CASE REPORT

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Infliximab- and azathioprine-related severe neutropenia and thrombocytopenia in a case with Crohn's disease

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A 25-year-old female patient with Crohn's disease had been using azathioprine and metronidazole for an extended period because of recurrent perianal and rectovaginal fistulae. Infliximab was added to the treatment regimen following postoperative recurrence of a rectovaginal fistula. Upon the development of severe neutropenia and thrombocytopenia after the third dose of infliximab, azathioprine and infliximab were stopped. Neutropenia work-up did not reveal any other cause. Neutropenia was ameliorated with use of granulocyte colony-stimulating factor. Treatment was restarted with infliximab alone upon leakage from the rectovaginal fistula with no hematologic toxicity. This case was considered as a serious adverse effect of infliximab and azathioprine combination therapy.

Key words: Crohn's disease, infliximab, neutropenia, thrombocytopenia, azathioprine

İnfliximab ve azathioprin'e bağlı ağır nötropeni ve trombositopeni gelişen bir Crohn olgusu

Crohn hastalığı olan 25 yaşında kadın hasta tekrarlayan perianal ve rektovajinal fistül nedeniyle uzun süredir azathioprin ve metronidazol kullanıyordu. Ameliyat sonrası rektovajinal fistül tekrarladığından tedaviye infliximab eklendi. Üçüncü infliximab dozundan sonra gelişen ağır nötropeni nedeniyle azathioprin ve infliximab kesildi. Nötropeni için yapılan incelemelerde başka neden saptanmadı. Nötropeni ancak granülosit koloni-stimulan faktör kullanımı ile düzeldi. Takibinde rektovajinal fistülden tekrar akıntı olması üzerine tek başına başlanan infliximab tedavisi herhangi bir hematolojik toksisiteye neden olmadı. Bu durum infliximab-azathioprin kombinasyonu sonrası gelişen nadir ciddi bir yan etki olarak değerlendirildi.

Anahtar kelimeler: Crohn hastalığı, infliximab, nötropeni, trombositopeni, azathioprin

INTRODUCTION

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine that is released in response to infectious or inflammatory stimuli. The TNF-α antagonists infliximab, etanercept and adalimumab are successfully used in the treatment of rheumatoid diseases such as rheumatoid arthritis and ankylosing spondylitis, and in Crohn's disease refractory to standard therapy (1). Generally well-tolerated, the most common side effects related to TNF-α inhibitors are reactions at the injection si-

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te, dyspnea, urticaria, and headache. Infusion reactions, anaphylaxis, development of tuberculosis and opportunistic fungal infections, congestive heart failure, and triggering of multiple myeloma attacks have also been reported (2). Although the mechanism of action is unclear, aplastic anemia, neutropenia and pancytopenia have been reported in association with anti-TNF-α treatment (2-4). Infliximab-related neutropenia is not common, and exists in the literature as case reports (3,5-7).

Azathioprine (AZA) and its active metabolite 6-mercaptopurine (6-MP) have been extensively used in the treatment of steroid-resistant Crohn's disease. A significant side effect of these drugs that inhibit DNA synthesis is bone marrow toxicity. This side effect usually occurs after doses greater than 2 mg/kg/day. This dose-dependent myelosuppression generally improves with lowering of the dose or suspension of treatment (8). However, an idiosyncratic severe myelosuppression may rarely occur with these drugs. Previous studies have not reported an increase in the prevalence of any adverse effect, including bone marrow toxicity, during combination therapy with AZA and infliximab (9,10).

