of ABMR in the index case or for at least the same period as the index case. The study was approved by our Clinical Research Ethics Committee (PR(AG)327/2015).

3.3. Definitions

ABMR was defined according to the Banff criteria in force at that time. [17–20] Patients were classified as having acute ABMR or chronic active ABMR based on the histopathological diagnosis. TCMR was also defined by the Banff criteria [17–20]. Concomitant TCMR and ABMR was established when diagnostic criteria for both types of rejection were met in the same kidney allograft biopsy [17–20].

CMV replication was established on detection of nucleic acid in whole blood samples. [21] CMV syndrome was defined as fever (temperature > 38 °C) for at least 2 days within a 4-day period, neutropenia, or thrombocytopenia, and CMV detection in blood. CMV end-organ diseases were defined according to the 2002 definitions in SOT. [22].

CMV prophylaxis was established when a patient received at least 3 months of valganciclovir treatment. In our center, high-risk KTR receive between 3 and 6 months of antiviral prophylaxis.

BKV viruria or viremia was defined as a positive nucleic acid test for BKV in urine or whole blood. BKV replication was considered significant at values of > 10^7 copies/mL in urine or > 10^4 copies/mL in whole blood. [23] BKV nephropathy was defined based on cytopathic changes due to the virus in renal allograft tissue, confirmed by immunohistochemistry for BKV proteins [24].

3.4. Outcome

The main outcome was the incidence of CMV replication and significant BKV replication during the first year after ABMR while patients were receiving immunosuppressive treatment. In controls, we analyzed the first year after the diagnosis of ABMR in the matched cases.

3.5. Data collection

Epidemiological, clinical, and microbiological data were obtained by chart abstraction and entered in a database created for the study. Acute ABMR was treated with plasmapheresis or immunoglobulins. Most patients also received rituximab. Treatment of chronic active ABMR was decided by the attending physician. Some of these patients were included in a double-blind, randomized clinical trial of intravenous immunoglobulins and rituximab versus placebo. [25] Since January 2000, all CMV and BKV determinations have been automatically registered in an electronic database system. We reviewed these electronic medical records, and all determinations and values for both viruses were recorded.

3.6. Microbiological results

Detection and quantification of CMV in blood was performed by a real-time PCR technique (RealStar® CMV PCR Kit, Altona Diagnostics, Hamburg, Germany) on a CFX96 instrument (Biorad). The analytical sensitivity of the technique was 0.42 IU/μL (95% CI, 0.30-0.83 IU/μL). The quantification standards were calibrated against the 1 st WHO International Standard for Human Cytomegalovirus for Nucleic Acid Amplification Techniques (NIBSC code: 09/162), and results were reported in IU/mL.

BKV detection and quantification in urine and blood was done with a real-time PCR technique (RealStar® BKV PCR Kit, Altona Diagnostics, Hamburg, Germany) on a SmartCycler instrument (Cepheid). Analytical sensitivity was 0.222 copies/μL (95% CI: 0.115-0.844 copies/μL), and results were reported in copies/mL.

3.7. Statistical analysis

Quantitative variables were tested using the Mann Whitney *U* test. Categorical variables were tested using the chi-square or Fisher exact test, as appropriate. Significance tests were two-sided and a p value of < 0.05 was considered statistically significant. When multiple comparisons were performed, p values were adjusted using a false discovery rate method. [26]

As the data were matched, we performed a conditional logistic model to analyze the CMV replication results between cases and controls adjusting by all possible risk factors for CMV replication. The number of CMV PCR determinations differed between cases and controls. Therefore, a new variable was designed for testing the relationship between case status and CMV determinations and replications. Individuals with no CMV determinations or replication were considered as reference. Individuals with determinations and no replication were placed in another group, and individuals with determinations and replication in a third group. The odds ratio (OR) obtained for each group was compared with the reference. After this adjustment, we analyzed main risk factors for CMV replication (retransplantation, ATG treatment

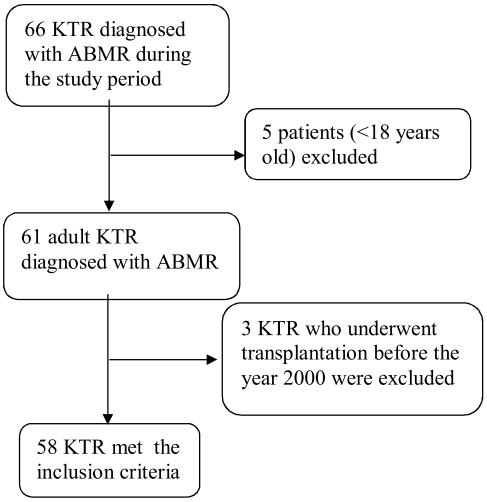

Fig. 1. Flow diagram of kidney transplant recipients diagnosed with antibody-mediated rejection included in the study.

for induction or rejection, methylprednisolone pulses for TCMR and CMV replication previously to ABMR) in an individual analysis. Statistically significant variables in this model were included in a final multivariate model to identify the odds ratio (OR) obtained for each variable in cases versus controls. All statistical analyses were done in R software, 3.4.0 version (R Core Team, 2017).

