Duodenal Post-Transplant Lymphoproliferative Disorder (PTLD) with History of Heart Transplant

by Karen Tsai, Thomas Coppola, Raluca Vrabie

Post-transplant lymphoproliferative disorder (PTLD) is the most common malignancy in adult transplant recipients. We present a case of PTLD in the duodenum in a 48-year-old, Epstein-Barr virus positive female who underwent remote heart transplant due to postpartum cardiomyopathy. Her PTLD manifested as acute onset hypoalbuminemia and severe diarrhea. The diagnosis was made from duodenal biopsies, which looked mildly nodular. Remission of PTLD and symptom resolution were seen with reduction of tacrolimus and increase in valacyclovir doses. Although a rare entity, PTLD is a relevant clinical diagnosis in solid organ transplant patients who have unexplained diarrhea.

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is a serious and potentially fatal complication after solid organ transplant. It is the most common malignancy post solid organ transplant in adults and occurs in up to 10% of patients.[1] With increasing number and improving survival of solid organ transplantations, clinicians should be aware of post-transplant complications. PTLD is an entity that is usually seen within the first few years post-transplant, mediated by the degree of immunosuppression and the EBV status of the patient. Clinical symptoms of PTLD can be highly variable, ranging from acute viral illness mimicking infective mononucleosis to organ-specific symptoms often making the diagnosis challenging.

Presentation

A 48-year-old female with a history of heart transplant 16 years ago from Coxsackie-induced postpartum cardiomyopathy presented to the hospital with complaints of fatigue and severe diarrhea for the past month. Her diarrhea was watery, non-bloody, occurring six times a day and unrelieved by intermittent loperamide use. She denied any sick contacts or recent travel. Her medical history consisted of renal insufficiency secondary to chronic tacrolimus toxicity, anal squamous cell cancer diagnosed two years ago (treated with surgery, Nigro chemotherapy and radiation), Epstein-Barr virus (EBV) infection, genital herpes and Kaposi sarcoma (excised). Her home medications included tacrolimus for transplant immunosuppression and valacyclovir.

On exam, she demonstrated whole body anasarca, abdominal ascites and 3+ pitting edema in her lower extremities bilaterally up to the knees and lower back. Her labs were significant for hypoalbuminemia (2.1g/dL; normal 3.5-4.8g/dL), and hypereosinophilia (absolute eosinophil 1.4K/uL; normal 0-0.5K/uL). Urinalysis was negative for hematuria and proteinuria. Tacrolimus level was 9.9ng/mL (normal 5-20ng/mL). An infectious gastroenteritis workup including ova and parasites, stool culture including Salmonella, Shigella, Campylobacter and Clostridium difficile was negative. Serum tissue transglutaminase and stool lactoferrin, pancreatic elastase and calprotectin were unremarkable. Liver enzymes were within normal limits.

The patient underwent upper endoscopy and colonoscopy with biopsies. The endoscopy was

Karen Tsai, BA, MD Candidate[1] Thomas Coppola, DO, Gastroenterology Fellow[2] Raluca Vrabie, MD Director of the Center for Inflammatory Bowel Diseases[2] [1]Stony Brook University School of Medicine, Stony Brook, NY, [2]Winthrop University Hospital, Department of Gastroenterology, Mineola, NY,

largely normal, with mildly nodular mucosa in the duodenal bulb (Fig. 1). The colonoscopy was grossly unremarkable. Pathology results from the duodenal bulb showed atypical lymphoid infiltrates consistent with PTLD and atypical cells that expressed CD20, CD79a and BCL-2 and were negative for CD10 (Fig. 2a, 3a). Small bowel mucosa showed eosinophilia and scattered cells tested positive for EBV (Fig. 2b). This atypical lymphoid infiltrate showed a kappa to lambda ratio of 8:1, which was consistent with her serum monoclonal gammopathy.

