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CASE REPORT | COLON

Dynamic Presentations of Recurrent Post-Transplant Lymphoproliferative Disorder in a Heart Transplant Recipient: A Rare Case Study

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ABSTRACT

Post-transplant lymphoproliferative disorders (PTLD) are complications that arise from post-transplantation immunosuppressive therapy. Although Epstein-Barr virus (EBV) viremia is often seen in PTLD, it is not a definitive feature for diagnosis. We report a rare case of recurrent PTLD in a 26-year-old heart transplant recipient on high-dose tacrolimus who presented with emesis, fatigue, and bloody diarrhea. Although substantial EBV viremia was seen in the first PTLD episode, the current episode was a gastrointestinal manifestation with barely detectable circulating EBV. The patient's history of gastrointestinal disease delayed definitive diagnosis, which was later established through endoscopy and biopsy sample analysis.

KEYWORDS: PTLD; EBV; Crohn's disease; inflammatory bowel disease

INTRODUCTION

Post-transplant lymphoproliferative disorders (PTLD) are uncommon but significant complications of solid organ and allogeneic hematopoietic cell transplantation. Although elevated Epstein-Barr virus (EBV) viremia is a common feature of EBV-positive PTLD, the absence of detectable EBV does not exclude a diagnosis of PTLD, and definitive diagnosis requires the histologic assessment of a tissue biopsy sample.[1-4] In this article, we present the case of a heart transplant recipient with inflammatory bowel disease (IBD) who developed a recurrent manifestation of PTLD in the absence of significant EBV viremia. Notably, the patient presented with gastrointestinal symptoms suggestive of a Crohn's disease exacerbation, which led to a delayed diagnosis. This case highlights the need for clinicians to maintain a heightened suspicion for PTLD in their differential diagnosis for transplant recipients and to adopt a low threshold for early endoscopy when patients with transplants are exhibiting a severe gastrointestinal-related illness.

CASE REPORT

A 26-year-old woman with an orthotopic heart transplant and Crohn's disease presented to the emergency department with escalating severe abdominal pain, emesis, fatigue, and bloody diarrhea. Her heart transplantation was performed 7 years previously because of viral myocarditis. Her donor organ was EBV-positive, whereas her serology was EBV-negative. She did not undergo induction immunosuppression for her transplant because of the high-dose immunosuppression she was already receiving for myocarditis, which included prednisone 60 mg daily and tacrolimus 2 mg twice daily. After transplant, mycophenolate 500 mg twice daily was added but eventually discontinued because of gastrointestinal intolerance. Notably, she was diagnosed with EBV-positive PTLD 3 years after transplantation and was successfully treated with rituximab and discontinuation of her prednisone. That PTLD presentation occurred after 2 episodes of mild rejection a year apart treated by solumedrol tapers and shortly after transitioning from vedolizumab to infliximab infusions while she was taking tacrolimus 3.5 mg daily and prednisone 15 mg daily. That presentation was associated with

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substantial EBV viremia (>700,000 copies/mL), EBV DNA in cerebrospinal fluid, diffuse lymphadenopathy, and a singular lesion in the left inferior temporal occipital junction.

