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CASE REPORT

Steroid-refractory ulcerative colitis and associated primary sclerosing cholangitis treated with infliximab

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Abstract

Primary sclerosing cholangitis is an infrequent extraintestinal manifestation of ulcerative colitis. Damage to bile ducts is irreversible and medical therapies to prevent progression of the disease are usually ineffective. We describe a patient with long-standing ulcerative colitis, which was refractory to corticosteroid therapy who developed primary sclerosing cholangitis (biochemical stage Ⅱ/Ⅳ) in the course of his pancolitis. Treatment with infliximab (5 mg/kg as an induction dose followed by maintenance doses every two months) was indicated because of steroid-dependent disease associated to primary sclerosing cholangitis as well as sacroiliitis and uveitis and previous episode of severe azathioprine-related hepatic toxicity. At present, after two years of follow-up, the patient is asymptomatic with normal liver tests and complete resumption of daily life activities. This case draws attention to the usefulness of anti-tumor necrosis factor-alpha therapy for the management of primary sclerosing cholangitis as extraintestinal manifestation of inflammatory bowel disease.

Key words: Ulcerative colitis; Infliximab; Monoclonal antibodies; Sclerosing cholangitis; Bile duct diseases; Tumor necrosis factor-alpha

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INTRODUCTION

Inflammatory bowel diseases are associated with extraintestinal manifestations involving almost every organ system in the body, including the musculoskeletal, dermatologic, hepatic, pancreatic, biliary, ocular, renal and pulmonary systems and can cause a significant challenge to physicians managing patients with Crohn's disease and ulcerative colitis[1-3]. Primary sclerosing cholangitis, a chronic, progressive disorder of unknown etiology that manifests as inflammation, stricturing, and fibrosis of medium and large intra- and extrahepatic bile ducts, is one of the most serious complications of inflammatory bowel disease, with an established strong relationship with ulcerative colitis[4]. At least 75% of patients with primary sclerosing

cholangitis have coexisting ulcerative colitis[2]. However, only 5% of patients with ulcerative colitis develop primary sclerosing cholangitis. The clinical course of sclerosing cholangitis bears no relationship with the underlying inflammatory bowel disease but damage to bile ducts is irreversible, no medical therapies have been shown to be effective at preventing the progression of the disease, and orthotopic liver transplantation is the only curative treatment.

The advent of biologic response modifiers, e.g., tumor necrosis factor-alpha (TNF-α) inhibitors, has improved the treatment of inflammatory bowel disease and its associated extraintestinal manifestations[5], such as arthritis and uveitis[6,7]. Current data suggest that infliximab is an effective alternative treatment option for patients with moderate to severe ulcerative colitis with an inadequate response to conventional glucocorticoid treatment[8]. However, the efficacy of infliximab in primary sclerosing cholangitis in patients with ulcerative colitis has not been previously assessed.

We report the case of a patient with steroid-refractory ulcerative colitis with intolerance to thiopurines and various extraintestinal manifestations, including ankylosing spondylitis and primary sclerosing cholangitis with favorable response to infliximab therapy.

CASE REPORT

We report here on a 68-year-old man in whom positive HLA B27 spondyloarthropathy and uveitis in the left eye were diagnosed at the age of 54. He was referred to the hospital because of an episode of subacute diarrhea with blood and mucous associated with mild iron-deficiency anemia. Also, he was diagnosed endoscopically and histologically of mild to moderate ulcerative rectosigmoiditis. He received oral and topical 5-aminosalicylic acid with good initial response. During the course of the disease, he presented multiple episodes of steroid-dependent ulcerative colitis and treatment with azathioprine was started 6 years after diagnosis. After 4 mo, azathioprine was discontinued due to severe hepatic cytolysis. Four years later, he was readmitted to the hospital because of bloody diarrhea and mucus (12-14 bowel movements daily, with generalized abdominal pain, proctalgia, fecal urgency and tenesmus without fever, and weight loss of 6 kg. Physical examination showed marked impairment of the patient's general condition, diffuse abdominal pain on palpation and functional limitation secondary to ankylosing spondylitis. Blood tests showed serum hemoglobin 10.5 g/dL, C-reactive protein 154 mg/dL and cholestasis hepatitis with bilirubin 1.2 mg/dL, aspartate aminotransferase (AST) 112 IU/L, alanine aminotransferase (ALT) 162 IU/L, alkaline phosphatase 281 IU/L, gamma-glutamyl transpeptidase (γ-GGT) 913 IU/L, and positive p-antinuclear antibodies 1/80. A diagnosis of moderate to severe episode of pancolitis was established. A cholangio-magnetic resonance imaging (MRI) study disclosed stenosis of the proximal common bile duct probably related to cholangitis. Causes of secondary sclerosing cholangitis were excluded as shown by the lack of abnormally elevated immunoglobulin G4 (IgG4) levels as shown in autoimmune pancreatitis or IgG4-related sclerosing cholangitis (IgG4 levels were < 100 mg/dL). Also, the patient showed increased values serum bilirubin and alkaline phosphatase of a lower magnitude that those suggestive of autoimmune pancreatitis, and radioimaging findings for enlargement of the pancreatic gland were absent. Also, the patient did not complain of abdominal symptoms suggestive of pancreatitis. All these data together with the presence of ulcerative pancolitis directed us to confirm the diagnosis of primary sclerosing cholangitis associated to inflammatory bowel disease and to exclude the diagnosis of autoimmune pancreatitis.

