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Gastrointestinal bleeding secondary to use of high-dose methotrexate: A case report

Yüksek doz metotreksat kullanımına ikincil gelişen gastrointestinal kanama: Olgu sunumu

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Abstract

A 69-year-old female patient was admitted to our emergency service with painful oral ulcers and rectal bleeding. She has been used methotrexate (MTX) because of rheumatoid arthritis (RA). The patient has been used methotrexate every day for 10 days instead of a weekly treatment. Pancytopenia was seen in laboratory tests. Rectal bleeding associated with gastrointestinal mucosal erosion was attributed to MTX toxicity and MTX-induced thrombocytopenia. The direct cause of MTX intoxication in this case was accidental daily use instead of a weekly use. This case demonstrates the importance of communicating adequately with health professionals and emphasizes that MTX should be used weekly. It is essential to describe in detail how the medication can be used and what adverse effects may occur as the result of taking MTX.

Keywords: Methotrexate, Rheumatoid arthritis, Thrombocytopenia

Öz

69 yaşında kadın hasta Acil Servis'e ağrılı oral ülserler ve rektal kanama ile başvurdu. Romatoid artrit (RA) sebebiyle metotreksat (MTX) kullanıyordu ve haftalık tedavi yerine 10 gün boyunca her gün olacak şekilde MTX kullanmıştı. Labaratuvar testlerinde pansitopeni görüldü. Gastrointestinal mukozal hasar birlikteliği ile olan rektal kanaması MTX toksisitesine ve MTX bağımlı trombositopeniye bağlandı. Bu olguda MTX intoksikasyonunun direkt sebebi haftalık kullanım yerine yanlışlıkla günlük olarak kullanım idi. Bu vaka sağlık çalışanları ile yeterli iletişim kurmanın önemini göstermektedir ve MTX'ın haftalık olarak kullanılması gerektiğini vurgulamaktadır. MTX tedavisi başlanacağı zaman detaylı bir şekilde ilacın nasıl kullanılacağı ve hangi yan etkileri oluşturabileceğini anlatmak elzemdir.

Anahtar kelimeler: Metotreksat, Romatoid artrit, Trombositopeni

Introduction

Methotrexate (MTX) is a folic acid antagonist with anti-inflammatory and immunosuppressive effects. It is mostly used in neoplastic diseases and in the treatment of inflammatory diseases such as Rheumatoid arthritis (RA). Rarely, it can cause severe side effects such as agranulocytosis on the basis of bone marrow suppression, inflammation in mucosal tissues, hepatic necrosis, cirrhosis of the liver, pulmonary fibrosis and renal dysfunction [1]. We presented a case of newly diagnosed pancytopenia, stomatitis and gastrointestinal hemorrhage in a 69-year-old woman who had been mistakenly used intramuscular MTX every day.

Case presentation

A 69-year old woman with no history of chronic disease except known hypertension was admitted to our clinic with complaints of nausea, vomiting, abdominal pain, bright red stool, oral mucositis and decreased oral intake for the last 3 days. An oral dose of 8 mg/day methylprednisolone and intramuscular MTX 15 mg/week was started 10 days prior with a diagnosis of RA in the rheumatology polyclinic. However, the patient administered methylprednisolone once a week and MTX every day. Vital findings of the case were the following: blood pressure 125/80 mmHg, pulse rate 98/min, temperature 36.8 °C, respiration rate 19/min.

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On the physical examination, there were numerous aphthous lesions in the mouth. The patient had tenderness on deep palpation but had no rebound tenderness, defense or organomegaly. The digital rectal examination was compatible with hematochezia. Significant pathological findings were not found in other system examinations of the patient. The laboratory findings were the following: WBC 1200 /mm^3, neutrophil 300/mm^3 [30%], Hgb 9.5 gr/dl, MCV (Mean Corpuscular Volume) 94 /Fl, thrombocyte 43000 /mm^3, sedimentation 42 mm/hr, CRP (C-Reactive Protein) 8 mg/dL (Table 1).

