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Cutaneous T-cell lymphoma in the setting of anti-tumor necrosis factor and immunomodulator therapy: A case report and literature review

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Abstract

Immunosuppressive therapy is well recognized as increasing the risk of lymphoma. Mycosis fungoides is a rare cutaneous form of T-cell lymphoma with a largely unknown etiology and not typically associated with immunosuppression. In this article, we describe our encounter with a 24-year-old male with Crohn's disease in remission on immunotherapy, specifically dual therapy with azathioprine and infliximab, presenting with a facial rash found to be consistent with mycosis fungoides on biopsy. The patient's rash resolved with treatment of topical steroids. In addition, the decision was made to discontinue his azathioprine to minimize his risks of developing future malignancies.

Keywords

Inflammatory bowel disease, immunotherapy, Crohn's disease, lymphoma, mycosis fungoides

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Introduction

Medical therapy to treat symptomatic Crohn's disease has advanced over the past decade, due to the development of biologic and immunomodulator drugs. Crohn's disease affects an estimated 3.2 per 1000 people in North America and has been increasing in incidence since the 1990s,[1] likely due to increased detection rates. Due to the progressive nature of the disease, those with Crohn's disease have a slightly reduced life expectancy[2] because of the increased risk of malignancies.[3] Crohn's disease has a relapsing and remitting nature; therefore, proactive monitoring and escalating treatment as necessary is recommended. Once remission is achieved, relapse should be prevented with continuing medical therapy.[4] Current data suggest treatment Crohn's disease with dual immunomodulator therapy, such as the combination of azathioprine and infliximab, is more effective than monotherapy in preventing relapse.[4,5] Despite improvements in medical therapy, an estimated 70% of patients with Crohn's disease will require some type of surgery to relieve their symptoms.[6]

The immunosuppressive therapies available to manage Crohn's disease include immunomodulators, such as azathioprine and methotrexate, and anti-tumor necrosis factor (TNF) agents, such as infliximab and adalimumab.[7,8] Given the long-term use of immunosuppressive drugs in patients with Crohn's, potential side effects should be proactively monitored and addressed. Adverse effects of these drugs include pancreatitis, myelosuppression, nausea, opportunistic infections, and hepatotoxicity.[8] Several studies suggest an increased risk of malignancy, particularly both non-Hodgkin- and Hodgkin-type lymphomas in patients with inflammatory bowel disease (IBD) who are treated with thiopurines.[9–13] In addition, this risk appears to increase gradually with continued use of azathioprine.[14]

Based on a meta-analysis by Kandiel et al.,[15] the number needed to harm to cause a case of lymphoma in patients treated with either azathioprine or 6-mercaptopurine was estimated to be 4357 for patients aged 20–29 years and 355 for patients aged 70–79 years. Other studies have found an association between azathioprine use and an increased

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incidence of other cancers, including nonmelanoma skin cancer[16] and cutaneous squamous cell carcinoma.[17] In addition, one case report describes a case of cutaneous mycosis fungoides in a patient with IBD treated with infliximab.[18] Whether the increased risk of malignancy is due to the underlying inflammatory nature of Crohn's disease or medication side effects remains unclear.

Case

A 24-year-old Caucasian male with ileocolonic Crohn's disease presented for follow-up at the gastroenterology clinic for a progressively worsening facial rash. He had a history of complicated Crohn's disease with perianal involvement requiring surgery but was in remission for the previous 2 years. He initially started treatment for Crohn's disease with 2-month taper of prednisone as well as azathioprine and eventually bridged to infliximab after cessation of prednisone. His regimen at the time of the initial visit included azathioprine 200 mg daily and infliximab 5 mg/kg every 8 weeks. About a year after starting treatment, he had thiopurine metabolites measured, which were within normal limits, and he had no evidence of toxicity.

