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Can Mucocutaneous Ulceration be a Part of Monitoring Guidelines for Methotrexate Toxicity ?

KEYWORDS: Cumulative, Idiosyncratic, Methotrexate, Mucocutaneous ulcerations.

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ABSTRACT *There are monitoring guidelines to prevent methotrexate toxicity. Pancytopenia and mucocutaneous ulcerations are the important early laboratory and clinical findings of methotrexate toxicity respectively. Mucocutaneous ulceration especially mucositis is an early predictor of methotrexate toxicity well before laboratory evidence. We are reporting three cases of psoriasis vulgaris with methotrexate toxicity. In 1st case, patient developed mucocutaneous erosions after single test dose of methotrexate without myelosupression suggestive of idiosyncratic reaction. In 2nd case, patient took methotrexate for longer duration without any monitoring and developed mucocutaneous ulcerations and myelosupression suggestive of cumulative toxicity. In our 3rd case, patient developed myelosupression and mucocutaneous ulceration due to daily dosing. Mucocutaneous ulceration is the consistant clinical sign of methotrexate toxicity observed in all cases and it can be seen even without myelosupression as in our 1st case. In our opinion, mucocutaneous ulcerations should be included as one of the clinical sign under methotrexate monitoring guidelines.*

INTRODUCTION

Methotrexate is a folic acid antagonist which competitively and irreversibly binds with dihydrofolate reductase enzyme and its action is specific for S-phase of cell cycle. High dose methotrexate (0.5-12 g/m^2) has antiproliferative activity and is used in treatment of cancer, while low dose methotrexate (10-40 mg/m^2) has anti inflammatory and immunosuppressive properties.[1] Methotrexate is a commonly used systemic drug in treatment of psoriasis due to its efficacy, easy availability and cost effectiveness.

Common signs of methotrexate toxicity are anorexia, nausea, vomiting, myelosupression, oral and gastrointestinal side effects in the form of mucositis. Ulceration of psoriatic plaques is rare sign of methotrexate toxicity. Hepatic and pulmonary toxicity is usually associated with long term use of methotrexate. It is pregnancy category x drug. The risk of methotrexate toxicity can be precipitated by several factors like age of patient (>55years), high dose of methotrexate, drug interaction, low serum albumin level & infection.

Low dose methotrexate therapy used in psoriasis rarely produces toxicity, and most of such cases occurs due to non adherence to the recommended guidelines.[2] Methotrexate induced toxicity usually occurs late after its intake suggesting a cumulative effect (dose & duration dependent). Idiosyncratic methotrexate toxicity is a dose independent reaction. We are presenting both cumulative and idiosyncratic reaction due to methotrexate toxicity.

CASE REPORTS

Case 1:

51 year old male patient presented with ulcerative lesions over psoriatic plaques involving extremities, trunk, buttocks, genitalia and oral cavity [Figure 1]. Patient took 5 mg test dose of methotrexate 7 days back and 3 days after which he developed above mentioned cutaneous lesions. Patient had not taken any other drugs. Routine blood counts were within normal limits. Methotrexate was stopped immediately & patient was put on parental folic acid (30 mg daily) for one week followed by oral tablets of folic acid (15mg daily) for two weeks with complete recovery of the patient.

Figure 1: Erosion and crusting involving upper limbs and neck.

Case 2:

57 year old female patient, a case of psoriasis vulgaris since 9 years presented with painful erosions and ulcerations with peri-lesional erythema involving psoriatic plaques over abdomen, lumbosacral area and extremities. Buccal mucosa showed erosive lesions. Patient was initially taking methotrexate under supervision in therapeutic dos-

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es. As the patient was familiar with methotrexate treatment he took weekly doses of methotrexate i.e.15mg/week for 7-8 months without supervision. Investigations on admission showed pancytopenia (Hb–6.1gm%, TLC–1450/cumm, Platlets-75000/cumm). Serum creatinine level was 1.8 gm%. Liver function test was normal. Methotrexate was stopped immediately & patient was put on parental folic acid (30 mg daily) followed by oral tablets. Adequate hydration was given. Blood transfusion was also done with complete recovery of the patient.

