Recurrent Gastrointestinal Bleeding, Intraabdominal Abscesses and Synchronous Candidemia and Meningitis Due to Leflunomide Therapy: Case Report

Leflunomid Kullanımı ile İlişkili Tekrarlayan Gastrointestinal Kanama, Batın İçi Apse, Kandidemi ve Menenjit Birlikteliği

Vedat TURHAN, MD,[a]
Ali ACAR, MD,[a]
Mehmet ÇOBAN, MD,[a]
Oral ÖNCÜL, MD,[a]
Şaban ÇAVUŞLU, MD[a]

[a]Department of Infection Diseases and Clinic Microbiology
GATA Haydarpaşa Educational Hospital
İstanbul

Geliş Tarihi/*Received:* 23.12.2008
Kabul Tarihi/*Accepted:* 02.06.2009

Yazışma Adresi/*Correspondence:*
Ali ACAR, MD
GATA Haydarpaşa Educational Hospital, Department of Infection Diseases and Clinic Microbiology, İstanbul, TÜRKİYE/TURKEY
draliacar@yahoo.com

ABSTRACT Leflunomide is a tumor necrosis factor-α (TNF-α) blocking agent which is commonly used in the management of rheumatoid arthritis (RA). We report a suspected case of leflunomide-induced recurrent gastrointestinal bleeding, intraabdominal abscesses with synchronous candidemia and then meningitis. A 63-year-old man was admitted to our Emergency Department with fever, mental confusion, and urinary incontinence. He had been used anticoagulants for ten years because of atrial fibrillation and leflunomide for two years because of RA. A history of two gastrointestinal bleeding attacks, intraabdominal abscess and candidemia during the leflunomide therapy had been documented. We diagnosed meningitis together with intraabdominal abscess, gastrointestinal bleeding, and candidemia in the third hospitalization of the patient. Leflunomide was discontinued, and the patient was treated with antimicrobials (antifungal and antibacterial) and surgical procedures consisting of drainage and resection of the intrabdominal abscess. Symptoms and signs of the patient were improved and he was discharged on the 25th day of hospitalization. There was no recurrence in following six months period. Leflunomide should be started after very strict evaluations to indicated patient. These evaluations should be focused on primarily tendency to bleeding especially in oral anticoagulant users and possible infectious complications of community acquired or nosocomial originated.

Key Words: Leflunomide; arthritis, rheumatoid; hemorrhage; candidiasis; meningitis

ÖZET Leflunomid, romatoid artrit (RA) tedavisinde sıklıkla tercih edilen tümör nekroz faktör-α (TNF-α) blokörü bir ajandır. Burada leflunomid kullanımına bağlı olduğunu düşündüğümüz tekrarlayan gastrointestinal kanama, batın içi apse, kandidemi ve menenjit gelişen bir olguyu rapor ediyoruz. Altmış üç yaşında bir erkek hasta acil servisimize ateş, mental konfüzyon ve üriner inkontinans semptomları ile başvurdu. Hasta atriyal fibrilasyon nedeniyle 10 yıldır oral antikoagülan (varfarin) ve RA nedeniyle de son iki yıldır leflunomid tedavisi almakta idi. Leflunomid kullandığı süre içinde iki kez gastrointestinal kanama, intraabdominal abse ve kandidemi atağı gelişmişti. Hastanın merkezimize üçüncü yatışında menenjit, batın içi abse, gastrointestinal kanama ve kandidemi tanıları konuldu. Hastanın leflunomid tedavisi kesilerek, antifungal ve antibakteriyel ajanların birlikte kullanılması ve absenin cerrahi olarak boşaltılması ile tedavi edildi. Semptom ve bulguları düzelen hasta yatışının 25. gününde kontrollere gelmek üzere taburcu edildi. Takip eden altı aylık süre içerisinde nüks saptanmadı. Leflunomid endike hastalarda çok sıkı bir değerlendirmeden sonra başlanmalıdır. Bu değerlendirme yapılırken oral antikoagülan kullanan hastalarda kanamaya eğilim olabileceği ve hastane veya toplum kökenli enfeksiyonlara bağlı komplikasyonlar gelişebileceği göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Leflunomid; romatoid artrit; kanama; kandidemi; menenjit

Turkiye Klinikleri J Med Sci 2010;30(6):2027-30

Leflunomide is a disease-modifying antirheumatic drug which reduces the signs and symptoms of inflammatory arthritis and delays the radiological progression of disease in adult patients with active

rheumatoid arthritis (RA).[1,2] Leflunomide may potentiate the effect of warfarin and may cause bleeding. It may also cause opportunistic infections due to suppression of cellular immunity.[1-3] We report a 63-year-old man with RA who had recurrent gastrointestinal bleeding, intraabdominal abscesses with synchronous candidemia and meningitis while he was receiving leflunomide.

