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Treatment of Concurrent Minimal Change Disease and Epstein Barr Virus–Driven Post-transplant Lymphoproliferative Disorder With Rituximab Following Hematopoietic Stem Cell Transplantation

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is increasingly used as first-line management in adults with aplastic anaemia even in the absence of a sibling donor. HSCT can be associated with a broad range of acute and chronic complications, including infections, graft versus host disease, and other immune complications. Renal complications are common following HSCT, including acute kidney injury (10%–70%), chronic kidney disease (7%–48%), and thrombotic microangiopathy and nephrotic syndrome (0.4%–4%).[1] In addition, renal manifestations of both acute and chronic graft versus host disease (GvHD) have been described, including nephrotic syndrome, which usually occurs as a late complication most commonly due to membranous nephropathy.[2–4]

Post-transplant lymphoproliferative disorder (PTLD) post HSCT occurs in up to 3.2% of allogeneic transplant recipients and is almost exclusively Epstein-Barr virus (EBV) related.[5] Management includes reduction of immunosuppression, rituximab, and/or chemotherapy in higher risk disease.

Minimal change disease (MCD) complicates Hodgkin disease in approximately 0.4%, and less commonly non-Hodgkin lymphoma.[6,7]

We present, to our knowledge, the first reported case of MCD associated with EBV-driven PTLD following HSCT and demonstrate an excellent response to rituximab with remission of nephrotic syndrome, normalization of Epstein-Barr viremia, and full clinical remission of PTLD.

CASE PRESENTATION

We report a 36-year-old white male with very severe aplastic anaemia who underwent allogeneic HSCT following a 3-month admission with pancytopenia, neutropenic fevers, and a fungal lower respiratory tract infection. His history includes stable ulcerative colitis, and he was on no regular medications.

He received an unrelated donor stem cell transplant with fludarabine, cyclophosphamide, and alemtuzumab conditioning. The transplant was a 10/10 human leukocyte antigen match with a permissive mismatch for human leukocyte antigen–DPB1, with recipient and donor cytomegalovirus IgG negative and anti-Epstein-Barr Nuclear Antigen IgG positive. Post-transplant 3 mg/kg cyclosporin was commenced on day −1, with neutrophil engraftment on day +10. Stage 1 acute kidney injury occurred day +15, urine microscopy demonstrated decoy cells, with a urinary BK level of >92,000,000 copies per milliliter. Both resolved with hydration and reduced cyclosporin dose, with mycophenolate mofetil then added. Acute skin GvHD occurred on day +24, treated with 1 mg/kg of i.v. methylprednisolone, followed by 1 mg/kg of prednisolone, which was weaned and discontinued by

