Demyelination-like syndrome in Crohn's disease after infliximab therapy

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An 18-year-old female patient with Crohn's disease involving the ileum and colon developed ankylosing spondylitis. After treatment of her spondylitis with multiple infliximab infusions, new onset of neurological symptoms developed, accompanied by detection of an abnormal white matter signal change on magnetic resonance imaging examination. Although infliximab treatment was terminated, the neurological symptoms and the magnetic resonance imaging changes persisted. Development of new neuropsychiatric changes in Crohn's disease should be thoroughly evaluated to exclude a concomitant demyelinating process. Infliximab infusions should be terminated if demyelination is suspected.

Key Words: *Ankylosing spondylitis; anti-TNF- α therapy; Crohn's disease; Demyelination; Infliximab; Multiple sclerosis; Rheumatoid arthritis*

Infliximab, a mouse-human chimeric monoclonal antibody to tumour necrosis factor- α (TNF- α), appears to reduce disease activity in Crohn's disease (1,2). Fistula drainage may also be reduced or terminated, but its role in complete resolution of fistulous tracts remains controversial (3,4). Recently, the adverse effects of infliximab in 500 patients with Crohn's disease treated at the Mayo Clinic (Rochester, Minnesota) were reviewed, including a single patient with evidence of demyelination (5). Additional details related to this specific case with neurological symptoms have also been published (6).

Infliximab, along with other forms of anti-TNF- α therapy (ie, etanercept), has also been used in the treatment of inflammatory arthritides, including rheumatoid arthritis and ankylosing spondylitis. Although the precise mechanism(s) leading to its therapeutic effect has not been defined, demyelination with anti-TNF- α therapy was previously recorded (7). The clinical syndromes have included multiple sclerosis (MS), optic neuritis and Guillain-Barré syndrome. In all, neurological events were temporally related to anti-TNF- α therapy with partial or

Syndrôme de pseudo-démýélinisation suivant un traitement par infliximab dans la maladie de Crohn

Une patiente de 18 ans atteinte de la maladie de Crohn affectant l'iléon et le côlon a développé une spondylite ankylosante. Après traitement de sa spondylite au moyen de plusieurs perfusions d'infliximab, de nouveaux symptômes neurologiques se sont installés, accompagnés d'une anomalie du signal généré par la substance blanche à l'IRM. Les signes neurologiques et les signaux anormaux ont persisté après la fin du traitement par infliximab. Il faut explorer soigneusement tout nouveau problème neuropsychiatrique dans la maladie de Crohn afin de s'assurer qu'un processus de démyélinisation ne soit pas déjà amorcé. Les perfusions d'infliximab doivent être suspendues si on soupçonne la présence de démyélinisation.

complete resolution on discontinuation in some treated patients (7). One patient also exhibited a positive rechallenge phenomenon (7). In addition, two patients with MS treated with infusions of infliximab during a phase 1 trial showed an increase in gadolinium-enhancing magnetic resonance imaging (MRI) lesions along with immune activation and increased disease activity leading to the recommendation that this agent should be avoided in MS treatment (8).

CASE PRESENTATION

An 18-year-old female patient developed diarrhea in February 1984. Barium studies of her upper and lower gastrointestinal tract showed ileal and colonic involvement with Crohn's disease. Sulphasalazine caused a skin rash and was discontinued. In 1985, a perianal abscess was drained, followed by treatment with metronidazole. After redevelopment of perineal drainage, she was referred to the University of British Columbia, Vancouver, British Columbia, for further evaluation. A perineal abscess was drained and multiple anal fistulas were excised