4. Results

4.1. Patient characteristics

In total, 66 patients were diagnosed with ABMR during the study period, and 58 met the inclusion criteria. A flowchart showing inclusion of all potential candidates for the study is shown in Fig. 1. We included two matched controls for each case (116 controls). The main epidemiologic and clinical variables in cases and controls are summarized in Table 1. Patients diagnosed with ABMR were recipients of more than one kidney graft, were given induction therapy with ATG, and had TCMR more often than controls. Consequently, ABMR patients received prophylaxis with valganciclovir more frequently. The duration of CMV prophylaxis was 3 months in 37 patients and 6 months in 9 patients.

The presence of CMV disease prior to ABMR was more common in patients with ABMR (9/58 15.5% vs 7/116 6%, p = 0.05). These diseases were mainly CMV syndromes, and three patients had colitis (two cases and one control).

Of the 58 patients with ABMR, 33 had chronic active ABMR and 25 acute ABMR. The median interval from transplantation to the ABMR diagnosis was 761 days (IQR 88–1380 days). Treatment of ABMR is detailed in Table 2.

4.2. Main outcomes after ABMR

Data on the main outcomes one year after the ABMR diagnosis are shown in Table 3. CMV replication was more common in patients with ABMR than in controls 9/58 (15.5%) vs 7/116 (6%). The median interval until CMV replication was globally 64 days (IQR 22–124); 113 (IQR 62–171) in cases and 20 (IQR 12–41) in controls (p = 0.007). There were no differences in viral load between the groups: median $\log_{10}$ was 2.97 IU/mL (IQR 2.7–3.47) in cases and 3.09 IU/mL (IQR 2.83–3.58) in controls (Fig. 2). During the study period, CMV PCR was requested more often in cases (46/58, 79.3%) than in controls (63/116, 54.3%, OR 4.58 CI 1.92–10.9 p = 0.01). There were no differences in

Table 1
Clinical and epidemiological characteristics in cases and controls.

Characteristics (n)	Cases (58)	Controls (116)	p value
Male sex	30 (52)	71 (61)	0.50
Age (years) at the time of diagnosis of ABMR, median [IQR]	49 (35-59)	56 (47-66)	0.02
Primary diagnosis:			0.46
• Glomerulonephritis	14 (24.1)	27 (23.3)	
• Polycystic kidney	5 (8.6)	18 (15.5)	
• Interstitial nephritis	6 (10.3)	11 (9.5)	
• Diabetic nephropathy	5 (8.6)	10 (8.6)	
• Renovascular disease	6 (10.3)	7 (6)	
• Other	22 (37.9)	43 (37.1)	
Donor type:			1
• Brain deceased donor	49 (84.5)	100 (86.2)	
• Living	7 (12.1)	12 (10.3)	
• Donation after circulatory death	2 (3.5)	4 (3.5)	
Number of HLA incompatibilities, median [IQR]	4 (3-4)	4 (3-5)	0.19
Number of HLA-DR incompatibilities, median [IQR]	1 (1-2)	1 (1-1)	0.528
Cold ischemia time (hours), median [IQR]	15,0 (13.5-19)	16,5 (11.8-19)	0.80
Retransplantation	23 (39.7)	14 (12.1)	0.002
Induction therapy:			0.08
• Anti-IL2 Receptor Antibody	27 (46.6)	67 (57.8)	
• Antithymocyte globulin	17 (29.3)	16 (13.8)	
• None	14 (24.1)	33 (28.4)	
Initial immunosuppressive therapy:			0.41
•TAC + MMF + PDN	56 (96.5)	113 (97.4)	
• CsA + MMF + PDN	2 (3.5)	3 (2.6)	
D +/R -	6 (10.3)	15 (12.9)	0.95
Cytomegalovirus prophylaxis	22 (37.9)	24 (20.7)	0.08
TCMR	18 (31)	11 (9.5)	0.004
• Previously	6 (10.3)	11 (9.5)	
• At the biopsy of ABMR diagnosis	12(20.7)	0	
Time (days) from previous TCMR until ABMR diagnosis, median [IQR]	973 (377-1320)	334 (171-817)	0.16
MPD intravenous pulses for TCMR	15 (25.9)	10 (8.6)	0.01
Antithymocyte globulin for TCMR	7 (12.1)	4 (3.5)	0.11
Serum creatinine (mg/dL) one month after transplant, median [IQR]	1.42 (1.21-1.80)	1.40 (1.20-1.73)	0.71
Serum creatinine (mg/dL) at time of ABMR, median [IQR]	1.90 (1.39-2.22)	1.40 (1.15-1.65)	< 0.001
mTOR inhibitor at time of ABMR	5 (9.8)	5 (4.4)	0.29
CMV Replication prior to ABMR	22 (37.9)	32 (27.6)	0.14
CMV Disease prior to ABMR	9 (15.5)	7 (6)	0.05
BKV significant replication prior to ABMR	6 (10.3)	10 (8.62)	0.70
BKV blood replication prior to ABMR	3 (5.2)	3 (2.6)	0.38
BKVAN prior to ABMR	1 (1.7)	1 (0.9)	0.62

