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Pott's disease and hypercalcemia in a patient with rheumatoid arthritis receiving methotrexate monotherapy

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Abstract

Methotrexate (MTX) may have adverse effects on multiple organs and system. A few cases of pulmonary tuberculosis in-patients with rheumatoid arthritis (RA) while receiving MTX monotherapy has been reported in the literature. We submit a case of vertebral tuberculosis with hypercalcemia in a patient receiving MTX monotherapy. Patient with RA taking MTX for 15 years developed pancytopenia, skin necrosis, tuberculous spondylodiscitis and hypercalcemia. The present case showed adverse effects of MTX therapy may occur even after years of continuous treatment. Due to pancytopenia in older patients, life-threatening tuberculosis at unusual sites may develop.

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Full Text

Introduction

Methotrexate (MTX) is the most common disease-modifying anti-rheumatic drug used in the treatment of rheumatoid arthritis (RA). MTX therapy may have adverse effects on multiple organs and systems, of which hematological and gastrointestinal adverse effects are most common. In MTX-treated RA patients, the prevalence of hematological toxicity - including leucopenia, thrombocytopenia, megaloblastic anemia and pancytopenia -

is estimated to be 3 %. [1] Pancytopenia is a serious and unpredictable adverse effect of low-dose MTX. Although, a large number of cases of tuberculosis in patients receiving a combination of MTX and biological agents have been reported in the literature, tuberculosis in patients treated with MTX monotherapy are scarce. [2] Intrestingly, in the present case, we observed that there was a development of tuberculous spondylodiscitis with hypercalcemia along with pancytopenia and skin necrosis which, to our knowledge, has not been reported earlier.

Case Report

In July 2012, a 74-year-old female patient with a 15-year history of well-controlled RA under MTX monotherapy (10 mg/week) was admitted with a 4-week history of gradually increasing generalized muscle weakness, fatigue, lumbar pain and ulcers on her lips and inguinal region. Her family physician prescribed an analgesic and muscle relaxant for pain relief (phenyramidol hydrochloride 2 × 100 mg/day). At the same time, she was taking treatment for hypertension (telmisartan 80 mg/day) and levothyroxine (100 mg/day) for Hashimoto thyroiditis.

Patient was referred to medicine department because of the worsening of her complaints and onset of fever. Physical examination of the patient revealed fever (temperature 38.5°C), erosions in the oral mucosa, hemorrhagic crusts on the lower lip and well-demarcated ulcers in the genital region and left medial thigh. Lumbar tenderness, 3/5 muscle weakness and reduced tendon reflexes in both lower extremities were also noted. Laboratory examination revealed pancytopenia along with elevated levels of C-reactive protein (CRP): 15.53 mg/dl (normal: 0-5 mg/dl), aspartate aminotransferase: 120 IU/L (normal: 7-38), alanine aminotransferase: 84 IU/L (normal: 7-35), serum creatinine: 2.01 mg/dl (normal: 0.6-1.2) and blood urea nitrogen (BUN): 53 mg/dl (normal: 8-23). Patient's calcium level was measured as 11.6 mg/dl (normal 8.8-10.2) [Table 1]. Patient's blood, urine, throat and stool cultures were taken: Owing to the absence, any additional medication or use of contrast substance, pancytopenia and elevated levels of CRP, transferases, BUN and creatinine were attributed to MTX therapy, which was withheld. Serum MTX level was measured higher than the normal therapeutic range. Folic acid treatment was initiated to overcome the toxic effects of MTX. Meropenem (3 g × 1 g intravenous) was started as an empirical initial treatment. Skin biopsy were performed by a Dermatologist revealed papillomatosis in the epidermis and dense eosinophilic infiltration consistent with drug reaction.{Table 1}

