A CASE REPORT

Gastrointestinal Bleeding Due to a Post Transplant Lymphoproliferative Disorder: A Complication of Renal Transplant

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Post-transplant lymphoproliferative disorder (PTLD) is a rare complication after solid organ or stem cell transplant, which is thought to be related to the immunosuppression medications used in this patient population. Although the gastrointestinal tract is a common location for proliferation, gastrointestinal bleeding (GIB) is rare in PTLD. We present a patient with history of renal transplant treated with prednisone, tacrolimus and azathioprine presenting with GIB. She was found to have multifocal jejunal B cell lymphoma. Outcomes in PTLD treated with immunosuppression reduction and chemotherapy are promising with response rates of 82-90%. Therefore, post-transplant care must include careful surveillance for PTLD.

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is any proliferation of lymphocytes occurring after solid organ or allogeneic stem cell transplant due to immunosuppression (IS) therapy. The most common extranodal location for PTLD is in the gastrointestinal tract. On average, PTLD occurs in 1-3% of renal transplant cases, though percentages vary based on patient’s age, type of transplant, and IS regimen. There is a higher frequency of PTLD amongst patients transplanted for autoimmune etiologies. This is thought to be due to more intensive immunosuppression regimens used in this population.

The presentation of PTLD is variable. B symptoms are seen in about 49% of cases. The initial presentation may be complications such as mass effect of tumor, gastrointestinal obstruction, perforation, or gastrointestinal bleeding (GIB).

Figure 1. Two endoscopic views of the irregular mass with diffuse erosions and shallow ulcerations (indicated by the yellow arrow) in the proximal jejunum.

GIB is a rare presentation with only a few case reports to date in the literature.

PTLDs were initially thought to occur within 1 year of transplant, however studies have shown that more than 70% cases occur later. Here we present a case of multifocal small bowel B cell lymphoma occurring 16 years after renal transplant.

Case Description

A 48 year-old female with history of end stage renal disease secondary to membranous

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glomerulonephritis, with living donor renal transplant 16 years prior, presented to the emergency department with generalized abdominal pain and fatigue. She reported intermittent dark-colored stools, generalized weakness, and a 10-lb weight loss in the preceding three months. She denied use of nonsteroidal anti-inflammatory drugs, alcohol and tobacco. The patient was on prednisone 5 mg daily, tacrolimus 3 mg twice daily, and azathioprine 50 mg daily for IS. She had no significant family history. Physical exam was benign except for positive occult blood on rectal exam. Laboratory workup revealed hemoglobin of 7.4 mg/dL, which was decreased from her baseline of 10 mg/dL three months prior. She also had mildly elevated BUN and creatinine at 30 mg/dL and 2.5 mg/dL respectively from a baseline creatinine of 1.4-1.6 mg/dL. Renal ultrasound with doppler was normal. Patient underwent an esophagogastroduodenoscopy and colonoscopy, which demonstrated only mild gastritis. Further workup with capsule endoscopy was positive for an ill-defined lesion in the proximal jejunum. Based on these results, the patient underwent push enteroscopy and was found to have an area of patchy inflammation with congestion and shallow ulcerations in the proximal jejunum (shown in Figure 1). Biopsy of this lesion showed focal ulceration and necrosis of the mucosa with underlying cellular infiltrate. The infiltrate was comprised mainly of large abnormal cells with scattered small lymphocytes and eosinophils (Figure 2A). The neoplastic cells were positive for CD20 (Figure 2B), CD79a (Figure 2C), PAX-5 (Figure 2D), and expressed monotypic lambda light chains (Figure 2E). The Ki-67 proliferation index was elevated at greater than 90%. The specimen was weakly positive for CD30 and negative for CD15. Due to strong suspicion for Epstein-Barr virus (EBV)-positive mucosal ulcers, EBV testing was conducted with both in situ hybridization for EBER and immunohistochemistry for EBV-LMP, though both were negative. Taken together, the above findings were consistent with monomorphic PTLD with features of diffuse large B-cell lymphoma.

The patient was subsequently referred to oncology for staging where a bone marrow biopsy was found to be normocellular with non-neoplastic lymphocytes on flow cytometry. Positron emission test/computed tomography (PET CT) demonstrated multifocal areas of intense hypermetabolism involving the GI tract including

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Figure 3. PET CT imaging demonstrating multifocal FDG uptake in small bowel.
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the distal gastroesophageal junction and multiple foci within the jejunum (Figure 3). There was no FDG avid lymphadenopathy. Although some bowel uptake can be physiologic, these findings were suggestive of multifocal small bowel disease given her biopsy-proven lymphoma in the jejunum.

Our patient’s IS dose was minimized with reduction of tacrolimus to 1mg twice daily and azathioprine was stopped. She was treated with six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). After initiation of treatment, the patient continued to have evidence of GIB with melena and slowly dropping hematocrit. Her blood counts were monitored closely and she was transfused as needed. PET/CT was performed after 3 cycles of chemotherapy, revealing resolution of the jejunal lesions and no new areas of abnormal FDG uptake. Her blood counts stabilized as therapy progressed.

DISCUSSION

GIB in a post-transplant patient is a complicated issue. With renal transplant specifically, renal dysfunction alone increases risk of GIB 8.7-fold, as uremia and nitric oxide accumulation contribute to impaired platelet function. Additionally, immunosuppressive agents can lead to GIB. Steroids and tacrolimus can impair gastrointestinal epithelium, thus predisposing patients to ulceration or other mucosal injury. Other agents, such as azathioprine, can cause thrombocytopenia. As demonstrated in this case, IS also predisposes patients to the development of PTLD which can cause GIB.

The pathogenesis of PTLD is not completely understood. EBV, known to provoke malignant transformation of B cells, is a major risk factor for the development of PTLD, accounting for more than 70% of cases. In the absence of EBV, as in our patient, the pathogenesis is not well understood. This patient was on an intensive IS regimen with three agents, which subjected her to increased risk for PTLD. IS, used for its inhibition of T cell function to prevent graft rejection, also allows for uncontrolled lymphoproliferation with potential for malignant transformation.

Mortality rates for PTLD ranges from 50-70%, with five year survival rate of 53-59%. Those with EBV positivity carry an unfavorable prognosis. Our patient possessed features thought to be good prognosticators, including female gender and inclusion of tacrolimus or azathioprine in IS regimen. These specific agents have more favorable prognosis as compared to patients on other IS regimens.

Treatment of PTLD requires a balance between eliminating the malignancy while also preserving the graft, with the key being dose reduction of IS. This allows for the re-engagement of the natural anti-tumor actions of the immune system. However, IS reduction is only effective in 10% of cases. Rituximab alone or combined with CHOP is an alternative in high risk cases. R-CHOP has a response rate of 82-90%. Given this favorable response to treatment, early identification of PTLD is key. With increasing number of solid organ transplants, it is important to consider PTLD as a potential complication in this population.

Acknowledgements

A special thank you to Dr. Hassan Dalal of the University of Connecticut Department of Pathology for providing pathologic figures for this case.

References