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Kidney Transplantation From Deceased Donors With Vaccine-induced Immune Thrombocytopenia and Thrombosis: An Updated Analysis of the UK Experience

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Background. The emergence and attendant mortality of vaccine-induced immune thrombocytopenia and thrombosis (VITT) as a consequence of vaccination against severe acute respiratory syndrome coronavirus 2 have resulted in some patients with VITT being considered as deceased organ donors. Outcomes after kidney transplantation in this context are poorly described. Because the disease seems to be mediated by antiplatelet factor 4 antibodies, there is a theoretical risk of transmission via passenger leukocytes within the allograft. **Methods.** We analyzed the experience of kidney transplantation from donors with VITT in the United Kingdom between January and June 2021. We followed-up all recipients of kidney-only transplants from donors with VITT to detect major postoperative complications or features of disease transmission and assess graft survival and function. **Results.** There were 16 kidney donors and 30 single kidney transplant recipients in our study period. Of 11 preimplantation biopsies, 4 showed widespread glomerular microthrombi. After a median of 5 mo, patient and graft survival were 97% and 90%, respectively. The median 3-mo estimated glomerular filtration rate was 51 mL/min/1.73 m^2. Two recipients had detectable antiplatelet factor 4 antibodies but no evidence of clinical disease after transplantation. Major hemorrhagic complications occurred in 3 recipients, all of whom had independent risk factors for bleeding, resulting in the loss of 2 grafts. The involvement of VITT could not be completely excluded in one of these cases. **Conclusions.** The UK experience to date shows that favorable outcomes are possible after kidney transplantation from donors with VITT but highlights the need for ongoing vigilance for donor-related complications in these patients.

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INTRODUCTION

Vaccine-induced immune thrombocytopenia and thrombosis (VITT) is a rare but serious syndrome that has emerged after the introduction of adenovirus vector vaccines for the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] Occurring predominantly after the first vaccine dose, it is characterized by antibodies to platelet factor 4 (PF4) that bind to and activate platelets, leading to profound thrombocytopenia and catastrophic thrombosis, with an apparent predilection for the cerebral venous system.[3] It shares features with heparin-induced thrombocytopenia, but the PF4 binding seen in VITT is independent of heparin.[4] Although treatment of VITT with anticoagulation, intravenous immunoglobulin, or plasma exchange may save lives, mortality is still high.[1,3] Some patients with VITT have become deceased organ donors, offering the potential of a lifesaving or life-enhancing operation to patients waiting for a transplant.

There have been reports of early thrombotic complications in recipients of kidney and liver transplants and concerns about the potential for transmission of VITT via passenger B cells within the graft.[5,6] As a result, some have advised caution when considering organ offers from donors with VITT.[7] A more detailed understanding of the risks of solid organ transplantation from donors with VITT has not yet been possible because of the small number of cases and limited follow-up. Longer-term data on significant numbers of transplants from donors with VITT are urgently required to gain a fuller picture of the risks of transplantation and thus to inform consent discussions.

The outcomes of liver transplants in the United Kingdom from donors with VITT have been reported elsewhere.[8] In this study, we analyzed outcomes in all UK kidney transplant recipients since the syndrome emerged, focusing on postoperative complications, patient and graft survival, and looking specifically for evidence of disease transmission.

MATERIALS AND METHODS

Study Design and Data Sources

This was a national case series of deceased donor kidney transplantation, using data from the UK Transplant Registry (UKTR), a database maintained by National Health Service Blood and Transplant (NHSBT), supplemented with follow-up information provided by transplant centers. Our study comprised all recipients of kidney-only transplants from deceased donors with VITT in the United Kingdom between January 1, and June 30, 2021. This period encompassed the time when most first doses of the ChAdOx1 nCoV-19 adenovirus vector vaccine were administered in the United Kingdom.

Case Detection

We identified donors with VITT using 3 methods: (1) prospective alerts to NHSBT from organ donation teams at the time of donor assessment; (2) retrospective search of the UKTR to find all deceased donors within the study period with any platelet count of $<150\times10^9$/L and a cause of death recorded as intracranial thrombosis or intracranial hemorrhage (ICH), to identify cases that were not reported at the time of assessment; and (3) correspondence with all UK kidney transplant centers to ask for submission of any additional cases.

