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CASE REPORT | INFLAMMATORY BOWEL DISEASE

The Persistent Wound: Plasmablastic Lymphoma in a Perianal Fistula

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ABSTRACT

Plasmablastic lymphoma is an aggressive subtype of diffuse large B-cell lymphoma associated with immunosuppression, particularly in HIV-positive patients. Although rare in HIV-negative individuals, patients with Crohn's disease experience immune dysregulation due to chronic immunosuppression that can predispose them to plasmablastic lymphoma. We present a case of a 54-year-old man with ileocolonic and perianal fistulizing Crohn's disease who developed plasmablastic lymphoma. This case emphasizes the importance of early recognition of plasmablastic lymphoma in patients undergoing chronic immunosuppressive treatment of Crohn's disease, as early diagnosis and timely intervention are crucial for improving outcomes.

KEYWORDS: plasmablastic lymphoma; Crohn's disease; HIV-negative; immune dysregulation

INTRODUCTION

Plasmablastic lymphoma (PBL) is a rare and highly aggressive variant of diffuse large B-cell lymphoma. PBL occurs in patients with compromised immune systems, specifically those with HIV, where it typically presents with a median survival between 4 and 15 months.[1–4] The disease is primarily seen in the oral cavity but has also been reported in other sites, including the gastrointestinal tract, bone marrow, and lungs.[5–7] While PBL in HIV-positive patients is well documented, cases in immunocompromised, HIV-negative individuals remain exceedingly rare.

Patients with Crohn's disease (CD) often require long-term immunosuppressive therapies, which may increase their risk of developing malignancies, including lymphoma.[8,9] Only 8 cases of PBL have been documented in HIV-negative patients with CD, making this an unusual but notable complication in this population. We report the case of a 54-year-old HIV-negative man with perianal and ileocolonic CD who developed PBL associated with persistent perianal fistulas in the setting of immunosuppressive therapy. This case highlights the need for early recognition of PBL in patients with CD on chronic immunosuppression.[10]

CASE REPORT

A 54-year-old man who presented with multiple episodes of perianal and rectal abscesses was diagnosed with ileocolonic and perianal fistulizing CD in 2014. He was initially treated with infliximab, but this was discontinued due to antibody formation resulting in a reaction. He was then started on standard-dose adalimumab (40 mg every 2 weeks) in 2016. Owing to persistent fistulizing perianal disease, chronic prednisone and azathioprine were added. He had a diverting colostomy in 2020 due to persistent perianal disease with recurrent abscess formation despite seton placements. The patient developed a chronic gluteal wound requiring treatment with prolonged antibiotic therapy with ertapenem and daptomycin. During treatment of his chronic gluteal wound in 2020, adalimumab and azathioprine were discontinued. The patient, however, continued to take prednisone.

In 2021, he was transferred to a large academic center for large-volume hematochezia associated with anemia. At the time of his presentation, he had tenderness in the perianal region with signs of active fistulizing disease. Hemoglobin was 8 g/dL. He remained afebrile and hemodynamically stable.

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Colorectal surgery performed an examination under anesthesia significant for friable granulation tissue in the perineum and multiple fistulous tracts, some associated with a small abscess. Biopsies were obtained and sent for pathological evaluation. Histology revealed large, atypical lymphoid cells with plasmacytic differentiation, characterized by prominent nucleoli and abundant cytoplasm (Figure 1). Immunohistochemical profile was as follows: CD20−/CD22−/CD30−/CD38−/CD45−/CD56+(weak, subset)/CD79a−/CD138+/Epstein Barr virus (EBV)+/ Epstein Barr virus encoded RNA in situ (EBER-ISH)+/HHV8−/κ+/λ−/multiple myeloma oncogene 1 (MUM1)+/PAX5−/Ki-67 (70%–80%), confirming PBL.

Staging with positron emission tomography/computed tomography was significant for hypermetabolic activity localized to the perianal region, without evidence of systemic disease. The patient was diagnosed with localized, stage IE PBL. HIV testing was negative.

Given the aggressive nature of PBL, the patient was initiated on a V-EPOCH chemotherapy regimen, which includes bortezomib, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin. V-EPOCH was selected due to its efficacy in addressing both the rapid cellular proliferation and immune-evasive characteristics of PBL. He completed a total of 6 cycles of V-EPOCH. At 6 months after treatment, he had an examination under anesthesia with biopsies demonstrating no evidence of disease recurrence. He was started on lenalidomide for maintenance therapy. Positron emission tomography scan a year from diagnosis was unremarkable for evidence of new tumor or metastasis.

