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Case Report
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Single Dose of Methotrexate Triggered Subacute Liver Failure in Patient with Adult Onset Still's Disease

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Abstract

Adult-onset Still disease (AOSD) is a rare systemic inflammatory condition of unknown origin. Treatment comprises non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and immunosuppressive drugs including methotrexate (MTX). Low dose of MTX has been shown to be effective and well tolerated. Here, we present a 61-year-old male patient with AOSD developed subacute liver failure after a single dose of methotrexate. His subacute liver failure has been cured by high dosage of corticosteroid which also leads to serious complication, such as infection. To our knowledge, this is the first reported case of serious hepatotoxicity after a single dose of 10mg MTX in patient with AOSD.

Keywords: Adult-onset still disease (AOSD); Herpes simplex virus (HSV); Human immunodeficiency virus (HIV)

Case Presentation

A 61 year old male with a past medical history of AOSD complaining fever and arthralgia was referred to our rheumatology clinics on 14, July, 2014. He was diagnosed with AOSD seven months ago, treated with 60mg/day methylprednisolone and slowly tapered to 12mg/day till July 2014. At this admission, his temperature was 39.2°C, blood pressure 145/80 mmHg and pulse rate 116/min. Physical examination showed diffuse joint tenderness and swelling on wrists, knees and ankles. Laboratory test indicated his white blood cell count was $26*10^9$/L, erythrocyte sedimentation rate 91 mm/h, C-reactive protein 49.19 mg/L and a very high ferritin level (more than 2000 mg/L), but liver and kidney blood tests normal.

During hospitalization, he was treated with 60 mg/day methylprednisolone. The medication has allowed the maintaining of apyrexia and the regression of joints pain, with improvement of biochemical parameters. 10 mg methotrexate was added on 30 July 2014. The patient began to suffer from drug rash on his trunk and pruritus in the same night. Loratadine and folic acid were administered to the patient, but lack of efficacy. In the morning of 4 Aug 2014, he developed a fever over 39°C, accompanied by chills and shivering. Complete blood count showed leukocyte count of $14.2*10^9$/L, hemoglobin 148 g/L, platelet count $244*10^9$/L. Liver function tests showed total bilirubin (TB) of 12 u mol/L, aspartate aminotransferase (AST) of 870 U/L, alanine aminotransferase (ALT) of 1591 U/L, gamma glutamate transpeptidase (GGT) of 590 U/L. Autoimmune workup including antinuclear antibody, rheumatoid factor, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody were all negative. Serology for viral hepatitis A, hepatitis B, hepatitis C, hepatitis E, herpes simplex virus (HSV), Epstein-Barr virus, Cytomegalovirus, human immunodeficiency virus (HIV) were also negative. Ultrasound of abdomen showed normal liver morphology with normal echogenicity. His fever subsided 3 days later, but liver function continued deteriorating although glycyrrhizin and polyene phosphatidylcholine were administered to the patient.

Discussion

On 25 Aug 2014, lab test showed TB of 148 umol/L, AST of 721 U/L, ALT of 325 U/L, GGT of 1042 U/L. MRCP was normal and extrahepatic biliary obstruction was excluded. He was diagnosed subacute liver failure and intrahepatic cholestasis. Intravenous methylprednisolone was administered at 120mg/day for 3 days, followed by down to 80 mg/d after then.

Six days after high dose of methylprednisolone therapy, the patient began to suffer from high fever of 39.7°C again, with chills and shivering. Complete blood count showed leukocyte count of 0.2*10^9/L triglyceride level was 3.63 mmol/L. No infectious source can be detected; blood cultures

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remained sterile. The patient was given teicoplanin and panipenem and granulocyte colony-stimulating factor (G-CSF) for his febrile neutropenia. Methylprednisolone was continued at the same dose. As the fever was continuous after 72 h, antibiotherapy was changed as vancomycin plus panipenem plus voriconazole. 13 days after high dose methylprednisolone therapy, his fever subsided and the neutrophils count was $12.0^{*}10^{9}$/L.

However, 3 days later, the patient was observed to have dark red bloody stools, 4 times a day. His haemoglobin levels dropped from 112 g/L to 83 g/L. PT 21.2s, APTT 34.4s. Vit K, cryoprecipitation, human fibrinogen and 4U of packed red blood cells were administrated to allow the amendment of rebreeding.

