

Crohn's Colitis Presenting With Node-Negative Colon Cancer and Liver Metastasis After Therapy With Infliximab: Report of Two Cases

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Infliximab (Remicade, Centocor Inc.) is a monoclonal antibody, cA2, targeted against tumor necrosis factor-alpha (TNF- α) approved for the treatment of Crohn's disease and rheumatoid arthritis. The mechanism of infliximab is to specifically inhibit the activity of TNF- α through the neutralization of the proinflammatory cytokine. The drug is able to bind to the transmembrane receptor and thus inhibit the inflammatory effects of TNF- α . Furthermore, the cells that have infliximab bound to the cellular receptors can be lysed *in vitro* by complement. By decreasing the levels of TNF- α , there is a decrease in the inflammatory response and immune reaction.^{1,2} By decreasing the levels of TNF- α in patients with Crohn's disease, signs and symptoms of the disease, including fistulas, have significantly improved. Infliximab is FDA approved for both induction and maintenance of remission of Crohn's disease.³

Reported adverse reactions to infliximab include respiratory tract infections, including cough, sinusitis, pharyngitis, and bronchitis, nervous system effects, including headache, dizziness, and pain, musculoskeletal effects, including arthralgias and back pain, abdominal pain, including nausea and diarrhea, and chills and fever.² Hypersensitivity reactions consisting of dyspnea, urticaria, and hypotension occur in approximately 10 percent of patients. Another complication of infliximab treatment is the reactivation of latent tuberculosis. By decreasing the immune response, tuberculosis can become symptomatic.

A potential side effect of an immune modifying medication is the possibility of initiating a malignancy. The most commonly reported malignancy is lymphoproliferative disorder. In a report evaluating infliximab, nine patients reportedly developed a lymphoproliferative disorder, eight of which were lymphomas.² It is unclear whether infliximab contributes to malignancy or whether the patient's disease condition itself leads to the malignancy. A few studies have indicated a possible association between infliximab therapy for Crohn's disease and the onset of lymphoma.⁴⁻⁶ However, a review of the literature did not produce any studies or case reports of infliximab treatment for Crohn's disease associated with adenocarcinoma of the colon and colonic metastasis. We

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report two patients who developed newly diagnosed metastatic colon cancer during the treatment with infliximab.

REPORT OF TWO CASES

This is a retrospective review of two patients with Crohn's colitis (1 patient had rheumatoid arthritis as well) who were being treated with infliximab; within 24 months of therapy, both patients were diagnosed with Stage IV adenocarcinoma of the colon.

Patient 1 was a 70-year-old female with a 10-year history of rheumatoid arthritis and a 30-year history of Crohn's disease. Ten years previously, she had a sigmoid resection for Stage I adenocarcinoma. Because of her long history of Crohn's colitis and Stage I adenocarcinoma of the colon, she was having yearly colonoscopy; her last colonoscopy was performed one year before the diagnosis of her second colon cancer. According to the colonoscopy report, there was no evidence of abnormalities. Random biopsies were taken of the cecum, ascending, hepatic flexure, transverse, splenic flexure, descending, sigmoid, and rectum. Each site had four biopsies for a total of 32 biopsies. There was no evidence of dysplasia in any of the biopsies. She was placed on infliximab (5 mg/kg) for intractable rheumatoid arthritis, not for Crohn's colitis, for the next two years and had an excellent clinical response. Her arthritis was responding to therapy and her colitis was in remission. However, after two years of treatment, she began to complain of abdominal discomfort and was referred to a gastroenterologist for evaluation of her Crohn's colitis. She underwent a colonoscopy, which revealed a partially obstructing ulcerative lesion in the proximal transverse colon. A preoperative CT scan of the abdomen and pelvis revealed a 4-cm × 4-cm lesion in the right lobe of the liver. The patient underwent an extended right hemicolectomy with ileocolic side-to-side anastomosis (Ethicon TLC, 75 mm) and incisional biopsy of the liver lesion. The pathology revealed a moderately differentiated colon cancer (T3N0) with metastasis to the liver. She received a six-month cycle of chemotherapy and then underwent a successful right hepatic lobectomy.