The patient was diagnosed of primary sclerosing cholangitis (biochemical stage Ⅱ/Ⅳ). He was treated with full doses of *i.v.* corticosteroids and urodesoxycholic acid 15 mg/kg body weight, without improvement. The patient received full doses of methylprednisolone, 1 mg/kg per day, with subsequent dose reductions at least on seven occasions over the course of 6 years. The situation of the patient was re-assessed and decided to start treatment with infliximab (5 mg/kg as an induction dose followed by maintenance doses every two months) because of steroid-dependent disease associated to primary sclerosing cholangitis, sacroiliitis and uveitis and previous history of an episode of severe azathioprine-related hepatic toxicity. At present, after two years of follow-up, the patient is still on treatment with infliximab and has remained asymptomatic, with improvement of anemia (hemoglobin 13.8 mg/dL) and biochemical evidence of cholestasis (bilirubin 0.4 mg/dL, AST 16 IU/L, ALT 20 IU/L, alkaline phosphatase 59 IU/L, γ-GGT 149 IU/L) and complete restoration of the quality of life. Annual endoscopic assessment did not show signs of dysplasia. Repeated cholangio-MRI performed during the follow-up was also unrevealing.

DISCUSSION

The incidence of primary sclerosing cholangitis varies between 0.9 to 1.6 per 100 000 persons/year[9]. More than two-thirds of patients are males and the most commonly associated condition is an inflammatory bowel disease which occurs in up to 70% of affected subjects. Inflammatory bowel disease in primary sclerosing cholangitis patients represents a distinct phenotype in that pancolitis is observed in 94% of patients with ulcerative colitis and in 96% of patients with Chron's disease[10]. It has been shown large differences between primary sclerosing cholangitis patients with and without concurrent inflammatory bowel disease. Patients with inflammatory bowel disease showed earlier appearance of primary sclerosing cholangitis than those without inflammatory bowel disease and are more likely to develop serious malignant complications and more likely to require liver transplantation[11].

In our patient, distal colitis was the initial manifestation of inflammatory bowel disease and later evolving to pancolitis, the time at which primary sclerosing cholangitis developed. Primary sclerosing cholangitis has been shown to be associated with greater anatomic extent of colitis[12-14]. It has been reported that development of primary sclerosing cholangitis in patients with ulcerative colitis may have a positive effect on colonic disease[15,16] with reduced disease activity and less use of steroids, azathioprine and surgery[17]. In other studies, ulcerative colitis associated with primary sclerosing cholangitis showed unique colonoscopic features (pancolitis, rectal sparing and backwash ileitis) with more frequent colorectal neoplasia development and worse prognosis than ulcerative colitis patients without primary sclerosing cholangitis[18]. In our patient the clinical course was characterized by severe ulcerative colitis refractory to steroid therapy. For this reason and taking into account the presence of other concomitant manifestations (uveitis, sacroiliitis) treatment with infliximab was started. However, indications of anti-TNF-α in well established primary sclerosing cholangitis should be carefully balanced due to immunosuppression and the risk of potentially fatal cholangitis.

The use of infliximab was followed by marked improvement in the patient's clinical condition, including the extraintestinal manifestations of ulcerative colitis and a favorable clinical and biochemical remission of primary sclerosing cholangitis. This suggests a direct effect of infliximab on hepatic inflammation. However, in a double-blind, placebo-controlled study of 24 patients with primary sclerosing cholangitis, no significant treatment benefit of infliximab was demonstrated[19], although in patients with primary sclerosing cholangitis and Crohn's disease treatment with infliximab was associated with improvement of liver function tests[20].

Currently, the use of anti-TNF-α treatment in primary sclerosing cholangitis is not well established. The observation that reduced T cell reactivity in liver infiltrating cells obtained from patients with primary sclerosing cholangitis was due to high local production of TNF-α provides support for the use of anti-TNF antibodies as an alternative treatment for these patients[21]. Contrarily, in the experience of Epstein *et al*[22] etanercept was well tolerated but not effective in a clinical series of 10 patients with clinically active primary sclerosing cholangitis. It is unknown whether early treatment with anti-TNF-α drugs may change the natural history of primary sclerosing cholangitis. Also, the use of this medication over years may raise financial concerns and secondary effects of this prolonged use. In the case here presented, although treatment with infliximab is expensive, the patient did not present recurrent episodes of colitis, uveitis, sacroiliitis or new episodes of cholangitis, allowing prompt resumption of work and social activities with an excellent quality of life and without further admissions to the hospital or the need of surgical operations, as a result of which direct and indirect costs have been markedly reduced in this particular case.

In conclusion, our report on a patient with steroid-refractory ulcerative colitis developing primary sclerosing cholangitis with favorable and maintained response to infliximab therapy draws attention to the usefulness of anti-TNF-α therapy for management of primary sclerosing cholangitis as extraintestinal manifestation of inflammatory bowel disease.

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