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CASE REPORT | PATHOLOGY

Recurrent, Multisubtype Posttransplant Lymphoproliferative Disorder Masquerading as Inflammatory Bowel Disease

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ABSTRACT

Posttransplant lymphoproliferative disorder (PTLD) is a severe posttransplant complication that occurs because of immunosuppression within the first year; however, recurrent PTLD or development of multiple histologic subtypes are rare. Our case demonstrates a renal transplant recipient with rare, recurrent PTLD with multiple histologic subtypes (monomorphic and polymorphic PTLD) despite a previous response to rituximab and resolution of inflammatory changes on endoscopy. It is essential that clinicians maintain a high suspicion for PTLD when caring for patients with previous transplantation and that they have a lower threshold for biopsy with endoscopic findings of nonspecific inflammatory changes.

INTRODUCTION

Posttransplant lymphoproliferative disorder (PTLD) is a serious posttransplant complication that occurs because of immunosuppression within the first year; however, recurrent PTLD or development of multiple histologic subtypes are rare.[1] The incidence of PTLD has been reported as highest after multiorgan transplants (>10% of cases), heart and lung (3%–9%), and lowest for kidney (1%).[1,2] Gastrointestinal (GI) manifestations of PTLD can occur in up to 25% of all PTLD cases, with a clinical presentation of nonspecific abdominal pain, bleeding, or perforation.[3,4] On endoscopy, GI-manifesting PTLD has been described as raised, rubbery, erythematous lesions with central ulcerations ranging in size from 5 to 15 mm in diameter.[3,5] PTLD appearance is similar to inflammatory bowel disease on endoscopy, which makes distinguishing the 2 diseases challenging. Our case depicts a renal transplant recipient presenting with recurrent PTLD of multiple histologic subtypes presenting as inflammatory changes on endoscopy.

CASE REPORT

An 80-year-old African American man presented for a 5-year colorectal cancer surveillance colonoscopy. His medical history included hypertension and end-stage renal disease with living-donor renal transplantation 10 years prior. The patient's initial immunosuppression regimen included mycophenolic acid, tacrolimus, valganciclovir, and a prednisone taper. Nine months posttransplant, he presented with a fever that warranted an inpatient diagnostic evaluation. Although the fever resolved with broad-spectrum antibiotics, abdominal computed tomography (CT) revealed an incidental finding of mural thickening in the cecum and ascending colon. A colonoscopy revealed a single 10-mm sigmoid polyp and discrete ulcers of the midascending colon. Polypectomy was performed, and biopsies were obtained with histopathology results consistent with early-PTLD. The patient was treated with rituximab and follow-up CT showing resolution of cecal and ascending colon thickening. Repeat colonoscopy 6 months later revealed no ulcers, erosions, polyps, or masses, and the patient was recommended a resumption of colorectal cancer surveillance in 3–5 years. He had yearly CT imaging to monitor for any lymphadenopathy or GI changes suggestive of PTLD recurrence, and at 5 years posttransplant, surveillance colonoscopy was unremarkable.

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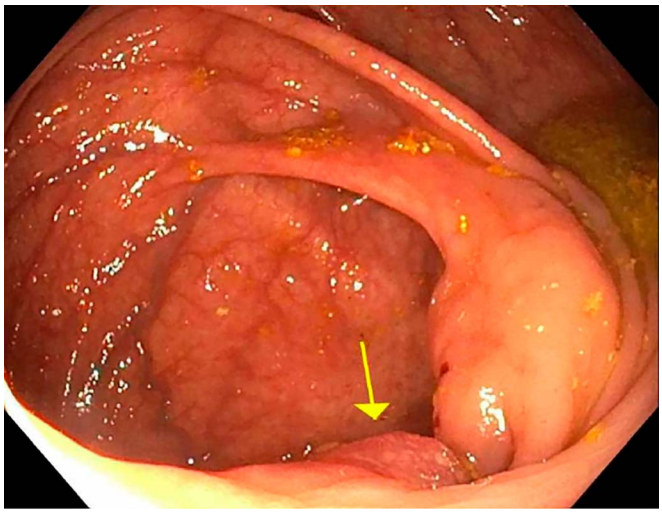

Figure 1. Ileocecal valve polyp.

