SHORT REPORT

Cutaneous lymphoma in a patient with ulcerative colitis after immunosuppressive therapy ☆,☆☆,★,★★

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Abstract

Introduction: Biologics are generally safe and well tolerated. However, the risk of haemato-poietic cancer in patients with inflammatory bowel disease receiving infliximab has been a growing concern.

Case presentation: We report the first case of cutaneous lymphoma after short use of infliximab in 75-year old Caucasian man with a 7-year history of ulcerative colitis.

Conclusion: Our current knowledge is not sufficient to rule out an increased risk of lymphoma associated with biologics, or allow definitive conclusions to be drawn about the association of infliximab and lymphoma. However, this case and others direct the attention to that both higher index of suspicion and closer follow up are required if patients are maintained on long-term infliximab together with other immunosuppressive therapy.

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1. Introduction

The treatment of ulcerative colitis has undergone a revolution with the advent of biologic therapies. Biologics are generally safe and well tolerated. During the past few years, the risk of hematopoietic cancer in patients with inflammatory bowel disease receiving infliximab, a chimeric IgG1 monoclonal antibody that binds specifically and directly to human tumor necrosis factor-α (TNF-α), has been a growing concern. However, most reported cases of lymphoma associated with infliximab were of the hepatosplenic T cell (HSTCL) or the B-cell non-Hodgkin’s types, and usually followed a long term use of infliximab. In this case report, we report a case of a cutaneous lymphoma after short use of infliximab.

2. Case presentation

75-year old; ex-smoker Caucasian man with a 7-year history of left ulcerative colitis (UC); his past medical history was unremarkable except for pulmonary embolism secondary to deep venous thrombosis (DVT) in 2004 and cerebellar infarction in 2008, with minimal residual effect and overall good performance. In November 2008, patient received biological therapy, infliximab (Remicade, Centocor) for an exacerbation. His maintenance treatment 1 year previously was azathioprine 200 mg daily (2.5 mg/kg/day), which was maintained from January 2005 to February 2009 plus on demand use of corticosteroids. The patient received three cycles of prednisone in the interval between August 2007 and November 2008, which was withheld with the start of infliximab treatment. Maximum doses were 60 mg/day. Until the time of withdrawal, interval between cycles was reduced progressively, with an average of 10 weeks interval between each cycle and the other. Infectivological screening revealed that hepatitis B virus; hepatitis C virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), and mycobacterial tuberculosis infections were negative. Epstein–Barr virus (EBV) serology showed that EBV VCA IgM was negative, and EBV VCA IgG and EBV EBNA IgG were positive. Infliximab induction therapy which consisted of three doses of 5 mg/kg at 0, 2 and 6 weeks was started after exclusion of contraindications. The third dose was in January 2009, with reported clinical improvement. Then he was planned to be included in the maintenance program, 5 mg/kg intravenous infusion every 8 weeks. Subsequent to the first course, in February 2009, he presented with progressively enlarged fronto-parietal swelling. The infliximab therapy was immediately discontinued. No lymphadenopathy can be detected either clinically or both by magnetic resonance imaging (MRI) and computed tomography (CT) scans of the head and neck. CT scans of the thorax and abdomen and ultrasound examination of the abdomen and groin were unremarkable. Excisional biopsy was done (Fig. 1). Histopathological and Immunohistochemistry evaluation showed diffuse infiltration of the dermis and subcutaneous tissue by large, atypical cells in a mixed inflammatory background, strongly positive for CD20 and CD30, consistent with the diagnosis of Hodgkin lymphoma (HL) with exclusive skin involvement. Surgical resection was done and treatment with five cycles of chemotherapy of (prednisone – lomustine – etoposide) was started. This produced marked symptomatic improvement and disappearance of the skin lesions. Immunosuppressive therapy was discontinued, and the UC was managed with oral and rectal mesalazine. In May 2010, the patient was admitted to the hospital with active colonic UC, confirmed by clinical, biochemical, endoscopic and pathological assessments, and he was started with oral daily doses of prednisone 50 mg/day, methotrexate 25 mg/week plus mesalazine 3.6 g/day. After the first dose of methotrexate, patient developed pancytopenia and methotrexate was withdrawn. Four months later, he presented again to hospital with moderate UC activity. Screening for potential superinfection role, revealed a positive Epstein–Barr virus (EBV) serology, virology by polymerase chain reaction (PCR), in colonic samples and in histopathology specimens, and negative cytomegalovirus (CMV) infection tests. In the view of the confirmation of the persistence of endoscopic activity, evidence of superinfection role and previous patient’s history, which discourage the use of immunosuppressive and biological therapy as first option of treatment; patient was assessed for possibility of total colectomy or granulocyte apheresis. Unfortunately, three weeks later, patient presented to the emergency room with refractory septic shock with multi-organ failure secondary to severe right lower lobe pneumonia that required Intensive Care Unit admission, and passed away in December 2010 despite intensive therapy.

