CASE REPORT OPEN ACCESS

Primary Gastrointestinal EBV-Associated Classical Hodgkin Lymphoma in Crohn Disease on Anti-TNF-α Therapy: A Rare Association

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ABSTRACT

Background: Lymphomas present a significant challenge in the field of gastrointestinal diseases, often being mistaken for other gastrointestinal tumors or inflammatory bowel disease conditions, causing clinical confusion. Early diagnosis plays a pivotal role in effective treatment. This case highlights the importance of recognizing lymphoproliferative disorders as a rare association of anti-tumor necrosis factor-α (TNF-α) therapy.

Case Presentation: A 41-year-old man with a 15-year history of Crohn disease on long-term therapy with adalimumab underwent a right hemicolectomy due to a semi-circumferential lesion at the ileocecal valve causing near complete obstruction and severe anemia (Hgb 6.4 g/dL). Previous biopsies of the mass showed an Epstein Barr Virus-positive (EBV+) classic Hodgkin lymphoma (CHL) in Crohn disease. At resection, the lymphoma showed transmural involvement of the ileum and regional lymph nodes.

Conclusion: Primary intestinal CHL comprises less than 5% of gastrointestinal lymphomas; CHL arising in the context of Crohn disease is even more rare. Most lymphomas associated with inflammatory bowel disease and/or immunosuppression are non-Hodgkin type. In this case, the long-term treatment with anti-TNF-α and EBV positivity suggested an iatrogenic immunodeficiency-associated lymphoma, an emerging group of lymphoproliferative disorders associated with the increased use of immunosuppressants.

1 | Introduction

Primary classic Hodgkin lymphoma (CHL) of the small intestine is extremely rare, comprising less than 0.9% of gastrointestinal (GI) lymphomas [1]. Patients with Crohn disease are likely to be at increased risk of developing lymphoproliferative disorders due to the coexistence of persistent chronic inflammation, a dysregulated immune response, and immunosuppressive treatment. However, epidemiologic studies do not support a clear association [2–7]. Most lymphomas in Crohn patients are of the non-Hodgkin type and are associated with thiopurine treatment [4, 8].

Anti-TNF-α agents, such as adalimumab, have been widely used for the management of inflammatory bowel disease (IBD) due to their efficacy in controlling inflammation and maintaining remission. Overall, these agents have a well-established safety profile, with most adverse effects related to infection risk and immune dysregulation rather than malignancy. However, concerns have been raised regarding their potential association