He sought medical attention 4 months prior to presentation at the dermatology clinic for the rash, which was exfoliative and initially unilateral on the malar surface of one cheek. He was given oral antibiotics for a presumed skin infection but returned to the clinic a few days later once the rash started to spread to the other side of his face. He reported significant sunlight exposure due to his work as a landscaper. He denied any other skin lesions or any musculoskeletal complaints. He also reported no gastrointestinal symptoms related to his Crohn's disease. A punch biopsy was performed and sent to the Mayo Clinic Laboratory. Prior to receiving the final biopsy report, he was given a topical steroid ointment by the dermatology clinic and noticed resolution of the skin rash in 3 days without any reoccurrence since then. At the time of this visit, his C-reactive protein (CRP) was 0.24 mg/dL, erythrocyte sedimentation rate (ESR) 2 mm/h, rheumatoid factor < 15 IU/mL, and anti-nuclear antibody (ANA) negative. Other recent laboratory studies, including complete blood count (CBC) and comprehensive metabolic panel (CMP), were unremarkable.

The final pathology report, available at the time of our office visit, described "atypical, superficial dermal lymphoid infiltrate with epidermotropism, consistent with mycosis fungoides." The risk of cutaneous lymphoma and other cancers while using immunomodulators was discussed with the patient. As he had significant risk factors, such as his age, race, and occupation, the decision was made to discontinue azathioprine. It was also recommended to continue treatment with infliximab to maintain remission of his Crohn's disease. He was also educated about routine sun protection and close follow-up with dermatology in order to prevent his skin rash from reoccurring and monitor for new skin lesions.

Discussion/Conclusion

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma, and it appears to be notably more common in males than females with an average age of onset between ages 45 and 55.[19] The cause of mycosis fungoides remains unknown; however, current hypotheses include genetic abnormalities and environmental exposures.[20,21] There have been reported cases of human T-lymphotropic virus type I in the peripheral blood or cutaneous lesions of some patients with mycosis fungoides,[22] although its role in the pathogenesis of the disease remains controversial. It has been noted that the progression of mycosis fungoides involves progression of immunodeficiency to avoid antitumor immunity, indicating that the disease may be more prevalent in those with immunocompromised states.[23,24]

The use of immunosuppressive drugs for IBD has allowed for better rates of remission.[25] However, one of the challenges in managing patients with IBD is balancing the benefits and risks of medical therapy. Due to the nature of these drugs, chronic use of immunosuppressive medications enables tumor cells to proliferate. In particular, azathioprine and other thiopurine analogues inhibit lymphocyte proliferation and cytotoxic T-cell and natural killer cell function, preventing cell-mediated immunosurveillance of cancers.[26]

There have been several studies examining the risk of lymphoma in IBD patients treated with thiopurine analogues. A meta-analysis performed by Kandiel et al.[15] pooled six single-center studies and obtained a standardized incidence ratio of 4.18 for lymphoma in patients with IBD treated with thiopurines. The CESAME cohort study demonstrated that patients on combination thiopurine and anti-TNF therapy had a markedly elevated risk of lymphoma, with a calculated standardized incidence ratio of 10.2 of lymphoma in patients on dual immunosuppressive therapy.[11] Therefore, there is a significant increased risk of cutaneous lymphomas in young, Caucasian males on dual immunosuppressive therapy for Crohn's disease such as our patient.

Given the increased risk of lymphomas with dual immunosuppressive therapy, it was decided to discontinue azathioprine and continue infliximab monotherapy for maintenance therapy. Although the rash resolved with the use of topical steroids, our patient would be predisposed to developing other skin lesions especially given his occupational risk factor.

As dual therapy with anti-TNF and immunomodulators is considered mainstay for initial treatment of Crohn's disease, consideration should be given for potential risks. Further examination of the association of immunosuppressive drugs and lymphoma is necessary to fully elucidate this risk for patients. All treatment risks need to be weighed against the impact of untreated IBD and the benefit these therapies can offer.

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Author contributions

J.D. and M.D. wrote the manuscript and reviewed the literature. D.M. reviewed the literature and made critical revisions to the manuscript.

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Informed consent

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