common causes of swelling in arteriovenous fistulae (AVFs) include thrombosis, infection, aneurysm, and superior vena cava (SVC) obstruction secondary to previous dialysis vascular catheter use. Malignancies confined in AVFs are rare and have been described in case series and case reports, mostly in immunosuppressed patients. Patients who undergo transplantation frequently have functioning or nonfunctioning AVFs. The risk of malignancy is increased in this patient group and thus should be considered in patients presenting with symptomatic AVF. The most common histopathological diagnosis is angiosarcoma. Plasmacytoma-like posttransplant lymphoproliferative disease (PTLD) confined in an AVF has not been previously described.

**CASE PRESENTATION**

A 43-year old Asian man with adult dominant polycystic kidney disease (ADPKD) started hemodialysis via a permanent dialysis right internal jugular line in 2011 and subsequently had a left branchio-cephalic AVF formed in 2013. He received a deceased-donor renal transplant in January 2016, with a single dose of 30 mg alemtuzumab and 500 mg methylprednisolone at induction, and was subsequently maintained on tacrolimus monotherapy with a steroid-sparing protocol (tacrolimus trough levels 6–8 ng/l). He presented in July 2017 with shortness of breath on exertion and head, neck, and left arm swelling where the functioning AVF was sited. There were no cutaneous manifestations such as cellulitis, discoloration, or lumps.

Initial investigations with chest X-ray showed bilateral pleural effusions (Figure 1a). Basic laboratory results were unremarkable, with stable serum creatinine 200 μmol/l and normal hemoglobin, white blood cell count, liver function test results, and C-reactive protein. A chest, abdomen, and pelvis computed tomogram with i.v. contrast demonstrated a large right and a smaller left pleural effusion, moderate pericardial effusion (measuring 20 mm), and a short occlusion of the SVC with marked dilated collateral veins in the chest wall and a large azygos vein. There was no evidence of malignancy or lymphadenopathy on the computed tomogram. An echocardiogram showed moderate pericardial effusion as described above, and preserved left ventricular and right ventricular function. A fistulogram was performed with a view to perform SVC venoplasty; however, the procedure was unsuccessful because of a total occlusion of the distal left innominate vein (Figure 1b, c). To improve symptoms from shunted arterial blood of the left-sided circulation to the right-sided circulation, the patient underwent AVF excision and ligation, with good response (Figure 1d).

The excised aneurysmal fistula was sent for routine histopathology examination as per our unit’s policy for all excised AVF specimens. Macroscopically, the tissue
examined measured 80 mm in length and 20 mm in diameter, with wall thickness ranging from 1 mm to 2 mm, and had a focal calcification with a completely blocked lumen from necrotic hemorrhagic material. Microscopic examination revealed thrombus with thickening and fibrosis of the vessel wall. The thrombus showed features of recanalization. A patchy inflammatory infiltrate was seen in the wall, composed of histiocytes, eosinophils, lymphocytes, and plasma cells. In 1 area, a particularly dense collection of plasma cells was noted. In the inflammatory infiltrate, most lymphoid cells were CD3- and CD5-positive T cells, with fewer CD20-positive B cells; cyclin D1 was negative in lymphoid cells. Plasma cells were CD138 positive, with lambda light chain restriction (Figure 2). Molecular diagnostistics performed on DNA extracted from formalin-fixed paraffin embedded tissue detected clonality in IgH and IgK (Qiagen QIAsymphony DSP DNA Mini kit [Hilden, Germany], Invivoscribe IdentiClone IgH and IGK B cell Clonality Assay, Applied Biosystems GeneMapper analysis software). Epstein–Barr virus–encoded RNA (EBER) in situ hybridization was negative. Features were in keeping with plasmacytoma-like PTLD.

