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Treatment of concurrent minimal change disease and Epstein Barr virus driven post-transplant lymphoproliferative disorder with Rituximab following haematopoietic stem cell transplantation

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Keywords

Nephrotic syndrome; minimal change disease; post-transplant lymphoproliferative disorder;
haematopoietic stem cell transplantation; Epstein-Barr virus; Rituximab

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Background

Haematopoietic 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%), thrombotic microangiopathy and nephrotic syndrome (0.4-4%)¹. Additionally, 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's 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, normalisation of Epstein Barr viraemia and full clinical remission of PTLD.

Case Presentation

We report a 36 year old Caucasian male with very severe aplastic anaemia (VSAA) who underwent allogeneic HSCT following a three 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 (HLA) match with a permissive mismatch for HLA-DPB1, with recipient and donor cytomegalovirus IgG negative and anti-Epstein Barr Nuclear Antigen (EBNA) IgG positive. Post-transplant 3mg/kg ciclosporin 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 millilitre. Both resolved with hydration and reduced ciclosporin dose, with mycophenolate mofetil then added. Acute skin graft versus host disease (GvHD) occurred day +24, treated with 1mg/kg of intravenous methylprednisolone, followed by 1mg/kg of prednisolone which was weaned and discontinued by day +40. Chimerism was assessed by peripheral blood analysis at day 100 showing 100% donor cells CD15/CD19 and 49% donors cells CD3, with lymphopenia.

Twenty weeks post-transplant the patient developed small volume cervical, occipital, posterior auricular lymphadenopathy with a whole blood EBV PCR of 40,000 copies per millilitre. Cervical lymph node biopsy demonstrated polymorphic PTLD with scattered EBV positivity (Figure.1) and Positron Emission Topography (PET) scan confirmed stage 3

disease. The patient continued on maintenance ciclosporin at this time, with no additional immunosuppression given.

Simultaneously our patient re-presented with oedema, frothy urine and 10 kg weight gain. Clinical examination highlighted pitting oedema, raised jugular venous pressure and crepitation's 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 375mg/m² leading to an undetectable EBV titre, resolution of palpable lymphadenopathy, normalisation of serum albumin, and improvement of urinary protein creatinine ratio to 66 mg/mmol eighteen 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 ciclosporin with a trough level of 30 ng/ml, and 3mg daily budesonide which was commenced 175 days after the onset of nephrotic syndrome, for skin and gastrointestinal GvHD and diarrhoea. Ten months following rituximab his CD19 cells had re-populated at 0.038, and his EBV titre became positive at 14,000 copies per millilitre and he received a further rituximab dose. His nephrotic syndrome has remained in remission.

Discussion:

Haematopoietic stem cell transplantation is potentially curative therapy for a range of haematological conditions, including aplastic anaemia. This is increasingly favoured over immunosuppression 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 ciclosporin 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, re-introduction of calcineurin inhibitors and rituximab. A small series of four patients with membranous nephropathy post HSCT receiving rituximab as a first or second line therapy showing complete and sustained remission in all cases.⁹ Urinary sediment abnormalities occur in 10% of patients with EBV viraemia which is associated with a range of renal pathologies including interstitial nephritis and MCD.^{5,10}

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 transplant, 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 PCR titre. There are four main histological categories of PTLD: monomorphic, polymorphic, T cell neoplasms and classical Hodgkin's 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.^{S11} Routine pre-transplant testing and post-transplant surveillance of EBV PCR is performed to detect primary or reactivated EBV infection. Treatment options include reduction of immunosuppression in order 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 pre-emptive rituximab can reduce the risk of EBV viraemia and PTLD, although the overall benefit is unclear.^{S12}

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's 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 role for tumour necrosis factor-alpha, c-maf inducing protein, and IL-13 which is highly expressed by Reed-Sternberg cells.^{S13-S15} Other hypotheses suggest a role for tumour necrosis factor-alpha, and c-maf inducing protein.^{S14, S15} MCD has also been reported as a rare complication of acute EBV infection.^{S16} 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.^{S17, S18} In a series of patients with MCD secondary to Hodgkin's 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, normalisation of EBV titres, and resolution of PTLD occurred with rituximab, without the need for high dose corticosteroid therapy induction treatment.

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, normalisation of EBV viraemia, and clinical remission of PTLD.

Abbreviations

PTLD – post lymphoproliferative disorder, GvHD – graft versus host disease, HSCT – haematopoietic stem cell transplant, EBV – Epstein Barr virus, VSAA – very severe aplastic anaemia, MDRD – Modification of Diet in Renal Disease Study, eGFR – estimated glomerular filtration rate

Declarations**Ethics approval and consent to participate**

Not applicable.

Consent for publication

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

Availability of data and material

Not applicable.

Competing interests

None of the listed authors has competing interests to disclose.

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Author's contributions

LA and SL produced manuscript, LH and MR formatted and interpreted histology, RP and KT reviewed and edited manuscript.

Data sharing is not applicable to this article as none were generated or analysed

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Supplemental Material

Supplementary references (PDF). Supplementary information is available at KI Report's website.

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Figure 1

Core biopsy of a right sided cervical level two lymph node showing effacement of the architecture by a proliferation of immunoblasts, plasma cells, plasmacytoid cells and medium-sized lymphocytes (A: H&E x100 and B: H&E x400). Mitotic features and Epstein-Barr virus-encoded small RNA positive cells are also seen (A; small window).