Two authors (G.G. and I.U.-L.) independently reviewed all potential donor cases detected by the above methods and identified likely cases using 5 diagnostic features consistent with published criteria[3]: symptom onset 5 to 30 d after SARS-CoV-2 vaccination, thrombosis in any vascular territory, platelet count of $<150\times10^9$/L at any time from hospital admission onward, elevated D-dimer (>4000 fibrinogen equivalent units [FEU]), and positive anti-PF4 antibodies on enzyme-linked immunosorbent assay (ELISA) testing. Finally, 2 experts in hemostasis and thrombosis (S.P. and B.J.H.) reviewed all potential cases; only deceased donors with "definite" or "probable" VITT were included.[3]

Clinical Parameters

Donors

Donor clinical and laboratory data came from the UKTR, including the type of vaccine received, time from vaccination to hospital admission, treatment of VITT received before death, cause of death, site(s) of thrombosis, type of donor (donation after brain death, donation after circulatory death), and relevant medical history (hypertension, diabetes, smoking). Laboratory parameters included SARS-CoV-2 RNA result, lowest platelet count from hospital admission onward, highest D-dimer result, lowest fibrinogen result, anti-PF4 ELISA result, terminal serum creatinine and terminal estimated glomerular filtration rate (eGFR; calculated from terminal creatinine using the Modification of Diet in Renal Disease equation, without adjustment for ethnicity).[9]

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When laboratory results required for VITT case confirmation (D-dimer, fibrinogen, or anti-PF4 antibodies) were missing, samples were tested in NHSBT laboratories using stored donor serum. To standardize donor characterization, serum from all donors was tested in NHSBT laboratories for anti-PF4 antibodies using the Lifecodes PF4 immunoglobulin G ELISA (Immucor); the threshold for a positive result using this assay was an optical density reading of >0.4.[10]

Recipients

Kidneys from donors with VITT were offered to transplant centers using existing pathways.[11] Implantation techniques and immunosuppression regimens were as per unit preference. Consent discussions were expected to follow national guidance.[12] Follow-up data on recipients of kidney-only transplants from donors with VITT came from the UKTR and from clinicians in their transplant centers. This included primary diagnosis of renal failure, graft number, dialysis status, high sensitization (defined as a calculated reaction frequency of ≥85%),[13] cold ischemia time (defined as the time from perfusion with cold preservation fluid in the donor to reperfusion with the recipient's blood), SARS-CoV-2 vaccination history, anticoagulation before transplantation (excluding heparin given on dialysis), and induction immunosuppression regimen.

National guidance recommends follow-up of recipients to detect possible VITT transmission.[12] Follow-up recipient laboratory parameters were as follows: platelet counts on the day of admission for transplantation and then the lowest result in postoperative weeks 1, 3, 4, 5 to 8, and 9 to 12; serum creatinine and eGFR (calculated using the Modification of Diet in Renal Disease equation in patients aged ≥18 y and the revised Schwartz formula with a constant [k] value of 36.5 in those aged under 18 y)[14] at 3 mo after transplantation in patients with functioning grafts; and all D-dimer, fibrinogen, and anti-PF4 antibody ELISA results from the day of transplant onward. We recorded anti-PF4 ELISA tests rather than heparin-induced thrombocytopenia screens (ie, rapid assays to detect anti-PF4 antibodies) because the latter have been shown to have poor sensitivity in the context of VITT.[10]

Outcomes

The outcomes of interest after transplantation were as follows: (1) major hemorrhagic or thrombotic complications, (2) early graft dysfunction, (3) graft failure, (4) death, and (5) recipient diagnosis of VITT.[3] Major complications were bleeds requiring open surgical or radiological intervention or thrombosis/thromboembolism proven on imaging in any venous or arterial territory. When this occurred, the clinical team judged whether it could have resulted from donor factors. Early graft dysfunction comprised delayed graft function (DGF), defined as the requirement for at least 1 session of dialysis/hemofiltration in the first 7 postoperative days, and primary nonfunction, defined as a failure to achieve independence from dialysis. We defined graft failure as the return to long-term dialysis or retransplantation and also recorded the cause of graft failure/death. Recipient follow-up ended on October 6, 2021.

Statistical Analysis

We used standard measures of dispersion to describe frequencies and time intervals, and summarized graft survival, censored at death, using a Kaplan-Meier curve. All data analyses used SAS Enterprise Guide V.7.13 (SAS Institute Inc, Cary, NC).