CASE REPORT

Our patient was a 63-year-old man. He had RA for 20 years. Until 2004 he had been treated with classical RA therapy (methotrexate, sulfasalazine, hydroxychloroquine and prednisolone) with inadequate response and he had been taking leflunomide (20 mg daily) in the previous two years. He had also received long-term anticoagulation with warfarin for recurrent thromboembolism and atrial fibrillation. In this history there were two reported bleeding attacks: one in the first year and one in the second year of leflunomide therapy. Both bleeding attacks had been cured by medical and replacement therapy. One month after the second bleeding attack he was hospitalized because of fever, abdominal distention and pain. A clinical diagnosis of intraabdominal abscesses was suspected and confirmed by ultrasound examination. Piperacilin-tazobactam (4.5 gr tid) was administered empirically and the abscess was drained surgically. No bacteria were isolated in samples taken during the surgical operation. Antibiotic therapy was continued for 15 days. Non-*albicans Candida* strain was concurrently isolated in the blood and catheter cultures on the tenth days of antibiotic therapy. According to culture-antibiogram results fluconazole therapy (2x400 mg/day IV) was administered for three weeks. After the surgical and medical treatment, the symptoms and signs of our case decreased and the abscesses disappeared. No microorganisms were isolated in the control cultures. He was discharged with improved health condition.

Four weeks later, he was admitted to our Emergency Department with fever, confusion, disorientation and urinary incontinence, on December 19, 2004. In physical examination, he had confusion, neck stiffness and his general condition was bad. The Glaskow coma scale score was 10. There were deformities and deviation on his phalanges and fingers. His skin was dry, shining and thin. The white blood cell count was 5400 /mm^3, the rate of polimorfonuclear leukocytes (PMNL), lymphocyte and monocyte were 57%, 18% and 25% respectively. Other blood parameters were normal except C-reactive protein (89.1 mg/dl). In lumbar puncture; increased cerebrospinal fluid (CSF) pressure, gray color and turbidness were identified. The cell count was 690/ml (60% lymphocyte, 40% PMNL) and CSF/blood glucose level was 40/94 mg/dl. The lactate dehydrogenase, chlorine and protein levels were 116, 123 and 129.9 mg/dl, respectively. The CSF's gram and Giemsa and Ehrlich Ziehl Nielsen staining were negative. CSF cultures yielded no microorganisms. *Mycobacterium tuberculosis* PCR was found as negative. Dilatation in ventricular cysterna and lacunar infarcts in left nucleus lentiformis and periventricular white zone were found. Cranial MRI findings revealed granulamatous lesions, ischemia and gliotic lesions in periventricular white zone. At the first admission day leflunomide was discontinued, and ceftriaxone was introduced 4 g daily. Four days later, non-*albicans Candida* was isolated in blood cultures, and liposomal amphotericine B was added to the therapy according to culture-antibiogram results. By the third day of liposomal amphotericin B therapy, gastrointestinal bleeding developed and intraabdominal abscesses (12x30 mm) were diagnosed by USG and confirmed by abdominal CT. The abscesses were drained surgically. Cultures of the abscess materials showed coagulase-negative oxacillin resistant. Staphylococci, Vancomycine was added to the therapy. In addition, non-*albicans Candida* strains were isolated from the blood, urine and catheter cultures taken simultaneously. Antibacterial therapy (ceftriaxone and vancomycine) was continued for 14 days while the antifungal was administered for 21 days. After the surgical and medical treatment, the symptoms and signs of the patient were improved and he was discharged on the 25th day of the hospitalization.

DISCUSSION

Leflunomide is a new class of immunomodulating drugs for use in transplantation. In 1985, the anti-inflammatory and immunomodulating properties of leflunomide were recognized, which differ from classical anti-inflammatory and immunosuppressive drugs. Because of its long half-life (11 to 16 d) in humans, the clinical development of leflunomide has been restricted to use in patients with a few autoimmune diseases such as RA.[1-3]

Leflunomide expresses its mechanism of action through inhibition of dihydroorotate dehydrogenase, an enzyme involved in *de novo* pyrimidine synthesis.[4,5] The most common side effects associated with leflunomide treatment are gastrointestinal problems like diarrhea, abdominal pain, nausea and vomiting.[6-8] The use of high doses of leflunomide for the treatment of RA patients is often accompanied with gastrointestinal problems suggesting that the drug affects some functions of mucosal epithelial cells. Suppressed proliferation and functions of gastrointestinal mucosal epithelial cells by leflunomide can increase not only the yeast colonization but also the risk of further fungal dissemination into internal organs.[9] In great possibility, candidemia and intraabdominal abscess due to *Candida* spp. was also developed by similar mechanism in our patient. Another explanation for these important infectious complications may be inhibition of neutrophil migration and phagocytosis failure as claimed by Kraan et al.[10] Grover et al. reported two cases with atypical and severe infectious complications associated with abscess formation while the patients were receiving leflunomide.[11] Our patient is a unique case with multiple complications, namely recurrent gastrointestinal bleeding, intraabdominal abscesses and candidemia followed by meningitis.

