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A Case Report on Methotrexate Overdose Induced Pancytopenia and Toxic Epidermal Necrolysis

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ABSTRACT

Methotrexate is commonly used for autoimmune diseases including rheumatoid arthritis, psoriasis, sarcoidosis, and eczema due to its anti-inflammatory and immunosuppressive effect. The following report describes the case of a 48-year-old female presenting with complaints of fever, erythematous rash and blister over upper limb and oral hemorrhagic mucositis. She was previously diagnosed with rheumatoid arthritis and left sided poliomyelitis and was on methotrexate 15 mg weekly, but the patient had taken it daily resulting in toxicity. she was hospitalized, treated with folic acid, injection leucovorin & inj. filgrastim. Our case highlights the importance of counselling to ensure adherence to the correct methotrexate treatment regimen to prevent toxicity and its side effect.

Keywords: Methotrexate, Rheumatoid Arthritis, Pancytopenia, Mucositis, Toxic Epidermal Necrolysis

INTRODUCTION

Methotrexate is a potent immunosuppressant and anticancer agent commonly used to treat conditions such as psoriasis, rheumatoid arthritis and cancer, however its use has been associated with severe adverse reactions, including Toxic Epidermal Necrolysis (TEN). The incidence of methotrexate induced TEN is relatively rare but is a serious concern due to its high mortality rate[1]. Methotrexate induced TEN is thought to result from the drug cytotoxic effect on rapidly dividing cells particularly in the skin and mucus membrane by involvement of immunological and genetic factors.

The onset of methotrexate induced TEN is often insidious, with patient initially presenting with flu-like symptoms, fever and malaise, which is followed by abrupt onset of a widespread exfoliative skin eruptions and mucosal involvement, leading to life threatening state of skin detachment and systemic inflammation, pancytopenia, mucositis with increased risk of bleeding. It has been shown that about 1.4% of patients develop pancytopenia [2]when treated with methotrexate. To prevent adverse effects on the hematopoietic system, folic acid, filgrastim (G-CSF), leucovorin should be given. Here we report a 48-year-old female patient of rheumatoid arthritis who had developed pancytopenia, mucositis and blister over skin after daily intake of methotrexate.

CASE REPORT

A 48-year-old female patient with rheumatoid arthritis and poliomyelitis had complaints of fever, erythematous rashes and blister over upper limb and oral cavity with bleeding manifestations. She is known case of RA who had wrongly taken methotrexate 15 mg injection once a week and tab methotrexate

15 mg three to four times in a week for 15 days consequently. After that her daughter noticed some rashes and blisters over skin associated with fever and took tab amoxicillin and plus clavulanic for 3 days; but she noticed worsening of erythematous rashes after antibiotics.

On the day of admission patient was conscious, oriented and her bp was 110/70 mmhg. Oral cavity examination showed ulcerated mucosa with bleeding from lips, blister over the upper limb and reddish black lesions over both upper and lower limbs. (Figure 1,2) she was advised to stop methotrexate. Blood count and peripheral blood smear were suggestive of pancytopenia [total leucocyte count (TLC) of 1200/ul ,HB -6.7g/dl and platelet count 59000/ul]. Liver function test suggestive of total bilirubin 1.8 mg. ALT-67 & AST-94 , Renal function test were normal urine routine was within normal limits . blood and wound swab sent for culture and sensitivity. testing for HIV, Hepatitis B, hepatitis C virus were negative .ultrasound of abdomen and pelvis showed no hepatomegaly and splenomegaly. Dermatology and hematologist opinion taken for treatment.

Keeping with this history, clinical presentation of mucocutaneous lesion with pancytopenia and elevated liver enzymes, methotrexate toxicity was suspected . patient was treated with intravenous piperacillin and tazobactam ,injection acyclovir 500 mg and injection fluconazole 200mg, but patient was not responding. On day 3, patient was started on recombinant human granulocyte colony stimulating factor (rHu-G-CSF)300MU injection per day subcutaneously till TLC increase above 4000/cumm , injection leucovorin calcium 50 mg bd for 3 days , folic acid 10 mg bd ,Two unit of Pack Cell Volume (PCV),Skin care with moisture retentive ointment[3] .After 3 days of treatment TLC was 6100/ul ,platelet count 15300 /ul and total bilirubin 1.0 mg % and AST 26 &ALT 36 patient gradually improved. bleeding from oral mucosa controlled. Later she was monitored in the ward. she was discharged on 13th day with follow up for rheumatoid arthritis with rheumatologist.

DISCUSSSION

Methotrexate in low weekly doses is a first line therapy for inflammatory diseases such as rheumatoid arthritis due to its effectiveness, low cost and ease of use .it is generally administered at a dose of 7.5-25 mg /week however several adverse effects like anemia, liver toxicity (increase transaminase), pancytopenia, mucositis, toxic epidermal necrosis and cutaneous ulceration may develop.

Toxic epidermal necrosis and Pancytopenia is mostly seen in patients with risk factors such as daily methotrexate dosing causing low folic acid levels, nausea, vomiting, weakness, dehydration. prolonged exposure of drug has more toxic effects on tissue and bone marrow. In our case daily intake of methotrexate instead of weekly, lack of folic acid supplement and lack of concomitant antibiotic cause resulted in toxicity.

Methotrexate induced hematological toxicity can be managed by discontinuing the drug followed by adequate hydration[4] and intravenous leucovorin and folic acid[5] ,recombinant growth factors , blood transfusion along with antibiotic and antifungal and antiviral coverage due high risk of infection .in our patient G -CSF[6] was given in view of worsening leucopenia .in this patient serum methotrexate level is not high but methotrexate toxicity is suspected irrespective of the blood methotrexate level in view of clinical features pointing towards toxicity. patient responded well to treatment. to avoid toxicity proper dosing of methotrexate and educate patient about disease. Also physicians should be aware about various attributing factor for toxicity that are preventable by regular monitoring and appropriate guidance

CONCLUSION

Managing methotrexate-induced toxic epidermal necrolysis (TEN) and pancytopenia requires a multidisciplinary approach, involving dermatologists, haematologists, and rheumatologist. Future directions in the management of these conditions focus on the development of targeted therapies to mitigate the severe cutaneous and hematologic manifestations experienced by affected patients. Additionally, there is a growing emphasis on the early identification of individuals at high risk of developing methotrexate induced TEN and pancytopenia through genetic screening and pharmacogenomic studies. This personalized medicine approach aims to minimize the incidence of these life-threatening adverse reactions [7]and improve patient outcomes. These innovative therapeutic strategies hold promise in reducing the morbidity and mortality [8]associated with these severe drug reactions. Finally, the education of healthcare providers [7]regarding the recognition, management, and reporting of methotrexate induced TEN and pancytopenia is of paramount importance. Proper counselling of the patient regarding dose of methotrexate is most important. Early diagnosis and intervention of methotrexate induced TEN can prevent serious complications like septicemia. Leucovorin and rHu G CSF both are very effective in managing methotrexate induced bone marrow suppression , hence should be introduced early.

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CONFLICT OF INTREST

The authors declared no conflict of interest. [9]

ABBREVATIONS

RA -Rheumatoid Arthritis, rHu G-CSF -Recombinant Human Granulocyte Colony Stimulating Factor TEN-Toxic Epidermal Necrosis

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