Ethics Statement

This was a service evaluation study, performed by NHSBT in collaboration with UK transplant units as part of its duty to monitor the safety of the national transplant program.[9] As such, additional ethical approval was not required. NHSBT uses patient identifiable data without consent under the terms of Articles 6(1) (e) and 9(2) (h) and (i) of the General Data Protection Regulations. All data were stored and analyzed within NHSBT, in accordance with existing policies.[15]

RESULTS

Donors

Among 568 deceased kidney donors during our study period, there were 16 with VITT (Table 1). This included 15 "definite" cases (fulfilling all 5 diagnostic

TABLE 1.

Characteristics of kidney donors with vaccine-induced immune thrombocytopenia and thrombosis

Characteristics	Donors with VITT (N = 16)
Female sex	12 (75)
Age (y)	44 (32–49)
Donor type	
DBD	15 (94)
DCD	1 (6)
Hypertension	1 (6)
History of smoking	7 (44)
Time from vaccination to hospital admission (d)	13 (12–16)
Time from hospital admission to donation (d)	4 (3–5)
Clinical features[a]	
Intracranial hemorrhage	15 (94)
Cerebral venous sinus thrombosis	13 (81)
Extracranial thrombosis[b]	6 (38)
Platelet count ($\times 10^9$/L)	
On admission to hospital	30 (16–56)
Lowest value before donation	13 (7–32)
Fibrinogen (g/L, NR 2–4)[c]	1.0 (0.9–1.6)
D-dimer (FEU, NR <500)[d]	40 000 (14 000–80 000)
Anti-PF4 antibodies (OD, assay cutoff 0.4)	2.58 (2.22–2.83)
Terminal creatinine (μmol/L)	57 (48–81)
Terminal eGFR (mL/min/1.73 m^2)	114 (85–139)
UK KDRI	0.99 (0.79–1.02)
US KDRI	1.09 (1.00–1.27)

Values are presented as n (%) or median (IQR).
[a]Features are not exclusive; 1 donor presented with intracranial hemorrhage only.
[b]Portomesenteric veins (2), pulmonary artery (2), splenic vein (2), and inferior vena cava (1).
[c]Lowest result reported by donor center.
[d]Highest result reported by donor center.
DBD, donation after brain death; DCD, donation after circulatory death; eGFR, estimated glomerular filtration rate; FEU, fibrinogen equivalent units; IQR, interquartile range; NR, normal range; OD, optical density PF4, platelet factor 4; UK KDRI, United Kingdom Kidney Donor Risk Index[16]; US KDRI, United States Kidney Donor Risk Index[17]; VITT, vaccine-induced immune thrombocytopenia and thrombosis.

criteria) and 1 "probable" case (fulfilling all criteria except documented thrombosis; cause of death was ICH). The median age was 44 y; 12 donors (75%) were female. The median age of all deceased kidney donors during the study period was 52 y. All donors had received a first dose of the ChAdOx1 nCoV-19 vaccine at a median (range) of 13 (9 to 18) d before admission. In total, 81% donors (13 of 16) presented with cerebral venous sinus thrombosis, 94% (15 of 16) had ICH, and 38% (6 of 16) had thromboses in other vascular territories (splenic vein, portomesenteric veins, inferior vena cava, and pulmonary artery). The lowest platelet count before donation ranged from 2 to 78×10^9/L. The median (interquartile range [IQR]) donor terminal creatinine was 57 (48–81) μmol/L. All donors had negative SARS-CoV-2 RNA results on nasopharyngeal swabs and endotracheal aspirates at the time of assessment.

Recipients

Thirty patients (including 2 aged <18 y) in 13 transplant units received a kidney-only transplant from a donor with VITT. The median (IQR) recipient age was 48 (36–59) y; 14 recipients (47%) were female (Table 2). Twenty-two recipients were on dialysis at the time of transplantation. Twenty-eight recipients had received at least 1 dose of SARS-CoV-2 vaccine at a median of 45 d before transplantation and 22 recipients had received 2 doses. Two recipients were taking warfarin before transplantation and restarted this on discharge. Median (IQR) recipient follow-up was 153 (122 to 170) d; all recipients had at least a 3-mo follow-up at the time of reporting.

Patient and Graft Outcomes

One recipient died from a cardiac arrhythmia on the day of transplantation. In the opinion of the local clinician, this was not related to the diagnosis of VITT in the donor. There were no other deaths in the recipient group by the end of the study period (patient survival 97%). Of the remaining 29 transplants, 24 had immediate graft function and 5 (17%) required a period of dialysis after transplantation (Table 3).