Her tacrolimus dose was decreased due to the development of PTLD. Her symptoms markedly improved, and she was discharged with repeat endoscopy and colonoscopy six months later. Repeat endoscopy with biopsies showed remission of PTLD (Fig. 3b). The patient continued to follow with her transplant physician and oncologist who recommended continuing the current dose of tacrolimus , evaluating the therapeutic level biweekly. Her valacyclovir was increased. After these medication adjustments, her albumin increased from 2.1g/dL to 3.7g/dL and she had complete resolution of diarrhea and anasarca.

Discussion

PTLD is a well-recognized complication that occurs after solid organ transplantation. It is primarily caused by a B-cell proliferation due to therapeutic immunosuppression after organ transplantation. Tacrolimus suppresses T cell immunosurveillance, which in certain circumstances can cause the EBV virus to proliferate in immunogenic tissues. Due to its high content of immunogenic tissue, the gut provides an ideal location for the proliferation of PTLD.

The prevalence of PTLD differs with different organ allografts, with the highest prevalence in multivisceral transplant recipients (13%–33% of cases), followed by bowel (7%–11%), heart-lung (9.4%), lung (1.8%–7.9%), heart (3.4%), liver (2.2%) and kidney (1%) recipients.[2] PTLD can occur years after transplantation with no inciting factor. Risk factors of PTLD include previous EBV infection, recipient age (<10 and >60 years-old show greater risk), degree of immunosuppression and host genetic factors.[3]

Known manifestations of PTLD include gastrointestinal bleeding, weight loss, abdominal discomfort, nausea and diarrhea. Protein-losing enteropathy with hypoalbuminemia is the most sensitive sign of gastrointestinal PTLD.[4] The duration of the post-transplant period is important because PTLD is most likely to develop in the first year following transplantation, with an incidence of 224 per 100,000 in the initial year, decreasing to 54 per 100,000 in the second year and 31 per 100,000 in the sixth year.[5] Our patient's presentation of PTLD happened 16 years after transplant which was quite unusual.

After tacrolimus and valacyclovir dose adjustments, our patient's symptoms improved markedly. Although no standard formula exists, decreasing tacrolimus or cyclosporine by 50% is often recommended.[6] Approximately 40% of patients respond to reduction in immunosuppression alone.[7] It is important to note is that although her tacrolimus levels were not elevated at

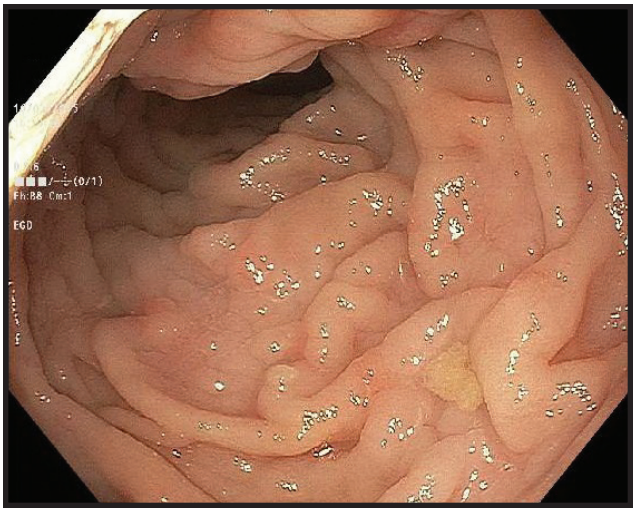

Figure 1. Initial endoscopy, where PTLD was diagnosed, was largely normal, with mildly nodular mucosa in the duodenal bulb.

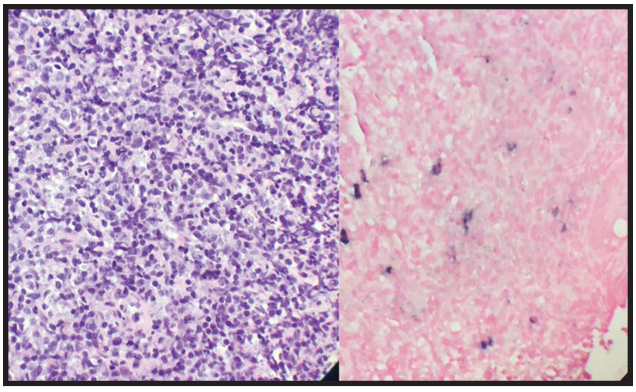

Figure 2. Duodenal biopsy images. a) Picture shows high power (40x) magnification of the basophilic cellular infiltrate of the duodenal biopsy site which shows a monomorphic, small, round cell infiltrate consistent with lymphocytes. b) Picture shows an in-situ hybridization (ISH) for EBV DNA that was performed to demonstrate positivity in scattered cells, including giant cells.

