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Lymphoma Complicating IBD Immunomodulator Therapy: A Reminder to be Vigilant

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Abstract

Patients with Inflammatory Bowel Disease (IBD) not responding to steroid treatment should be considered for immunomodulator therapy. The risk of lymphoma in IBD patients treated with immunomodulators is a well-documented but rare complication and remains a subject of controversy. Here, we present two patients treated successfully in outpatient clinics on thiopurine immunomodulators who were admitted within weeks of each other with a diagnosis of lymphoma. Both patients were found to have a positive Epstein - Barr Virus (EBV) status. These cases should serve as a reminder to be vigilant of this complication when patients present with systemic symptoms.

Keywords: IBD; Crohns disease; Ulcerative Colitis; Lymphoma; EBV; Immunomodulatory Therapy

List of Abbreviations: IBD: Inflammatory Bowel Disease; IFX: Infliximab; EBV: Epstein-Barr virus; TNF: Tumour Necrosis Factor

Introduction

Patients with steroid-dependent IBD frequently require immunomodulator therapy such as thiopurines. The risk of lymphoproliferative disorders and opportunistic infections in IBD patients treated with immunomodulators is a concern, prompting clinicians to be vigilant whenever reviewing patients. This risk of lymphoma is increased in patients with a positive EBV status. Combination therapy (thiopurines plus biologics such as anti-Tumour Necrosis Factor (TNF) agents) is perceived to have higher complication rates and there is more concern about the risk of lymphoproliferative disease than for patients on single modality therapy.

We present two reports of patients treated with combination therapy for IBD who presented with lymphoma within weeks of each other and review the evidence for the increased risk with this therapy.

Case Presentations

Patient 1

A 45-year-old female was diagnosed with distal ulcerative colitis in 2005 following smoking cessation. She was treated with oral and topical mesalazine and episodic steroid courses. In 2010, re-evaluation confirmed severe extensive colitis which prompted initiation of azathioprine, followed by Infliximab (IFX) a few months later. She achieved a steroid-free clinical remission.

After 12 months, IFX was discontinued, and she was maintained on azathioprine. In 2013, IFX was restarted due to recurrent flare-ups needing steroids, with prompt symptomatic response. She continued with regular 8-weekly infusions. In May 2014, azathioprine was discontinued due to a leucopenia of 3.1×10^9/L (neutrophils 1.8×10^9/L). One week later she presented with dizziness, dyspnea, cough, fatigue, weight loss, fevers and drenching night sweats. She was pyrexial (40 °C) with a tender left supraclavicular lymph node and a clear chest and abdomen. Investigations included Hb 99g/L, WBC $1.5x10^9$/L, platelets $94x10^9$/L, neutrophils $1.3x10^9$/L, lymphocytes $0.1x10^9$/L and CT imaging showed bulky para-aortic and paracaval nodes, retrocrural nodes, nodes in the sigmoid mesentery and the left supraclavicular area and splenomegaly. She was EBV IgG positive.

Lymph node biopsy showed a replacement of the normal architecture with patchy nodular infiltrate composed of large atypical cells. These cells stained positive for CD30, PAX5 and EBER. These morphological features were consistent with a classical Hodgkin's lymphoma, nodular sclerosis type, staged as IIIB. IFX was discontinued.

She received 6 cycles of ABVD chemotherapy and had a negative CT PET in August 2014 representing a complete response to chemotherapy. Her colitis has remained in clinical remission off all therapy. At last review in March 2016, she was in remission from Hodgkin's disease and the colitis.

Patient 2

A 49-year-old male was diagnosed with colonic Crohn's disease in 2005. He had complex multiple fistulae involving the scrotum and perianal area with an anal stricture. Despite azathioprine and IFX combination therapy from 2005, he required a defunctioning loop ileostomy to control severe rectal and perianal disease in 2012. His IFX regime was escalated to 6-weekly infusions in combination with azathioprine 175mg. Although there was clinical and biochemical response, azathioprine had to be discontinued due to deranged LFTs in late 2012. In July 2013, MRI of the pelvis documented radiological remission with resolution of the complex perianal disease.