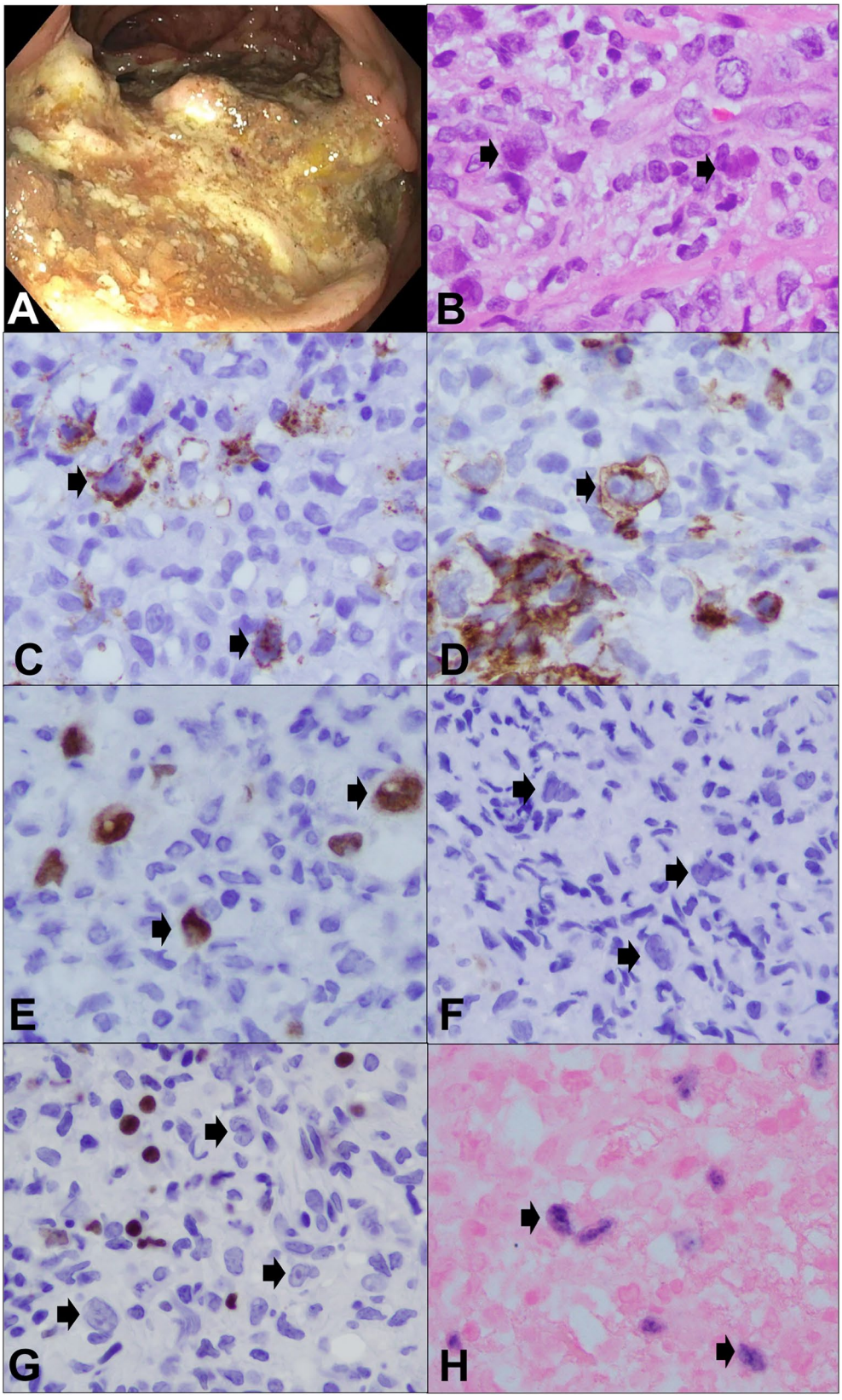

FIGURE 1 | Colonoscopy revealed a large, ulcerated semi-circumferential mass at the ileocecal valve (A). Histologic examination of mucosal biopsies showed severe active Crohn disease and scattered large mono-, bi- and polylobated cells with large eosinophilic nucleoli (B) that were positive for CD15 (C), CD30 (D), PAX5 (E), while negative for BOB1 (F) and OCT2 (G) consistent with Hodgkin/Reed-Sternberg cells (HRS). HRS cells were positive for EBV-encoded small RNA (EBER) in situ hybridization (H). Black arrows highlight HRS cells in microscopic images.

