



CASE REPORT

A 13 year-old boy with post-transplantation lymphoproliferative disorder presenting with obscure gastrointestinal bleeding: a case report [v1; ref status: indexed, <http://f1000r.es/2p0>]

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Abstract

One well recognized and potentially serious complication of chronic immunosuppression in organ transplant recipients is post-transplantation lymphoproliferative disorders (PTLD). This accounts for 20% of all malignancies in transplant recipients, which is four times higher than the general population^{1,2}. The diagnosis of PTLD is often difficult, due to various manifestations resulting in late diagnosis. We report an unusual presentation of PTLD in a pediatric patient where the diagnosis was achieved only after extensive investigation.

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Invited Referee Responses

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Case presentation

This case involves a 13 year-old Caucasian boy with a history of cystic fibrosis status post deceased donor *EnBloc* combined liver and pancreas transplantation, presenting with gastrointestinal bleeding. His immune suppression regimen after the transplant included tacrolimus 1.5 mg twice daily.

Two years after his transplant, the patient presented to the hospital with “a few days of dark tarry stool”. He did not complain of any nausea, vomiting, or abdominal pain. He denied taking any anti-platelet agents or non-steroidal inflammatory drugs. On admission, the patient was hypotensive with a blood pressure of 70/50 mmHg and tachycardic with a heart rate of 112 beats per minute. His hemoglobin was 7.4 g/dL, which represented a drop from a baseline hemoglobin of 10 g/dL. After fluid resuscitation, the patient was started on pantoprazole continuous infusion at 5 mg/hour and sulcrafate suspension 300 mg four times daily. He then underwent an urgent upper endoscopy, which revealed multiple small prepyloric and duodenal ulcerations without signs of recent hemorrhage. Biopsies of these ulcers showed acute inflammation. A capsule endoscopy was then performed, which showed scattered duodenal erosions and two adjacent erosions in the distal duodenum without stigmata of recent bleeding. During the work-up, the patient continued to have melena, necessitating transfusions every three days. This prompted a second upper endoscopy, which showed complete healing of the prior ulcers. Interestingly, portal hypertensive gastropathy and a gastric varix were also noted. To target bleeding lesions potentially related to portal hypertension, octreotide continuous infusion at 2 mcg/kg/hour was initiated. Unfortunately, his melena persisted. The patient underwent a technetium-labeled red blood cell bleeding scan, where a potential bleeding source “near the anastomosis of the native to transplanted duodenum or proximal jejunum” was identified. A visceral arteriogram was obtained but it failed to detect a bleeding source. Following these radiological tests,

a deep enteroscopy was performed. No signs of recent bleed within the suspected proximal hepatic limb of the Roux were detected. In the jejunum, however, there was a 10 mm clean-base, friable ulcer with significant oozing when it was biopsied. The pathological diagnosis of the ulcer was reported as follows: “the morphologic and immunophenotypic features indicate involvement of this patient’s jejunum of a large B-cell lymphoproliferative disorder consistent with diffuse large B-cell lymphoma (DLBCL). These findings thus support the diagnosis of a post-transplantation lymphoid disorder, involving small intestinal mucosa”. Epstein-Barr virus (EBV) was positive in the biopsied sample (See [Figure 1](#)).

Follow-up and outcome

An abdominal MRI performed a few days later demonstrated a mild thickening of the segments of small bowel in the left upper quadrant and portal hypertension. No lymphadenopathy was found in the abdomen and pelvis. The patient was then evaluated by the pediatric oncology service. A bone marrow biopsy reassuringly showed a normocellular marrow. The patient was started on cyclophosphamide, rituximab, and prednisone. His gastrointestinal bleeding eventually stopped a few weeks later.

Discussion

PTLD are rare but potentially fatal complications of solid organ transplantation³. The overall incidence of lymphoproliferative disorders in the transplant population is approximately 1% at 10 years, which is significantly higher than the general population³. The risk increases with the intensity of induction or rescue immunosuppression, and particularly following monoclonal or polyclonal anti-lymphocyte therapy⁴⁻⁶. The EBV serostatus of the recipient is another risk factor⁷, although PTLD can occur in EBV-negative diseases as well. Time post-transplant is also a key factor as the majority of PTLD occurs within the first year post-transplant⁸. Over half of the patients with PTLD present with extranodal masses⁹.

