Düşük doz Methotrexatın indüklediği Henoch-Schönlein Purpurası

Henoch-Schönlein Purpura induced by Low-Dose Methotrexate

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Abstract

Methotrexate (MTX) is an antiproliferative folic acid antagonist used in the treatment of various malignancies and chronic inflammatory diseases. Commonly observed side effects in patients receiving low-dose, weekly MTX treatment are nausea and stomatitis. Henoch-Schönlein purpura (HSP) is a condition generally induced by infectious agents, exposure to cold, insect bites, foods, and drugs. In this paper, we presented together with a review of the literature a case of HSP that developed in the third week of treatment of a 14-year-old male patient started on low-dose methotrexate for juvenile idiopathic arthritis.

Key words: Henoch-Schönlein Purpura, Juvenile Idiopathic Arthritis, Methotrexate

Özet

Metotreksat (MTX), çeşitli malignite ve kronik inflamatuvar hastalıkların tedavisinde kullanılan antiproliferatif bir folik asit antagonistidir. Düsük doz, haftalık MTX tedavisi alan hastalarda sık görülen yan etkiler bulantı ve stomatittir. Henoch-Schönlein purpurası (HSP) genellikle, infeksiyon ajanları, soğuk, böcek ısırması, besinler veya ilaçlara bağlı olarak tetiklenir. Bu yazıda juvenil idiyopatik artrite yönelik düşük doz metotrexate başlanan 14 yaşındaki erkek hastada tedavinin 3. haftasında ortaya çıkan HSP literatür eşliğinde sunulmuştur.

Anahtar Kelimeler: Henoch-Schönlein Purpura, Juvenile Idiopathic Artrit, Metotreksat

Introduction

Methotrexate (MTX) is an antiproliferative folic acid antagonist used in the treatment of various malignancies and chronic inflammatory diseases. Commonly observed side effects in patients receiving low-dose, weekly MTX treatment are nausea and stomatitis. Rarely observed side effects include the suppression of the bone marrow, and hepatic and pulmonary toxicities. At significantly high doses, MTX can lead to the erosion of psoriatic plaques and ulcers (1,2).

Henoch-Schönlein Purpura (HSP) is the most

commonly observed type of vasculitis in childhood. It mainly affects the gastrointestinal system, the articulations, and the kidneys, and may also affect the other organs in rare cases (3). Although its etiology has not yet been fully elucidated, infectious agents, exposure to cold, insect bites, foods, and drugs have generally been held responsible for inducing HSP (4). In this paper, we presented together with a review of the literature a case of HSP that developed in the third week of treatment of a 14-year-old male patient started on low-dose methotrexate for juvenile idiopathic arthritis.

Case

A 14-year-old male patient was admitted to our clinic with complaints of swelling and pain in the left knee that had been ongoing for two weeks. No distinctive characteristics were noted in the patient's medical history and family history. The following values were recorded during the patient's physical examination: weight: 35 kg (50-75 p), height: 155 cm (50-75 p), body temperature: 37.8 °C, pulse: 100/min, and blood pressure: 110/70 mmHg. Swelling and an increase in temperature were observed in the left knee. The patient had a left antalgic gait. The patellar shock test was positive. Articular movements in the left knee were painful, and flexion and extension were limited at 15° and 5°, respectively. No pain or limitation of movement was identified during the examination of other articulations. White blood cell count was determined as 10,200/mm^3 by the complete blood count. The erythrocyte sedimentation rate (ESR) was 45 mm/hour, the C-reactive protein (CRP) value was 61.7 mg/L, and the antistreptolysin O (ASO) value was 260 IU/ml. In addition, the rheumatoid factor was determined as 10.7, the antinuclear antibody (ANA) value as 0.99 (negative), and the anti-dsDNA value as 3.14 (negative), while the HLA B27, Brucella tube agglutination, the urine and blood cultures, and the FMF panel were all identified as negative. No significant findings were observed in the patient's full urinalysis. Furthermore, the patient's fasting blood sugar, thyroid, liver and kidney function tests, vitamin D levels, lung radiography, and full abdominal ultrasonography were normal.