Three recipients developed a perinephric hematoma between 3 d and 2 mo posttransplant. All of these occurred in the context of other risk factors for bleeding (known hemostatic disorder, enhanced thromboprophylaxis, percutaneous nephrostomy insertion). In 2 cases, the complications were unrelated to donor factors, whereas the clinical team could not completely exclude the involvement of VITT in the third. These complications resulted in the infarction and loss of 2 grafts. There was 1 other graft failure, the cause of which is not known. Therefore, 3-mo death-censored graft survival was 90% (26 of 29). Figure 1). Among 26 patients with functioning grafts, median (IQR) serum creatinine at 3 mo was 127 (103–143) μmol/L and median (IQR) eGFR at 3 mo was 51 (40 to 59) mL/min/1.73 m^2.

Graft Pathology

Seventeen (57%) kidneys had multiple petechiae identified prior to implantation 2 (12%) of those grafts had DGF and the remainder had immediate graft function. Eleven grafts (37%) were biopsied at the time of implantation. Four biopsies showed widespread glomerular

TABLE 2.

Baseline characteristics of recipients of kidney transplants from donors with vaccine-induced thrombosis and thrombocytopenia

Characteristics	Kidney transplant recipients from donors with VITT (N = 30)
Female sex	14 (47)
Age (y)	48 (36–59)
Cause of renal failure	
Diabetes	7 (23)
Polycystic kidney disease	6 (20)
Hypertension/renovascular disease	4 (13)
Glomerulonephritis	3 (10)
Other	10 (33)
On dialysis at transplant	26 (87)
Graft number	
First	26 (87)
Second	4 (13)
Time on waiting list (mo)	28 (20–48)
Highly sensitized (cRF ≥85%)	4 (13)
HLA mismatch grade[18]	
1–2	7 (23)
3–4	23 (77)
Cold ischemia time (h)	15 (12–19)
Induction agent[a]	
Basiliximab	28 (93)
Other[b]	2 (7)

Values are presented as n (%) or median (IQR).
[a]In addition to corticosteroids, mycophenolate mofetil and tacrolimus.
[b]Antithymocyte globulin (1), alemtuzumab (1).
cRF, calculated reaction frequency; IQR, interquartile range; VITT, vaccine-induced thrombosis and thrombocytopenia.

TABLE 3.

Clinical outcomes in kidney transplants from donors with vaccine-induced thrombosis and thrombocytopenia

Clinical outcomes	Kidney transplant recipients from donors with VITT (N = 30)
Early graft function	
Immediate	24 (80)
Delayed	5 (17)
Not determined[a]	1 (3)
Postoperative laboratory results	
Nadir platelet count ($\times 10^9$/L)	144 (102–230)
Nadir fibrinogen (g/L, NR 2–4)	3.1 (2.3–3.9)
Peak D-dimer (ng/mL, NR <500)	2000 (1000–5700)
3-mo serum creatinine (μmol/L)	127 (103–143)
Anti-PF4 antibodies detected[b]	2 (7)
Major postoperative complications[c]	
Hemorrhage	3 (10)
Thrombosis	1 (3)
Graft failure	3 (10)
Death	1 (3)

Values are presented as n (%) or median (IQR).
[a]Death on day of transplant.
[b]Sample/cutoff value ratio ≥1.0.
[c]Requiring return to theater or radiological intervention.
IQR, interquartile range; NR, normal range; PF4, platelet factor 4; VITT, vaccine-induced thrombosis and thrombocytopenia.

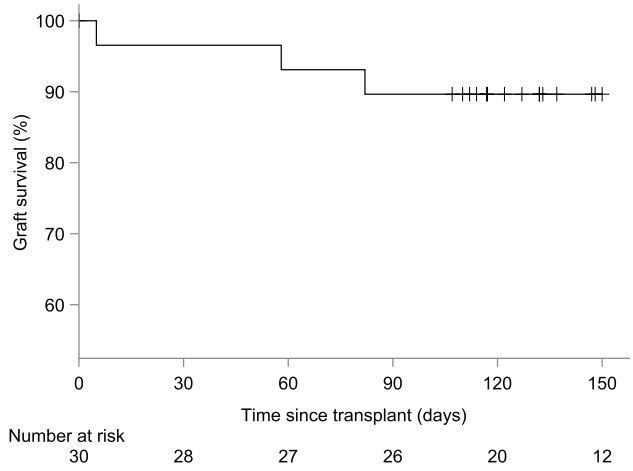

FIGURE 1. Kaplan-Meier curve of death-censored graft survival in kidney transplants from donors with vaccine-induced immune thrombocytopenia and thrombosis.

microthrombi (Figure 2). Three of those grafts had immediate function and 1 had DGF; 2 subsequently failed, whereas the other 2 had good function at the end of follow-up.

