

Post-transplantation lymphoproliferative disorder with gastrointestinal involvement

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Abstract

Post-transplantation lymphoproliferative disorders (PTLDs) are lymphoid proliferations or lymphomas that are the second most common tumors in adult transplant recipients. Most cases of PTLD are attributed to Epstein-Barr virus, which induces B-cell proliferation and occurs in the setting of severe immunosuppression after solid organ or bone marrow transplantation. The disorder is seen in 1-3% of liver transplant recipients and has a variable presentation chronology. Herein, we chronicle a case of aggressive B-cell lymphoma (PTLD WHO class-3) presenting with isolated gastrointestinal involvement in an Epstein-Barr virus-negative patient with living-donor liver transplantation, 4 years after receiving the transplant. While typical symptoms may be elusive in the immunocompromised setting, clinicians should be vigilant for underlying PTLD with isolated gastrointestinal involvement. Prompt detection and characterization by endoscopic evaluation with biopsy should be particularly stressed in such patients.

Keywords Post-transplantation lymphoproliferative disorder, gastrointestinal, intussusception, iron-deficiency anemia, awareness, treatment

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Introduction

Post-transplantation lymphoproliferative disorders (PTLDs) encompass a spectrum of heterogeneous entities ranging from benign polyclonal lymphoproliferation, polymorphic PTLD and monomorphic PTLD to classic Hodgkin's lymphoma-like PTLD [1]. Monomorphic disease includes diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma, plasma cell myeloma/plasmacytoma, and rarely T-cell neoplasms [1]. PTLD present with varying clinical

features, ranging from asymptomatic Epstein-Barr virus (EBV) seroconversion to monoclonal B-cell proliferation with nodal, extranodal, and disseminated disorder [2,3]. In one study, PTLD patients showed extensive symptomatic disease: extranodal disease (79%), poor performance status (68%), elevated lactate dehydrogenase (LDH) (71%), and advanced stage by Ann Arbor criteria (68%) [4]. Recently, PTLD has been highlighted as an important consideration in patients who develop iron-deficiency anemia (IDA) following solid organ transplantation [5]. Furthermore, intussusception is a known cause of intestinal obstruction. However, to our knowledge, it has rarely been reported in association with PTLD in adults secondary to liver transplant. In this article, we present a case of PTLD with isolated gastrointestinal (GI) involvement and review the pertinent medical literature.

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Case report

This study involves a 60-year-old Pakistani male with a history of hepatitis C virus-related decompensated cirrhosis status post living-donor liver transplantation. His immunosuppression regimen included tacrolimus

1.5 mg/day. Four years after transplant, he presented with unintentional weight loss, easy fatigability, recurrent vomiting for 1 month and 10-pound weight loss over 3 months. Review of systems was negative for fever, dysphagia, chills, or night-sweats. He was non-alcoholic, non-smoker, and drug-free.

Physical examination revealed pallor and temporal wasting. Laboratory evaluation was notable for hemoglobin 7.7 g/dL (13.5-17.5 g/dL), iron 42 µg/dL (55-160 µg/dL), and ferritin 23 ng/mL (20-500 ng/mL), consistent with IDA. He underwent esophagogastroduodenoscopy, which revealed multiple umbilicated masses with central ulceration in the body of the stomach (Fig. 1). The small bowel did not show any mucosal abnormalities. Colonoscopy was

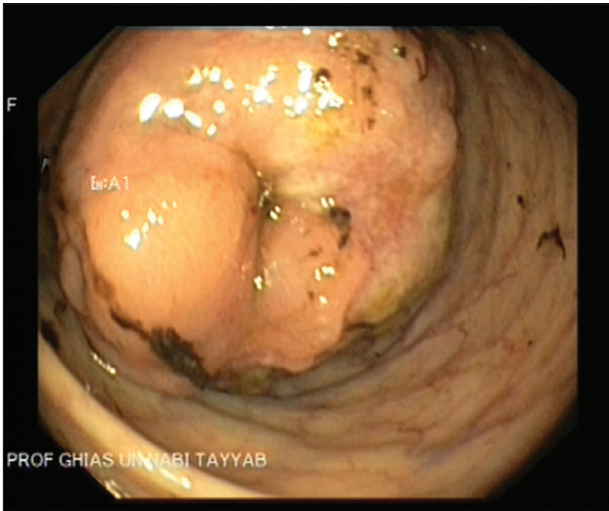


Figure 1 Esophagogastroduodenoscopy showing multiple umbilicated masses with central ulceration in the body of the stomach

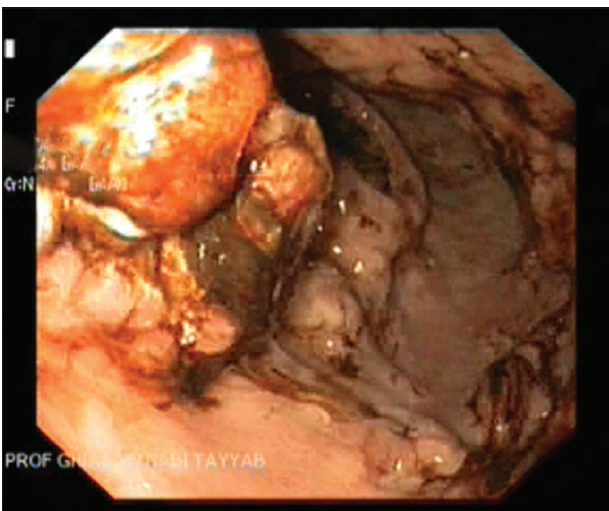


Figure 2 Colonoscopy showing tumor intussusception in the ileocecal region

notable for a tumor intussusception in the ileocecal region (Fig. 2). Contrast-enhanced computed tomography (CT) of the abdomen showed marked nodular thickening of the stomach (Fig. 3) and tumor intussusception in the ileocecal region (Fig. 4 A, B). Histopathological analysis of gastric and colonic specimens was consistent with the diagnosis of monomorphic, aggressive, B-cell lymphoma with Burkitt's-like features. Serum EBV polymerase chain reaction remained undetectable. A tumor staging positron emission tomography (PET)-CT demonstrated enhancement only in the stomach and colon. Bone marrow biopsy was negative for PTLD.

