Double trouble: Cyclosporine-induced thrombocytosis in a patient with methotrexate toxicity: Are they related?

Cherukuri Tejaswi, Saritha Mohanan, Rangaraj Murugaiyan, Kaliaperumal Karthikeyan

Department of Dermatology, Sri Manakula Vinayagar Medical College and Hospital, Kalitheerthalkuppam, Puducherry, India

Received: 09-05-2014 **Revised: 21-06-2014** **Accepted: 22-01-2015**

ABSTRACT

Psoriasis is a common, chronic, disfiguring, inflammatory, and proliferative condition of the skin. It manifests with varying degrees of severity and can be treated with various immune modulators. This is a case report of a 57-year-old male patient of psoriasis on long-term oral methotrexate, who developed methotrexate toxicity when given an injection of methotrexate for unstable psoriasis. After recovery, the patient was started on cyclosporine 100 mg twice a day. After a week, he developed thrombocytosis, which reverted a week after cyclosporine was stopped. The patient is currently being managed with acitretin. The aim of this case report is to emphasize the various unpredictable adverse reactions encountered during treatment of psoriasis, especially when a combination or sequential treatment is used. There is a need for caution, as late sequelae of long-term administration of the systemic agents used in the treatment of psoriasis are still unknown.

Key words: Cyclosporine, methotrexate, thrombocytosis

INTRODUCTION

Psoriasis is a common, chronic, disfiguring, relapsing, inflammatory, and proliferative condition of the skin.[1] Long-term treatment of moderate-to-severe psoriasis is challenging and often requires a combination, rotational or sequential therapy, with two or more systemic agents.[2] Although it had been avoided earlier, combination therapy with methotrexate and cyclosporine is being increasingly found to be safe and useful in the management of psoriasis.[3] We report here the case of a 57-year-old patient with unstable psoriasis, who developed unexpected methotrexate toxicity and cyclosporine-induced thrombocytosis in a span of two weeks of being given both drugs sequentially. We present this case to highlight the as-yet-unknown toxicities and interactions encountered with the administration of methotrexate and cyclosporine in the treatment of psoriasis.

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.162005

CASE REPORT

A 57-year-old male, who was known to be suffering from psoriasis vulgaris for the past 10 years, presented to us with features of unstable psoriasis for a duration of two weeks. He had been previously treated for multiple exacerbations with methotrexate (cumulative dose - 2285 mg), cyclosporine, and topical steroids, on separate instances. There was no history

Address for correspondence:
Saritha Mohanan, Department of Dermatology, Sri Manakula Vinayagar Medical College and Hospital, Kalitheerthalkuppam, Madagadipet, Puducherry - 605 107, India. E-mail: saritha_mohanan@yahoo.co.in

of any adverse effects in the past. The patient had been on maintenance treatment with Tab.methotrexate 5 mg/week prior to this exacerbation. He was a known diabetic for the past 10 years, on regular treatment with tablet metformin 500 mg twice a day. His baseline complete blood count showed leukocytosis (leucocyte count - 18,300 cells/mm^3; platelet count- $5 \times 10^5/mm^3$) and the liver function tests were within normal limits.

In view of the suspicion of unstable psoriasis, Inj. Methotrexate 10 mg IM was given on admission. After 24 hours, he developed multiple pustules over the nape of the neck and multiple oral erosions, resulting in severe odynophagia, with the existing lesions becoming more erythematous [Figure 1]. The hemogram showed a fall in the leukocyte counts (7,700 cells/mm^3). Methotrexate toxicity was diagnosed and the patient was started on intravenous folinic acid. He showed signs of improvement in three days. Improvement in his blood count was also noted, as they returned to normal in four days (leucocyte count - 9,700 cells/mm^3; platelet count - $4.11 \times 10^5/mm^3$). The causality assessment, done using the Naranjo algorithm, revealed a probable adverse drug reaction.