On presentation to our service for his repeat 5-year surveillance colonoscopy (10 years after PTLD diagnosis), the patient reported no GI complaints, fevers, night sweats, or unexplained weight loss. His outpatient medications included mycophenolate and tacrolimus, and his physical examination was unremarkable. Colonoscopy was significant for a 12-mm sessile polyp at the ileocecal valve, (3) 2–4 mm sessile polyps in the sigmoid and transverse colon, and diverticulosis of the ascending and sigmoid colon (Figure 1). Of note, there was diffuse inflammation in the rectosigmoid colon characterized by congestion, erosions, erythema, pseudopolyps, and deep ulcerations raising a concern for underlying inflammatory bowel disease (Figure 2). Polypectomy was performed, and histopathology of the ileocecal valve indicated polypoid fragments of mucosa with focal inflammation and lymphoid aggregates consistent with polymorphic-PTLD; staining showed CISH-kappa, CISH-lambda polytypic staining of plasma cells; CD20+ B-cells; CD3+ T-cells; and EBV+, CMV- samples (Figure 3). Histopathology of the rectosigmoid biopsies were consistent with monomorphic-PTLD; staining showed CISH-kappa, CISH-lambda light chain restriction in CD138/MUM1+ plasma cells; CD20+, bcl-2+, and PAX5+ B-cells; CD3+, CD5+ T-cells without coexpressions of B-cells and cyclin-D-, EBV+ samples (Figure 3). Further subclassification of the rectosigmoid specimen revealed extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). The hematology-oncology service was consulted, and the patient underwent a reduction of immunosuppressants and rituximab therapy. At this time, the patient continues to be followed by hematology-oncology, transplant nephrology, and gastroenterology for comprehensive care.

DISCUSSION

PTLD is a serious and often fatal complication that involves uninhibited B or T cell proliferation in the context of post-transplant drug-induced immunosuppression and is also largely associated with the Epstein-Barr virus, particularly if PTLD occurs within the first year after transplant.[6] The World Health Organization classifies PTLD into 4 subtypes: early lesions, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma-type PTLD (Table 1).[7,8] The most common immunosuppressive agents with evidence of increased association for PTLD include antithymocyte globulin, calcineurin inhibitors, anti-CD3 (OKT3), tacrolimus, and cyclosporine.[9,10]

Clinically, PTLD can present with B symptoms of fevers, chills, night sweats, or unexplained weight loss of >10% of body weight but is unique among lymphomas as lymphadenopathy is often absent.[11] Symptoms usually reflect the involved organ that was transplanted, but extranodal disease is common. GI manifestations can occur in up to 25% of all PTLD cases with nonspecific abdominal pain, bleeding, or perforation, with the colon as the most common GI site involved.[3,4] Interestingly, although being one of the less likely transplanted organs to present with PTLD, renal transplants have a high association for

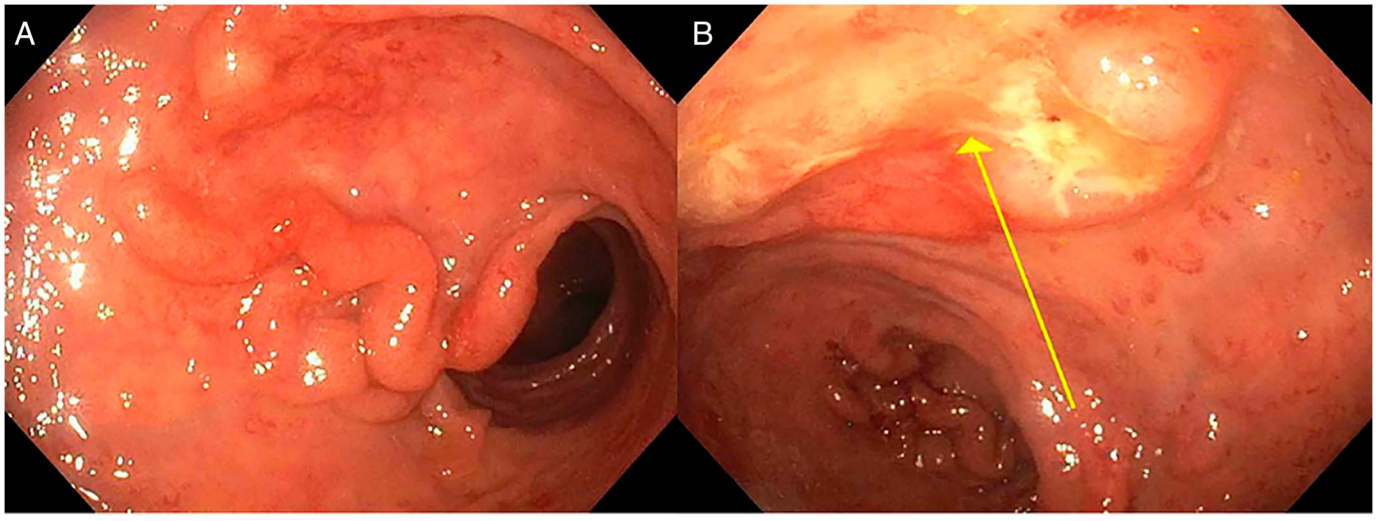

Figure 2. (A) Sigmoid colon inflammation. (B) Rectal inflammation.