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with placement of Seton sutures. The excised fistulas showed inflammatory change with fibrosis and granulomas. Colonoscopy demonstrated multiple areas of discrete ulceration, while mucosal biopsies showed focal inflammatory changes. Because of recurrent diarrhea and weight loss, prednisone was administered over six weeks. Her diarrhea resolved and the Seton sutures were removed. In 1987 and 1988, diarrhea and colonic ulceration recurred. Oral 5-aminosalicylate (Asacol, Procter & Gamble Pharmaceuticals, Canada) and prednisone led to resolution of her diarrhea so she continued on 5-aminosalicylate 800 mg twice daily. In 1991, colonoscopy and biopsies were normal, but barium studies of the upper gastrointestinal tract showed persistent ileal stricture formation, estimated to be approximately 10 cm. From 1993 to 1994, diarrhea and colonic ulceration recurred. Increased 5-aminosalicylate resolved her diarrhea and colonic ulcers.

In 1997, she first developed polyarthralgias, and the diarrhea recurred. Oral ileal release budesonide 3 mg twice daily led to symptom resolution. In 1999, colonoscopy and biopsies were normal, but in 2000, the diarrhea recurred and colonoscopy showed recurrent ulcers despite 5-aminosalicylate 1 g twice daily. A further course of budesonide 3 mg twice daily was associated with resolution of diarrhea and the colonic ulcers. However, recurring polyarthralgias in multiple joints along with back stiffness and pain resulted in a rheumatological consultation which documented a restricted range of movement in the lumbar region (ie, modified Schober's test estimated to be less than 3 cm, no lateral flexion or extension). Cervical spine rotation and forward flexion were reduced, while lateral flexion and extension were minimal. Chest expansion was estimated to be approximately 3 cm. Peripheral joint evaluation showed reduced shoulder range of movement with metacarpophalangeal and proximal interphalangeal joint tenderness. In her lower extremities, there was some localized tenderness at the right ankle. Radiographs and a computed tomography scan of her lumbar spine and sacroiliac joints showed changes of a severe axial spondyloarthropathy with particularly marked changes of sacroiliitis consistent with the clinical diagnosis of ankylosing spondylitis. Cervical spine radiographs were normal. HLA-B27 was positive. Anti-inflammatory medications provoked nausea, vomiting and abdominal pain with weight loss. In 2000, upper gastrointestinal endoscopy and biopsies of the stomach and duodenum showed a 'reactive' gastritis, but no granulomas. Barium studies showed persistent ileal narrowing, while a colonoscopy and biopsies were normal. Budesonide was not effective. She refused an immunosuppressive agent and, in March 2002, an ileal resection was performed. The resected specimen showed ileal ulceration with stricture formation. Following surgery, another 5-aminosalicylate formulation was provided (Pentasa, Ferring Inc, Canada), 1 g twice daily. In 2003, her joint symptoms became worse with pain and diminished range of movement. She was treated with intravenous infliximab 300 mg followed by additional infusions at two, six and then every eight weeks. Before treatment, a chest radiograph and tuberculin skin test were negative. Despite repeated infusions, she reported no improvement in her joint symptoms. In September 2003, she complained of a new onset of headache as well as numbness in her left arm and tingling and cramping discomfort with numbness in the lateral aspect of her left leg. In October 2003, a computed tomography head scan was normal but, in

January 2004, an MRI scan (Figures 1 to 3) showed a single, small high-signal lesion in the right superior frontal white matter on both fast spin echo T2 and fluid-attenuated inversion recovery sequences. There were no corpus callosal lesions and the posterior fossa was normal. The cervical spine was normal. A solitary lesion, such as in this case, may be considered a nonspecific finding and does not fulfill the McDonald criteria for MS (9), but is compatible with demyelination. Because of the failure of infliximab to provide any symptomatic rheumatological improvement and the detection of the imaging changes on MRI, the infliximab infusions were discontinued. In September 2004, neurological symptoms were still present and a second MRI scan showed no changes compared with the original images, and no new lesions.