Patient 2 was a 47-year-old female with a 20-year history of Crohn's colitis, which had been controlled with intermittent steroids and 6-mercaptopurine. She had been undergoing surveillance colonoscopy every two years for the past ten years. The random biopsy

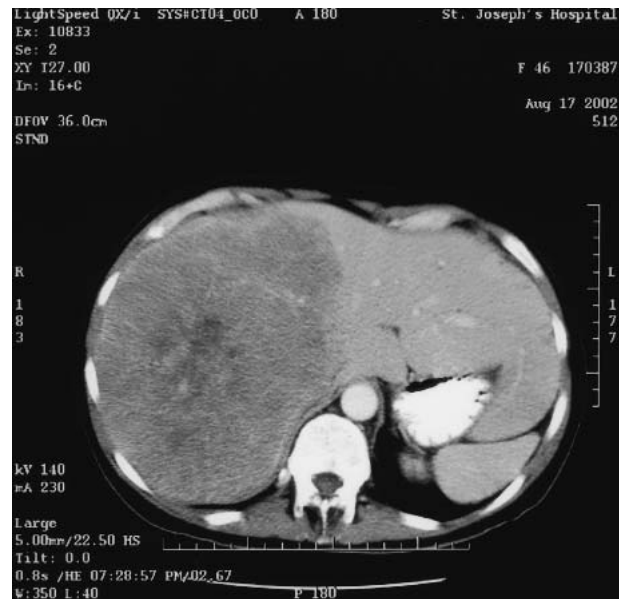


Figure 1. CT scan of Patient 2 demonstrating extensive colon metastasis in the liver.

pattern was four specimens from different sites of the colon and rectum: cecum, ascending, hepatic flexure, transverse, splenic flexure, descending, sigmoid, and rectum (total of 32 biopsies). The colonoscopy two years before the diagnosis of adenocarcinoma of the colon revealed pseudopolyps with skip areas of inflammation of the cecum, ascending, transverse colon, and rectosigmoid. Biopsies of the ascending and transverse colon revealed mild dysplasia in the presence of inflammation. One year after the previous colonoscopy, she had another colonoscopy and biopsies were taken from the same areas; there was no evidence of dysplasia. For the last two years, she experienced increasing symptoms of Crohn's colitis and was started on infliximab therapy. The patient received two courses of infliximab (5 mg/kg) during a two-year interval. Five months after her last treatment, she developed a palpable abdominal mass in the right upper quadrant. A CT scan revealed a 19-cm lesion in the liver with a partially obstructing lesion in the transverse colon (Fig. 1). She underwent a colonoscopy and biopsy of the lesion in the transverse colon; access beyond the lesion was not possible because of the high-grade stenosis. A transverse colectomy and incisional biopsy of the liver lesion were performed. The pathology report was a poorly differentiated adenocarcinoma of the transverse colon (T3N0) with metastasis to the right lobe of the liver. Her postoperative course involved a postoperative anastomotic leak, which required a laparotomy. At the time of the

laparotomy, a completion colectomy was performed with an end ileostomy and mucus fistula of the rectosigmoid colon. The pathology report of the rest of the colon revealed three other synchronous poorly differentiated lesions (T2N0). She has received more than six months of chemotherapy, and initially the size of the liver lesion decreased to 14 cm and a marked improvement of right upper-quadrant pain. However, during the last two months the liver lesion has increased to >22 cm in size. She died during October 2003.

DISCUSSION

The two patients in our study developed metastatic node-negative adenocarcinoma of the colon within one year of therapy with infliximab for Crohn's disease. The patients before beginning treatment did not have any evidence of colon cancer and were both receiving surveillance colonoscopy. The first case had a previous sigmoidectomy for Stage I adenocarcinoma; the second had evidence of dysplasia on routine colonoscopy. Each patient was treated for at least two years with infliximab and was diagnosed with Stage IV adenocarcinoma of the colon. We propose in patients with colitis who have a "precancerous" colon or a history of colonic malignancy, careful consideration should be given before instituting therapy with infliximab. These cases may demonstrate the ability of cancer to progress to a metastatic stage at an accelerated rate with the institution of therapy with anti-TNF- α medication.

A landmark article in 1949 by Warren and Sommers recognized that precancerous lesions existed in patients with inflammatory bowel disease (IBD), especially those with ulcerative colitis.⁷ In 1967 Morson and Pang proposed that dysplasia could be used as a marker for developing of colon and rectal cancer in patients with IBD.⁸ In patients with IBD colitis with high-grade dysplasia have at least a 42 percent chance of having an associated invasive carcinoma of the colon.⁹ In patients with low-grade dysplasia in IBD colitis have at least a 19 percent incidence of having an associated invasive carcinoma of the colon.¹⁰ In an article from the Cleveland Clinic Foundation, intestinal adenocarcinoma in Crohn's disease was studied. They reviewed their experience during a 20-year period of 30 patients with intestinal carcinoma, of 2,883 cases of resected Crohn's disease. Only six of their patients (20 percent) had disease limited to the colon.