At this emergency department presentation, she reported that she had been treated for recurrent IBD flares over the preceding months and recently initiated another round of budesonide therapy before her symptoms escalated and prompted her to seek further care. Her current immunosuppression regimen consisted of tacrolimus 8 mg daily, budesonide 9 mg daily, and vedolizumab 300 mg every 4 weeks. Initial laboratory tests revealed no leukocytosis, high C-reactive protein (20.8 mg/L), barely detectable EBV viral load (<50 IU/mL), and no lymphocyte abnormalities per peripheral smear. Computed tomography imaging revealed severe pancolonic wall thickening and fat stranding accompanied by multiple prominent mesenteric and pericolonic lymph nodes. Initially, considering her history, abdominal symptoms, imaging results, normal lymphocytes, and low EBV viremia, she was started on methylprednisolone for presumed Crohn's flare. Because of a lack of clinical response, colonoscopy was pursued on the third day of admission and showed inflammation with deep ulcerations in a continuous and circumferential pattern from the rectum to the sigmoid, with pronounced serpiginous ulcers in the sigmoid colon (Figure 1). Pathology analysis of colonic biopsy specimens revealed colonic mucosa with architectural distortion, Paneth cell metaplasia, focal active inflammation, and increased lamina propria plasmacytic inflammation. Further histologic staining revealed EBV-positive plasma cell hyperplasia with no evidence of cytomegalovirus or granulomata (Figure 2). Considering the patient's cardiac transplant history, ongoing immunosuppressive therapy, and histologic findings, she was ultimately diagnosed with recurrent early PTLD. Her tacrolimus was reduced to 5 mg daily, budesonide and vedolizumab were discontinued, and she was transitioned to ustekinumab 90 mg every 8 weeks. Within 2 weeks, her symptoms significantly improved, and a follow-up colonoscopy with biopsy confirmed the resolution of both inflammation and ulcers.

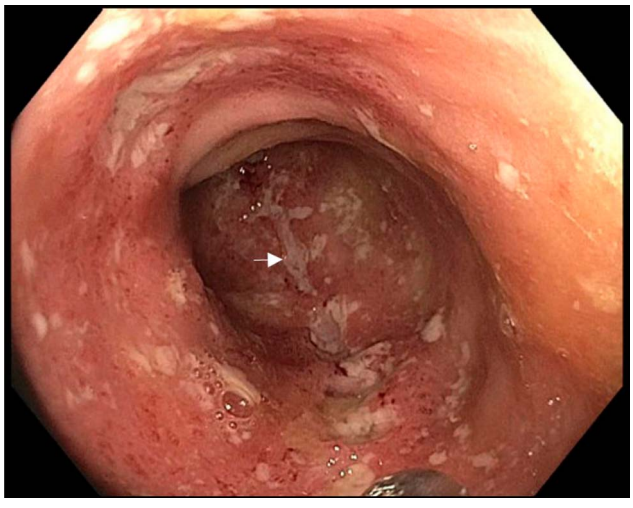

Figure 1. Sigmoid colon—deep serpiginous ulcer (white arrow).

DISCUSSION

PTLD are a continuum of diseases characterized by lymphoid or plasmocytic proliferations arising from immunosuppression after solid organ or allogeneic hematopoietic cell transplantation and are often, but not always, associated with EBV viremia.[1–5] PTLD may be difficult to diagnose because patients may present with complications ranging from benign conditions to aggressive lymphomas.[3,4] Because of our patient's history of IBD, severe abdominal symptoms resembling a Crohn's flare, and low EBV viremia, she was initially treated for IBD flare; however, subsequent endoscopy and comprehensive investigation of colonic tissues revealed a recurrent manifestation of PTLD.

PTLD's pathophysiology usually involves proliferation of B cells latently infected with EBV deriving from either the host or organ donor. Viral replication in infected B cells leads to viral protein expression that transforms the cells into immortalized lymphoblastoid cells, leading to PTLD.[6] The foremost recognized factor contributing to PTLD risk in transplant recipients is the extent of immunosuppressive therapy, which can impair T-cell–mediated immunity by reducing T-cell surveillance and cytotoxic responses, thus creating a conducive environment for unchecked proliferation of latently infected B cells.[7,8] Therefore, PTLD typically occurs within the first year after transplantation, coinciding with the most intense period of immunosuppressive therapy, and it is more frequently seen in heart transplant recipients, who undergo more potent immunosuppression than other solid organ transplant recipients.[9–11] Specifically, high-dose tacrolimus is associated with increased PTLD risk, particularly in pediatric patients.[11–13] Moreover, individuals with EBV-negative serology who receive an EBV-positive donor organ are at markedly higher risk of developing PTLD.[14,15] Our patient had several of these risk factors, including having been a pediatric heart transplant recipient, having received an organ that was donor-positive for EBV, and receiving high immunosuppression. However, the timing of her disease was unusual, with the initial EBV-positive event occurring 3 years after transplant surgery and the recurrent low-EBV viremia event occurring 7 years after transplantation in the setting of multiple IBD flares, delaying diagnosis.