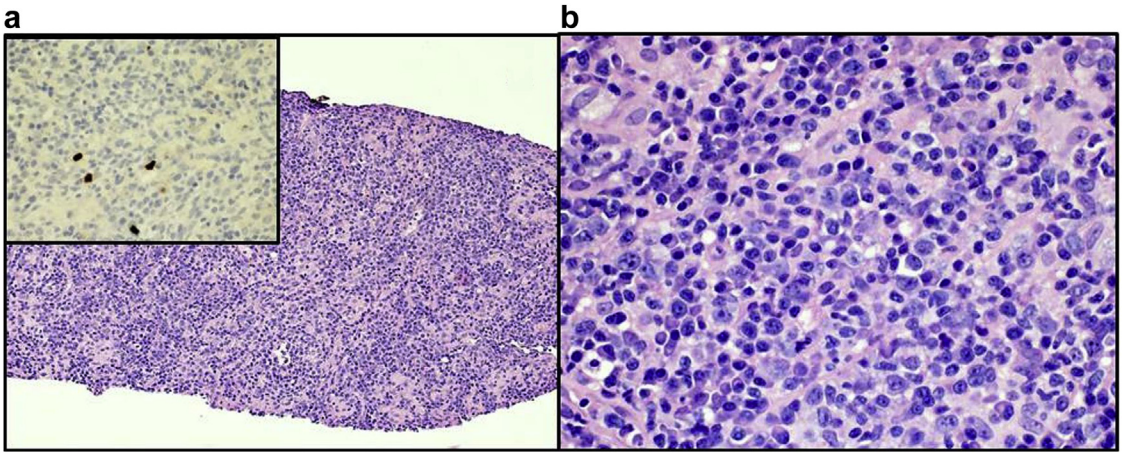

Figure 1. Core biopsy of a right-sided cervical level 2 lymph node showing effacement of the architecture by a proliferation of immunoblasts, plasma cells, plasmacytoid cells, and medium-sized lymphocytes (a: hematoxylin-eosin, original magnification ×100; and b: hematoxylin-eosin, original magnification ×400). Mitotic features and Epstein-Barr virus–encoded small RNA-positive cells are also seen (a; small window).

day +40. Chimerism was assessed by peripheral blood analysis at day 100 showing 100% donor cells CD15/CD19 and 49% donor cells CD3, with lymphopenia.

Twenty weeks post-transplant, the patient developed small volume cervical, occipital, posterior auricular lymphadenopathy with a whole blood EBV polymerase chain reaction of 40,000 copies per milliliter. Cervical lymph node biopsy demonstrated polymorphic PTLD with scattered EBV positivity (Figure 1) and positron emission tomography scan confirmed stage 3 disease. The patient continued on maintenance cyclosporin at this time, with no additional immunosuppression given.

Simultaneously, our patient re-presented with edema, frothy urine, and 10 kg weight gain. Clinical examination highlighted pitting edema, raised jugular venous pressure, and crepitations bibasally on chest auscultation. Table 1 summarizes the relevant investigations confirming nephrotic syndrome, and a renal biopsy was performed confirming a diagnosis of MCD (Figure 2).

Rituximab was commenced with 3 weekly doses of 375 mg/m^2 leading to an undetectable EBV titer, resolution of palpable lymphadenopathy, normalization of serum albumin, and improvement of urinary protein-creatinine ratio to 66 mg/mmol 18 days after the first dose of rituximab. No corticosteroids were given during this period. On submission, the patient's nephrotic syndrome and PTLD remain in clinical remission. He continues on cyclosporin with a trough level of 30 ng/ml, and 3 mg daily budesonide, which was commenced 175 days after the onset of nephrotic syndrome, for skin and gastrointestinal GvHD and diarrhea. Ten months following rituximab, his CD19 cells had repopulated at 0.038, and his EBV titer became positive at 14,000 copies per milliliter and he received a further rituximab dose. His nephrotic syndrome has remained in remission.

DISCUSSION

HSCT is potentially curative therapy for a range of hematological conditions, including aplastic anaemia. This is increasingly favored over immunosuppression

Table 1. Investigations

Investigation	Result
Hemoglobin	102 g/dl
White cell count	4.4 × 10^9/l
Platelets	213 × 10^9/l
Sodium	141mmol/l
Potassium	4.5 mmol/l
Creatinine	121 micromol/l
Estimated glomerular filtration rate	61 ml/min per 1.73 m^2
Serum albumin	16 g/l
Alanine transaminase	14 IU/l
Alkaline phosphatase	88 IU/l
Bilirubin (total)	7 μmol/l
Adjusted calcium	2.37 mmol/l
Immunoglobulins	
IgA	0.84 g/l
IgG	7.08 g/l
IgM	2.64 g/l
Serum electrophoresis and immunofixation	Paraprotein too faint to quantify
Hepatitis C ribonucleic acid, hepatitis B core-antibody and surface antigen, HIV antibodies	All negative
Whole blood cytomegalovirus, adenovirus and BK polyomavirus polymerase chain reaction	Not detected
Epstein-Barr virus polymerase chain reaction	40,000 copies per milliliter
Trough cyclosporine level	40 ng/ml
Antinuclear antibodies, anti-cytoplasmic neutrophil antibodies, anti-glomerular basement membrane antibodies, double-stranded DNA, and rheumatoid factor	All negative
Complement factor C3	0.58 g/l
Complement factor C4	0.17 g/l
Urine protein-creatinine ratio	937 mg/mmol
Ultrasound kidneys	13.6 cm and 13 cm unobstructed kidneys with normal corticomedullary differentiation