Following histological diagnosis, the patient underwent further workup. Lactate dehydrogenase, adjusted calcium and β2-microglobulin levels were normal. Imaging with nuclear medicine whole-body fluorodeoxyglucose (FDG) positron emission tomography/computed tomography did not show evidence of FDG avid disease elsewhere. An M-spike was undetectable on protein electrophoresis/immuno fixation and urine electrophoresis/immuno fixation. Serum kappa/lambda light chain ratio was normal. The serum Epstein–Barr DNA titer was <500 copies/ml. Immunosuppression was reduced, aiming for tacrolimus trough levels of 4 to 5 ng/ml. The patient remains on regular renal and hematological follow-up 12 months after the excision of the AVF, with no evidence of disease recurrence. The pleural effusion has significantly improved (Figure 1d). The patient’s renal allograft function during the acute presentation and, on follow-up through the reduction of immunosuppression, has remained stable (serum creatinine 170–200 μmol/l, Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] 35–42 ml/min per 1.73 m²).

**DISCUSSION**

This is the first description of localized extramedullary plasmacytoma-like PTLD presenting in a disused AVF following transplantation. Initial presentation, laboratory testing, and imaging modalities performed did not raise the suspicion of malignant disease. Monoclonal restriction was suggested only after microscopic examination of the excised tissue from the AVF, which is performed routinely in all AVF specimens in our unit. Diagnosis was confirmed with molecular diagnostistics. This case highlights the importance of histopathology in the diagnosis and management of an extramedullary plasmacytoma-like PTLD confined in the AVF that could easily be missed.

Posttransplant lymphoproliferative disease is the second most common malignancy after skin cancer in adult solid organ transplant recipients, with reported incidence ranging from less than 2% to as high as 10%. In renal transplantation, the reported incidence was 1% at 5 years posttransplantation, increasing to 2.1% by 10 years, in a French kidney transplant registry. Posttransplant lymphoproliferative disease is a recognized complication of immunosuppression regimens that can occur at any time in the posttransplantation period but that has a higher incidence in the first year. The previously reported PTLD mortality rates of up to 50% have improved in the modern era with the use of rituximab; however, the magnitude of this improvement is difficult to ascertain because of the lack of large national or international studies and the variability of factors that affect prognosis, such as the histologic subtype, timing of presentation, and other clinical, disease, and treatment approach characteristics. Most types of PTLD derive from B cells as high-grade non-Hodgkin’s lymphomas. T-cell neoplasms constitute around 15% of all PTLDs, and rare natural killer cell lineages are also reported. The oncogenic role of EBV is well described. It causes B-cell blastic transformation and uncontrolled proliferation, leading to development of lymphomas in the context of diminished immune surveillance and decreased EBV-specific cytotoxic T lymphocytes as a result of immunosuppression.

However, EBV-negative PTLDs are more common than previously thought and were reported in up to 40% to 50% of cases in recent studies. Established risk factors for the development of PTLD include the use antithymocyte globulin leuko-depleting antibodies at induction, tacrolimus maintenance, young age, small bowel and lung transplantation, and EBV seronegativity before transplantation. Posttransplant lymphoproliferative disease commonly presents with extranodal involvement, and thus a high index of suspicion is important for early diagnosis. Histopathology and cellular markers are important to determine the cell lineage and to provide an accurate diagnosis to guide treatment approaches. B
cells possess CD19, CD20, CD72, and CD79a, whereas T cells express CD2 and CD3. CD45 may be found on both T and B cells. CD20-expressing lesions are likely to benefit from rituximab. CD30, expressed in several anaplastic lymphoproliferative disorders, is found to be upregulated in EB-transformed B cells.

In the current World Health Organization (WHO) Classification, most types of PTLD are classified into 6 categories as follows: (i) plasmacytic hyperplasia, (ii) infectious mononucleosis–like PTLD, (iii) florid follicular hyperplasia, (iv) classic Hodgkin’s lymphoma–like PTLD, (v) polymorphic PTLD, and (vi) monomorphic PTLD (B-cell, T-cell, or natural killer–cell types). Monomorphic PTLDs are further subclassified according to the lymphomas that they resemble (i.e., diffuse large B-cell lymphoma, Burkitt lymphoma, peripheral T-cell lymphoma, etc.).