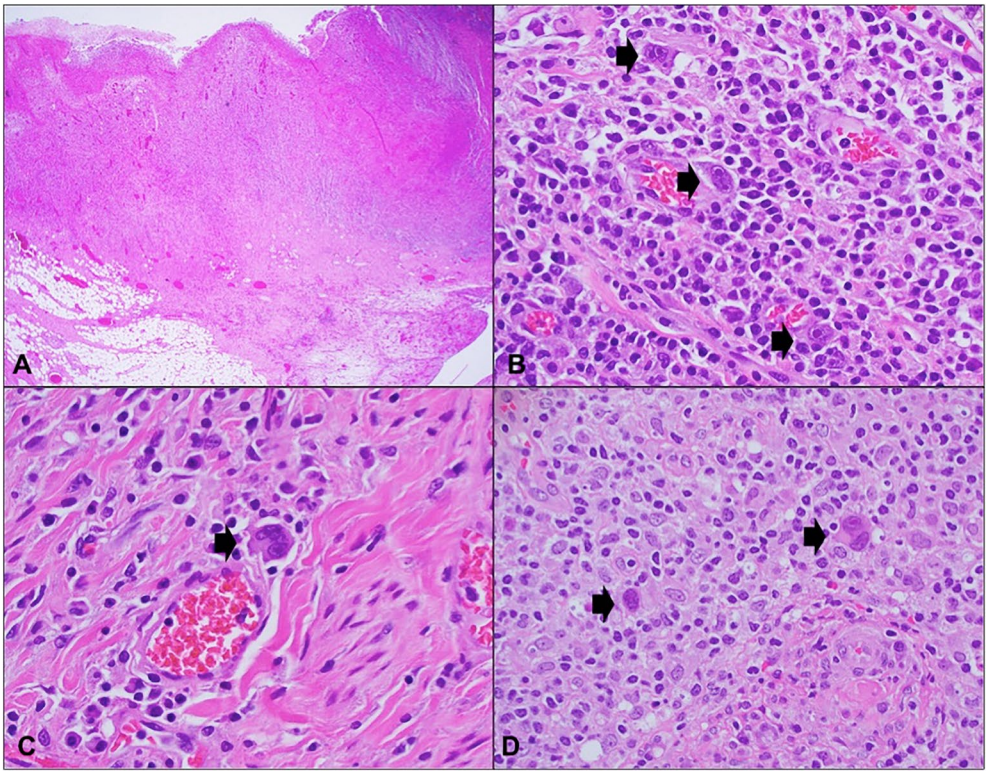

FIGURE 2 | Histological examination of the hemicolectomy specimen showed transmural Crohn disease and EBV (+) Hodgkin lymphoma involving the ileocecal intestine (A). Scattered HRS cells embedded in a polymorphous inflammatory infiltrate within the submucosa (B), subserosa (C), and regional lymph nodes (D). Black arrows highlight HRS cells in microscopic images.

with lymphoproliferative disorders, particularly in EBV-positive individuals or those receiving concurrent immunomodulatory therapy.

We describe an extremely unusual case of a primary ileocecal Epstein Barr Virus-positive (EBV+) CHL in a patient on long-term adalimumab therapy for Crohn disease. Current guidelines recommend routine clinical monitoring of patients on anti-TNF-α therapy, including periodic evaluation for opportunistic infections and malignancies, although no specific screening strategies for lymphoma in this population have been established. We performed a literature review attempting to demonstrate this rare association with anti-tumor necrosis factor-alpha (TNF-α) therapy, which is widely used to treat inflammatory bowel disease.

2 | Case Report

A 41-year-old man with a 15-year history of ileocecal Crohn disease maintained on long-term immunosuppression with adalimumab (subcutaneous injection, 40 mg/0.4 mL every 2 weeks) presented with hematochezia and severe anemia (Hgb 6.4 g/dL). Colonoscopy revealed a large, ulcerated semi-circumferential mass at the ileocecal valve (Figure 1A). Mucosal biopsies showed severe active Crohn disease and scattered large mono-, bi-, and polylobated cells with large eosinophilic nucleoli (Figure 1B) that were positive for CD15 (Figure 1C), CD30 (Figure 1D), PAX5 (Figure 1E), BCL6, MUM1, while negative for CD3, CD20, CD45 (LCA), BOB1 (Figure 1F) and OCT2 (Figure 1G), consistent with Hodgkin/Reed-Sternberg cells (HRS). HRS cells were positive for EBV-encoded small RNA (EBER) in situ hybridization (Figure 1H). All cells were negative by immunohistochemistry for cytomegalovirus and herpes simplex virus. According to the International Consensus Classification of Mature Lymphoid Neoplasms (ICC), it is crucial to differentiate these cases from EBV+ diffuse large B-cell lymphoma with a T-cell/histiocyte-rich large B-cell lymphoma-like pattern and from EBV+ mucocutaneous ulcer, given their increased incidence in immunosuppressed individuals. Expression of B-cell markers in more than 50% of the tumor cells can be demonstrated in these entities, requiring the use of an extended B-cell antibody panel. [9] Based on the 2024 WHO classification guidelines (WHO) [10], a diagnosis of EBV+ CHL arising in Crohn disease was made. Despite the lymphoma diagnosis, a right hemicolectomy was performed due to near-complete obstruction and significant bleeding. Histopathologic examination of the resection specimen showed transmural Crohn disease and EBV+ CHL involving the ileocecal intestine and regional lymph nodes (Figure 2A–D). Postoperatively, adalimumab was discontinued, and the patient was referred to hematology-oncology for further management. Evaluation with PET-CT at the time of resection revealed adenopathy above and below the diaphragm, along with spleen involvement. The patient was treated with 6 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy. Interim and posttreatment PET-CT showed no evidence of systemic disease, supporting a diagnosis of primary GI CHL, with complete remission at the six-month follow-up. The patient is currently under observation and surveillance, off all immunosuppressive therapy for colitis, and not on any active treatment.