DISCUSSION

Chronic immunosuppression in patients with CD is essential for disease control but may increase risk of malignancies. Prolonged use of prednisone can lead to poor wound healing, immunosuppression, and increased lymphoma risk.[11] Anti-TNF agents like adalimumab have also been linked to an elevated risk of lymphoproliferative disorders. A nationwide cohort study found that the risk of lymphoma was higher among patients exposed to anti-TNF monotherapy (adjusted hazard ratio, 2.41) and even higher with combination therapy (adjusted hazard ratio, 6.11) compared with unexposed patients. Similarly, a prospective registry study found that patients receiving anti-TNF therapy had a 2 to threefold increased risk of lymphoma, especially with adalimumab and infliximab (standardized incidence ratio 4.1 and 3.6, respectively).[12] This increased risk is thought to be due to the immunosuppressive effects of these therapies, which can lead to reactivation of latent EBV and subsequent lymphomagenesis.[13,14]

Of the cases in the literature that report PBL in a patient with HIV-negative CD, 7 of these patients had prior anti-TNF exposure while the remaining case received 6-mercaptopurine with budesonide (Table 1).[15,16] In our case, the patient's prolonged prednisone use, combined with immunomodulator and adalimumab, as well as the chronic inflammatory state from his persistent fistulas likely created a pro-oncogenic environment.

The diagnosis of PBL requires a high index of suspicion, especially when patients present with unusual symptoms like persistent bleeding, ulcerative lesions, or constitutional signs that are unresponsive to conventional CD treatment modalities. Immunohistochemical markers such as CD20, PAX5, CD138 and MUM1 are critical for confirming the diagnosis. EBV-encoded RNA positivity in PBL also suggests a viral contribution to its pathogenesis.[22] EBV is known to infect B cells and

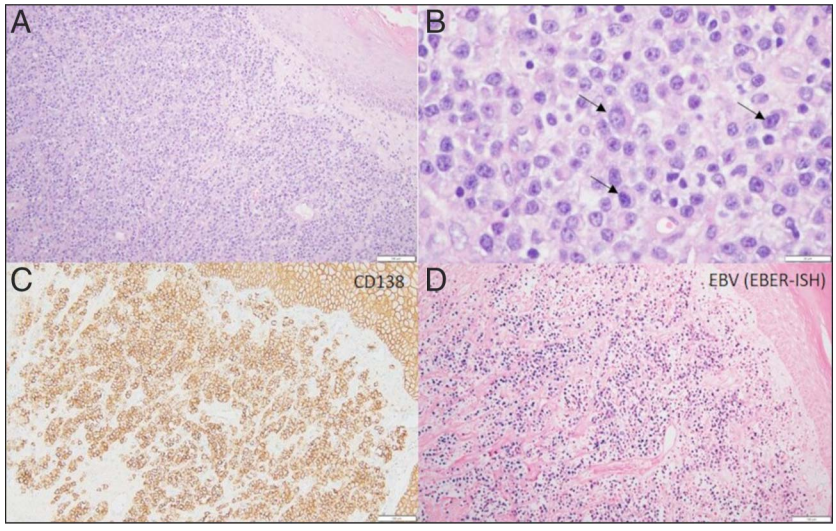

Figure 1. (A and B) Perianal fistulous tract biopsy section stained with hematoxylin and eosin stain—(A) low power view 100× and (B) high power view 600×—(C) section stained with CD138; (D) section stained with EBV (EBER-ISH). A dermal diffuse infiltrate of pleomorphic plasmacytoid cells with prominent nucleoli (B–arrows), positive for CD138 (C) and EBER-ISH (D). EBER-ISH,Epstein Barr virus encoded RNA in situ; EBV, Epstein-Barr virus.

