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CASE REPORT

Oral ulcerations are associated with the loss of response to infliximab in Crohn's disease

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We describe a 25-year-old Caucasian man with a 13-year history of inflammatory Crohn's disease (CD) who was suffering recurrent severe oral and esophageal ulcerations for the past 3 years. His CD had been treated with infliximab infusions among other medications. The loss of efficacy was confirmed by antibodies to infliximab (ATI) and serum infliximab tests that showed high levels of ATIs and undetectable levels of infliximab respectively. These findings were consistent with significant immunogenic response to infliximab leading to loss of effect. Infliximab infusions and prednisone were discontinued and treatment of the CD was instituted with adalimumab, a human anti-tumor necrosis factor (TNF)-α biologic agent, to control the inflammatory small intestinal disease and dapsone for the oral and esophageal CD ulcerations. The patient's oral and esophageal lesions as well as the enteric CD are under control after 5 months of therapy.
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The patient was a 25-year-old male who was diagnosed with inflammatory enteric Crohn's disease (CD) in 1990. He underwent a small bowel resection and three stricturoplasties in 1994, and a second small intestinal surgery and five stricturoplasties in 2000. The patient had also received a variety of medications for CD including sulfasalazine, mesalamine, prednisone, azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, and infliximab.

In March 2000, the patient began treatment with infliximab for active CD. His enteric disease was under good control until December 2000. However, after several infliximab administrations, the patient developed severe oral and esophageal ulcers about 3 weeks after receiving an infliximab infusion. Eventually, infliximab was stopped in December 2000, and treatment with thalidomide was instituted without benefit for the oral and esophageal ulcerations. Thalidomide was discontinued in August 2001 as a result of excessive sedation.

Then, infliximab therapy was instituted again from August 2001 to December 2001 with no benefit of the oral and esophageal ulcerations. The infliximab was discontinued in December 2001 in order to participate in a clinical trial of anti-interleukin-12 antibody. This was administered until April 2003, when infliximab therapy was restarted again at a 5 mg/kg dose every 4 weeks. In October 2003, he was referred to the Division of Gastroenterology at Mayo Clinic for evaluation of severe intractable oral and esophageal ulcers. At that time, an extensive evaluation was undertaken including esophagogastroduodenoscopy, colonoscopy, small bowel and chest radiography, completed blood studies, fungal and viral serologies, and immunologic studies such as antibodies to infliximab (ATI), antinuclear antibodies (ANA), double-stranded DNA antibodies (dsDNA), antibodies to extractable nuclear antigens (ENA), antibodies to histones, rheumatoid factor, complement, cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies (cANCA and pANCA), and serum infliximab levels.

After this initial consultation, the patient was referred for dermatologic, otorhinolaryngologic, and rheumatologic consultations. The patient presented for the dermatologic consultation with limited ability to tolerate oral intake and weight loss because of the oral and esophageal ulcerations. The patient medications were prednisone 30 mg daily, 6-mercaptopurine 75 mg daily, infliximab 5 mg/kg every 4 weeks, sucralfate 1 g twice a day, sertraline hydrochloride 50 mg daily, mirtazepine 15 mg daily, clotrimazole lozenges 10 mg five times daily, clindamycin hydrochloride 300 mg twice daily and a monthly injection of vitamin B_{12}. The last dose of infliximab was in September 2003.

Oral examination revealed oral ulcerations and linear cobblestone lesions in the left and right buccal mucosa characteristic of oral lesions of CD (Fig. 1). An oral biopsy was taken from the left buccal mucosa was

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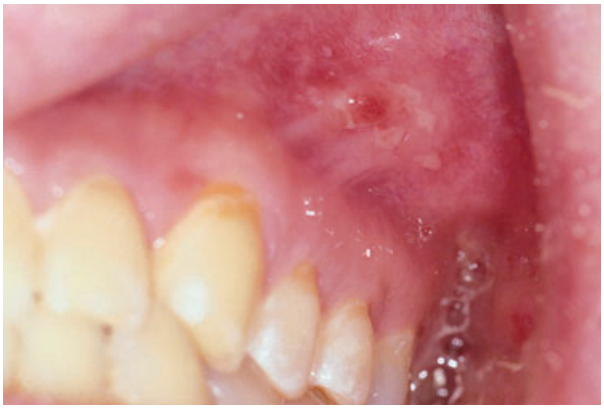

Figure 1 Clinical appearance of severe ulcerations in the upper right buccal mucosa.

studied by routine histology and direct immunofluorescence testing (DIF). The DIF examination was negative. The routine histology showed evidence of epithelial hyperplasia with neutrophilic and lymphocytic spongiosis. In the lamina propia hemorrhage, edema, and a mixed infiltrate composed of lymphocytes, histiocytes, plasma cells, neutrophils, eosinophils, and small aggregates of epithelioid and multinucleated histiocytic giant cells were identified (Fig. 2). These histologic and clinical findings were consistent with the diagnosis of oral CD.

All the requested examinations and laboratory tests were essentially normal with the exception of a positive ANA, which can occur in the context of infliximab treatment, positive ATI and serum infliximab tests that showed high levels of antichimeric antibodies, and undetectable levels of infliximab 5 weeks after the last administration of infliximab. These findings were consistent with significant immunogenic response to infliximab leading to loss of effect. His treatment plan included the discontinuation of infliximab infusions.