TABLE 1 | Reports of Hodgkin Lymphoma in Crohn disease treated with anti-TNF-α therapy: Cases published between 1999—present (including our case).

Source		Age/sex	Clinical presentation	Duration of Crohn disease (*y*)	Site of involvement	Immunomodulatory therapy	EBV status
1999	Bickston et al. [8]	29/M	Intermittent cramping, abdominal pain, weight loss, recurrent perirectal fissures	4	Ileum and colon	Azathioprine/ steroids/infliximab	Not reported
2006	Bai et al. [11]	35/M	Severe, continuous anal pain and diarrhea	8	Rectum	Infliximab	Positive (by IHC and ISH)
2009	Castrellon et al. [12]	66/M	Diarrhea, lower abdominal pain	5	Ileum and colon	Methotrexate/ leflunomid/infiximab/6-mercaptopurine/ steroids	Positive (by ISH)
2011	Cassaday et al. [13]	54/F	Abdominal pain, diarrhea, fever	16	Ileum and colon	Azathioprine/steroids/ adalimumab	Positive (by ISH)
2012	Sagüés et al. [14]	20/M	Lymphadenopaty, not otherwise specified	6	Ileum and colon	Azathioprine/infliximab	Positive (by serology)
2014	Salgueiro et al. [15]	37/M	Acute exacerbation, not otherwise specified	20	Colon and rectum	Azathioprine/infliximab	Positive (by IHC)
2015	Moran et al. [16]	53/F	Rectal hemorrhage	Since teenage years	Colon and rectum	Azathioprine/steroids/ methotrexate/infliximab	Positive (by ISH)
2017	Carvalho et al. [17]	40/M	Lymphadenopathy, not otherwise specified	17	Ileum and colon	Azathioprine/ steroids/infliximab	Positive (by IHC)
2018	Barzilai et al. [18]	54/M	Anal pain, fever, weight loss, enlarged inguinal lymph node, perianal fistula	6	Ileum and colon	6-mercaptopurine/ iinfliximab/vedolizumab	Positive (by ISH)
2022	Current case	41/M	Hematochezia, severe anemia	15	Ileum and colon	Adalimumab	Positive (by ISH)

Abbreviations: EBV, Epstein–Barr virus; IHC, immunohistochemistry; ISH, in situ hybridization.

3 | Discussion

We describe a case of primary ileocecal EBV+ CHL in a patient with Crohn disease undergoing long-term anti-TNF-α therapy. This rare association between iatrogenic immunosuppression and the development of EBV+ CHL in the context of inflammatory bowel disease prompted us to conduct a comprehensive systematic literature review to examine similar cases and better understand the underlying mechanisms and potential clinical implications. Our search was conducted using PubMed, with keywords including "lymphoma", "Crohn disease", "EBV", "anti-TNF therapy", and "immunosuppression". The first case of CHL arising in a Crohn disease patient receiving anti-TNF-α therapy was described by Bickston et al. [8]. Since then, eight additional cases have been reported as individual case reports [11–18], which are listed in Table 1. All cases had previously received treatment with immunomodulators [8, 11–18].

One case was a relapse in a patient with a history of treated systemic CHL in remission [13]. Interestingly, this patient had a complete spontaneous regression of the lymphoma after refusing any further pharmacologic treatments and opting for hospice care, suggesting that iatrogenic immunosuppression played a central role in her EBV+ CHL [8].