Data are presented as the number and percentage unless otherwise indicated.
ABMR: Antibody mediated rejection, CMV: Cytomegalovirus, D+/R-: CMV donor seropositive and seronegative recipient, HLA: Human leukocyte antigen, HLA-DR: Human leukocyte antigen-antigen D related, IL-2: Interleukin 2, MMF: Mycophenolate mofetil, MPD: Methylprednisolone, mTOR: Mechanistic target of rapamycin, PDN: Prednisone, TAC: Tacrolimus, TCMR: T-cell mediated rejection.

Table 2
Therapeutic regimens for patients diagnosed with antibody mediated rejection.

Type of treatment	Acute ABMR (25)	Chronic active ABMR (33)
Rituximab + PP + Igs	14 (56)	10 (30.3)
PP + Igs	11 (44)	2 (6.1)
Rituximab + Igs		3 (9.1)
PP + Rituximab		4 (12.1)
No treatment		14 (42.4)

Data are presented as the number and percentage.
ABMR: Antibody mediated rejection, Igs: Immunoglobulins, PP: Plasmapheresis.

Table 3
Univariate analysis of main outcomes.

Characteristics (n)	Cases (58)	Controls (116)	OR	95% CI	p value
CMV Replication after ABMR	9 (15.5)	7 (6.0)	4.21	1.10-16.16	0.04
CMV PCR determinations after ABMR	46 (79.3)	63 (54.3)	4.58	1.92-10.9	0.01
CMV Disease	1 (1.7)	0 (0)	–	–	–
CMV Replication prior to ABMR	22 (37.9)	32 (27.6)	1.75	0.84-3.63	0.14
Retransplantation	23 (39.7)	14 (12.1)	5.95	2.38-14.88	0.002
ATG treatment for induction or/and TCMR	23 (39.7)	20 (17.2)	3.08	1.49-6.35	0.01
MPD intravenous pulses for TCMR	15 (25.9)	10 (8.6)	5.42	1.91-15.34	0.01
BKV significant replication	2 (3.5)	4 (3.5)	1	0.16-6.42	1
BKV blood replication	1 (1.7)	2 (1.7)	–	–	–
BKVAN	0	0	–	–	

Data are presented as the number and percentage.
ABMR: Antibody mediated rejection. ATG: Antithymocyte globulin. BKV: BK virus. BKVAN: BK virus associated nephropathy, CMV: Cytomegalovirus. MPD: Methylprednisolone.

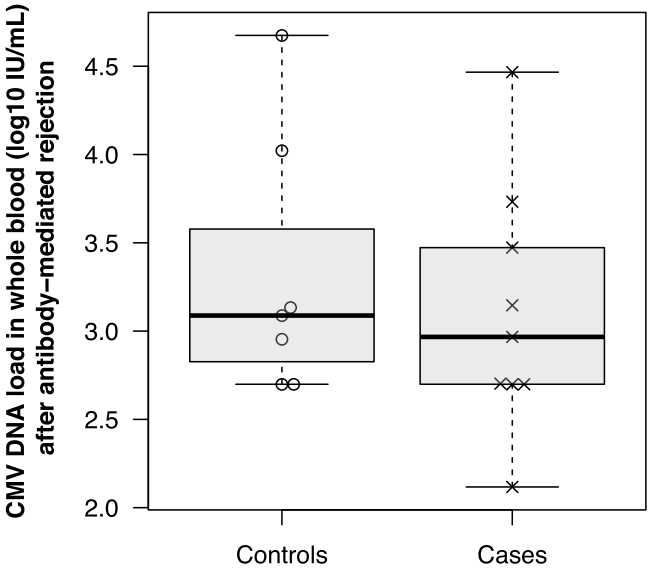

Fig. 2. CMV DNA load in whole blood (log10 IU/mL) after antibody-mediated rejection.