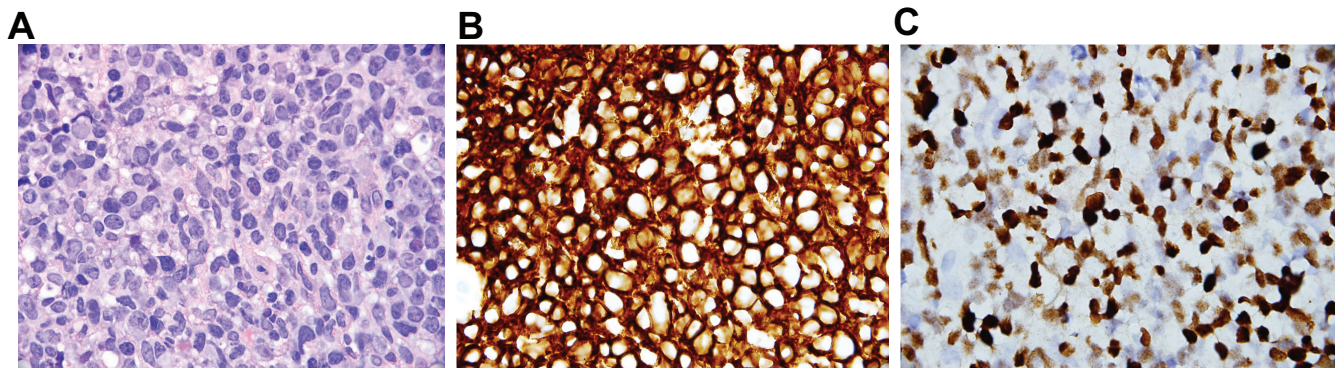


Figure 1. Biopsy of jejunal ulcer. **1A:** Haematoxylin & Eosin stain, 1000x. Large, centroblastic lymphoid cells with hyperchromatic, pleomorphic nuclei and moderate cytoplasm. These tumor cells almost completely efface the jejunal mucosa. Scattered mitotic activity and apoptotic debris are present as well. **1B:** Immunohistochemical stain for CD20, 1000x. Diffusely positive membranous staining in the tumor cells is indicative of lymphoid differentiation. In the context of the morphology seen in Figure **1A**, the findings are compatible with a Diffuse Large B-Cell Lymphoma (DLBCL). Per the 2008 World Health Organization (WHO) classification, a lymphoid proliferation that meets the criteria for a high grade malignancy (in this case DLBCL) that occurs in a recipient of a solid organ, bone marrow, or stem cell transplant is diagnostic of a post-transplant lymphoproliferative disorder (PTLD). **1C:** *In situ* hybridization for Epstein-Barr virus encoded RNA (EBER), 1000x. Strong nuclear positivity is seen in the majority of the tumor cells, a finding seen in many monomorphic PTLD cases.

PTLD can affect many organs, including the gastrointestinal tract, lungs, liver, central nervous system, and the allograft itself. Clinical manifestations vary, ranging from benign polyclonal lymphoproliferation (infectious mononucleosis-type acute illness) to aggressive and disseminated malignant disease. Gastrointestinal features typically include abdominal pain, fever, and bowel perforation in serious cases. There have been case reports describing gastrointestinal bleeding as the initial presentation of PTLD in the pediatric population^{10–13}, but this is less common. This case highlights the importance of considering the diagnosis of post-transplantation lymphoproliferative disorders in transplant recipients presenting with unexplained gastrointestinal hemorrhage.

Consent

Informed consent for publication of clinical details and clinical images was obtained from the next of kin.

Author contributions

EH: acquisition of data, interpretation of data, drafting of manuscript, assistance in clinical care.

VG: preparation and processing of pathology slides, interpretation of data.

MM, JO: acquisition of data, interpretation of data, guidance of clinical management plan, revision of manuscript.

Competing interests

No competing interests were disclosed.

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Current Referee Status:



Referee Responses for Version 1



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Referee Report: 04 August 2014

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This is an interesting case report that emphasizes the need to consider the diagnosis of PTLD in post-transplant recipients who present with GI bleeding. It is a well-written report but could be improved by additional details.

1. Readers could benefit from a focused discussion on the treatment of PTLD in the post-transplant setting, including reduction in immune suppression, modulation of immune suppression (e.g. transition from a calcineurin inhibitor to sirolimus), single agent therapy with rituximab, or multi-agent therapy with prednisone, cyclophosphamide, and rituximab. In this case based on the pathology, multi-agent chemotherapy was the appropriate treatment, but in other instances less aggressive measures are sometimes used.
2. Additional details including imaging of his extra-abdominal compartment by CT or PET-CT, EBV viral load, and LDH would be helpful. Also, more details on the length and response to treatment would be of interest (was he reimaged or re-scoped?).

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



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Approved: 07 May 2014

Referee Report: 07 May 2014

doi:[10.5256/f1000research.3492.r4391](https://doi.org/10.5256/f1000research.3492.r4391)

This is an interesting case that highlights the importance of considering PTLD in the differential diagnosis of gastrointestinal bleeding occurring after transplantation. The case report is well written, but requires a

few minor revisions.

Article content

- A few clinical details, important for the diagnosis of PTLT, such as EBV status at transplantation, EBV DNA at diagnosis and at treatment re-evaluation, and LDH at diagnosis, should be inserted.
- Was a PET scan performed to complete PTLT assessment? In order to increase the clinical value of this report, I believe it is important to add data on patient imaging assessment at diagnosis (small bowel MRI and, if performed, total body PET scan, as figure 2 a and b). If PET scan or CT scan were not performed, add a comment on the reasons for not performing imaging assessment.

References

- The reference for 2008 World Health Organization (WHO) classification (cited in the legend to Figure 1) ought to be reported.
- Reference 3 relates to stem cell rather than solid organ transplantation. The authors need to replace this reference with a more appropriate one, possibly published within the last 10 years.
- Reference 8 is very outdated. The same author has published a review on the same topic in 2003 ([Opelz & Dohler, 2003](#)), thus the authors should replace the 1993 article with the 2003 review.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.