In addition to her transplant immunosuppression the patient was on vedolizumab, an α4β7 integrin antagonist, that is primarily associated with gut-specific immunosuppression. Systematic reviews of the long-term safety data of vedolizumab show that vedolizumab does not significantly increase the risk of malignancies, including those related to EBV.[16,17] To the best of our knowledge, there are no documented cases of vedolizumab use leading to EBV PTLD, and it is unknown whether its concomitant use with the post-transplant immunosuppression contributed to her presentation.

Patients with PTLD may present with nonspecific symptoms, including weight loss, fatigue, fever, and additional symptoms

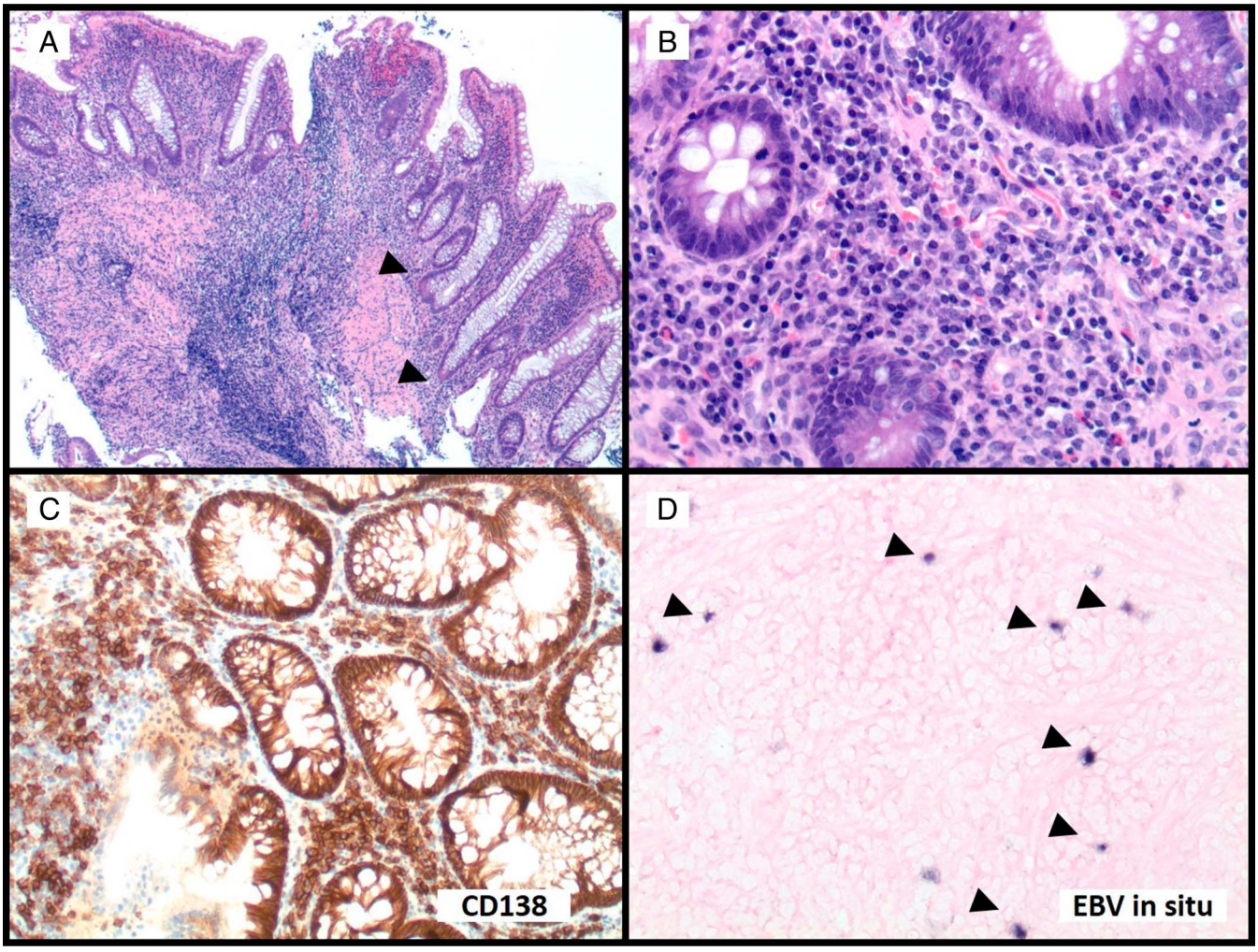

Figure 2. A hematoxylin and eosin stained section at 4× magnification (A) from the sigmoid colon biopsy showing colonic mucosa with architectural distortion and Paneth cell metaplasia (arrowhead) and (B) increased lamina propria plasmacytic inflammation. (C) Immunostaining for CD138 highlights numerous plasma cells in the lamina propria, which were polyclonal per kappa and lambda in situ stains (not pictured). CD138 immunostaining revealed normal expression in the colonic epithelium. (D) An EBV in situ stain highlights scattered lamina propria inflammatory cells (arrowhead). The features were most consistent with EBV-positive plasma cell hyperplasia described for early post-transplant lymphoproliferative disorder lesions. EBV, Epstein-Barr virus.

that vary depending on organ involvement. Thus, timely diagnosis demands a heightened level of suspicion. Although PTLD are classified within 2 classification schemas, no clear definitions for high-risk patients exist. Importantly, significant EBV viremia is a common feature of EBV-positive disease, underscoring the importance of early monitoring for EBV viral load when PTLD is suspected; however, the absence of EBV viremia does not preclude a PTLD diagnosis.