Table 1: Laboratory findings of the patient

Day/Parameter	Wbc x10^3/uL	Neu x10^3/uL	Hgb gr/dl	Plt x10^3/uL	Ast U/L	Alt U/L	Crt mg/dl
Pre-treatment	1.2	0.3	9.5	43	25	20	0.7
Day 1	1.3	0.4	9,6	59	69	92	0.8
Day 3	1.3	0.4	9.5	54	44	85	0.7
Day 4	1.6	0.7	9.7	155	26	65	0.7
Day 7	2.6	1.5	9.8	160	35	21	0.8
Day 9	29	25	10.4	380	22	19	0.7

Wbc: White blood cell, Neu: Neutrophil, Hgb: Hemoglobin, Plt: Platelet, Ast: Aspartate aminotransferase, Alt: Alanine aminotransferase, Crt: Creatinine

Erythrocytes were normocytic hypochromic, few neutrophils and mature lymphocytes were present, clumping of platelets was observed and no atypical cells were detected upon the examination of peripheral blood smear. Chest X-ray and electrocardiography of the patient were normal. The biochemical values were usual. There was no significant pathologic finding in abdominal CT (Computed Tomography) of the patient who had abdominal pain. No pathology was detected in the direct microscopic examination of stool specimens and in microscopic-macroscopic examinations of the patient with bloody stool. Colonoscopy showed a mucosal-like appearance throughout evident in the descending colon and there were locally ulcerated sites (Figure 1). Pancytopenia secondary to the use of high-dose MTX, mucositis and gastrointestinal bleeding were considered for the patient. MTX was discontinued and intravenous Folinic Acid rescue protocol was administered at 5 mg/day for 4 days. Filgrastim subcutaneous 48 IU 1x1 was initiated for pancytopenia, thrombocytopenia on the 7th day, pancytopenia and gastrointestinal system bleeding stopped on the 9th day of admission. Her pancytopenia improved, she had no bloody stool complaints and lesions in her mouth receded and then, the patient was discharged.

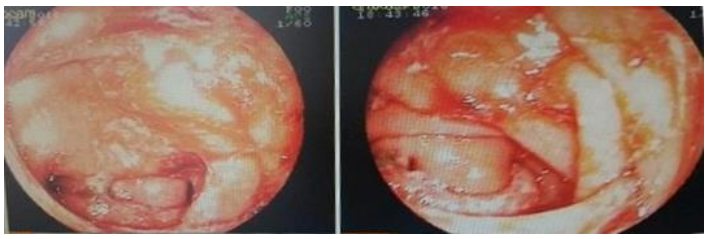

Figure 1: Mucositis and ulcer areas in the descending colon

Discussion

RA characterized by a symmetric, erosive, synovitis and sometimes with multisystem organ involvement is an autoimmune disease with unknown etiology [2]. In RA treatment, disease modifying drugs are used to prevent progression of the disease. The first preferred drug is MTX within this group of drugs [3,4]. MTX is regarded as the leading drug in RA treatment because it has many features such as its long-term use by patients, high clinical reliability, and being able to be combined with biological agents [5]. When MTX therapy is initiated, its effect starts at 3-6 weeks and is usually well-tolerated. Although it is generally well-tolerated, MTX use may cause pancytopenia, hepatotoxicity, pulmonary toxicity, nephrotoxicity, high fever, gastrointestinal adverse effects, and skin eruptions [6,7]. The gastrointestinal tract and bone marrow toxicity of MTX may be dose-dependent, whereas pneumonitis, liver and cardiac toxicity may be dose-independent. In our case, there was a pancytopenia that developed due to a high-dose use of MTX every day. MTX-induced pancytopenia toxicity may be due to high-dose use of MTX or may be due to low-dose [8, 9]. A study conducted by Ohosone et al. [10], found that about 1.4% of patients using a low-dose MTX developed pancytopenia. In the case of MTX-induced pancytopenia, treatment options include the use of the first granulocyte colony-stimulating factor [11,12]. In our case, 48 IU filgrastim therapy improved leukopenia on the 7th day complete blood count. It rarely can have adverse effects on gastrointestinal system mucosa because of the antimitotic and antiproliferative effect of MTX. Intestinal mucositis, bleeding and ulcers are known toxic effects in gastrointestinal tract. In the present case, there were findings compatible with intestinal mucositis in the entire colon, especially in descending colon in the colonoscopy. It is thought that MTX may be associated with increased immune response and gastrointestinal blood flow, although it is not fully elucidated how MTX causes mucositis. In the literature, Tsukada et al. [13] reported a case of gastrointestinal mucosal necrosis developed in a patient using a dose of MTX at 8 mg/week. Unlike our case, there was no high-dose use history and the patient had mucosal necrosis on the gastrointestinal examination.

In conclusion, MTX use in RA therapy may cause unexpected and life-threatening complications as a result of unconscious use although it is effective, safe and tolerable. Patients should be informed how to use the medication and what adverse effects may occur in detail when MTX therapy is initiated. MTX toxicity should be kept in mind when symptoms such as pancytopenia, oral ulcers, and gastrointestinal bleeding occur in patients with RA.

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