

Case Report

METHOTREXATE INDUCED MYELOSUPPRESSION IN PSORIASIS: THE NEED FOR CLOSE HAEMATOLOGICAL MONITORING

***Jatin Munjal, Shashi Bansal, Narayani Joshi, Nag B.P. and Tashi Agarwal**

Department of Pathology, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan

**Author for Correspondence*

ABSTRACT

Methotrexate is an effective antipsoriatic agent. It has been widely used to treat severe psoriasis since the 1960s, especially in acute generalized pustular psoriasis, psoriatic erythroderma, psoriatic arthritis and for extensive chronic plaque psoriasis in patients who are inadequately controlled by topical therapy alone. The most important potential side-effect of methotrexate is myelosuppression and when used in chemotherapy it causes profound suppression of the bone marrow. Even at low doses it is often associated with bone marrow suppression and is the cause of most of the rare deaths attributed to the use of methotrexate therapy for psoriasis. Myelosuppression occurs more likely in the elderly, particularly in patients with renal impairment and/or folate depletion, and with overdose or drug interactions. However, in comparison with other therapies it is inexpensive and with the correct use its safety profile is favorable. We report a case of 65 year old female treated with low dose methotrexate for psoriasis. She presented with pancytopenia, and was found to have MTX related myelosuppression. This case report also highlights the importance of close monitoring and regular laboratory investigations of patients on methotrexate therapy, even when used in low doses.

Key Words: *Psoriasis, Methotrexate, Myelosuppression, Bone Marrow*

INTRODUCTION

Gubner *et al.* (1951) noted the rapid clearing of psoriatic skin lesions in patients with psoriatic arthritis treated with the anti-metabolic drug aminopterin. Later this drug was replaced by the more stable and less toxic derivative methotrexate (MTX).

Psoriasis is considered to be a polygenetically influenced, immune-mediated, organ-specific disease of deregulated inflammation that is triggered by environmental factors such as infections, medications, and physical and/or emotional stress. It is recognized as one of the most prevalent skin diseases, affecting 2% to 3% of Caucasian populations. Major advances in understanding of disease pathogenesis indicate that patients with psoriasis have an increased risk of co-morbidities such as metabolic syndrome and cardiovascular disease.

Despite significant progress in alternative systemic treatment regimens, such as retinoids, cyclosporin A, and photochemotherapy with UVA (PUVA), folic acid antagonist, MTX remains in clinical use as a standard systemic therapy for psoriasis. Low-dose methotrexate (MTX) is one of the classical agents and is still one of the most frequently used systemic treatments for psoriasis worldwide. A favourable efficacy and safety profile has been established for MTX in a large number of clinical trials, as well as in common practice.

However, in MTX-treated psoriatic patients, the prevalence of haematological toxicity, including leucopenia, thrombocytopenia, megaloblastic anaemia and pancytopenia, is estimated to be 3%. The extent of pancytopenia, a serious and unpredictable adverse effect of low-dose MTX, may be underestimated and needs attention.

CASES

A 65 years old female presented with eruptions all over body since 10 months. The eruptions were associated with itching. The patient also complained of joint pain since 10 months. There is history of oral ulcers and mild grade fever since last 10 days. The patient had been treated with long term methotrexate

Case Report

(15 mg oral dose weekly). On examination vital signs were within normal limits and there was evidence of pallor. Also, multiple well defined erythematous plaques with psoriasiform scales, in symmetric distribution were present all over the body. There was no history of tuberculosis, diabetes mellitus and hypertension.

Investigations

CBC revealed: White blood cell count: 970/ μ L, Hemoglobin: 6.9 g/dL, Platelet: 1.51 lac/ μ L. Differential count showed: Neutrophils: 10%, lymphocytes: 76%, monocytes: 08% and 06% eosinophils.

Peripheral blood film findings were, red blood cells showed mild anisocytosis with hypochromia. Microcytes, macrocytes, tear drop cells also seen. White blood cells had markedly reduced total count. Rheumatoid factor was negative.