Following this, the patient was started on cyclosporine 100 mg, twice a day, to control the unstable psoriasis. One week after administration of cyclosporine, it was noticed that the platelet count increased three times from the baseline values ($9.0 \times 10^5/mm^3$) when tested, on multiple occasions. Cyclosporine was stopped due to suspicion of drug-induced thrombocytosis. The platelet count dropped to a high normal value ($5 \times 10^5/mm^3$) four days after withdrawing the drug, thus confirming our suspicion. The Naranjo scale scoring was 7, which again implied a probable adverse drug reaction. The patient was then started on acitretin 50 mg once a day and was discharged after resolution of the lesions [Figure 2]. The patient is currently in remission, while on acitretin.

DISCUSSION

Methotrexate and cyclosporine are considered to be the foremost treatment options of moderate-to-severe psoriasis. As both carry possible side effects and complications, guidelines have been formulated for their use in psoriasis.[4] Methotrexate toxicity is a well-recognized, yet rare occurrence. Factors predictive of methotrexate toxicity in patients with rheumatoid arthritis include absence of folate supplementation, high Body Mass Index, prior gastrointestinal events, lower age group, female sex, renal impairment, change in dose, drug interactions, and infection.[5,6] There are no similar studies on factors predicting methotrexate toxicity in psoriasis. However, our patient did not have any such factors. It remains unexplained as to why this patient, who had received methotrexate for many years, suddenly developed methotrexate toxicity after a relatively low dose. He was given a low dose of parenteral methotrexate, as he developed unstable psoriasis while on a low dose of oral methotrexate. The role of change of route of administration in causing methotrexate toxicity remains to be studied.

Cyclosporine-induced thrombocytosis is a rare entity.[7] An alternative explanation for thrombocytosis in our patient could be a reactive thrombocytosis set off by methotrexate toxicity or by the disease itself.[8] However, the normal platelet count after withdrawal of cyclosporine is more suggestive of the former.

Reactive thrombocytosis is the exaggerated physiological response to a primary stimulus and is also known to accompany chronic inflammatory diseases like psoriasis.[9] Yasumoto *et al*. also reported reactive thrombocytosis in two patients with psoriasis, with associated raised IL-6 (Interleukin-6) levels, thus supporting the theory that thrombocytosis could be caused by the disease *per se*.[10] However, the fact that IL-6 also has a role in the pathogenesis of psoriasis as T memory/effector

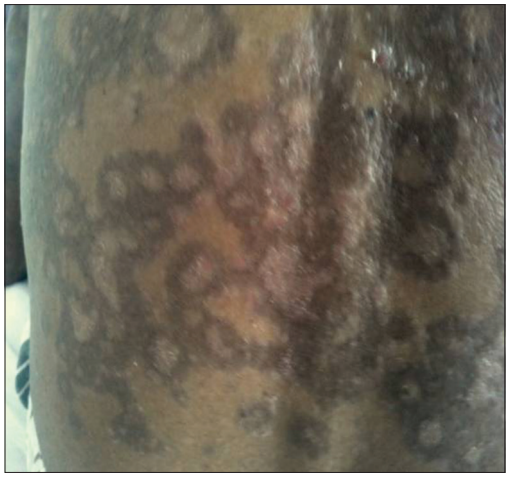

Figure 1: Mild erythema and hyperpigmentation of plaques three days after starting methotrexate and folinic acid

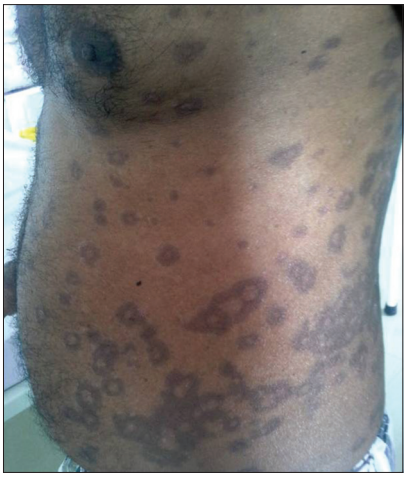

Figure 2: Complete clearance of lesions with post-inflammatory hyperpigmentation

cells that are chronically activated and poorly suppressed by regulatory T cells must be remembered. IL-6 signals through STAT3 and allows the escape of T memory/effector cells from T regulator-mediated suppression in a murine system. Cyclosporine is also reported to increase IL-6 production, while methotrexate has no correlation.[11,12] Cyclosporine can induce IL-1β expression in circulatory leukocytes and this may be sufficient to induce IL-6 production in some tissues. This is a plausible explanation to the increase in platelet counts during cyclosporine therapy in our patient.[9]