His chronic immunosuppression regimen was reduced and single-agent rituximab was administered, which resulted in a remarkable response with resolution of GI symptoms within a few weeks. At the 1-year follow up, he continues to do well, with no evidence of disease recurrence.

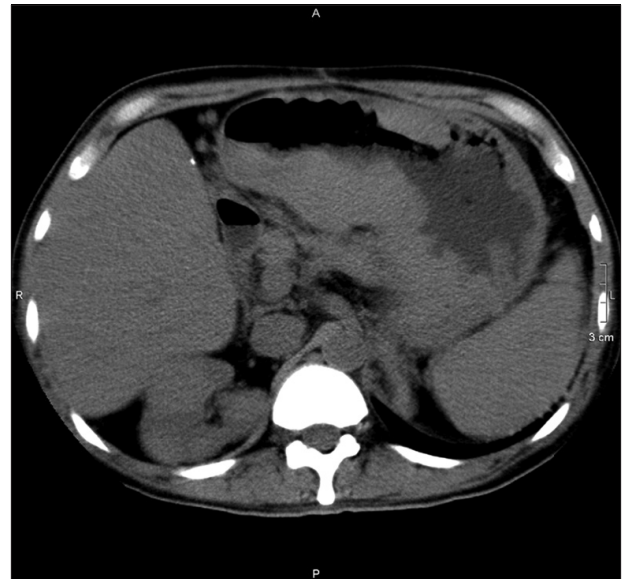


Figure 3 Contrast-enhanced computed tomography of the abdomen showing marked nodular thickening of the stomach



Figure 4 Computed tomography of the abdomen showing tumor intussusception in the ileocecal region. (A) Axial view, (B) coronal view

Discussion

The incidence of PTLD is variable based on the transplanted organ: 1-3% in kidney or liver transplants, 1-6% in heart transplants, 4-10% in lung transplants, and up to 20% in small intestine transplants [1]. An average time period between transplantation procedure and the diagnosis of PTLD is approx. 5.5 years. However, in a French registry of adult kidney and kidney pancreas recipients, GI PTLD mostly occurred late, from the 6th to the 10th post-transplant year [2].

Principal risk factors for PTLD include the degree of T-cell immunosuppression, EBV serostatus, time post transplant, recipient age, type of allograft, sex, and ethnicity [2]. EBV seroconversion is one of the most important risk factors, especially in pediatric transplant recipients and in early onset PTLD [2]. There is a known correlation between the type and duration of immunosuppression and the development of this disorder. Male sex, white race, and younger age at transplantation are additional independent risk factors for PTLD [3].

The pathogenesis of PTLD in most patients relates to the outgrowth of EBV-positive B-cell proliferations in the setting of chronic T-cell immunosuppression. However, EBV-negative tumors and T-cell tumors can also occur. The degree of T-cell immunosuppression is considered more important than the degree of immunosuppression overall, because of the impairment of EBV-specific T cell-mediated immunity. EBV-infected B cells are thought to be normally “held in check” by cytotoxic T cells, but this defense mechanism is impaired by T-cell dysfunction, eventually promoting the development of PTLD [3].

The literature lacks a consensus regarding the diagnosis of PTLD. Radiological evidence of a mass, or elevated serum markers, such as serum LDH levels, are suggestive of PTLD; positive PET scanning also favors the diagnosis. However, an accurate diagnosis should absolutely involve histopathological confirmation [4].

PTLD with isolated GI involvement is less common. O'Connor *et al* described 6 pediatric liver-transplant patients presenting with nonspecific GI symptoms, anemia, and failure to thrive. Endoscopy detected rubbery, raised, and ulcerated lesions in the colon and stomach [6]. Additionally, a few pediatric cases were reported to present with GI bleeding. In adult patients, Shitrit *et al* presented a review of isolated GI PTLD in 17 lung-transplant recipients [7] who manifested vague GI symptoms. Furthermore, isolated GI involvement has been described in 19% of 181 adult French renal-transplant recipients with PTLD [1].

A few reports have described PTLD-associated intussusception in pediatric liver-transplant patients, but it is rare in adult patients [8]. Management usually includes surgery but in selected cases, close follow up without surgical intervention can be considered, as in our patient [8]. Based on these data, it is imperative to consider urgent endoscopy

to establish an early diagnosis of PTLD with isolated GI involvement.

Treatment options may include reduction of immunosuppression, chemotherapy, anti-B-cell antibodies, or cytokine-based therapies [9]. The management of late PTLD involves the underlying histological lymphoma subtype with appropriate chemotherapeutic regimens, but rituximab, as in the present case, has frequently been used as either a single-agent or combination therapy in B-cell PTLD [10]. Prognosis varies with clonality and extent of disease; overall survival rates range between 25% and 35%. Mortality with monomorphic PTLD has been reported to be as high as 80%, with an extremely poor prognosis in T-cell lymphomas [10].

In conclusion, physicians should consider isolated GI PTLD as a possible etiology in post-transplant, immunocompromised patients who present with GI symptoms. A prompt endoscopic investigation is warranted in such patients to diagnose potentially curable PTLD early in the course of the disease, ultimately improving clinical outcomes.

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