Anti-tumor necrosis factor therapies are still suspected of contributing to malignancy development, though it remains unproven. A 53-year-old female patient was admitted to our clinic with the complaints of fatigue, weight loss and rectal bleeding. She suffered from ankylosing spondylitis and had been treated with infliximab. Colonoscopic examination showed bleeding and ulcerated polypoid tumor in the cecum. Pathological examination of the material revealed adenocarcinoma. We discuss the high probability of a serious adverse effect of infliximab as an anti-tumor necrosis factor agent.

**Key words:** Ankylosing spondylitis, anti-tumor necrosis factor, infliximab, malignancy, adenocarcinoma

**INTRODUCTION**

Anti-tumor necrosis factor-α (TNF-α) treatment is effective in the treatment of various rheumatologic diseases, particularly rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, and Crohn’s disease (1). Infliximab is a chimeric (mouse/human) IgG-1 anti-TNF-α monoclonal antibody that binds to soluble transmembrane TNF-α with high affinity and forms a complex with its receptor (2). The results of preliminary clinical studies have demonstrated that infliximab significantly improved clinical outcomes, quality of life and spinal inflammation in patients with AS (3). Anti-TNF-α treatment-associated cancer risk has been poorly explored and the long-term risk is unknown.

We herein present an AS patient who developed colon adenocarcinoma 17 months after the initiation of infliximab treatment.

**CASE REPORT**

A 53-year-old female patient was admitted to our outpatient clinic in November 2005 with the complaint of rectal bleeding. In 1980, she had been diagnosed in another medical center as having AS with inflammatory back pain and bilateral symmetric sacroiliitis. She had been treated with non-steroidal anti-inflammatory drugs (NSAIDs) for about 20 years. In 2002, the disease activity could not be controlled with NSAIDs, and sulfasalazine (SSZ) was started as 2 g/day. Methotrexate (MTX) 7.5 mg/week was added to the treatment in 2003.

Infliximab therapy was started as 5 mg/kg every 6 weeks in July 2004 in another rheumatology center due to resistant disease activity. Seventeen months after the initiation of infliximab, she was admitted to our rheumatology clinic with the complaints of rectal bleeding, fatigue and weight loss (5 kg in 3 months). Her past medical history revealed hypertension. In her family history, her sister had been diagnosed as having AS. No malignant disorder had been diagnosed in her family. Her physical examination revealed limited motion in the lumbar spine. The laboratory evaluation revealed: hemoglobin 8.45 g/dl, mean corpuscular volume (MCV) 75.11 fL, platelet count 573 x10⁹/μL, serum iron level 11 μg/dl (25-156), and serum iron binding capacity 287 μg/dl (70-390). Erythrocyte sedimentation rate was 59 mm/hr, and C-reactive protein level was 3.43 mg/dl (0-0.5). Tumor markers CA 19-9 and CEA were within normal limits. Colonoscopy demonstrated bleeding and an ulcerated, nearly 2 cm-thick polypoid tumor in the cecum (Figure 1, arrow). The pathological examination of the material revealed adenocarcinoma of the colon.
DISCUSSION

Tumor necrosis factor (TNF) has a documented tumor-reducing capacity, and treatment with anti-TNF drugs might thus theoretically promote formation of tumors (4).

There has been only one large national cohort of patients with AS that aimed to determine the overall cancer risk in AS. In this Swedish population-based cohort study, no overall increase in cancer risk was found. Colon cancer risk was not significantly increased, and moreover, rectal cancer was less common. Decreased risk of rectal cancer was thought to be due to the use of NSAIDs (5). Another study from Scotland quantified and compared risks for malignancy in patients with rheumatic conditions, and concluded that the risk of development of colorectal cancer was reduced in those patients (6). Bongartz et al. (7) recently reported a meta-analysis regarding the risk of malignancies in anti-TNF antibody-administered patients with RA. The authors concluded a dose-dependent increased risk for malignancies in those patients. Pharmacokinetic studies have already shown that infliximab doses beyond 3 mg/kg every 8 weeks lead to a high risk of overexposure with an excessive binding of TNF (8). However, in AS patients, the recommended infliximab dose is 3 to 10 mg/kg, and the recommended dose interval is every 6 weeks. There are a few reported cases demonstrating the development of gastrointestinal adenocarcinoma in patients with RA after infliximab therapy. St. Clair et al. (9) reported gastrointestinal adenocarcinoma in the 12th month of therapy in their randomized controlled trial with infliximab for early RA. The dose of infliximab was 6 mg/kg every 4 weeks. Lipsky et al. 10 reported another patient who developed gastrointestinal adenocarcinoma after 26 weeks of infliximab therapy for RA at a dose of 10 mg/kg every 4 weeks. To our knowledge, there has been no report of a patient with AS who developed gastrointestinal cancer after infliximab. In this paper, we report an AS patient who developed gastrointestinal cancer after administration of this agent. Our patient had been treated with 5 mg/kg infliximab (400 mg) per 6 weeks for 17 months. There were no other risk factors for the development of malignancy. It has been suggested that long-term use of NSAIDs reduces the risk of development of colorectal cancer. The reduced need for NSAIDs after infliximab might also have increased the tumorigenesis.

In summary, we report herein an important possible serious adverse event of infliximab therapy in an AS patient. Although there is currently no definitive proof of a relation between infliximab therapy and colon cancer, thorough screening for subclinical malignancies may be needed in patients who are being considered for anti-TNF antibody treatment.

The authors declare that they have no competing interests. Written consent was obtained from the patient.

REFERENCES