CASE REPORT

A 25-year-old female patient was first admitted to our clinic 7 years ago with the complaint of abdominal pain and diarrhea. After clinical, endoscopic and histologic examinations, an ileocolonic Crohn's disease was diagnosed. Her Crohn's Disease Activity Index (CDAI) score was 530, and a clinical remission was achieved with mesalazine 3 g/day and a prednisolone course of 40 mg/day. She remained in remission for one year with mesalazine. After one year, a perianal fistula developed, and AZA 2 mg/kg/day was started together with a six-week metronidazole course. Following two years in remission, a rectovaginal fistula developed and the patient was operated. Postoperative metronidazole was started for non-closure of the fistula and the development of new perianal fistulae. Being well-tolerated, the AZA dose was increased to 3 mg/kg/day in order to obtain more effective therapeutic effect, and later discontinued due to mild bone marrow suppression [white blood cell count (WBC): 3000/mm^3, polymorphonuclear neutrophils (PMNs): 1450/mm^3, hemoglobin (Hb): 10.9 g/dl, platelet count: 155.000/mm^3)]. Treatment with AZA was restarted after three months, up to 100 mg (nearly 2 mg/kg - the patient's body weight was 54 kg at that time) with increments of 25 mg. There was no decrease in leukocyte count. The perianal disease did not improve after six months of therapy with AZA. Furthermore, new perianal fistulae and fissures developed, and leakage from the patient's rectovaginal fistula persisted. Infliximab was therefore added to the treatment at 5 mg/kg on weeks 0, 2 and 6. The patient presented with complaints of fatigue, fever and diarrhea 10 days after the third infliximab dose. Fever was 39°C, WBC: 350/mm^3, PMNs: 130/mm^3, platelet: 34000/mm^3, and Hb: 10.8 g/dl. The patient was hospitalized and placed under therapy with wide-spectrum antibiotics, and AZA was discontinued. On day 5, the patient still had high fever, and neutropenia and thrombocytopenia had not improved. Granulocyte colony-stimulating factor (G-CSF) was administered at doses 30 MU/day for five days. Blood counts started to increase after the second day of G-CSF treatment. Cultures were negative. Testing for the other possible etiologies of neutropenia and thrombocytopenia showed no pathologies (antinuclear antibody (ANA), anti-DNA, extractable nuclear antigens (ENA) profile, anti-neutrophil cytoplasmic antibody (ANCA), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and parvovirus tests were all negative). The patient was discharged on mesalazine alone with normal temperature and blood count. Upon leakage from the rectovaginal fistula two months after discharge, treatment with infliximab alone at a dose of 3 mg/kg was initiated. The patient's hemogram was normal, and the third dose was administered as 5 mg/kg. No hematologic toxicity was observed after the eighth dose of infliximab treatment. There was marked improvement in the rectovaginal and perianal fistulae.

DISCUSSION

The known risk of severe myelosuppression in patients with inflammatory bowel disease using thiopurine therapy warrants monitoring the patients during their first two months of therapy. Manufacturers recommend weekly WBCs for the first eight weeks of therapy followed by blood tests at least every three months. Less frequent monitoring (weekly within the first 4 weeks of the therapy and every 6–12 weeks thereafter) may be sufficient. It is just as important to advise patients to report promptly should a sore throat or other sign of infection occur. Tailoring or optimization of thiopurine therapy can occur before or during treat-

ment. Clinicians should aim for a maintenance dose of AZA of 2–2.5 mg/kg/day and of 6-MP of 1–1.5 mg/kg/day in both ulcerative colitis and Crohn's disease. The maximum dose will differ between individuals, and effectivity means that level at which leukopenia develops (11).

Drug-induced bone marrow suppression is related to infectious complications and increased mortality (12). Although bone marrow suppression is quite rare with infliximab, it is a more common side effect with AZA. In our case, the previous AZA-related mild neutropenia had improved upon discontinuation of the drug, and was not observed with dose increase in small increments up to the 2 mg/kg of body weight. Thus, we think that our patient's first myelotoxicity was related to the high-dose of AZA. After the third dose of infliximab, neutropenia persisted despite discontinuation of AZA and infliximab. The neutropenia reported by Montané et al. (3) within 2-3 weeks of etanercept treatment only improved 1-2 months after discontinuation of the drug. Treatment could not be resumed, as similar side effects were observed with repeated doses of etanercept, and later with infliximab. Favalli et al. (5) reported serious neutropenia following the second dose of infliximab in a patient with enteropathic spondyloarthropathy. Marchesoni et al. (13) described an additive effect of potentially myelosuppressive agents such as allopurinol and leflunomide being co-administered with infliximab in relation with a case with rheumatoid arthritis who developed neutropenia. Vidal et al. (6) also mentioned an additive effect in their report of severe neutropenia and thrombocytopenia in a patient with rheumatoid arthritis after the third dose of infliximab in combination with methotrexate. We also suggest that our patient's second myelotoxicity was related to the coadministration of AZA and infliximab, because the patient had no myelotoxicity with separate uses of AZA 100 mg/day and/or infliximab. There is no data in the literature regarding the two drugs' interaction during metabolism (14). However, myelosuppression, a side effect of both drugs, is enhanced in combined use. As our patient's need for anti-TNF treatment continued, AZA was discontinued and infliximab dosage was increased in small increments, thereby avoiding bone marrow toxicity.

In conclusion, infliximab treatment in Crohn's disease in combination with AZA can cause serious myelosuppression. Patients under treatment with this combination should be closely monitored for hematologic complications.

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