Late-onset post-transplant lymphoproliferative disease presenting as massive occult gastrointestinal haemorrhage

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ABSTRACT

Post-transplant lymphoproliferative disease (PTLD) is a widely-recognised complication of solid organ transplants with a myriad of clinical presentations. We report a 56-year-old Chinese woman who developed PTLD 17 years after a renal transplant. She initially presented with constitutional symptoms, and a diagnosis of diffuse large B-cell lymphoma was confirmed on liver biopsy. Staging computed tomography demonstrated widespread adenopathy. Initial treatment consisted of reduction of immunosuppression and Rituximab. Prior to institution of chemotherapy, she presented with life-threatening melaena. Laparotomy revealed a mid-jejunal ulcerating tumour which was resected. Histology confirmed necrotic diffuse large B-cell lymphoma and the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy regime was subsequently commenced. The aim of this case report is to highlight the unique challenges in the management of PTLD in the context of an acute abdomen.

Keywords: Epstein-Barr virus, gastrointestinal bleeding, lymphoproliferative disorders, post-transplant, renal transplantation

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INTRODUCTION

Post-transplant lymphoproliferative disease (PTLD) is now a widely-recognised complication of solid organ and haematopoeitic stem cell transplants. The prevalence of lymphoproliferative disorders post-renal transplant, has been reported to be 1%–2%.[1,2] The risk of developing PTLD is highest within the first year after the transplant, and the probability decreases thereafter.[3] Most patients have extranodal disease with the gastrointestinal tract being the most common site of clinical presentation.[2,4] We report a patient, who presented with massive gastrointestinal bleeding requiring emergency laparotomy, due to lymphoproliferative disease of the small bowel which developed 17 years post-renal transplant.

CASE REPORT

A 56-year-old Chinese woman with end-stage renal failure secondary to chronic glomerulonephritis underwent a cadaveric renal transplant in 1989. Her immunosuppressive regimen included azathioprin and cyclosporin. She was well until March 2006, when she presented with loss of appetite and low grade fever. Ultrasound scans showed hypoechoeic lesions in the left lobe of the liver. Magnetic resonance imaging showed involvement of the liver parenchyma and portal triad by the lesion. A liver biopsy showed diffuse large B-cell lymphoma. Epstein-Barr virus (EBV) *in situ* hybridisation was positive (Figs. 1a–d). Staging computed tomography (CT) showed an infiltrative mass in the left hepatic lobe and adenopathy in the supraclavicular, gastric, small bowel mesentery, hepatic artery, left paraaortic and aortocaval regions. Azathioprine was stopped, the cyclosporin dose attenuated and five cycles of rituximab given. Interval CT revealed interval disease regression and chemotherapy was planned.

She presented again two months later with abdominal discomfort, melaena and hypotension. Colonoscopy showed multiple ulcers in the ascending and transverse colon with no active bleeding. The ileum was intubated and blood was seen, but there was no fresh bleeding. Oesophagogastroduodenoscopy and mesenteric angiogram were essentially normal. Tagged red blood cell scan showed active bleeding in the lower abdomen, likely at the region of proximal ileum or distal jejunum. The patient continued to have fresh melaena and multiple episodes of hypotension requiring fluid challenges and blood products. A decision was made for an exploratory laparotomy, and the findings included a hard mass in the mesentery of the small bowel at mid-jejunum, extending to the root of the mesentery, and ulcerating into the lumen of the bowel at two sites (Figs. 2a & b). Resection of a 40-cm segment, starting from the small bowel to the