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 immunoglobulins (G, A and M), complement (C3 and C1q), BKV, and EBV. A) Medium power image showing three morphologically normal glomeruli surrounded by well-preserved tubules (Haematoxylin and eosin x20). B) High power image of a morphologically normal glomerulus (Periodic acid methamine silver, x40). 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 x2000).

Table 1

Investigation	Result
Haemoglobin	102 g/dL
White cell count	4.4 x 10 ⁹ /L
Platelets	213 x 10 ⁹ /L
Sodium	141mmol/L
Potassium	4.5 mmol/L
Creatinine	121 micromol/L
Estimated glomerular filtration rate	61 ml/min/1.73 ³
Serum albumin	16 g/L
Alanine transaminase	14 IU/L
Alkaline Phosphatase	88 IU/L
Bilirubin (total)	7 umol/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, human immunodeficiency virus 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 millilitre
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	13.6cm and 13 cm unobstructed kidneys with normal corticomedullary differentiation
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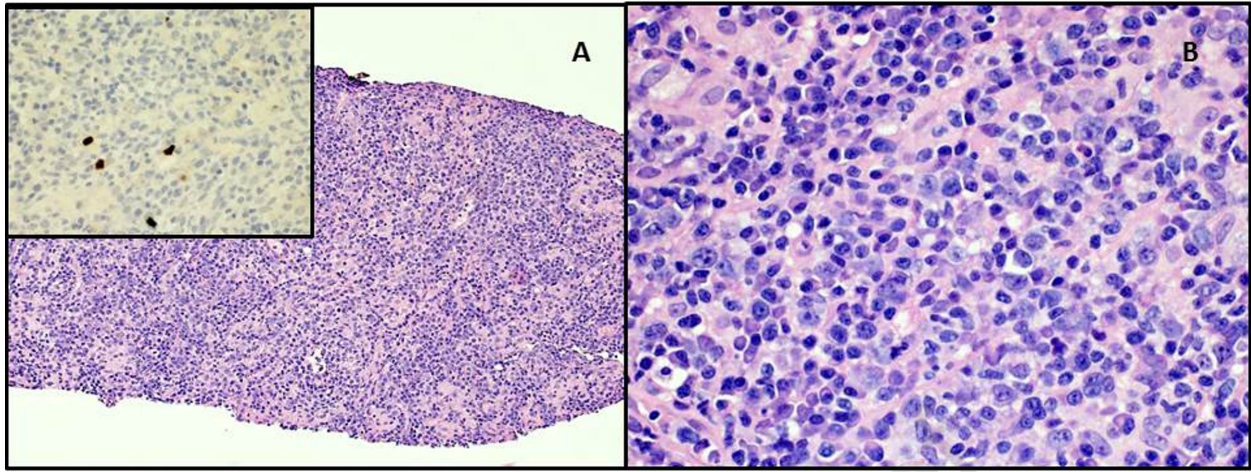
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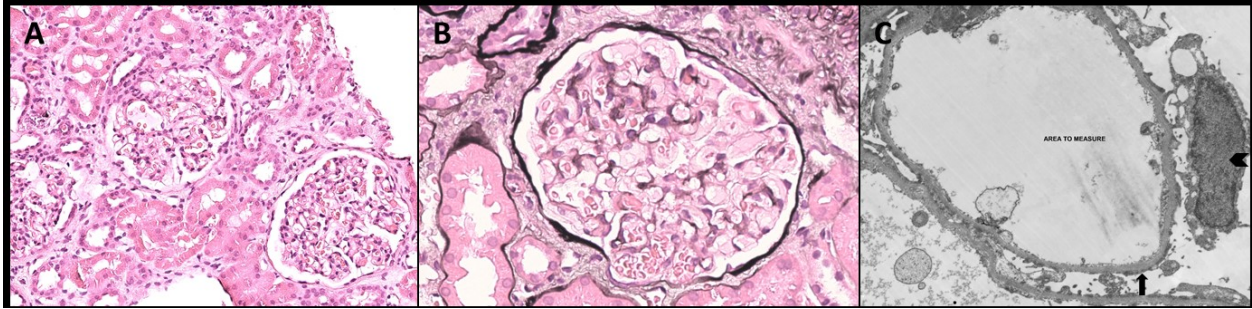
1 Table 2: Teaching points

<ul style="list-style-type: none">• Nephrotic syndrome following haematopoietic stem cell transplantation (HSCT) is rare, with membranous nephropathy accounting for 2/3's of cases
<ul style="list-style-type: none">• Minimal change disease complicates ~0.4% of Hodgkin's lymphoma cases
<ul style="list-style-type: none">• Remission of nephrotic syndrome occurs with treatment of the underlying lymphoma
<ul style="list-style-type: none">• Minimal change disease is reported with acute Epstein Barr virus (EBV) infection
<ul style="list-style-type: none">• Rituximab successfully treats EBV re-activation/ PTLD following HSCT in 70% of patients.
<ul style="list-style-type: none">• Small case series highlight a role for Rituximab in minimal change disease
<ul style="list-style-type: none">• To our knowledge this is the first published report of minimal change disease complicating post-transplant lymphoproliferative disorder (PTLD) following HSCT

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