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Bowel perforation due to methotrexate therapeutic error: an insidious adverse reaction

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Abstract. – OBJECTIVE: Methotrexate (MTX) is widely used in the treatment of rheumatic and non-rheumatic disorders. Severe adverse effects are often associated with therapeutic errors, such as daily intake rather than weekly intake. Among them, the risk of bowel perforation is extremely rare (0.1%). We describe a case of bowel perforation, occurred following daily intake of MTX.

CASE REPORT: A 68-year-old man was prescribed to take MTX 7,5 mg orally once a week, while waiting for switch to abatacept for a recent reactivation of rheumatoid arthritis. After 10 days he started having pharyngodynia, hematochezia and general malaise. At medical examination he presented oral and nasal mucositis; moreover, blood exams showed thrombocytopenia. The anamnesis revealed that he had been taken the prescribed dosage of MTX daily, instead of weekly. Therapy with Lederfolin 1000 mg (mg/m²/die) and urine alkalinization started. After 7 days of hospitalization, there was an abrupt worsening of clinical conditions and an emergency CT scan revealed millimetric gas bubbles indicating bowel perforation. The patient underwent an emergency exploratory laparotomy that resulted in peritoneal toilette and sigma resections. Anatomopathological findings were suggestive of MTX poisoning.

CONCLUSIONS: The patient was discharged on the 17th day in good clinical condition.

Key Words:
Methotrexate, Adverse drug reaction, Bowel perforation, Rheumatoid arthritis, Mucositis.

Introduction

Methotrexate (MTX) is an immune system suppressant agent widely used in treatment of autoimmune disorders, such as rheumatoid arthritis (RA)[1]; as antimetabolite, it is used also in a wide range of malignant and non-malignant diseases[2].

Mild adverse effects during therapeutic use are common, but severe toxicity is mainly associated with therapeutic errors due to misunderstanding of the posology by the patients[2,3]. Indeed, high dosage, wrong timing and/or long-time administration can result in serious morpho-functional alterations mainly involving gastrointestinal (GI) tract and bone marrow[1,4]. Potentially life-threatening events, such as bowel perforation, have been rarely registered[5].

Case Report

A 68-year-old man was sent to the Emergency Department after presenting with mucositis and thrombocytopenia at its programmed rheumatology visit. He was under treatment for RA with etanercept 50 mg/week and prednisone 10 mg/day; to treat disease reactivation, his therapy was changed, and methotrexate was prescribed instead of etanercept. The prescribed treatment was 7.5 mg/week, but the patient took 7.5 mg daily for ten days instead.

At admission, the patient presented pharyngodynia, asthenia, low blood pressure, gum bleeding, epistaxis and hemorrhagic diarrhea; blood tests showed thrombocytopenia. Patient was diagnosed having acute MTX toxicity and treatment with calcium levofolinate pentahydrate 1000 mg (mg/m²/die) divided into four daily administrations, and urine alkalinization using bicarbonate 8.4% infusion was started. MTX blood value was within therapeutic range (0.05 µg/ml).

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In the following days, fever was registered but blood culture was negative for pathogens. Since platelets value kept going down (PLT: 7000 U/l), three platelet units were transfused with good response. On the 7th day of hospitalization, the patient showed an abrupt worsening of clinical conditions, with board-like rigid abdomen and intense pain. An emergency CT scan was performed that showed diffuse mesenteric edema, hyperemia of small and large bowel, and millimetric gas bubbles under diaphragmatic left zone and periumbilical and pelvic areas, indicating bowel perforation (Figure 1). The patient underwent to an emergency exploratory laparotomy that resulted in peritoneal toilette and sigma resections. The anatomopathological examination showed linfo-granulocytosis flogosis and necrotic areas in colonic walls with some abscessed zones, hemorrhagic spots and severe acute perivisceral inflammation; these findings were compatible with acute intestinal MTX toxicity.

The patient has been discharged in 17th day in good clinical condition with planned rheumatologist controls for therapy management. The patient's clinical course is summarized in Figure 2.

Discussion

MTX is a competitive inhibitor of dihydrofolate reductase (DHFR) with a much stronger binding affinity than folates; it decreases the *de novo* synthesis of purine and pyrimidine required for DNA and RNA production by rapidly dividing malignant cells. Moreover, its anti-inflammatory activities have been explained by other mechanisms, such as release of adenosine and inhibition of polyamines[2].

In RA, MTX is used as long term and low dose therapy, with weekly dosage ranging from 5 to 20 mg[2].

Side effects, such as myelosuppression, hepatotoxicity and GI symptoms are quite common. The most common GI side effects are mucositis, nausea, peptic ulcer and hemorrhagic enteritis, while bowel perforation is extremely rare (0.1% of cases), although much more dangerous[1].

Severe MTX toxicity is often related to therapeutics errors, such as daily intake rather than weekly intake, especially when the drug is self-administered[3].

Our patient initially presented with general malaise and mild gastrointestinal symptoms, with a concerning worsening thrombocytopenia. Once this last adverse effect was corrected and general condition was improving, the bowel perforation unexpectedly occurred.

Very few cases of MTX-related bowel perforation have been described in the literature[4]. However, chronic intake of corticosteroids and presence of diverticulitis has been identified as significant risk factors for developing bowel perforation during MTX therapy[4]. Our patient presented just one of these factors, the chronic intake of low-dose corticosteroids, while a recent colonoscopy showed a slight perivisceral inflammation without identifying diverticular disease.

Today, there is still no clear explication of the pathogenic mechanisms that may lead to a bowel perforation during MTX treatment[2]. Genetic polymorphisms can make some individuals more susceptible to drug actions, predisposing them to develop serious adverse effects, even after a short time exposure[6]. Unfortunately, nowadays these specific tests are not routinely available.