There is an interaction between leflunomide and warfarin. Leflunomide usually causes an increase in the patient's international normalized warfarin ratio. Leflunomide inhibits cytochrome *P*4502C9 and can increase the bioavailability of drugs metabolised by cytochrome *P*4502C9, such as warfarin and phenytoin.[12] It was thought that the recurrent gastrointestinal bleeding in our case developed due to interaction between leflunomide and warfarin.

In our case, the cause of abscesses and meningitis was thought to be related to *Candida*. Several possible explanations may have played a role. First, *Candida* was isolated from blood cultures in the same periods of recurrent intraabdominal abscesses and candidemia synchronously. Second, good clinical and laboratory response in the abdominal abscesses and meningitis were provided by antifungal therapy. Third, although the *Candida* strains were sensitive to fluconasole in the first attack, they were resistant to fluconasole in the second attack. Fourth, no specific microorganisms were isolated from abscess samples.

As a conclusion, the leflunomide therapy may enhance the risk of invasive candidal infections in patients with RA, especially if they are hospitalised frequently. On the other hand, it could increase the bleeding effect of warfarin and gastrointestinal bleeding may occur. Therefore, clinicians should frequently measure INR and adjust the warfarin dosage accordingly to maintain therapeutic anticoagulation. During leflunomide therapy taken into consideration must be patients should be followed carefully and opportunistic infections even as a nosocomial infection.

REFERENCES

1. Jenks KA, Stamp LK, O'Donnell JL, Savage RL, Chapman PT. Leflunomide-associated infections in rheumatoid arthritis. J Rheumatol 2007;34(11):2201-3.
2. Top C, Terekeci H. [Disease-modifying antirheumatic drugs in the treatment of rheumatoid arthritis: medical education]. Turkiye Klinikleri J Med Sci 2008;28(3):387-98.
3. Gummert JF, Ikonen T, Morris RE. Newer immunosuppressive drugs: a review. J Am Soc Nephrol 1999;10(6):1366-80.
4. Bartlett RR, Brendel S, Zielinski T, Schorlemmer HU. Leflunomide, an immunorestoring drug for the therapy of autoimmune disorders, especially rheumatoid arthritis. Transplant Proc 1996;28(6):3074-8.
5. Cherwinski HM, Byars N, Ballaron SJ, Nakano GM, Young JM, Ransom JT. Leflunomide interferes with pyrimidine nucleotide biosynthesis. Inflamm Res 1995;44(8):317-22.
6. Kalden JR, Smolen JS, Emery P, van Riel PL, Dougados M, Strand CV, et al. Lefunomide in combination therapy. J Rheumatol 2004;71 (Suppl):25-30.

7. van Riel PL, Smolen JS, Emery P, Kalden JR, Dougados M, Strand CV, et al. Leflunomide: a manageable safety profile. J Rheumatol 2004;71(Suppl):21-4.
8. Smolen JS, Emery P, Kalden JR, Van Riel PL, Dougados M, Strand CV, et al. The efficacy of leflunomide monotherapy in rheumatoid arthritis: towards the goals of disease modifying antirheumatic drug therapy. J Rheumatol 2004;71(Suppl):13-20.
9. Dimitrova P, Ivanovska N. Influence of leflunomide on gastrointestinal Candida albicans infection induced in naive and arthritic newborn mice. Int Immunopharmacol 2006;6(11): 1682-9.
10. Kraan MC, de Koster BM, Elferink JG, Post WJ, Breedveld FC, Tak PP. Inhibition of neutrophil migration soon after initiation of treatment with leflunomide or methotrexate in patients with rheumatoid arthritis: findings in a prospective, randomized, double-blind clinical trial in fifteen patients. Arthritis Rheum 2000;43(7):1488-95.
11. Grover R, Dhir V, Aneja R, Arya V, Galle A, Marwaha V, et al. Severe infections following leflunomide therapy for rheumatoid arthritis. Rheumatology (Oxford) 2006;45(7):918-20.
12. Lim V, Pande I. Leflunomide can potentiate the anticoagulant effect of warfarin. BMJ 2002;325(7376):1333.