Laboratory Results and Disease Transmission

Figure 3 shows the trend of platelet counts in all recipients in the first 3 mo after transplantation; 15 recipients (50%) developed thrombocytopenia (platelet count $<150\times10^9$/mL). This occurred in postoperative week 1 (n = 8), weeks 4 to 8 (n = 3), and month 3 (n = 4) and was generally mild (75 to 150×10^9/mL in 12 of 15; 50 to 75×10^9/mL in 2 of 15; 25 to 50×10^9/mL in 1 of 15). The median (IQR) peak D-dimer result after transplantation was 2000 (1000–5700) FEU, occurring between postoperative days 1 and 36 (**Figure S1, SDC**, http://links.lww.com/TP/C444). The median (IQR) nadir fibrinogen result was 3.1 (2.3–3.9) g/L, occurring between day 1 and 59. There were no recipient fibrinogen results of <2 g/L after transplantation.

Nineteen recipients were tested for anti-PF4 antibodies (using ELISA testing) between 1 and 58 d after transplantation; no anti-PF4 tests were performed before transplantation. Two recipients had positive anti-PF4 antibody results. In both cases, the positive result was the first test performed after transplantation and the antibody titer reduced on repeat testing (**Figure S2, SDC**, http://links.lww.com/TP/C444). In the first recipient, who had received their second dose of ChAdOx1 nCoV-19 vaccine 25 d before transplantation, the first positive anti-PF4 result was detected at 7 d posttransplant (sample/cutoff value ratio 2.1). This recipient developed concurrent thrombocytopenia (platelet count, 102×10^9/mL) and elevated D-dimer levels (peak 7000 FEU), which subsequently resolved. In the second case, in which no vaccination for SARS-CoV-2 had been received before transplantation, the first positive result was detected at 31 d posttransplant (sample/cutoff value ratio 1.5); the platelet count and D-dimer results remained within normal ranges. Both recipients with positive anti-PF4 results had immediate graft function, no hemorrhagic or thrombotic complications, good graft function (creatinine 84 and 44 μmol/L, respectively), and normal platelet counts at the end of follow-up. All 3 recipients who suffered major postoperative complications had negative anti-PF4 antibody results. No recipients were diagnosed with VITT after transplantation.

DISCUSSION

In this follow-up national case series, we have found 97% and 90% patient and graft survival, respectively, with a minimum 3-mo follow-up in 30 recipients of