On the 19th day of high dose methylprednisolone therapy, the patient complaint of oral discomfort and burning sensation. On intraoral examination, there was multiple mycotic stomatitis. Throat swab and sputum culture showed multiresistant candida, sensitive to amphotericin B only. So amphotericin B was added. 20 days later, mycotic stomatitis disappeared. Antibiotics were discontinued. The patient's icterus disappeared and bilirubin levels normalized on the 68th day after subacute liver failure was diagnosed. He was discharged on 40 mg day -1 methylprednisolone.

Adult-onset Still disease (AOSD) is an inflammatory condition of unknown origin. Treatment comprises NSAIDs, corticosteroids and immunosuppressive drugs with MTX being the most common immunosuppressants [1,2]. Low dose MTX (5~25mg/week) has been demonstrated to be well tolerated [3]. Side effects of methotrexate commonly include nausea, vomiting, loss of appetite, and mild liver problems [4]. The mean cumulative dose of MTX at the onset of hepatotoxicity was 552.3 mg [5].

Hepatic involvement usually is frequently seen in AOSD [6]. Factors inducing ALF include AOSD itself, infection, drug and others. In our case, we conclude that the liver failure was triggered by a single dose of MTX based on the following clues; 1) transpeptidase increased dramatically from normal range immediately after administration of MTX; 2) drug rash and pruritus suggested allergy to MTX; 3) AOSD was controlled well evidenced by improved biochemical parameter; 4) no evidence of infection was found at that time.

It is reported that RFC1 A80G (rs1051266) and MDR1 C3435T (rs1801131) polymorphisms increased the risk for overall MTX toxicity, while MTHFR A1298C (rs1045642) polymorphism had a protective effect on overall MTX toxicity [7]. Our patient's rs1051266 is AG, rs1801131 is AA, rs1045642 is CC which suggest out patient had high risk to MTX toxicity.

High dosage of corticosteroid was effective in our patient for the treatment of liver injury, but also leads to serious complication such as infection. Febrile neutropenia (FN) was onset on the 6th day of high dose of steroid therapy in our case. In our patient, FN can be caused by either infection or AOSD. However, as the patient did not manifest arthralgia, rash or sore throat, flare of AOSD was excluded. We conclude that the cause of FN is infection. Remission of FN by prompt treatment of antibiotics further supported our conclusion.

Another urgent complication in our case was acute gastrointestinal hemorrhage. This manifestation may be due to sevaral pathogenisis: 1) coagulation defects caused by liver dysfunction, 2) invasive fungal disease combined with mycotic stomatitis and stomachache. Meanwhile, mega dose pulse methylprednisolone therapy could also increase the risk of bleeding digestive symptoms were remitted by treatment with hemostasis and liposomal amphotericin.

To our knowledge, this is the first reported case of serious hepatotoxicity after a single dose of 10 mg MTX in patient with AOSD. In our case, dramatic response improvement in liver enzymes and DILI occurred following high dose methylprednisolone pulse therapy and refrained from liver transplantation. Prompt initiation of high dose methylprednisolone pulse therapy may be indicated effective treatment in drug-induced liver failure.

References

1. Efthimiou P, PK Paik, L Bielory. Diagnosis and management of adult onset Still's disease. Ann Rheum Dis. 2006; 65: 564-572.
2. Franchini S, Dagna L, Salvo F, Aiello P, Baldissera E, Sabbadini MG. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. Arthritis Rheum. 2010; 62: 2530-2535.
3. Weinblatt ME. Methotrexate in rheumatoid arthritis: a quarter century of development. Trans Am Clin Climatol Assoc. 2013; 124: 16-25.
4. Lopez-Olivo, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2014; 6: CD000957.
5. Ng LC, Lee YY, Lee CK, Wong SM. A retrospective review of methotrexate-induced hepatotoxicity among patients with psoriasis in a tertiary dermatology center in Malaysia. Int J Dermatol. 2013; 52: 102-105.
6. Valluru N, Tammana VS, Windham M, Mekonen E, Begum R. Rare Manifestation of a Rare Disease, Acute Liver Failure in Adult Onset Still's Disease: Dramatic Response to Methylprednisolone Pulse Therapy -A Case Report and Review. Case Rep Med. 2014: 375035.
7. Bohanec Grabar P, Logar D, Lestan B, Dolzan V. Genetic determinants of methotrexate toxicity in rheumatoid arthritis patients: a study of polymorphisms affecting methotrexate transport and folate metabolism. Eur J Clin Pharmacol. 2008; 64: 1057-1068.