3. Discussion

This case of cutaneous HL in a patient on short-term maintenance therapy with infliximab and azathioprine for UC is unusual for these reasons: to our knowledge, this is the first case of cutaneous HL presenting in a patient with UC, occurring after treatment with infliximab and azathioprine. Although few case reports have indicated that an extremely rare, but universally fatal lymphoma may occur in patients treated with the antibody TNF-α inhibitors, particularly when used in combination with thiopurines in patients with IBD; most of these infliximab associated lymphomas are mainly of HTSCL or the B-cell non-Hodgkin’s types and usually followed prolonged use of infliximab. The development of lymphoproliferative disorders is a known complication of immunosuppressive therapy. Chances of lymphoma development irrespective of the underlying...
disease increase if infliximab is used with another immuno-suppressive agent as cyclosporine and methotrexate. This patient was also on azathioprine. Indeed, data from observational studies, clinical trials, and meta-analyses have generally indicated a favorable risk profile of TNF-α inhibitors with respect to lymphoma. Meta-analyses of randomized controlled studies, which limit the concerns of channeling bias associated with observational studies, have yielded conflicting results. Although, one meta-analysis has failed to show a statistically significant risk of lymphoma with TNF-α inhibitors, a recent one done exclusively for Crohn's disease patients reported that TNF-α inhibitors are slightly associated with increased risk of NHL. Albeit, meta-analyses of RCT are considered the gold standard of evidence based medicine, in this instance, they are poorly suited to fully address lymphoma risk due to the short duration of exposure to these agents as well as relatively limited statistical power to rule out associations which may be clinically important. Additionally, long-term use of azathioprine, which is used to maintain remission and as a steroid-sparing agent in patients with UC, has previously been implicated in the pathogenesis of reversible lymphoma in patients with IBD. Some cases of HSTCL reported in patients treated with a thiopurine utilized alone for IBD. These observations seem to suggest that there may be a synergistic effect with infliximab and thiopurines, although it is also possible that the heightened awareness of this rare disease resulted in an increase in reported cases above that seen with thiopurines alone. On the other hand, although IBD per se, is proposed to be associated with development of extra-intestinal HL, regardless the use of immunosuppressive therapy, this correlation is not universally accepted. While, Palli et al. and Loftus et al. reported a possible increase risk lymphoma in patients with IBD, Lewis and colleagues cannot confirm this association. Moreover, most of these reports implicate UC more than Crohn's disease in this issue, even without immunosuppressive therapy. By analysis of these reports and our case, the possibility that UC may be directly implicated as potential predisposing risk factor in pathogenesis of HL in our patient cannot be ruled out, putting in mind its possible occurrence in the extra-intestinal organs. Further studies are required in this issue to clarify the role of genetic basis and host factors in predisposition for increasing risk of HL in patients with UC either per se, or with the use of immunosuppressive therapy.

Another crucial aspect of immunosuppression associated lymphomas is the well-distinguished relationship between many of these malignancies and EBV infection. EBV is also a known cofactor in several AIDS-related non-Hodgkin’s lymphomas. Although EBV is likely to have a role in tumorigenesis, the pathophysiology is unclear. In a recent Dutch nationwide study, a distinct correlation between EBV-positive lymphoma and AZA/6-MP use was observed. In this patient evidence of infection with this virus was positive in blood serology and virology, in colonic samples and in histopathology specimens. Presumably, the patients compromised immune status allowed an EBV-driven proliferation to develop, similar to that seen in post-transplant and HIV-positive patients.

In conclusion, this is the first case of cutaneous HL presenting in a patient with UC, occurring after treatment with infliximab. However, our current knowledge is not sufficient to rule out an increased risk of lymphoma associated with biologics, or allow definitive conclusions to be drawn about the association of infliximab and lymphoma. However, its benefits clearly outweigh the risk of lymphoma, and justify its use in our case, and in others. Moreover, we cannot confirm that infliximab alone can be held responsible for the pathogenesis of HL in this patient as he had two other risk factors namely his primary disease and the use of azathioprine. Further studies are keenly needed to provide answer, whether this risk increases with prolonged use of infliximab or with concomitant use of thiopurines. Albeit, it is likely that the absolute risk of HL associated with infliximab is very low, given that they have not been observed outside of spontaneous reports, both higher index of suspicion and closer follow up are required if patients are maintained on long-term infliximab together with other immunosuppressive therapy.

References