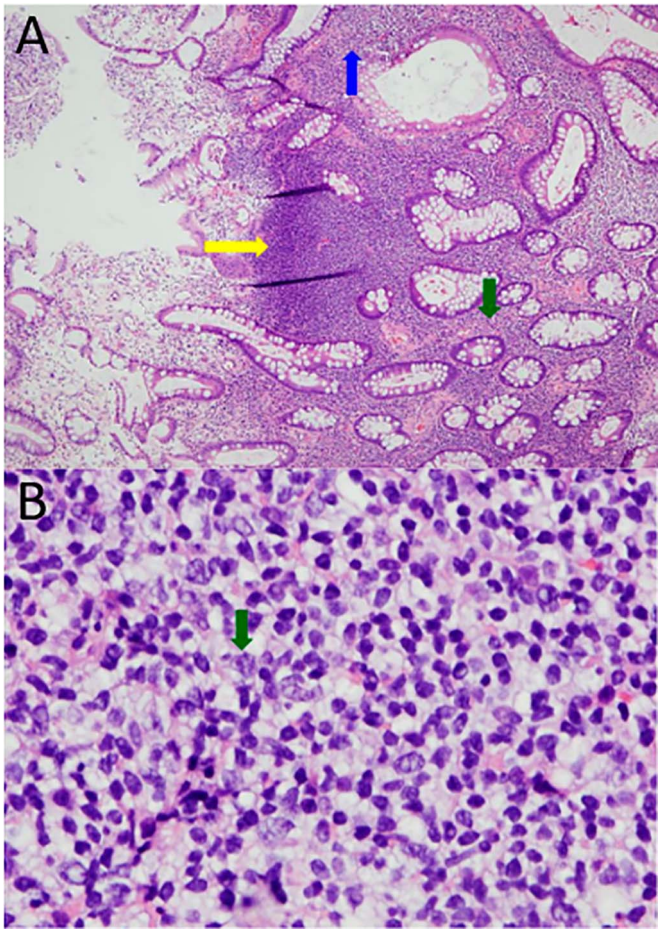

Figure 3. (A) Polymorphic posttransplant lymphoproliferative disorder—histopathology of the ileocecal valve at low power (magnification 4×) showing proliferation of interglandular, small bland lymphocytes and lamina propria (green arrows), focal proliferation of small, irregular lymphoid cells (yellow arrows), and increased lamina propria plasma cells (blue arrows). (B) Monomorphic posttransplant lymphoproliferative disorder—histopathology of the rectosigmoid colon at medium power (magnification 40×) showing sheets of medium sized lymphoid cells (green arrows) with irregular nuclei, small nucleoli, and moderate cytoplasm.

GI manifesting disease when compared with the heart, lung, or liver.[1,3] On endoscopy, GI-manifesting PTLD has been described as raised, rubbery, erythematous lesions with central ulcerations and can range in size from 5 to 15 mm in diameter.[3,5] Diagnosis is made by tissue biopsy.[12]

There is no definitive treatment for PTLD, with general consensus focusing on the preservation of the transplanted organ while alleviating disease progression and symptoms. Thus, a reduction in immunosuppression is the first step in the management for patients, followed by immunologic treatments such as rituximab with or followed by chemotherapy. In rare cases, surgery or radiation may be considered.[13,14] Although reduction in immunosuppression is the most widely used first step in management, it has a wide variance of remission rate ranging from 0% to 70%.[13,14]

Table 1. PTLD subtypes

Subtype[7]	Summary of key features[1,8]
Early PTLD type	Early lesion-PTLD is made up of a mixed cell population consisting primarily of small lymphocytes with scattered plasma cells and immunoblasts. This type exhibits minimal if any cytologic atypia.
Polymorphic PTLD type	Polymorphic PTLD subtype consists of mixed small and medium sized lymphocytes, atypical immunoblasts, mature plasma cells, and Reed-Sternberg-like cells and involves the destruction of tissue architecture with malignant features such as high mitotic rate, nuclear atypia, and necrosis.
Monomorphic PTLD type	Monomorphic PTLD consists of large lymphocytes and plasma cells with a uniform appearance and must fulfil the criteria for one of the B or T/NK cell lymphomas recognized in immunocompetent patients such as diffuse large B cell lymphoma or Burkitt lymphoma.
Hodgkin lymphoma-type PTLD	Hodgkin lymphoma-type PTLD is similar to typical Hodgkin lymphoma patients in that they are typically EBV+ with biopsies showing Reed-Sternberg cells and occurs usually in renal transplant patients.

EBV, Epstein Barr virus; NK, natural killer; PTLD, posttransplant lymphoproliferative disorder.

To our knowledge, the recurrence of PTLD after remission is a rare phenomenon. Few case studies have noted recurrence; 1 case involved polymorphic PTLD with recurrent monomorphic PTLD after treatment and another case of recurrent monomorphic PTLD occurring after a heart transplant.[15] Both cases used a reduction in immunosuppression, followed by chemotherapy for treatment.

In summary, our case demonstrates a renal transplant recipient with rare, recurrent PTLD with multiple histologic subtypes despite a previous response to rituximab and resolution of inflammatory changes on endoscopy. It is essential clinicians maintain a high suspicion for PTLD when caring for transplant patients and have a lower threshold for biopsy with endoscopic, nonspecific inflammatory changes. Importantly, this recurrence was found 10 years after initial diagnosis, which signifies the importance of serial monitoring for possible recurrence of the disease.

DISCLOSURES

Author contributions: S. Mussarat and K. Houston wrote the manuscript and reviewed the literature. P. Parekh supervised, edited the manuscript, and is the article guarantor.

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