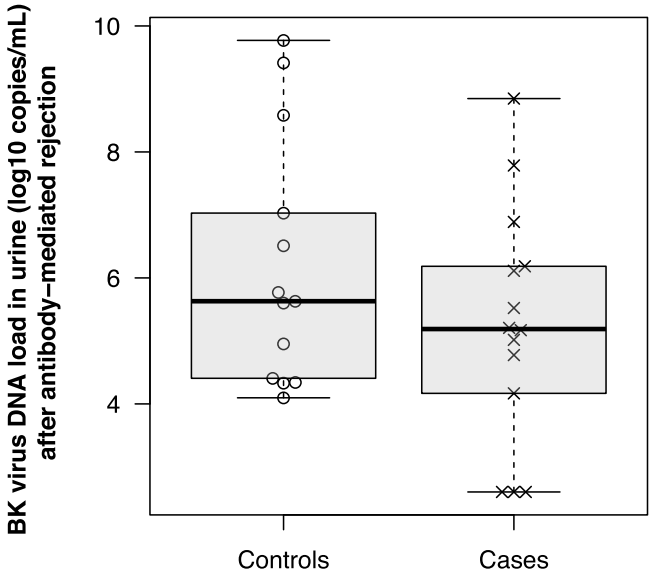

Fig. 3. BK virus DNA load in urine (log10 copies/mL) after antibody-mediated rejection.

the treatment for CMV replication with antiviral agents (2/58, 3.45% in cases vs 1/116 0.86% in controls, p = 0.26) or in immunosuppressive therapy changes (no cases and only one control patient discontinued mycophenolate mofetil). There was only one case of CMV disease during the study period.

All statically significant variables in Table 3, were included in a multivariate model (Table 4). In this model, after adjusting for all the main risk factors such as CMV PCR determinations after ABMR, re-transplantation, ATG treatment and methylprednisolone intravenous pulses, CMV replication remained more frequent in cases, with an OR of 2.41. However, the difference was not statistically significant (CI 0.49–11.73, p = 0.28).

Table 4
Multivariate model to analyze CMV replication in cases versus controls.

Characteristics (n)	OR	95% CI	p value
CMV Replication after ABMR	2.41	0.49-11.73	0.28
CMV PCR determinations after ABMR	4.43	1.59-12.34	0.01
Retransplantation	4.73	1.55-14.39	0.01
ATG treatment for induction or/and TCMR	2.03	0.75-5.5	0.16
MPD intravenous pulses for TCMR	4.84	1.55-14.39	0.01

Data are presented as the number and percentage.
ABMR: Antibody mediated rejection. ATG: Antithymocyte globulin. CMV: Cytomegalovirus. MPD: Methylprednisolone. TCMR: T-cell mediated rejection.

Regarding BKV replication, two ABMR patients and four control patients showed significant BKV replication. From these six patients, one patient of each group presented also CMV replication after ABMR. There were no differences in BKV viral load in urine (Fig. 3). None of the patients were diagnosed with BKVAN after ABMR.

We performed a separate analysis in order to detect viral replication differences between ABMR patients treated with rituximab and the controls. The analysis showed fewer differences between these two subgroups than in the overall analysis (Table 5).

5. Discussion

The results of this study in KTR show that CMV replication was more common during the year after the ABMR diagnosis in cases than in controls. In contrast, we did not find any differences in BKV replication. On multivariate analysis, a trend toward more frequent CMV replication was observed in ABMR patients. To the best of our knowledge, there are no previous studies evaluating CMV and BKV infection following ABMR in KTR.

Two studies have reported an association between CMV infection and the presence of TCMR. [2,3] In D+/R- kidney and liver recipients, allograft rejection was identified as a major predictor of late-onset CMV disease [2]. Moreover, in a cohort of seropositive KTR, acute rejection

Table 5
Analysis of main outcomes after antibody mediated rejection in cases treated with rituximab and their matched controls.