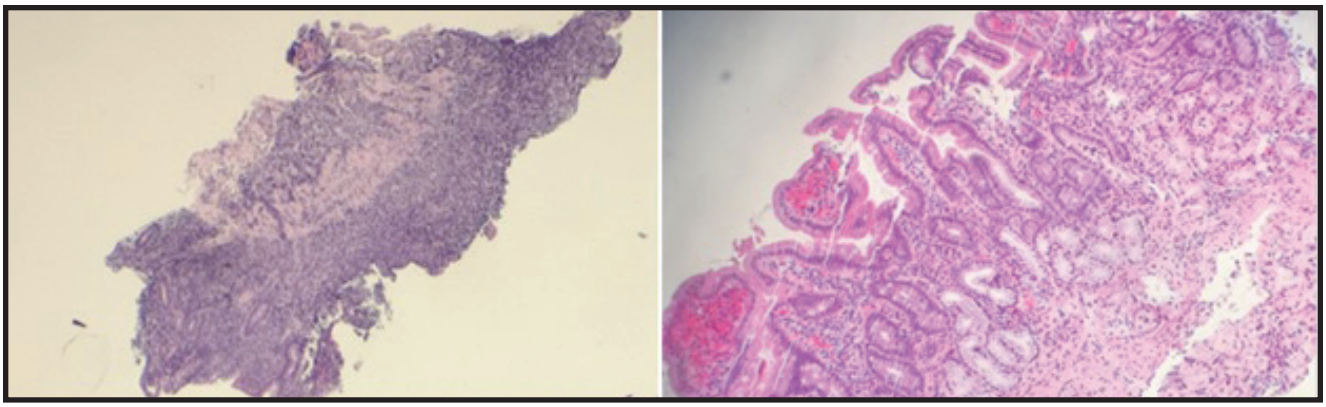

Figure 3. Duodenal biopsy at low power (10x): a) Picture shows a fragment of the initial duodenal biopsy whose architecture has been altered by the presence of a basophilic cellular infiltrate. b) Picture shows a fragment of duodenum done at follow up biopsy that shows preserved villous architecture of the duodenum with a mild increase in chronic inflammation. There was no evidence of a monomorphic inflammatory infiltrate.

time of presentation, she still developed PTLD.

Antivirals such as valacyclovir can possibly reduce the incidence of PTLD by lowering EBV viral loads, especially since EBV infection is associated with PTLD in up to 8% of transplant recipients.[8] Since the patient was taking valacyclovir for her genital herpes, this may help explain the late PTLD presentation. Current treatments, such as rituximab-based regimens, are starting to become more defined in B-cell lymphoproliferative disorders because they express CD20 and treatment with rituximab is considered to be relatively non-toxic compared with traditional chemotherapeutic agents.[3] Currently, primary prevention of PTLD includes EBV vaccination and chemoprophylaxis via antivirals such as acyclovir or ganciclovir.[8]

PTLD is a serious and feared complication in the post-transplant patient. This case is unique because of the patient's late presentation, dramatic response to adjustments in tacrolimus and valacyclovir and the fact that the patient developed PTLD in the setting of normal tacrolimus levels. Understanding PTLD and having a greater awareness is crucial due to its high mortality rate and late diagnosis. Further research on PTLD can focus on exploring universal screening techniques and defining preventative strategies and optimal therapy. ■

Learning Points

- Consider PTLD in a patient with gastrointestinal symptoms with history of solid organ transplant
- Diagnosis of PTLD is made by endoscopy and colonoscopy with biopsies so gastroenterologist consultation should not be delayed when there is suspicion of PTLD

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