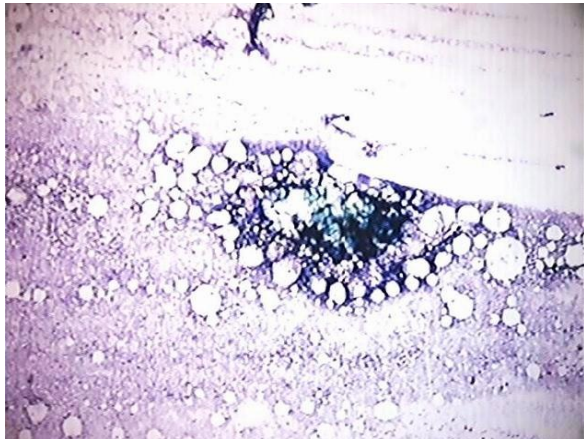


Figure 1: Bone marrow aspirate showing particle which shows variable cellularity. (H&E \times 188)

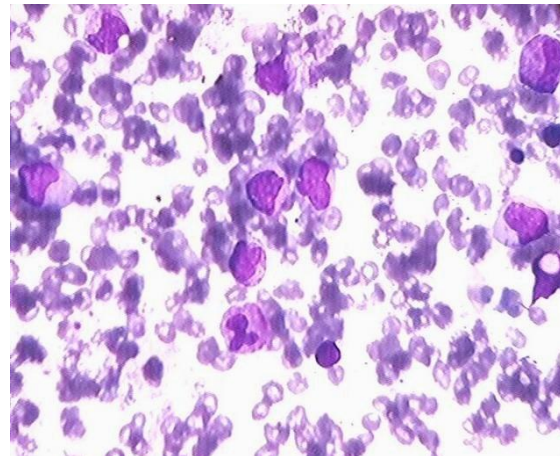


Figure 2: Bone marrow aspirate showing the myeloid series with slight increase in immature precursors and presence of hypogranularity of cytoplasm. Giant stab forms also seen. (Giemsa stain \times 970)

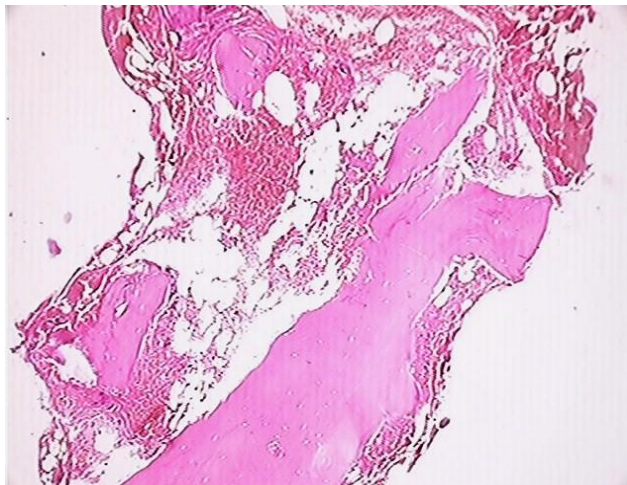


Figure 3: Bone marrow biopsy shows bony trabeculae enclosing marrow space along with areas of haemorrhage. The marrow is hypocellular for age with 78% fat and 28% cellularity. (H&E \times 377)

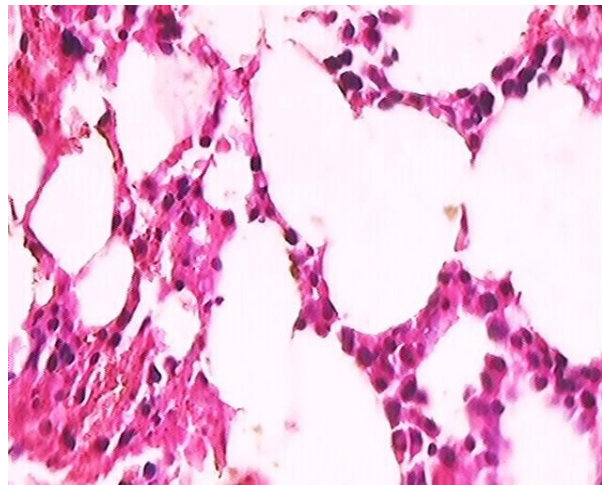


Figure 4: Bone marrow biopsy showing all the three series: erythropoietic, granulopoietic and megakaryocytic suppressed. (H&E 970)

Case Report

Bone marrow examination: Bone marrow aspiration revealed particle which shows variable cellularity. The myeloid series showed slight increase in immature precursors with presence of hypogranularity of the cytoplasm, giant stab forms also seen. M: E ratio - 1:1.15.