On stepping down the frequency back to 8-weekly IFX infusions he had a recurrence of fistulae including one at the base of the penis. In February 2014 he was unwell with weight loss of 15kg over 4 months, occasional drenching night sweats and passing urine through the base of the penis. His CRP was 217mg/L, albumin 15g/L, Hb 79g/L and WBC 11.5×10^9/L. CT scan showed pelvic, inguinal and para-aortic lymphadenopathy and splenomegaly.

Inguinal node biopsy showed a poorly differentiated neoplasm with loss of normal nodal architecture and a patchy infiltrate of pleomorphic large cells. This was proven to be an EBV-driven large cell lymphoproliferative condition, which lacked definitive lineage markers, staining with PAX5 and CD2. EBV status showed active and previous infection more than 8 weeks previously. Chemotherapy achieved symptomatic improvement and resolution of disease, shown on a CT-PET scan done in July 2014. In view of the persistence of his fistulae, he required a formal proctectomy and formation of end ileostomy. He is now thriving in remission from both the lymphoma and the Crohn's disease.

Discussion

Since the earliest studies of azathioprine in Crohn's disease and ulcerative colitis, there have been concerns about drug toxicities, including the risk of malignancies. The risk of development of lymphoma in IBD remains controversial [1]. Numerous studies have concluded that the risk may be only slightly higher than in the general population but the rare occurrence of lymphoma makes the risk difficult to calculate [2]. The number needed to treat to cause one additional lymphoma ranges from 400-4000 in patients treated with thiopruines [3]. Possibilities have been postulated as to the cause of this complication, including a link to the increase in incidence of bowel cancer in IBD patients, particularly those with ulcerative colitis [4]. Increased risk of lymphoproliferative disorder has been noted in patients on immunomodulator therapy following solid organ transplant with strong links to EBV infection in a number of these patients [5]. A possible reason is the increased susceptibility to infections whilst on immunomodulation and EBV infection has been linked to lymphoma development with EBV serostatus being an important risk factor alongside young age [6-8]. It has been suggested that EBV drives lymphoproliferation by reducing immunosurveillance of latent EBV [9]. The use of immunomodulators may result in iatrogenic immunosuppression which could lead to this increased susceptibility. The French CESAME Study was the largest population based prospective study which included 19,486 patients with IBD, and they showed an increased hazard ratio of 5.28 for lymphoma in patients exposed to thiopurines [10]. There was an association with EBV infections and the risk reduced to baseline once thiopurines were discontinued.

Anti-TNF therapy is almost always used alongside other immunomodulators so the independent risks have been difficult to establish. One study of thiopurine-only therapy showed a strong association with EBV-positive lymphoma [11]. Recent meta-analyses and larger population based studies have not revealed any increase risk of cancer in anti-TNF exposed patients [12]. Whilst the absolute risks of lymphoma are low, the concern should be acknowledged before commencing therapy with evaluation of the risk-benefit ratio. National guidelines still include immunomodulators as treatment for IBD due to their effectiveness in controlling disease and reducing the need for steroids but NICE guidelines state that treatment must be reassessed after 12 months to ensure that the risk-benefit ratio is maintained. The risk has not been shown to be dose-dependent so this need not be considered [6]. Screening for EBV status prior to starting thiopurines is advisable and these drugs should be avoided in EBV-naïve patients to reduce the risk of fatal post mononucleosis proliferation, especially in males [13]. However there are no serological or histological predictors of lymphoma in IBD patients.

In summary, the overall benefits outweigh the absolute risk, especially in young patients where the risk of non-Hodgkin's lymphoma is lower. In spite of concerns, thiopurines remain the mainstay of IBD management and are used in approximately 40% of patients [10]. Consensus remains that the benefits of thiopurines outweigh the risks of lymphoproliferative diseases and combination therapy probably does not confer any added risk. Decisions to continue treatment, whether combination therapy or single agent therapy, needs to be tailored to each patient and incorporate clinical factors such as disease activity, response to therapy, age of the patient and prior complications such as previous cancers.

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