Table 1. Literature review and case study summary of plasmablastic lymphoma in patients with Crohn's disease

Author Year	Age Sex	CD duration	CD treatment	PBL symptoms	PBL location	HIV	PBL treatment	Outcome
Sato 2020[17]	66 M	42 y	5-ASA (10 y) AZA (10 y) IFX (10 y)	Enlarging red nodule	Right abdomen	(−)	VCD	DOD
Plaza 2011[8]	57 F	25 y	AZA (3 mo) IFX (4 mo) Steroids	Gluteal fistula with drainage	Inguinal lymph nodes	(−)	Hyper-CVAD	Cardiac arrest
Ghosh 2017[18]	29 F	10 y	5-ASA (1 y) ADA (1 y) CTZ (1 y) IFX (1 y) MTX (1 y) Natalizumab (1 y) Steroids (1 y) Ustekinumab (3 y)	Loose stool, abdominal pain	Colon	NR	V-EPOCH	Remission
Liu 2013[19]	33 F	9 y	ADA (1 y)	None	Colon	(−)	EPOCH	Remission
Redmond 2007[20]	32 M	17 y	AZA IFX (2 y) Steroids	Back pain, night sweats, weight loss	Paravertebral	(−)	Hyper-CVAD	Remission
Maung 2015[21]	50 M	12 y	6-MP IFX (9 mo) SSZ Steroids	Vomiting, abdominal pain, diarrhea	Small intestine	(−)	EPOCH	Remission
Luria 2014[6]	41 M	15 y	6-MP (13 y) Budesonide (13 y)	Abdominal pain, diarrhea, weight loss	Ileum	NR	Hyper-CVAD	DOD
Luria 2014[6]	65 M	11 y	Budesonide IFX Steroids	Acute bowel obstruction	Ileum	(−)	Hyper-CVAD	Remission

(−), negative; 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; ADA, adalimumab; AZA, azathioprine; CD, Crohn's disease; CTZ, certolizumab pegol; DOD, dead of disease; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; F, female; hyper-CVAD, cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, dexamethasone; IFX, infliximab; M, male; MTX, methotrexate; NR, not reported; PBL, plasmablastic lymphoma; SSZ, sulfasalazine; VCD, bortezomib, cyclophosphamide, and dexamethasone; V-EPOCH, bortezomib + EPOCH.

drives their transformation through the expression of latent membrane proteins and Epstein-Barr nuclear antigens. These viral proteins disrupt normal B-cell differentiation and promote proliferation in both HIV-positive and immunocompromised patients.[23] In this case, the positive EBV status in the patient's tumor tissue further supports the role of chronic immunosuppression in PBL development.

Although there is no universally accepted standard treatment of PBL, combination therapy is frequently used. Regimens such as bortezomib, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (V-EPOCH), CHOP, and hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone are often used. However, comparative studies between V-EPOCH and cyclophosphamide, doxorubicin, vincristine, and prednisone and hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone have shown superior overall survival for V-EPOCH.[15,24] This has led to a recommendation by the National Comprehensive Cancer Network for V-EPOCH as first-line treatment for PBL, which led to the decision of using V-EPOCH therapy on this patient.[16,25]

This case illustrates the importance of maintaining a high index of suspicion for PBL in patients with Crohn's disease undergoing chronic immunosuppressive therapy. Although PBL is uncommon in HIV-negative individuals, with only 8 cases reported in patients with CD, it can develop in the context of prolonged immunosuppression, particularly when combined with persistent inflammation from complications such as perianal fistulas. Anti-TNF agents, corticosteroids, and immunomodulators collectively contribute to a pro-oncogenic environment, increasing the risk of malignancies like PBL. Early recognition is essential, especially when patients with CD present with atypical symptoms. Diagnostic confirmation relies on immunohistochemical markers, including CD20 and PAX5 negativity, with EBV positivity further indicating a viral contribution to lymphomagenesis. From a clinical perspective, this case highlights the need for monitoring patients with CD on

long-term immunosuppressive regimens. While treatment options remain limited, regimens such as V-EPOCH have emerged as effective and safe. Further research is warranted to establish the mechanisms linking chronic immunosuppression, EBV reactivation, and PBL development in HIV-negative populations. Clinicians should be aware of the potential for PBL in immunosuppressed patients and include it in the differential diagnosis when atypical lesions or symptoms arise. Given the aggressive course of PBL and the limited survival outcomes with current treatment options, early diagnosis is essential.

DISCLOSURES

Author contributions: SC Lutfallah, JFG Bobo, and N. Loganantharaj conceptualized the research; All authors were responsible for data acquisition and interpretation. SC Lutfallah and N. Loganantharaj drafted the manuscript; All authors were responsible for revision of the manuscript. N. Loganantharaj supervised the study. N. Loganantharaj is the article guarantor.

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