Except for swelling in the soft tissues, no particular findings or features were identified in knee radiographies taken while the patient was standing. The sacroiliac radiography was also normal. Except for synovitis and effusion in the intra-articular space, no pathologies were identified during the examination of the left knee with magnetic resonance imaging. Twenty cc of synovial fluid was aspirated from the left knee under sterile conditions. Examination of the fluid revealed a cloudy color, a white blood cell count of 32,000/mm^3 and a polymorphonuclear leukocyte (PMNL) ratio of 40%. No bacteria were identified in the synovial fluid, and no growth was observed in the synovial fluid culture. The patient's electrocardiography and echocardiography tests were also normal. No findings indicative of uveitis were identified during the patient's eye examination. The patient had no subcutaneous nodules, erythema marginatum, aphthae, psoriatic skin lesions, enthesitis or dactylitis.

The patient was diagnosed with idiopathic monoarthritis, and prescribed with 220 mg naproxen three times a day. The patient was also advised to perform cold applications to the left knee four times a day for five minutes. The patient was then placed under follow-up. Following the application of these recommended treatments, partial relief was observed in the patient's complaints. As the patient's arthritis in

the left knee continued for more than six weeks, a diagnosis of early onset oligoarticular juvenile idiopathic arthritis (JIA) was considered, and the patient was accordingly started on a treatment of prednisolone (10 mg/day, oral), methotrexate (10 mg/week, tablet), folic acid, and proton pump inhibitor (PPI). However, on the third week of his follow-up, the patient applied once again to our clinic with swollen, red-purple purpuric skin eruptions on both lower extremities, especially on their posterior side (Figure I), which did not fade when pressed. The patient did not describe any complaints related to stomach pain, or associated with the urinary or respiratory tracts. The complete blood test, liver test and kidney function test values of the patient were all within normal limits. The dermatology department was consulted, and the histopathological evaluation of the biopsy obtained from the skin lesions was reported as a "leukocytoclastic vasculitis associated with IgA deposits in the arterioles and venules." Values for the CRP, ESR, full urinalysis, liver function test, prothrombin time (PT), active partial thromboplastin time (apTT), serum IgA level, and the complements (C3, C4) were all within normal limits. The patient was diagnosed with HSP based on the examination findings and his medical history. The MTX treatment was discontinued, and the patient was instead started on a treatment of methylprednisolone (35 mg/day).

The purpuric lesions began to regress and fade starting from the second day of the clinical follow-up. By the third month of follow-up, the patient's skin symptoms associated with HSP had completely resolved. The complete blood test, liver test, and kidney function test values and the acute phase reactants of the patient were all within normal limits.

Discussion

Methotrexate is a folic acid antagonist which, through several mechanisms, inhibits numerous metabolic pathways dependent on folic acid, including purine metabolism. The most important among these mechanisms is the inhibition of the enzyme dihydrofolate reductase (DHFR), which prevents the reduction of folic acid into dihydrofolate and tetrahydrofolate Methotrexate thus demonstrates its effects by inhibiting the functions of inflammatory cells involved in rheumatologic processes. The dose usually administered for rheumatologic cases is 10 mg/m^2/week; administration as a single dose and once a week is generally recommended (5).

It has been reported that one-third of patients using MTX eventually discontinue the drug due to its side effects, and that only 1% of these side effects are serious.[1] Certain predisposing factors such as folate deficiency, drug use at high doses, renal failure, and the use of modifying or non-steroidal anti-inflammatory drugs can increase the likelihood of toxic effects. The main side effects associated with MTX use are loss of appetite, nausea, vomiting, diarrhea, weight loss, leucopenia, thrombocytopenia, megaloblastic anemia, pancytopenia, renal toxicity, transient oligospermia, increased incidence of lymphoma, hypersensitivity pneumonitis, increased liver function test values, and decreased serum albumin levels. Furthermore, side effects that involve the skin including alopecia, sensitivity to sunlight, erythema, urticaria, cutaneous vasculitis, increased number of rheumatoid nodules, toxic epidermal necrolysis, anagen effluvium and the erosion of psoriatic plaques are also observed (6). Aside from the administration of low-dose MTX and the use of folic acid support, the current case had no other predisposing factors for HSP.