[1–4,18] Rather, a definitive PTLD diagnosis requires confirmation of certain histologic, immunophenotypic, and genetic features of tissue biopsy specimens.[3,4] This is a crucial consideration in recurrent EBV PTLD, which frequently manifests as new, distinct lesions in different locations that are histologically and clonally different from previous occurrences, and thus may present with different clinical features in each episode, including changes in the presence of EBV viremia.[19,20]

In conclusion, this case illustrates the challenge of diagnosing a recurrent manifestation of early PTLD in a heart transplant recipient who had a different clinical manifestation than her first episode. Our patient's situation was complicated because she presented with symptoms resembling an IBD flare alongside very low EBV viremia, unlike her first PTLD episode which was diagnosed with high EBV viremia. Clinicians are advised to maintain a heightened suspicion for PTLD and adopt a low threshold for early endoscopy with biopsy analysis for EBV in transplant recipients manifesting gastrointestinal-related symptoms as recurrent episodes of PTLD may have different clinical manifestations. This is particularly critical because PTLD treatment necessitates reducing immunosuppression, whereas managing a Crohn's flare involves a stepwise approach of increasing immunosuppression—2 divergent strategies whose incorrect application could lead to detrimental outcomes. This proactive stance can help ensure timely identification and

prompt treatment, especially when clinical presentations overlap with other pre-existing conditions.

DISCLOSURES

Author contributions: A. Toiv, KB Harris, and MZ Khan reviewed the literature and wrote the manuscript. BK Theisen prepared the biopsy slides, evaluated them, and wrote the figure legends explaining the pathology. A. Varma, C. Fain, and N. Kaur participated in clinical assessment and treatment and edited the manuscript. N. Kaur is the article guarantor. All authors approved the article.

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