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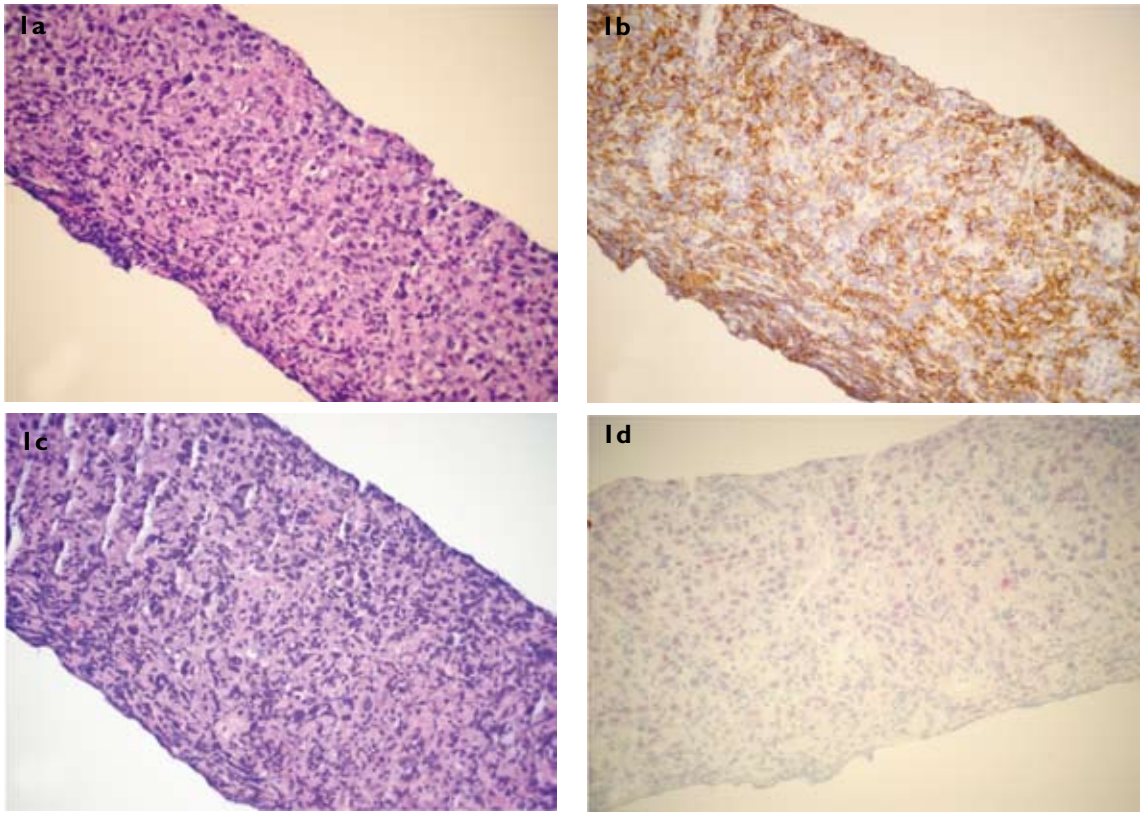


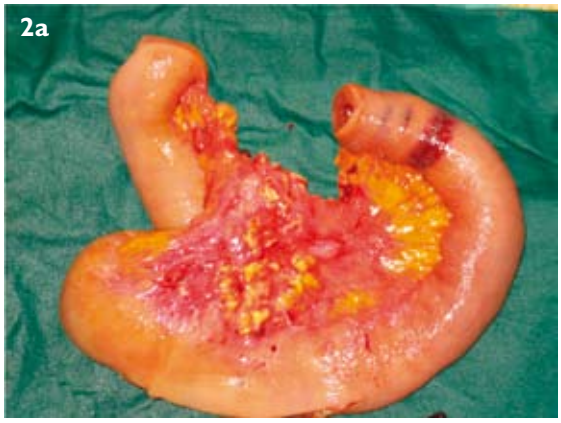
Fig. 1 (a) Photomicrograph of the liver biopsy shows diffuse infiltrate of medium- to large-sized lymphoma cells (Haematoxylin & eosin, x 200). (b) Photomicrograph of the lymphoma cells in the liver shows irregular nuclei and prominent nucleoli (Haematoxylin & eosin, x 400). (c) Photomicrograph of the lymphoma cells in the liver shows diffuse positivity for B-cell marker, CD20 (Immuno-peroxidase, x 400). (d) Photomicrograph shows *in-situ* hybridisation for Epstein-Barr virus early encoded RNA is positive in the lymphoma cells (ISH, x 400).

root of the mesentery, was performed, with primary anastomosis done. Histology showed a tumour with mucosal ulceration, contiguous with the adjacent matted group of the lymph nodes. Microscopical features were consistent with necrotic diffuse large B-cell lymphoma (Figs. 3a–c). Postoperatively, the patient recovered well and was started on the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regime.