Plasmacytoma-like PTLD is a rare variant of B-cell monomorphic PTLD, which resembles the extramedullary plasmacytomas in the nontransplant population and has been described in only case reports and small cases series (Table 1). Unlike other PTLDs, plasmacytoma-like PTLD presents late after transplantation, in some cases more than 10 years, suggesting that long-term antigen stimulation plays a role in the pathogenesis of this subtype of PTLD. Extramedullary involvement is common, usually without bone marrow involvement or bone lytic lesions. Review of all

Figure 1. (a) Chest X-ray (CXR) on presentation. (b) Superior vena cava (SVC) obstruction with collateral veins. (c) Curved multiplanar image of computed tomographic venogram, showing short-distance occlusion at the confluence of left innominate vein (LT INV) and SVC. Ao, aorta. (d) CXR after arteriovenous fistula (AVF) excision.
published case studies and case series showed that bone lesions were present in 4 of 32 cases reporting bone involvement. Three of 30 cases with available bone marrow results had bone marrow involvement. Remarkably, the primary site of disease was skin in 20 of 54 cases, which highlights the importance of dermatological surveillance and skin biopsies in immunosuppressed patients (Table 1). Paraprotein detection by serum electrophoresis is not possible in all cases, and, if detected, Ig levels are usually lower compared to those in plasma cell myeloma. Free kappa/lambda light chain ratios were not reported consistently in these case studies. Histopathologically, plasmacytoma-like PTLDs resemble myeloma in non-immunosuppressed patients. They are characterized by well-differentiated Marschalko-like plasma cells with light chain restriction, expressing CD138 and lacking CD20, although, in a minority of cases, CD20 positivity has been reported. Epstein—Barr virus—encoded RNA in the tumour using EBER in situ hybridization is positive in approximately 50% in the case studies. Importantly, immunohistochemical staining for the latent membrane protein 1 (LMP-1), Epstein—Barr nuclear antigen 2, Epstein—Barr ZEBRA antigen when reported, was usually negative, underscoring the importance of EBER in situ hybridization. Epstein—Barr virus—DNA titers in serum were inconsistently reported. Treatment approaches were tailored to the individual cases and included reduction of immunosuppression with or without surgery, and irradiation for localized disease and addition of anti—plasma cell chemotherapy in more advanced disease. Some case studies reported curative responses with reduction of immunosuppression but had a wide range of follow-up times. Overall, among 49 case reports that reported on survival, 18 (37%) patients died. In a national study of US renal transplant recipients from the United States Renal Data System (USRDS), multiple myeloma—PTLD had the lowest 10-year survival rate (26%) compared to other subtypes of PTLD, although plasmacytoma-like PTLD was not differentiated in this study.

Figure 2. Biopsy specimen. (a) Posttransplant lymphoproliferative disease (PTLD) granulomas show presence of granulomata within the lesion. (b) PTLD shows the infiltrate with many eosinophils, histiocytes, plasma cells, and lymphocytes. (c) CD138 highlights the many plasma cells within the lesion. (d) Plasma cells express lambda light chain and are restricted for lambda light chain (seen on lambda original magnification stain).
Table 1. Published case studies and case series of plasmacytoma-like posttransplant lymphoproliferative disease