Primary GI CHL is rare, comprising less than 5% of GI lymphomas [19–21]. The stomach is the most commonly affected site, followed by the small intestine and colon [22]. There is conflicting data about whether the incidence of lymphomas is increased in inflammatory bowel disease (IBD). Some groups have reported an increased incidence of non-Hodgkin and EBV+ lymphomas in IBD [23–25]. However, most large epidemiologic studies and meta-analyses have not identified significant differences compared to the general population, indicating that if a risk exists, it is very low [2, 3, 5, 26, 27]. While the independent influence of IBD on the development of EBV-associated lymphomas remains unclear, it is evident that IBD patients on immunosuppressive therapy are at a higher risk. The association between anti-TNF therapy and EBV+ CHL may be mediated through several immunological and cellular mechanisms. Anti-TNF-α agents, such as infliximab and adalimumab, are known to suppress the inflammatory response in patients with autoimmune conditions, such as Crohn disease. While this provides therapeutic benefit by reducing inflammation, immunosuppression hinders the immune system's ability to control latent EBV infection, allowing the virus to reactivate and promote the proliferation of EBV-infected B-cells, potentially leading to the development of lymphoma. Anti-TNF therapy has been shown to alter cytokine profiles and suppress both innate and adaptive immune responses, further favoring the development of lymphoproliferative disorders in patients with latent EBV infection. Moreover, EBV+ Hodgkin cells activate NF-κB signaling pathways, promoting cell survival and proliferation while downregulating MHC class I molecules, thus preventing effective immune surveillance [28].

In regard to IBD therapies and the risk of lymphoma, thiopurines are associated with a 4 to 5-fold increased risk of non-Hodgkin lymphoma [29, 30]. By contrast, an association with anti-TNF-α therapy in epidemiologic studies has been reported only by a few investigators [4] and refuted by most [2, 3, 5]. Finally, some case reports and small case series have suggested an association between GI CHL, Crohn disease, and EBV infection [31–35]. However, larger studies have not shown statistically significant differences in the EBV viral load of Crohn disease patients and controls, regardless of anti-TNF-α therapy. Nonetheless, a few patients did experience transient high viremias linked to disease flare-ups [18, 36–41].

From a clinical perspective, our case highlights the importance of individualized risk assessment in patients receiving long-term immunosuppression. Although the absolute risk of lymphoma remains low, clinicians should maintain a high index of suspicion in patients who present with atypical masses, unexplained anemia, or persistent constitutional symptoms while on anti-TNF-α therapy. Practical recommendations include regular clinical monitoring, baseline laboratory assessments (including complete blood count and inflammatory markers), and periodic imaging for patients with complicated or refractory disease.

Regarding EBV screening, there is currently no consensus on routine pre-treatment testing before initiating biologics. However, given the role of EBV in lymphoproliferative disorders, EBV serologic testing (EBV IgG/IgM and possibly EBV DNA quantification) could be considered in high-risk individuals, such as those with prior immunosuppressive exposure, a history of EBV-driven disease, or concurrent thiopurine therapy. For patients with detectable EBV viremia at baseline, closer surveillance with periodic viral load monitoring may be warranted, although further studies are needed to define the utility of this approach.

In conclusion, primary intestinal EBV+ CHL in patients with Crohn disease on anti-TNF-α therapy is a very rare type of iatrogenic immunodeficiency-associated lymphoproliferative disorder affecting a very small subset of IBD patients. There is no epidemiologic evidence that this constellation represents an emerging syndrome that would require disease-specific surveillance strategies in IBD patients. Clinicians should be aware of this rare entity that may present as an inflammatory mass in the setting of refractory Crohn disease. Pathologists should perform a careful review of histology with the aid of immunophenotyping studies for the presence of Hodgkin/Reed-Sternberg cells that may be embedded within a polymorphous inflammatory infiltrate present in active Crohn disease.

Ethics Statement

We confirm all relevant ethical guidelines have been followed. We consulted with the Institutional Review Board/Research Ethics Committee of Indiana University, who determined that ethical approval was not applicable because this article does not contain any studies with human or animal subjects.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data generated for this research are available from the corresponding author upon reasonable request.

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