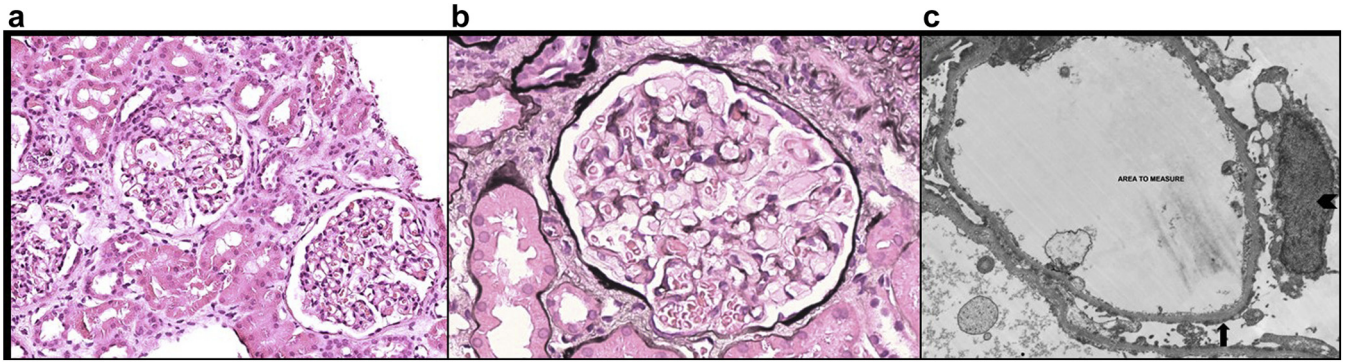

Figure 2. Renal biopsy capturing 12 glomeruli, with no sclerosis, crescents, spikes, amyloid material, or duplications, and normal mesangial matrix and cell numbers. Immunohistochemistry was negative for IgG, IgA, and IgM; complement (C3 and C1q), BK virus, and Epstein-Barr virus. (a) Medium power image showing 3 morphologically normal glomeruli surrounded by well-preserved tubules (hematoxylin-eosin, original magnification ×20). (b) High-power image of a morphologically normal glomerulus (Periodic acid methenamine silver, original magnification ×40). (c) Electron micrograph showing a capillary loop with effacement of the podocyte foot processes (arrow) and a podocyte nucleus (arrowhead); no electron-dense deposits were found, and the glomerular basement membrane was morphologically normal (image courtesy of Leicester Royal Infirmary electron microscopy department, original magnification ×2000).

in young, fit patients. Matched unrelated donor transplants are now considered, where previously only a sibling donor would be considered due to improved and more comparable outcomes.

Acute kidney injury is common post HSCT, with multiple causes including sepsis, transplant-associated thrombotic microangiopathy, volume depletion from gastrointestinal losses, and nephrotoxic medications, including cyclosporin and chemotherapy. Nephrotic syndrome post HSCT is rare, with membranous nephropathy accounting for two-thirds, MCD in one-quarter, and a wide spectrum of other renal pathology for the remainder.[8] GvHD is diagnosed simultaneously in 47%, often coinciding with immunosuppression withdrawal.[4] Treatment strategies include corticosteroids, mycophenolate mofetil, reintroduction of calcineurin inhibitors, and rituximab. A small series of 4 patients with membranous nephropathy post HSCT receiving rituximab as a first- or second-line therapy showed complete and sustained remission in all cases.[9] Urinary sediment abnormalities occur in 10% of patients with EBV viremia, which is associated with a range of renal pathologies, including interstitial nephritis and MCD.[S1]