| No. | Reference | Age (yr) | Type of Tx | Site | Ind.IS | Maint. IS | Time Post TX (mo) | CD 138 | CD 20 | LC | EBER | Ser. | Treatment | Bone | FU (mo) | RS | Outcome |
|-----|-----------|----------|------------|------|--------|-----------|-----------------|--------|------|----|------|------|-----------|------|---------|----|---------|
| 1   | S13       | 37       | Liver      | Lymph N.| NR    | Tac       | 59              | Y      | N    | L  | N    | NR   | RIS, Chemo | N    | 100     | CR | Death   |
| 2   | S13       | 48       | Liver      | Lymph N.| NR    | CsA       | 77              | N      | Y    | K  | Y    | NR   | RIS, Chemo | N    | 101     | CR | Alive (relapse) |
| 3   | S13       | 17       | Heart      | Adenoids| NR    | Tac       | 114             | Y      | N    | L  | N    | NR   | RIS       | N    | 27      | CR | Alive   |
| 4   | S13       | 52       | Kidney     | Skin   | NR    | CsA       | 86              | Y      | N    | Y  | L    | NR   | RIS       | N    | 42      | CR | Alive (relapse) |
| 5   | S12       | 56       | Kidney     | Stomach| NR    | CsA, MMF, S | 131            | Y      | N    | L  | N    | NR   | RIS       | N    | 18      | CR | Death   |
| 6   | S12       | 51       | Lung       | Adenoids| NR    | CsA, AZA | 168             | Y      | N    | K  | Y    | NR   | Unchanged, IR | N    | 10      | CR | Alive   |
| 7   | S12       | 68       | Heart      | Adenoids| NR    | CsA, AZA | 48              | Y      | N    | K  | Y    | NR   | RIS, Chemo | N    | 14      | DP | Alive   |
| 8   | S12       | 69       | Liver      | Liver   | NR    | Tac, MMF, S | 8              | Y      | N    | NR | Y    | NR   | RIS       | N    | 5       | SD | Death   |
| 9   | S11       | 53       | Heart      | Adenoids| NR    | Tac       | 71              | Y      | N    | K  | N    | NR   | RIS, Chemo | N    | 68      | CR | Alive   |
| 10  | S11       | 65       | Lung       | Skin   | NR    | CsA, MMF, S | 167            | Y      | N    | NR | Y    | N    | RIS, surgery, IR | N    | 1       | SD | Death   |
| 11  | S11       | 56       | Kidney     | GI     | NR    | CsA, AZA, S | 172            | Y      | N    | NR | Y    | NR   | --        | NR   | 89      | CR | Alive (relapse) |
| 12  | S11       | 62       | Liver      | Liver   | NR    | Tac       | 16              | Y      | N    | NR | Y    | NR   | RIS, Chemo, IR | NR   | 12      | DP | Death   |
| 13  | S11       | 71       | Heart      | Adenoids| NR    | Tac, AZA | 70              | Y      | N    | NR | N    | NR   | RIS, Chemo, IR | NR   | 12      | DP | Alive   |
| 14  | S11       | 54       | Kidney     | Skin   | NR    | CsA      | 288             | Y      | N    | NR | Y    | NR   | RIS       | N    | 9       | CR | Alive   |
| 15  | S11       | 53       | Kidney     | Adenoids| NR    | Tac, MMF, S | 44             | Y      | N    | NR | N    | NR   | Surgery     | NR   | 3       | CR | Alive   |
| 16  | S15       | 33       | Heart      | Heart   | NR    | FK, MMF, S, R | 60             | Y      | NR  | L   | N    | NR   | RIS, Chemo | N    | 36      | -- | Alive   |
| 17  | S19       | 45       | Kidney     | Adenoids| NR    | CsA, AZA, S | 84             | Y      | N    | L  | Y    | NR   | RIS, IR    | N    | 84      | CR | Death (relapse) |
| 18  | S20       | 56       | Kidney     | Skin   | NR    | Unknown   | 166             | Y      | N    | NR | Y    | --   | RIS, surgery, IR | NR   | 9       | CR | Death (DP) |
| 19  | S21       | 59       | Heart      | Skin   | NR    | CsA, AZA, S | 118            | NR    | NR  | K   | NR   | NR   | Chemo      | Y    | 7       | SD | Alive   |
| 20  | S21       | 61       | Heart      | Skin   | NR    | CsA, AZA, S | 118            | NR    | NR  | L   | NR   | NR   | NR        | NR   | 6       | CR | Alive   |
| 21  | S22       | 63       | Heart      | Skin   | NR    | CsA, AZA, S | 96             | NR    | NR  | K   | N    | N    | Chemo, IR  | N    | 60      | CR | Alive   |
| 22  | S23       | 57       | Heart      | Skin   | NR    | CsA      | 122             | Y      | N    | L  | Y    | NR   | RIS, surgery, IR | N    | 60      | RD | Death (relapse) |
| 23  | S24       | 74       | Kidney     | Skin   | NR    | CsA, AZA, S | 96             | Y      | N    | K  | N    | NR   | RIS, Chemo, IR, RX | N    | 100     | CR | Alive (relapse) |