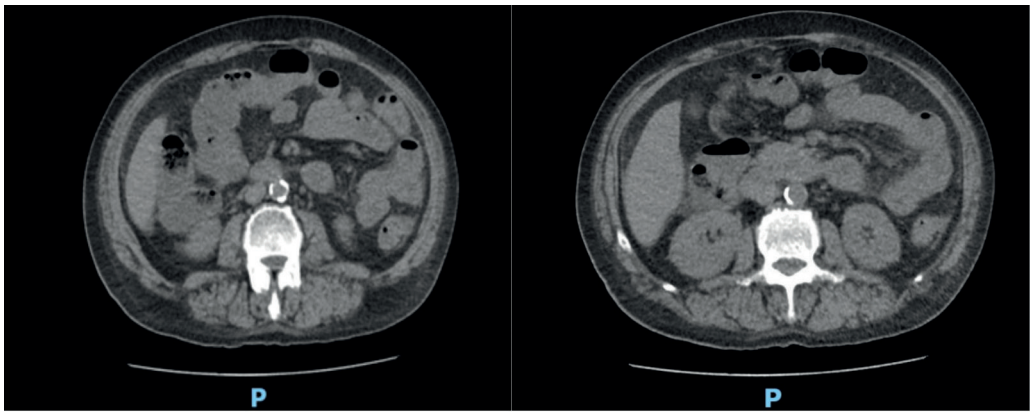

Figure 1. Abdomen CT Scan images showing gas bubbles indicating bowel perforation.

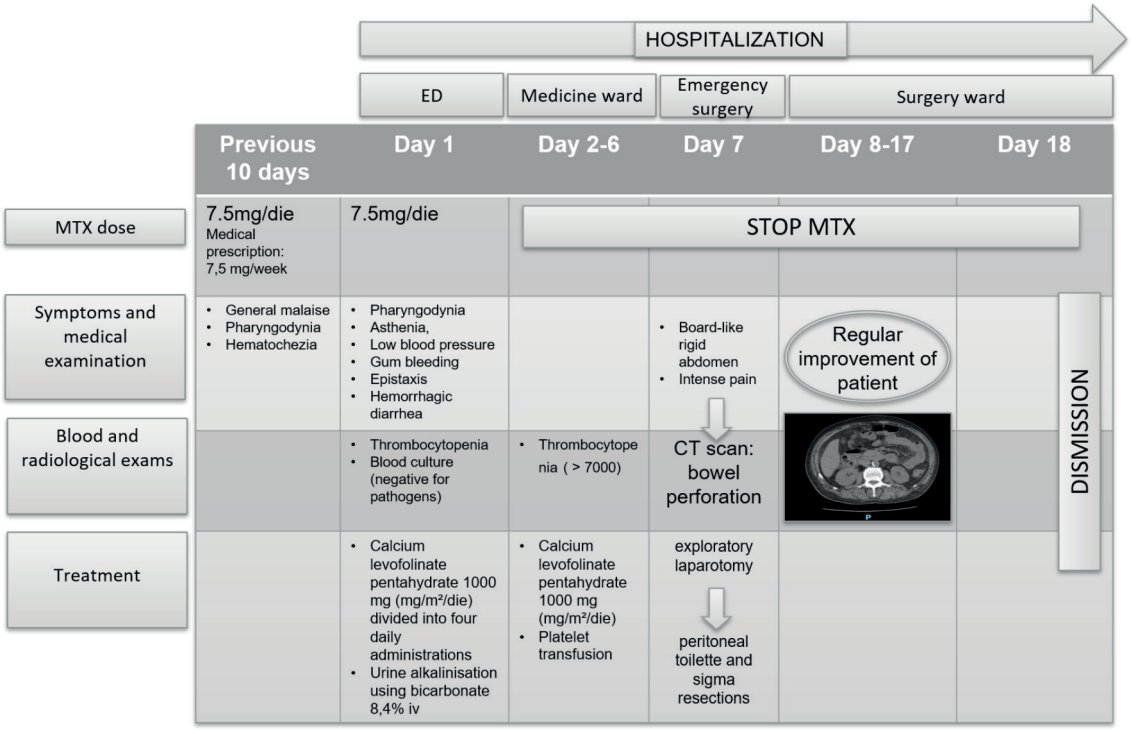

Figure 2. Patient's clinical course.

Nevertheless, supporting this hypothesis, a more detailed medical history of our patient revealed that in the past he was forced to discontinue treatment with MTX for the onset of gastrointestinal distress and increased liver enzymes after two weeks of low dose subcutaneous MTX.

There is a widely scientific agreement about supplementing MTX therapy with folic and folinic acid during chronic administration, in order to reduce the potential toxicity[5]. In our case, folic acid was not prescribed together with MTX because the treatment was set for a short period. On the other hand, calcium levofolinate was promptly started after diagnosis of MTX poisoning in order to decrease the toxicity, along with urine alkalinization to increase MTX kidney clearance.

Finally, our case suggests that serum MTX concentration is not related to symptoms severity and cannot be considered useful to guide the clinical management.

Conclusions

MTX therapeutic errors are quite common, and symptoms are often mild. However severe reaction, as bowel perforation, may occur and be potentially lethal. It is appropriate to consider that there is an individual susceptibility and a genetic predisposition to the development of adverse effects, although specific tests are not routinely available today. Furthermore, any concomitant risk factors, such as steroid therapy or a pre-existing diverticulitis disease, should always be considered during medical prescription of MTX.

Patient Consent

Written informed consent for publication of this report was obtained from the patient by the author.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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