HSP is a systemic vasculitis that is generally

observed during childhood. It is generally self-limiting, and has good prognosis. Between 30% to 50% of patients have a history of upper respiratory tract infection 1 to 3 weeks prior to the disease. Group A β hemolytic streptococcus (GABS) infections are commonly observed in cases of HSP (7). Other than GABS, numerous bacteria and viruses that are potentially associated with HSP have also been reported in various publications. These include bacteria such as mycoplasma pneumonia, hemophilus influenza, legionella, salmonella, shigella, and mycobacterium tuberculosis; and viruses such as the Epstein-Barr virus, parvovirus, adenovirus, hepatitis A and B, the rubeola virus, the rubella virus, and the varicella virus. HSP might develop following traumas, vaccination (rubeola, cholera, typhoid, and yellow fever), incest bites, exposure to cold, ingestion of certain foods, and the use of certain drugs. Drugs that might potentially cause HSP can be listed as salicylates, penicillin, tetracycline, sulfonamide, allopurinol, colchicine, quinidine, indomethacin, phenacetin, and diphenylhydrazine (8). The current case had no history of infection or drug use that might have been associated with the development of HSP. Aside from skin lesions typical of HSP, the patient's organs, such as his kidneys and gastrointestinal system, were not affected. We believe that the lack of any side effects on the organs might have been related to the patient's steroid use (albeit at a low dose), as steroids play an important role in the treatment of HSP. It has been reported that symptoms of arthritis in HSP may appear one or two days before the skin lesions (3). In our case, arthritis developed approximately two months before the skin lesions. For this reason, we believe that the patient's arthritis was unrelated to HSP.

Discontinuation of the drug and the administration of calcium folinate play an important role in the management of MTX toxicity (9). In our case, self-limiting skin lesions had appeared with the use of low-dose MTX. In addition, no impairment was observed in the patient's complete blood test, liver test, and kidney function test values. For this reason, discontinuation of MTX and increasing the dose of the already-used low-dose steroid was sufficient for ensuring the regression and fading of the lesions within a few days.

In conclusion, patients started on MTX should be informed in detail regarding the potential toxic effects of the drug and the reactions it can induce. They must also be closely followed and monitored, especially during the early period of treatment. Furthermore, it also important to remember questioning patients admitted to the clinic for HSP with regards to MTX use.

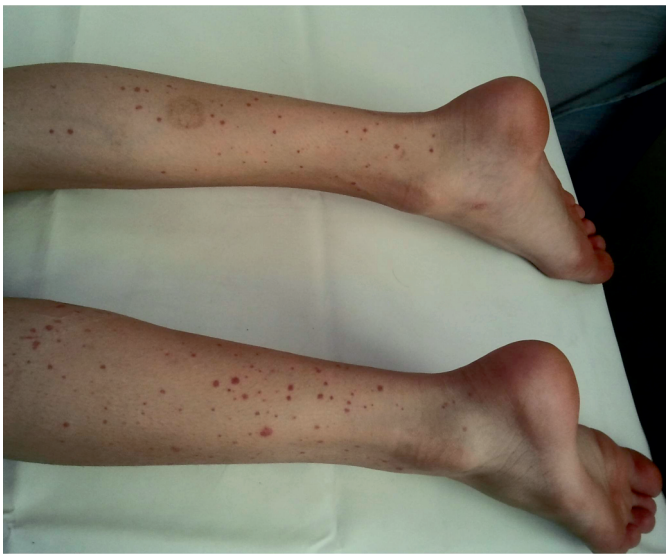

Fıgure 1. Purpuric eruptions observed on the posterior side of both lower extremities of a patient with Henoch-Schönlein purpuric eruptions.

Yazarlarla ilgili bildirilmesi gereken konular (Conflict of interest statement) : Yok (None)

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