DISCUSSION

Given the temporal relationship between infliximab treatment for her spondylitis and new-onset neurological symptoms concurrent with the detection of abnormal and persistent MRI changes, a demyelination-like syndrome was suspected in this patient with Crohn's disease. Although the MRI findings by themselves are not specific for demyelination, concomitant neurological symptoms in the present case led to the termination of anti-TNF treatment. Recently, a case from the Mayo Clinic (with no documented arthritis) also indicated that anti-TNF- α therapy may directly cause neurological findings in Crohn's disease or, conceivably, have an indirect effect by unmasking a subclinical demyelinating process (6).

The findings here and in the earlier Mayo Clinic report (6) are consistent with earlier studies. Demyelinating lesions have been detected in the brain and spinal cord of patients with various inflammatory arthritides, treated with different formulations of anti-TNF- α , including infliximab and etanercept (7) as well as infliximab in MS (8). Most significantly, in at least one patient with arthritis, a positive rechallenge was also described (7). Together, new neurological or psychiatric findings accompanied by MRI-detectable lesions consistent with demyelination in different disorders treated with anti-TNF- α therapies, particularly infliximab, provide compelling evidence that TNF- α has a direct role in the etiopathogenesis of demyelination, or in changes seen in demyelinating disorders, such as MS.

Some reports have noted that demyelination disorders may be increased in inflammatory bowel disease per se, particularly ulcerative colitis. In a study from Olmsted County (10), an increased rate of inflammatory bowel disease and MS was recorded. Other reports from Canadian investigators (11,12) have also recorded MS with chronic inflammatory bowel disease. Later, sporadic case reports of Crohn's disease with MS were also noted (13,14). If Crohn's disease patients are predisposed to develop MS, then TNF- α inhibition may well lead to an increased risk for demyelination.

In 65% of patients with inflammatory arthritides treated with infliximab, the most common neurological symptoms that developed were paresthesias in different sites (7), as in the present patient with Crohn's disease. Other changes included visual and gait changes, confusion, facial palsy and a Guillain-Barré form of ascending paralysis. Some of these patients developed neurological symptoms during treatment, while others first noted symptoms only after more than a year from initiation of infliximab. Because visual or neuropsychiatric

Figure 1) Sagittal fluid-attenuated inversion recovery sequence magnetic resonance image. A single hyperintense focus in the white matter of the right frontal lobe is present

symptoms in patients treated with Crohn's disease may be minimal or possibly attributed to other causes (eg, metronidazole-induced peripheral neuropathy, steroid-induced psychiatric effects, other immunoneuropathological comorbidities, including an inflammatory myelopathy), recognition of demyelination may be difficult. Moreover, specialist gastroenterologists likely have some limitations in their skills for the detection of subtle neurological or psychiatric changes. Moreover, the long latent period before clinical expression of demyelination is not only disconcerting, but may also add to diagnostic difficulties.

Precise management guidelines are difficult to provide based on current information. From a medicolegal perspective, anti-TNF- α therapies, such as infliximab, would appear to pose a 'materially significant risk' to cause or unmask a demyelinating process and possibly result in a full-blown MS-like disorder in Crohn's disease. As a result, a treating physician should disclose this potential risk to patients before infliximab administration to patients with Crohn's disease. The concern has already been expressed that infliximab should be avoided in Crohn's disease with concurrent MS (or presumably in patients with neurological findings that suggest an occult demyelinating process) (15). Although there is no evidence to date supporting MRI screening in all patients with Crohn's disease, it seems prudent that those with concomitant or new-onset neurological or psychiatric findings undergo thorough clinical evaluation, including MRI scanning, before the initiation of new or ongoing infliximab treatment. If demyelination-like lesions are documented, then it appears advisable to avoid further treatment with this agent.

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Figure 2) Axial fluid-attenuated inversion recovery sequence magnetic resonance image. Same hyperintense focus as seen in Figure 1

Figure 3) Axial fast spin echo T2 magnetic resonance image. The hyperintense focus seen in Figures 1 and 2 is slightly harder to appreciate because the cerebral spinal fluid signal is not attenuated

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