Case 3:
71 year old male patient was a case of psoriasis vulgaris since 6 years. Initially he took methotrexate (7.5 mg/weekly) under supervision but later on he took it for 5 years without consultation. To get rid of intense pruritus he took methotrexate 5mg/ day for 10 days without any medical advice and presented with painful, edematous, erosions on pre-existing psoriatic lesions over neck, cubital & popliteal fossa, groin, buttocks and thighs [Figure 2 and 3].

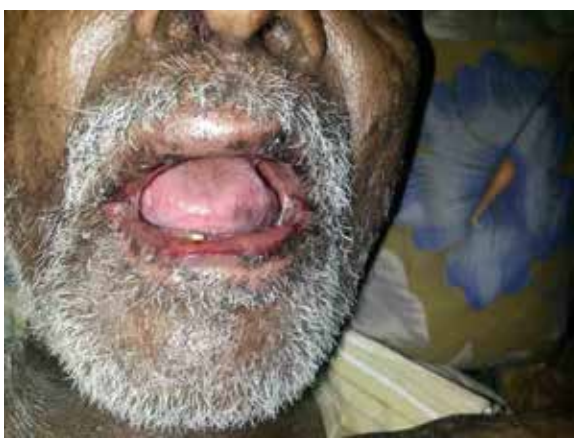

Figure 2: Erosion and crusting involving lips.

Upper & lower lip showed erosions and crusting. Investigations showed pancytopenia (Hb-11 gm/dl, white cell count-1500 cumm and platelet-76,000/cumm). SGOT was 63 IU/L. Total bilirubin level was 1.39 mg%. Serum urea was 63 mg%.

Figure 3: Erosion and ulcer involving upper limb.

Methotrexate was stopped immediately and parental folic acid (60 mg in divided doses) and systemic antibiotics were given. Adequate hydration was maintained. Blood transfusion was planned. But unfortunately patient died. Old age and impaired renal function are important additional risk factors associated with methotrexate toxicity.

DISCUSSION

In 1st case, patient developed mucocutaneous erosions after single test dose of methotrexate without myelosupression suggestive of idiosyncratic reaction. This case is presented to sensitize the physicians regarding idiosyncratic reaction to methotrexate.[3] In 2nd case patient took methotrexate for longer duration without monitoring and developed side effects (mucocutaneous and myelosupression) suggestive of cumulative toxicity. In 3rd case patient developed myelosupression and mucocutaneous ulceration due to daily dosing leading to detrimental effect on rapidly proliferative cells of gastrointestinal tract and bone marrow.

Usually methotrexate induced pancytopenia is dose dependent but rarely it can be idiosyncratic. Agrawal V et al in their article quoted that a single dose of methotrexate was responsible for pancytopenia and mucositis.[4] Development of pancytopenia following the first dose of methotrexate points towards an idiosyncratic reaction.[4] Skin ulcerations within the psoriasis plaques usually occur within one month of starting or restarting therapy,[5] however such events have been reported following chronic administration of methotrexate.[6,7]

The mucosal cells are more sensitive to methotrexate than the precursor cells in the bone marrow because of greater accumulation and persistence of methotrexate in the intestinal epithelium. Mucositis usually appears 3-7 days after the drug administration and precedes the onset of fall of leucocytes and platelet counts by several days.[8] The first laboratory parameter suggestive of methotrexate toxicity is thrombocytopenia and to monitor this absolute platelate count is routinely advised after one week of methotrexate intake. But idiosyncratic reaction can developed within few days (<1week) after 1st test dose as found in our first case.

Hocaoglu N et al also observed mucocutaneous ulceration and pancytopenia as early as 3 days after initiation of methotrexate therapy.[9] Therefore in idiosyncratic reaction mucocutaneous ulceration can be used as an early clinical marker of methotrexate toxicity which can be developed well before laboratory evidence of pancytopenia. Mucocutaneous ulceration is the consistant clinical sign of methotrexate toxicity as observed in various cases reported in literature and it can be seen even without myelosupression as in our 1st case.

CONCLUSION

In our opinion pretreatment counseling of patients regarding occurrence of methotrexate induced mucocutaneous ulceration is must and mucocutaneous ulcerations should be included as one of the clinical sign under methotrexate monitoring guidelines. So that methotrexate can be stopped immediately with early management of toxicity.

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