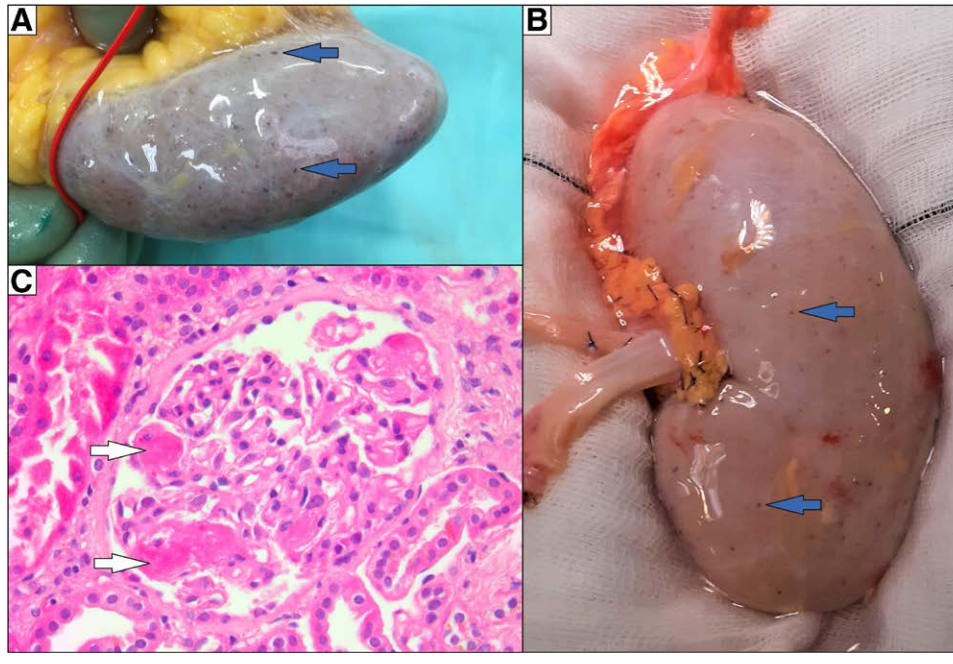

FIGURE 2. Preimplantation images of kidneys from donors with vaccine-induced immune thrombocytopenia and thrombosis. A and B, Photos of kidneys before implantation, showing multiple petechiae on the surface of the organ (blue arrows). C, Histology slide (hematoxylin and eosin stain) of preimplantation biopsy, showing multiple glomerular microthrombi (white arrows). Image created with BioRender.com.

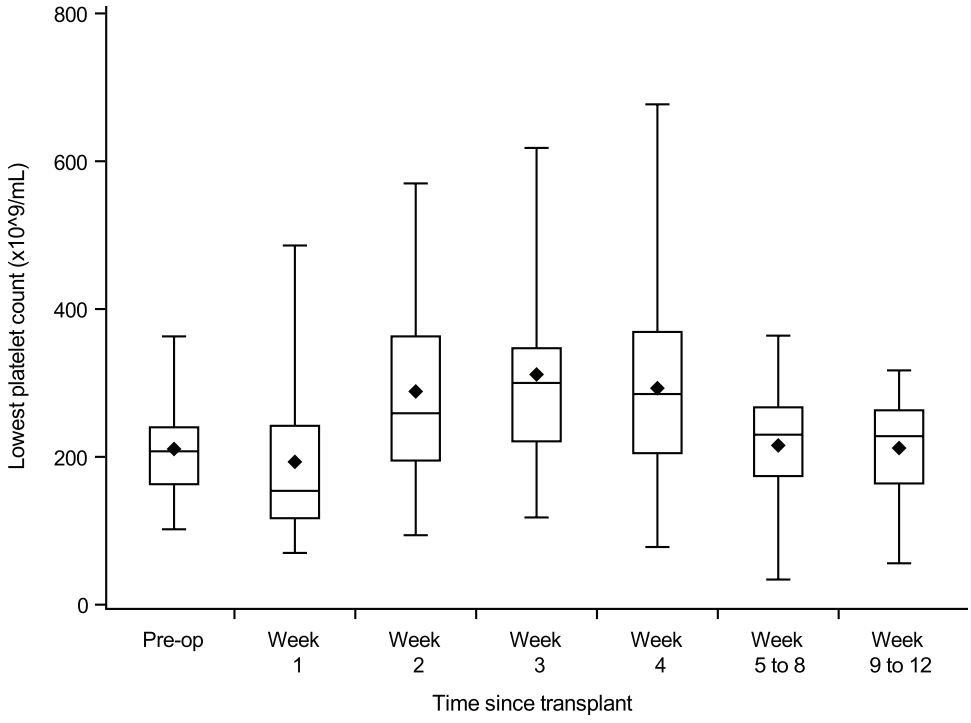

FIGURE 3. Box and whisker plot of platelet counts over time in recipients of kidney transplants from donors with vaccine-induced immune thrombocytopenia and thrombosis. Diamond, mean; line, median; box, interquartile range; whiskers, minimum/maximum. Values are the lowest platelet count reported in each time period.

kidney transplants from donors with confirmed VITT.[5] There were early hemorrhagic complications affecting three recipients, resulting in the loss of two grafts. All of these occurred in patients with independent risk factors for bleeding; in one of these cases the clinical team could not completely exclude a contribution of VITT in the donor. Following transplantation, 2 recipients had detectable anti-PF4 antibodies without any other features of VITT. None of the recipients have yet been diagnosed with VITT.