DISCUSSION

PTLD has been reported in up to 15% of solid organ transplant recipients.[3] It is a heterogeneous group of abnormal lymphoid proliferations ranging from B-cell hyperplasia to immunoblastic lymphoma. The incidence rate of PTLD varies with the type of organ transplanted,[5] EBV status of the donor and recipient,[6,7] degree of immunosuppression, and the immunosuppressive agent used. The single most important risk factor for developing PTLD is EBV infection. This association is well established,[6,7] and 80%–90% of PTLD cases are associated with primary EBV infection or reactivation of previously-acquired EBV. With immunosuppression, diminished cytotoxic T-cell activity may allow EBV reactivation, viral replication, EBV oncogene expression and malignant transformation of B-cells. Recent studies have suggested that late onset PTLD (occurring more than one year after the transplant) are EBV negative. This could be due to continued immunosuppression causing cells to acquire more mutations, resulting in an aggressive lymphoma which requires more robust treatment.[5,8]

The clinical presentation of PTLD is highly variable, ranging from infectious mononucleosis-like symptoms (fever, lymphadenopathy, pharyngitis, tonsillar enlargement) and mass effects from tumour growth, to allograft dysfunction. Involved organs include the gastrointestinal tract, lungs, skin, liver, central nervous system and infiltrative lesions in the allograft. Extranodal involvement occurs in more than 50% of the cases. The gastrointestinal tract is predominantly involved with an increased propensity for ulceration and perforation.[2,9] PTLD can present at any time post-transplant, as is illustrated in our case, where the patient presented 17 years after her renal transplant. Most cases of PTLD occur as nodal diseases, but these can present with localised symptoms. As in this case, the small bowel mesenteric lymph nodes had most likely eroded in the bowels and caused massive gastrointestinal bleeding. The work-up and differential diagnosis of occult bleeding from the gastrointestinal tract should be no different between transplant and normal patients. However, in patients with previous transplanted organs, the possibility of PTLD must be considered, especially as PTLD in the gastrointestinal



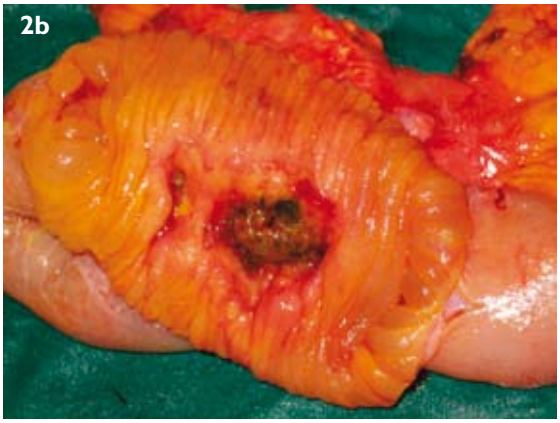
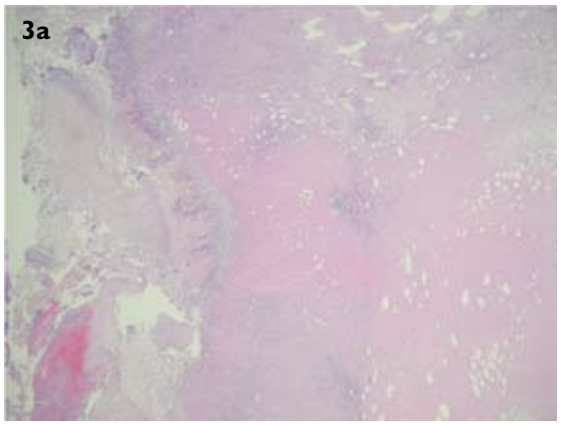
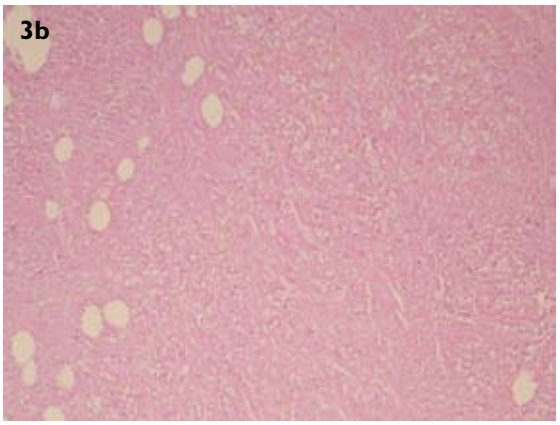