| 24  | S25       | 53       | Heart      | Skin   | NR    | CsA, AZA, S | 180            | Y      | N    | K  | Y    | NR   | RIS       | IR   | N    | 9   | SD      | Death |
| 25  | S26       | 56       | Heart      | Pentoneum| NA    | NA        | 36             | NA     | NA  | L   | NA   | NA   | NA        | NA   | NA      | NA | NA      | NA |
| 26  | S27       | 58       | Lung       | Adenoids| NR    | Tac, S, Sr | 118            | Y      | N    | L  | Y    | NR   | RIS, IR    | Y    | 6       | DP | Death   |
| 27  | S28       | 55       | Liver      | Pleura, kidney | NA  | NA        | 6              | NA     | NA  | L   | N    | NA   | NA        | RIS, Chemo | NA  | NA  | PR    | Death |
| 28  | S29       | 66       | Liver      | Liver   | NR    | Tac, MMF, S | 2              | Y      | NR  | L   | Y    | NR   | RIS       | N    | 2       | CR | Alive   |
| 29  | S30       | 52       | Liver      | Abdo, bladder | NA  | NA        | 17             | NA     | NA  | K   | Y    | NR   | RIS, IR    | IR   | NA      | NA | CR      | Alive |
| 30  | S31       | 59       | Kidney     | Rennal graft | NA  | NA        | 84             | NA     | NA  | K   | N    | NA   | RIS, IR    | NA   | 24      | CR | Alive   |
| 31  | S32       | 63       | Kidney     | Adenoid | NA    | NA        | 72             | Y      | N    | L   | N    | NA   | NA        | NA   | NA      | NA | NA      | NA |
| 32  | S33       | 33       | Kidney     | Lymph N. | NA    | NA        | 118            | NA     | NA  | K   | N    | NA   | NA        | NA   | NA      | NA | NA      | NA |
| 33  | S34       | 52       | Kidney     | Rt flank | No   | Tac, MMF, S | 11             | Y      | N    | K  | NA  | NA   | RIS, IR, ASCT | N    | 31      | CR | Alive (relapse) |
| 34  | S35       | 10       | Kidney     | Lt groin | NA    | CsA, AZA, S | 60             | Y      | NA  | L   | Y    | NA   | RIS       | NA   | 20      | CR | Alive   |
| 35  | S36       | 59       | Kidney     | Skin, abdomen | NR  | CsA, AZA, S | 60             | Y      | N    | K  | Y    | NR   | RIS, Chemo, IR | N    | 2       | Death |
| 36  | S37       | 65       | Kidney     | Adenoid | NR    | CsA, S    | 136            | Y      | N    | K  | Y    | NR   | RIS, Chemo, IR, ASCT | NR   | 8       | PR | Death   |
More recently, Rosenberg et al. attempted a prognosis and survival analysis study of plasma cell myeloma-PTLD from the Scientific Registry of Transplant Recipients (SRTR) in the United States by comparing outcomes with matched multiple myeloma (MM) controls from the general population. Approximately one-half of the myeloma-PTLD case had extramedullary disease, although plasmacytoma-like PTLD was not reported independently. The study reported inferior outcomes of the myeloma/PTLD patients compared to MM controls in the early study period (2000–2006), which subsequently ameliorated, demonstrating similar overall survival in the 2 groups for the latter study period (2007–2010). This was attributed to the improvement of non-PTLD-specific mortality due to the use of novel, less cytotoxic agents.

Advanced age, Caucasian race, elevated serum creatinine at baseline, and the use of OKT3 at induction negatively affected overall survival. We have previously reported the first case of diffuse large B-cell lymphoma confined in a disused AVF posttransplantation. In this report, we describe the first case of plasmacytoma-like PTLD in a renal transplant patient presenting with swollen functioning AVF. Appropriate histopathological workup was critical in unraveling the underlying hematological diagnosis and guiding management decisions in a multidisciplinary approach with hematology, renal, and histopathology input.
panel and staining with additional molecular diagnostics is important for early diagnosis and improved patient outcomes (Table 2).

**DISCLOSURE**

FWKT is the chief investigator of an international clinical trial of spleen tyrosine kinase inhibitor in IgA nephropathy (funded by Rigel Pharmaceuticals, San Francisco, California, USA); has received research project grants from Baxter Biosciences, Boehringer Ingelheim, and MedImmune; and has consultancy agreements with Rigel Pharmaceuticals and Novartis. All the other authors declared no competing interests.

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**SUPPLEMENTARY MATERIAL**

Supplementary References.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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