Earlier reports from the period when VITT was emerging as a novel clinical syndrome found some catastrophic early complications in recipients of liver transplants from donors with VITT,[5,8] resulting in a moratorium on liver transplants from these donors in the United Kingdom except in exceptional circumstances.[12] Although the follow-up is relatively short, our results in kidney transplant recipients are reassuring, with outcomes comparable with national data and no evidence of transmitted disease.[19]

Organ transplantation carries an unavoidable but low risk of disease transmission from donor to recipient. Because VITT is believed to be antibody-mediated, there is a possible risk of donor-transmitted disease in recipients of organs from donors with VITT via graft passenger leukocytes. During our study period, as the international community learned more about this novel disease, transplant clinicians and their patients have had to balance the unknown risk of disease transmission against the benefit of accepting organs from relatively young and otherwise healthy organ donors with VITT. In the context of VITT, the transfer and persistence of antibody-producing donor lymphocytes, so-called passenger leukocyte syndrome,[20] could theoretically manifest as a spectrum of syndromes, from transient detection of anti-PF4 antibodies to overt clinical sequelae and development of life-threatening VITT in the recipient. The incidence and severity of thrombocytopenia in our case series were in keeping with that seen in recipients from non-VITT donors.[21,22] To date, 1 case of thrombocytopenia and elevated anti-PF4 antibodies (without confirmed thrombosis) has been reported in the recipient of a liver transplant from a donor with VITT.[23] At the time of writing, there are no other published reports of detectable anti-PF4 antibodies in recipients of kidney transplants from donors with VITT. The only other case series in this area to date is a report from France that found good early outcomes in 6 kidney transplants from 3 donors with VITT.[6] In contrast to this study, the donors in our series were relatively young with little comorbidity; this may reflect differences in national vaccine rollout.

The clinical significance of the anti-PF4 antibodies detected in 2 recipients in our case series is uncertain. It is reassuring that neither patient experienced significant postoperative complications nor were they diagnosed with VITT. Recent evidence from patients with VITT suggests that antibody levels wane after diagnosis.[24]

It is notable that over half of the kidneys in this case series had multiple petechiae noted before implantation, suggesting established VITT-related microvascular renal pathology. The outcomes in these grafts were similar to those with normal appearances. This suggests that parenchymal petechiae may not be a significant concern in this context.[6] The clinical significance of glomerular microthrombi on preimplantation biopsies is uncertain; although we do not have follow-up biopsies in our series, previous studies have demonstrated rapid resolution and little or no impact on subsequent graft function.[16,25]

This is the largest case series of transplant recipients from donors with VITT to date. The follow-up period is

sufficient to exclude disease transmission with reasonable confidence, given existing evidence on the expected period within which passenger lymphocyte syndrome manifests in solid organ transplant recipients.[17,20] The UKTR has national coverage and good data completeness, permitting reliable identification of donors with VITT and complete recipient outcome reporting.

Our study has some limitations. Donors with VITT were selected according to national policies and clinical judgment, so our findings do not mean that all individuals dying because of VITT would be suitable and safe organ donors. The relatively small number of transplants limits the comparison of outcomes and complications with published data. Only two-thirds of our recipient cases underwent anti-PF4 antibody testing after transplantation, despite recommendations in national guidance, which limits the interpretation of these results.

Current UK guidance issued by NHSBT advises cautious use of organs from donors with VITT, and vigilance for features that may herald the development of VITT in the recipient. Serial monitoring of the platelet count, anti-PF4 antibodies, D-dimer, and fibrinogen levels is recommended for at least the first month after transplantation. A fall in the platelet count, rise in the D-dimer or anti-PF4 antibody level, or evidence of new thrombosis should prompt heightened surveillance. In recipients with suspected disease transmission, clinicians should consider alternative causes of thrombocytopenia, avoid platelet transfusions and heparin-based anticoagulants, seek urgent expert clinical hematology input, and inform the national transplant authority. At present, it is recommended that liver, lung, small bowel, and pancreas transplantation should be avoided, unless in exceptional circumstances, because the risk of donor-transmitted disease may be greater in organs with a high passenger leukocyte burden.[12] Recently published evidence may begin to challenge these recommendations.[8]

The emergence of VITT, a novel syndrome that is theoretically transmissible, has resulted in challenges for the international transplant community. The optimal donor management, organ retrieval, and recipient immunosuppression strategies remain unclear. Our findings advance existing knowledge and provide reasonable reassurance that good outcomes are likely after kidney transplantation from donors with VITT.[5,6,8,23] There remains an ongoing need for vigilance for donor-related complications in these recipients.

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