Section from the bone marrow biopsy shows bony trabeculae enclosing marrow space along with areas of haemorrhage. Marrow is hypocellular for age showing 78% fat and 28% cellularity. Erythropoietic series- Predominantly normoblastic reaction, few megaloblasts seen. Granulopoietic series- Shows features of dysplasia. All three series: erythropoietic, granulopoietic and megakaryocytic are suppressed. No parasitic pathology seen.

On follow up, the white blood cell count was 16,020/uL, haemoglobin was 8.6g/dL. Differential count was neutrophils: 76%, lymphocytes 20%, monocytes 3%, eosinophils 1%.

DISCUSSION

Methotrexate is a folate analogue with anti-inflammatory, anti-proliferative and anti-neoplastic properties widely used in the treatment of rheumatoid arthritis, psoriasis and cancers.

The guidelines on MTX therapy for psoriasis have been revised several times since 1972 and have been approved by the FDA. MTX inhibits dihydrofolate-reductase competitively, reducing metabolism of dihydrofolic acid to tetrahydrofolic acid which results in the suppression of intracellular synthesis of various folic acid derivatives that play an important role as cosubstrate in the transport of C1 units. Synthesis of purin, thymine and DNA is disturbed as a consequence which in turn interferes with DNA synthesis, DNA repair, and cellular replication. The immune system is a likely target for the antipsoriatic effects of MTX. In addition, MTX interferes with epidermal cell kinetics.

Boffa *et al.*, (1996) reported that the most important potential side-effect is myelosuppression. Myelosuppression is more likely in the elderly, in patients with renal impairment and/or folate depletion, and with overdose or drug interactions.

Grove *et al.*, (2001) concluded that pancytopenia, a rare but potentially fatal complication of MTX therapy, may develop suddenly and without warning signs. It can occur early (within 1–2 months of starting MTX, independently of dose and route of administration), when it is rarely avoidable, possibly reflecting an idiosyncratic reaction. More commonly, however, it occurs late suggesting a cumulative effect.

Stomatitis has been shown to precede or accompany pancytopenia and should be a warning sign. Patients with mucositis and neutropenia have a relative risk of septicemia that is greater than four times that of individuals without mucositis. Long-term therapy carries with it a risk of hepatotoxicity, liver fibrosis and cirrhosis which is related to the dosage regimen employed, and is increased by exposure to other hepatic toxins, particularly alcohol.

Haustein (2000) concluded that Low-dose MTX is an effective therapy for extensive and severe forms of psoriasis if patients are selected carefully and monitored regularly, particularly with respect to liver and bone marrow toxicity. This helps to reduce severe side-effects even during long-term treatment.

Lim *et al.*, (2005) report on their experience with 25 cases in five years that, MTX-induced pancytopenia is more common than expected and is probably under-reported.

Because they can occur at any time during therapy, it is necessary to follow patients on Methotrexate closely. Most adverse reactions are reversible if detected early. Baseline assessment should include haematology at least monthly (a complete blood count with differential and platelet counts), liver function and renal function every 1 to 2 months (hepatic enzymes, renal function tests) and a chest X-ray. During initial or changing doses, or during periods of increased risk of elevated Methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated i.e. 7 days after starting MTX as well as after any dose increase. Thereafter, the blood counts can be monitored every 2 to 4 weeks for the first few months as concluded by Kalb *et al.*, (2009).

Bright (1999) said that MTX therapy according to the guidelines is relatively safe and still has a place in the systemic treatment of psoriasis with 40 years of experience and an acceptable safety record.

Case Report

REFERENCES

- Boffa MJ and Chalmers RJ (1996).** Methotrexate for psoriasis. *Clinical and Experimental Dermatology* **21** 399-408.
- Bright (1999).** Methotrexate in the treatment of psoriasis. *Cutis* **64**(5) 332-4.
- Grove ML, Hassell AB, Hay EM and Shadforth MF (2001).** Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. *Quarterly Journal of Medicine* **94** 309-19.
- Haustein UF and Rytter M (2000).** Methotrexate in psoriasis: 26 years' experience with low-dose long-term treatment. *Journal of European Academy of Dermatology Venereology* **14**(5) 382-8.
- Kalb RE, Strober B, Weinstein G and Lebwohl M (2009).** Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *Journal of American Academy of Dermatology* **60** 824-37.
- Lim AY, Gaffney K and Scott DG (2005).** Methotrexate-induced pancytopenia: Serious and under-reported? Our experience of 25 cases in 5 years. *Rheumatology* **44** 1051-1055.