Fig. 2 Intraoperative photographs show (a) a hard mass of the matted lymph nodes in the small bowel mesentery; and (b) an ulcerated tumour in the mid-jejunum.





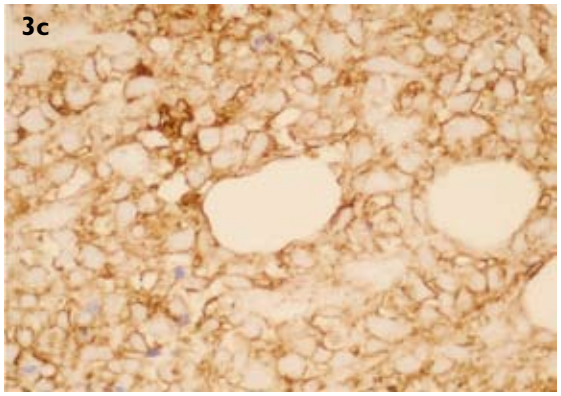


Fig. 3 Photomicrographs show (a) a necrotic tumour in the small intestine with mucosal ulceration (Haematoxylin & eosin, x 40); (b) the tumour cells in the small intestine are completely necrotic (Haematoxylin & eosin, x 200); and (c) the necrotic tumour cells in the small intestine are immunoreactive for the B-cell marker, CD20 (Immunoperoxidase, x 400).

tract has a propensity for ulceration.

The diagnosis of PTLD is based on histological confirmation of the suspected tissue. Staging of the disease is based on the same system that is used for non-Hodgkin's lymphoma. CT of the abdomen and thorax, as well as a bone marrow biopsy are recommended. The efficacy of positron emission tomography (PET) for the staging and follow-up of lymphomas have been studied, and they have been shown to be useful, especially in non-Hodgkin's lymphomas.[10,11] Integrated PET with CT have also been shown to be more accurate than either CT or PET alone. Following this trend of thought, PET should be useful in the evaluation of PTLD. Two recent studies have shown that PET/CT is a useful tool in the staging and follow-up of PTLD patients.[12,13] In these studies, PET has been shown to be able to identify all disease sites, clarify site of uncertain significance and detect additional disease in some patients. However, the PET scan results resulted in a change in management for only some patients. Both these studies were conducted as a small case series but as the results were encouraging, further studies should be done to evaluate the usefulness of PET in the staging and follow-up of PTLD.

Treatment of PTLD is a major challenge. Initially, immunosuppression is reduced to increase antitumour activity. Chemotherapy is commonly used next when this fails. Anti–B-cell antibodies, like Rituximab, are increasingly being used as it may allow for lower dosages of chemotherapy. Surgery has a definite role to play in selected patients. Complete surgical excision of localised disease has been shown to be effective. PTLD-related mortality rates of 0%–25% have been reported when definite local therapy (surgery or radiation), combined with immunosuppression reduction, is used. As prognosis tends to be excellent, surgical excision of the node, mass or affected organ should be done, when possible, in the

elective setting.[14] Few studies have specifically looked at surgery as a treatment option for PTLD in the elective or emergency setting. Emergency surgery is warranted in cases of gastrointestinal perforation or massive bleeding. Given that PTLD has been shown to respond well to medical treatment, and that the outcome appears to be similar to non-PTLD cases with good peri- and postoperative management, surgery should be considered where possible.

PTLD is a unique disease with a myriad of presentations and the diagnosis should be considered in post-transplant patients. Complete surgical excision of the localised disease is warranted in an emergency setting, and is recommended in an elective setting for the control of symptoms. PET may be useful in the initial evaluation of PTLD to screen for potential disease sites, but further studies should be done to validate this.

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