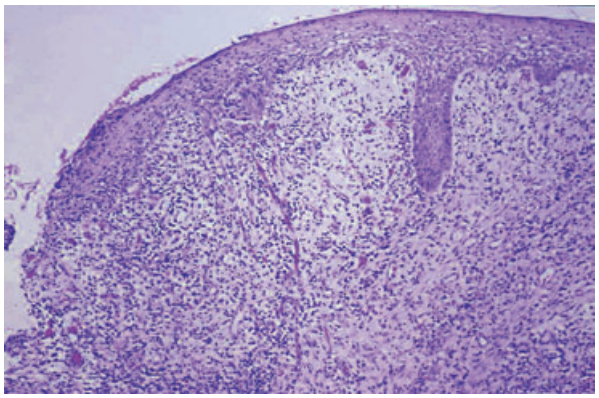

Figure 2 Microphotograph of the tissue section showing evidence of epithelial hyperplasia, neutrophilic and lymphocytic spongiosis with exocytosis. In the submucosa, there was hemorrhage, edema, and a mixed infiltrate composed of lymphocytes, histiocytes, plasma cells, neutrophils, eosinophils, and small aggregates of epithelioid and multinucleated histiocytic giant cells [hematoxylin and eosin (H & E) stain, original magnification ×10].

Treatment of the CD was instituted with an human anti-tumor necrosis factor (TNF) antibody drug adalimumab (loading dose of 80 mg subcutaneously followed by maintenance therapy with 40 mg subcutaneous dose every week) to control the inflammatory component of his small intestinal disease and dapsone (25 mg/day for 3 days, then 50 mg/day for 3 days then 75 mg/day for 3 days and then 100 mg/day up to 150 mg/day if the patient is not responding) for the oral and esophageal CD. Additionally, the patient continued the treatment with 6-mercaptopurine at the previous dose. The patient is monitored for evidence of hemolytic anemia while on dapsone. With this treatment regimen, the patient's oral and esophageal lesions are under control and there has been no further recurrence. In addition, the enteric CD remains quiescent.

Comments

Crohn's disease is a chronic relapsing inflammatory disorder of the intestines and a common cause of gastrointestinal morbidity in young people with a peak age of onset between 15 and 25 years of age. The etiology of CD of inflammatory bowel disease is unknown, but host, genetic, and environmental influences are considered important (1). Standard first-line therapies for CD include sulfasalazine, and corticosteroids for inflammatory CD, and antibiotics for anal and fistulizing CD. Although corticosteroids are highly effective in suppressing the symptoms, their use is limited due to their significant side effects. Alternative treatments for unresponsive patients include the use of drugs such as 6-mercaptopurine, azathioprine, methotrexate, cyclosporine, and anti-TNFα therapy (2).

Biologic agents have recently been introduced for the treatment of CD. Infliximab, a chimeric (75% human protein and 25% murine protein) monoclonal immunoglobulin (Ig)G1 antibody to TNFα, has been proven to be effective in the treatment of both fistulizing and inflammatory CD (2). The mechanism of action of this antibody is not well understood, but the down-regulation of inflammation seems to be far more complex than just the neutralization of circulating TNFα.

Infliximab reduces the mucosal content of proinflammatory cytokine-producing T cells, perhaps due to increased apoptosis (3). Adverse effects of infliximab include infusion reactions, delayed hypersensitivity-like reactions, and the potential for rare events such as reactivation of latent tuberculosis and the development of drug-induced lupus erythematous (1). The immunogenicity of this drug is an emerging issue, which may limit the long-term efficacy of infliximab re-treatment through the formation of ATIs (4). The immunogenicity of infliximab is assessed using an assay developed by the manufacturer (Centocor, Malvern, PA, USA) that measures anti-idiotype antibodies to epitopes on the murine variable region of infliximab as well as antiallotype antibodies to the human IgG1 constant region (5). ATI may develop in up to 27% of patients treated with the drug (1). The detection of these antibodies are associated with an increased incidence of infusion

reactions and a loss of response, although they may develop less frequently in those patients taking immunomodulators or corticosteroids (4, 5).

The patient described here was plagued by severe oral and esophageal ulcerations while receiving multiple medications including infliximab, prednisone, and 6-mercaptopurine for the treatment of his CD. It has recently been suggested that administration of a single dose of infliximab without concomitant immunosuppressive therapy is an immunogenic event that frequently leads to the formation of ATIs and that the high concentration of ATIs leads to adverse patient outcomes in the form of shortened duration of benefit or complete loss of effect (5). Therefore, to minimize the formation of ATIs, two optimization strategies has been suggested. The first treatment strategy would be to use an immunosuppressive treatment with azathioprine or 6-mercapturine for 2–3 months or methotrexate for 6–8 weeks prior to initiating infliximab with subsequent long-term continuation of the same immunosuppressive agent as concomitant therapy with infliximab. This approach was first used in this patient without benefit. The second approach includes the discontinuation of infliximab and its replacement with a less immunogenic alternative such as humanized or fully human therapeutic molecule. In this case report, the treatment was switched to adalimumab, a fully human anti-TNFα antibody drug, which is providing satisfactory results.

In conclusion, in this case, the development of oral and possibly esophageal CD occurred in association with the formation of ATIs, and the high concentration of ATIs led to adverse patient outcomes in the form of complete loss of therapeutic efficacy of infliximab.

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