PTLD is well-described post HSCT. The vast majority of PTLD involves EBV-driven transformation of B cells, usually within the first few months following transplantation, before reconstitution of effective T-cell immunity. The disease comprises a heterogeneous group of pathological entities and can range from an indolent to a highly aggressive disorder. Presenting features include fever, lymphadenopathy, and rising EBV polymerase chain reaction titer. There are 4 main histological categories of PTLD: monomorphic, polymorphic, T-cell neoplasms, and classic Hodgkin lymphoma-like. The diagnosis of proven EBV disease requires EBV nucleic acid or protein detection on tissue and clinical symptoms or signs. Risk factors for PTLD include mismatched donor, T-cell depletion, severe GvHD, second HSCT, and EBV mismatched transplant.[S2] Routine pretransplant testing and post-transplant surveillance of EBV polymerase chain reaction is performed to detect primary or reactivated EBV infection. Treatment options include reduction of immunosuppression to allow restoration of cytotoxic T cells, anti-CD20 monoclonal antibodies, chemotherapy, EBV- cytotoxic T lymphocytes, or donor lymphocyte infusion. Approximately 70% of patients treated with rituximab have a positive outcome.[5] There is some evidence that the use of preemptive rituximab can reduce the risk of EBV viremia and PTLD, although the overall benefit is unclear.[S3]

MCD accounts for 20% of nephrotic syndrome in adults and up to 90% in children. Most cases are idiopathic, but secondary causes include infection, drugs, and malignancy, with Hodgkin lymphoma one of the commonest. Despite this, MCD remains a rare complication of Hodgkin lymphoma, occurring in up to 1:2000 patients. Proposed pathological mechanisms include a

Table 2. Teaching points

• Nephrotic syndrome following hematopoietic stem cell transplantation (HSCT) is rare, with membranous nephropathy accounting for two-thirds of cases.
• Minimal change disease complicates ~0.4% of Hodgkin lymphoma cases.
• Remission of nephrotic syndrome occurs with treatment of the underlying lymphoma.
• Minimal change disease is reported with acute Epstein-Barr virus (EBV) infection.
• Rituximab successfully treats EBV reactivation/post-transplant lymphoproliferative disorder (PTLD) following HSCT in 70% of patients.
• Small case series highlight a role for rituximab in minimal change disease.
• To our knowledge, this is the first published report of minimal change disease complicating PTLD following HSCT.

role for tumor necrosis factor-alpha, c-maf inducing protein, and interleukin-13, which is highly expressed by Reed-Sternberg cells.[S4–S6] MCD has also been reported as a rare complication of acute EBV infection.[S7] Treatment of primary MCD is with corticosteroid therapy, with consideration of calcineurin inhibitors in the context of frequently relapsing or steroid-dependent disease. Small studies show a role for rituximab in inducing remission and preventing recurrence, in steroid-dependent and frequently relapsing MCD.[S8,S9] In a series of patients with MCD secondary to Hodgkin lymphoma, effective lymphoma treatment led to remission of nephrotic syndrome in all patients. Those provisionally treated with corticosteroids alone had a higher frequency of steroid resistance than found in primary MCD.[6] In our case, complete remission of nephrotic syndrome, normalization of EBV titers, and resolution of PTLD occurred with rituximab, without the need for high-dose corticosteroid therapy induction treatment.

CONCLUSION

In conclusion, we present a case of EBV-driven minimal change related nephrotic syndrome in the setting of PTLD post HSCT for which rituximab monotherapy led to a full remission of nephrotic syndrome, normalization of EBV viremia, and clinical remission of PTLD (Table 2).

DISCLOSURE

All the authors declared no competing interests.

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This case report has been produced and submitted with the patient's written consent.

AUTHOR CONTRIBUTIONS

LA and SL produced manuscript, LH and MR-J formatted and interpreted histology, and RJP and KT reviewed and edited manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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