Characteristics (n)	Cases (31)	Controls (62)	OR	95% CI	p value
CMV Replication	4 (12.9)	4 (6.5)	4,0	0.41-39	0.23
CMV Disease	0	0	–	–	–
BKV significant replication	0	1 (1.5)	–	–	–
BKV blood replication	0	0	–	–	–

Data are presented as the number and percentage.
ABMR: Antibody mediated rejection. BKV: BK virus. BKVAN: BK virus associated nephropathy, CMV: Cytomegalovirus.

was an independent risk factor for tissue-invasive CMV disease (8% vs 3%) [3].

Treatment for TCMR could also increase the risk of CMV replication. Use of ATG has been associated with CMV disease, especially when is used for treating rejection. [1] Furthermore, ATG induction therapy in KTR led to increases in CMV infection [27]. In our study, ATG induction was used more often in ABMR patients, and this group also had a higher incidence of TMCR requiring specific therapy. These factors could explain part of CMV replication in ABMR patients. However, after performing a multivariate analysis cases, still had an OR of 2.4 for CMV replication, although not significantly. The difference observed in the median interval until CMV replication after ABMR is explained by the fact that controls with CMV replication were those of cases diagnosed with acute ABMR very close to the transplant procedure when the net state of immunosuppression was higher.

The CMV immune response is highly complex and the humoral response is an important component. [4] Hypogammaglobulinemia has been identified as a risk factor for developing CMV infection after SOT [4,28]. Low anti-CMV immunoglobulin titer at 7 days after heart transplantation was found to be an independent risk factor for CMV disease [6]. In another study, a low pre-transplant CMV antibody titer was significantly associated with CMV infection [29]. Furthermore, in seropositive lung transplant recipients, anti-CMV antibody levels at the time of stopping antiviral prophylaxis were significantly higher in patients who did not develop CMV viremia [30]. These data suggest that humoral immunity has an important role in CMV infection in SOT and support our hypothesis.

Of note, in heart transplant recipients with CMV disease, the use of nonspecific IV immunoglobulin (Ig) treatment has led to more favorable outcomes than treatments without Igs. [31] Forty of our 58 ABMR patients were treated with non-specific Igs, and the results suggest that these may prevent the development of CMV replication. Unfortunately, due to the retrospective nature of our study, serum gamma globulin levels were not available in our patients.

Regarding BKV replication, we found no differences between KTR with or without ABMR at one year after the diagnosis. Only a few patients in each of these groups showed significant replication or whole blood replication. These low percentages of BKV replication (3.5%) in our patients could be considered a limitation to finding differences. Nonetheless, although the values were low, they were similar in the two groups, and we believe they are sufficiently conclusive to rule out our initial hypothesis.

Rituximab was the most used drug to treat ABMR in our study. It remains uncertain whether rituximab is a risk factor for CMV infection in SOT. In BKV infection, the related studies have shown discordant results. Desensitization with intravenous immunoglobulins and rituximab in KTR was the major predictor of BKV viremia in one study. [32] Nonetheless, in another study polyomavirus replication was not associated with rituximab therapy [33]. In our experience, there were no differences regarding viral replication between ABMR patients treated with rituximab and their matched controls.

Our study has some limitations, the first being those inherent to its observational and retrospective design. However, the main outcome variables, such as CMV and BKV replication, were automatically recorded in an electronic medical system, minimizing the risk of recording bias in the results. Second, because of the retrospective design, monitoring of viral replication differed in ABMR cases and the controls. The attending physician decided when and how often viral replication would be monitored in each patient, and this may have affected the results of the study. On the other hand, all patients included were managed in daily clinical practice, and this fact enhances the applicability of the results to the real-life setting. Moreover, a multivariate model was constructed to adjust for the number of CMV PCR determinations in both groups. Third, this is a single-center study with a limited sample size.

In conclusion, KTR diagnosed with ABMR presented CMV replication more often during the first year after the ABMR diagnosis. These results suggest that CMV should be monitored following the diagnosis and treatment of ABMR in KTR. There were no differences in BKV replication after the ABMR diagnosis; hence this infection may not require specific monitoring in this clinical situation.

Author contribution statement

Ibai Los-Arcos: Data curation, Formal analysis, Original draft
Oscar Len: Conceptualization, Formal analysis, Methodology, Supervision, Review & Editing
Manel Perello: Data curation, Review & Editing
Irina Torres: Data curation, Formal analysis, Review & Editing
Gemma Codina: Investigation, Review & Editing
Juliana Esperalba: Investigation, Review & Editing
Joana Sellares: Data curation, Review & Editing
Francesc Moreso: Conceptualization, Formal analysis, Supervision, Review & Editing
Daniel Serón: Supervision, Review & Editing
Joan Gavaldà: Conceptualization, Supervision, Review & Editing

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Competing interests

None declared

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