After treatment, resolution in the skin and oral lesions was observed. Because of an accompanying hematological disease, bone marrow aspiration and biopsy of the patient were performed and sent for pathological and microbiological evaluation. A normocellular bone marrow with granulomatous foci suggesting megakaryocytosis was reported [Figure 1]. Gram- and acid-resistant staining of the aspirated specimen revealed no bacteria. Due to the patients's lumbar pain, a bone scintigraphy was performed which revealed a pathological involvement in the L4. Further examination with positron emission tomography (PET) (F-18 fluorodeoxyglucose) showed a pathological involvement consistent with inflammation [Figure 2]. A lumbar magnetic resonance imaging (MRI) revealed a psoas abscess causing spinal stenosis consistent with tuberculous spondylodiscitis. A computed tomography (CT)-guided biopsy of the vertebral lesion was performed but no malignancy was reported. Gram- and acid-resistant staining of the vertebral biopsy specimen revealed no bacteria; a culture of this specimen was also obtained. A performed QuantiFERON test was positive. Because all gathered information about the patient was consistent with tuberculosis, tuberculosis treatment was initiated without waiting for the results of the culture specimens. No other additional pathology was found to explain hypercalcemia other than granulomatous foci in the bone marrow and vertebral lesions. Mycobacterium tuberculosis was isolated in cultures of the specimens from the patient's bone marrow and lumbar region. The patient was diagnosed with pancytopenia, renal failure, tuberculous spondylodiscitis and hypercalcemia due to the use of MTX. Anti-tuberculosis therapy yielded an improvement in the patient's clinical status and as well as her hematological and biochemical parameters [Table 1].{Figure 1}{Figure 2}

Discussion

While MTX therapy has adverse effects on multiple systems in the human body, the most common adverse effects are supression of the hematopoietic system and gastrointestinal injury. Pancytopenia and agranulocytosis are rare, but potentially serious side-effects. Lim et al. reported that their 25 patients had developed pancytopenia between 1999 and 2004 due to MTX therapy. In this study, it was suggested that pancytopenia might occur even after years of MTX therapy. Furthermore, renal failure, hypoalbuminaemia, high dose MTX, no folic acid supplementation and elevated transaminase levels were shown as potential risk-factors for the development of pancytopenia due to MTX therapy. [1] Deighton reported that none of their RA 248 patients using MTX had developed pancytopenia in the follow-up period between 1990 and 2004 and that leukopenia was observed in only seven patients. [3] Our case had severe pancytopenia, similar to and also having the potential risk factors suggested by Lim et al., such as renal failure, hypoalbuminaemia, no folic acid supplementation and elevated transaminase levels. Our patient had developed pancytopenia after 15 years of MTX therapy, which is consistent with the suggestions of Lim et al. The partial recovery of pancytopenia with folic acid supplementation and withdrawal of MTX therapy and later the recovery with anti-tuberculosis therapy made us to consider that tuberculosis might also have an effect on pancytopenia besides MTX therapy. Studies have reported tuberculosis in patients with RA using a combination therapy of MTX and corticosteroids or biological agents, tuberculosis in patients receiving MTX monotherapy is scarce. Binymin and Cooper reported a patient who had a history of vertebral tuberculosis at the age of 7 and developed a relapse at the age of 57 due to MTX monotherapy. [2] In our case, the patient had no history of tuberculosis. Furthermore, the existence of pancytopenia, skin lesions, renal failure, bone marrow involvement and hypercalcemia has not been reported earlier.

Skin and oral mucosal lesions are well-established with an adverse affects of MTX therapy. These lesions may vary in a broad spectrum from superficial ulcers to toxic epidermal necrolysis. [4] Our patient had oral ulcers and skin lesions with an erythematous base. Because biopsy of the lesions reported them as a drug reaction and because

of the improvement of the lesions after withdrawal of MTX and folic acid supplementation, these skin manifestations were attributed to MTX therapy.

That granulomatous infections by 1-α-hydroxylase activity may cause an increase in the synthesis of vitamin D and eventually hypercalcemia is well-known. Elevated calcium levels were reported in some studies investigating tuberculosis patients. [5] In our case, the patient's calcium level was higher than the normal range but, symptoms of hypercalcemia were not deleted.

Conclusion

We suggest that although MTX therapy in RA patients seems to be safe in long-term, these patients should be closely monitored for an adverse affects of MTX therapy, particularly for the occurrence of life-threatening infections that may occur after years of treatment with MTX.

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