Of 22 patients with colorectal adenocarcinoma, 13 (59 percent) had poorly differentiated adenocarcinoma. The incidence of dysplasia associated with adenocarcinoma of the colon in this study was 87 percent. In this cohort all adjacent and distal dysplasia was of high-grade and only one case had a combination of low and high-dysplasia. In none of their reported cases was there mention of synchronous lesions or a history of previous malignancy of the colon as in our two cases.¹¹

The relationship of colon and rectal cancer with ulcerative colitis has been universally accepted.¹²⁻¹⁵ However, the relationship between colon and rectal cancer and Crohn's disease has remained more controversial.¹⁶⁻¹⁹ The malignancies most commonly associated with Crohn's disease have been lymphoma, adenocarcinoma of the small bowel, chronic fistula tract, or in a defunctionalized or by-passed segment.¹¹ The occurrence and location of the cancer developing in fistula tracts, in intestinal segments, corresponds to areas of active and chronic inflammation. This area of chronic inflammatory condition causes a cellular transition to dysplasia and then malignant transformation.²⁰

Dysplasia is defined as an unequivocal neoplastic alteration of the colonic epithelium. Riddell *et al.*⁹ discussed the difficulty of diagnosing dysplasia in a setting of active IBD. He proposed the category of indefinite for dysplasia for lesions that are not unequivocally neoplastic.

In our case the patient had low-grade dysplasia in the setting of active Crohn's colitis. One year later, biopsies did not reveal any evidence of dysplasia. She was then treated for her Crohn's colitis with infliximab. Patients with Crohn's disease are believed to have an increased incidence of adenocarcinoma of the colon and rectum. The exact increased risk and incidence of cancer and Crohn's disease is still uncertain but an association is accepted. In a study by Weider *et al.*,²¹ 449 patients with Crohn's disease were evaluated for overall risk of colon and rectal cancer. The patients with Crohn's disease had a 20-fold increase risk of colon and rectal cancer over the general population. Ekbom *et al.*¹⁵ in 1990 indicated the relative risk of colon and rectal cancer was increased 2.5 times in patients with Crohn's disease compared with the general population. The same study indicated a relative risk of malignancy of 5.6 times greater in the patients with Crohn's colitis. Other studies have indicated an increased relative risk of colon cancer ranging from 3.4 to 23.8.^{16,17} Most of

the larger studies not only indicated an increased risk of colon and rectal carcinoma but at an earlier age of onset. However, some studies have suggested that there is not a significant increase risk of colon cancer in patients with Crohn's disease compared with the general population.²² These studies are based on smaller study populations and many of the patients underwent early operations thus influencing the overall results.

Could the use of anti-TNF- α antibodies enhance the transition to malignancy in some high-risk patients with Crohn's colitis? The use of infliximab in patients with rheumatoid arthritis and Crohn's disease and possible increased incidence of malignancy is a concern.²¹ Numerous studies have evaluated the association of infliximab therapy and lymphoproliferative disease.^{4-6,22-25} In clinical trials of infliximab therapy in 1,372 patients, 18 developed new or recurrent lymphoproliferative malignancies.² It was concluded that a direct or casual relationship between infliximab and lymphoma could not be established.² In another study by Brown *et al.*⁴ with the FDA, 26 patients developed lymphoproliferative disorders during treatment with TNF- α antagonist in a population that was monitored by Med Watch reports. The study concluded that lymphoma did occur in the patients treated with anti-TNF- α medications; however, a direct or causal relationship between anti-TNF- α medication and lymphoma could not be established.

None of the clinical trials involving infliximab-associated neoplasms have identified a case adenocarcinoma of the colon and rectum. Furthermore, there have been no studies evaluating the effects of anti-TNF- α agents used for patients who have a history of dysplasia of the colon or history of colon cancer. These two case reports are of concern because both had recent colonoscopies, then were treated with infliximab, and within 24 months of initiation of therapy were diagnosed with Stage IV colon cancer.

CONCLUSIONS

These case reports present an interesting clinical issue and possibly a trend that may be starting with the increased "site-specific" immune modulating therapy for patients with inflammatory bowel disease. The use of infliximab could inhibit the natural immune surveillance mechanism allowing premalignant cells to transform into malignant cells and further enhance their ability to metastasize. These two cases

may be just a statistical phenomenon without association to infliximab therapy. This report also may encourage other similar cases to be reported.

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