The role of platelets in the inflammatory process is increasingly being recognized, in addition to their function in hemostasis and thrombosis.[1] Hence, the effect of the inflammatory process of unstable psoriasis on the platelet counts or vice versa is also an interesting postulate in our case; the temporal course of events do not, however, suggest a correlation. We found it curious that our patient developed cyclosporine-induced-thrombocytosis a week after he recovered from unexplained methotrexate toxicity. There are no reports on similar hematological manifestations because of the potential interactions between methotrexate and cyclosporine when administered concurrently or sequentially. However, a study on the cytogenetic effect of methotrexate on human cells *in vivo* showed that methotrexate had a chromosome-breaking effect on human bone marrow cells.[13]

Recent studies have highlighted that methotrexate and cyclosporine can be co-administered in patients with difficult-to-treat psoriasis.[2,3] However, this case shows that there is still a need for caution, as late sequelae of long-term administration of the drugs are still unknown.

CONCLUSION

Studies on predictors of methotrexate toxicity in psoriasis are the need of the hour. We present this case to highlight that unknown long-term toxicities and unexplored interactions between systemic agents used for psoriasis still remain a chink in our therapeutic armamentarium for this common disease. This defect can be repaired by well-planned cohort studies and meticulous documentation of records of patients.

REFERENCES

1. Tamagawa-Mineoka R, Katoh N, Ueda E, Masuda K, Kishimoto S. Elevated platelet activation in patients with atopic dermatitis and psoriasis: Increased plasma levels of beta-thromboglobulin and platelet factor 4. Allergol Int 2008;57:391-6.
2. Aydin F, Canturk T, Senturk N, Turanli AY. Methotrexate and ciclosporin combination for the treatment of severe psoriasis. Clin Exp Dermatol 2006;31:520-4.
3. Mohanan S, Ramassamy S, Chandrashekar L, Thappa DM. A retrospective analysis of combination methotrexate-cyclosporine therapy in moderate-severe psoriasis. J Dermatolog Treat 2014;25:50-3.
4. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, *et al*. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009;23 Suppl 2:1-70.
5. Hoekstra M, van Ede AE, Haagsma CJ, van de Laar MA, Huizinga TW, Kruijsen MW, *et al*. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:423-6.
6. Tan KW, Tay YK. A case of acute methotrexate toxicity. Ann Acad Med Singapore 2011;40:97-9.
7. Itami N, Akutsu Y, Yasoshima K. Thrombocytosis after cyclosporin therapy in child with nephrotic syndrome. Lancet 1988;2:1018.
8. Ogston D, Dawson AA, Philip JF. Methotrexate and the platelet count. Br J Cancer 1968;22:244-9.
9. Davidovici BB, Sullivan-Whalen MM, Gilleaudeau P, Krueger JG. Differing effect of systemic anti psoriasis therapies on platelet physiology - A case report and review of literature. BMC Dermatol 2010;10:2.
10. Yasumoto S, Imayama S, Hori Y. Increased serum level of interleukin-6 in patients with psoriatic arthritis and thrombocytosis. J Dermatol 1995;22:718-22.
11. Storogenko M, Pech-Amsellem MA, Kerdine S, Rousselet F, Pallardy M. Cyclosporin-A inhibits human endothelial cells proliferation through interleukin-6-dependent mechanisms. Life Sci 1997;60:1487-96.
12. Elango T, Dayalan H, Subramanian S, Gnanaraj P, Malligarjunan H. Serum interleukin-6 levels in response to methotrexate treatment in psoriatic patients. Clin Chim Acta 2012;413:1652-6.
13. Jensen MK, Nyfors A. Cytogenic effects of methotrexate on human cells *in vivo*: Comparison between results obtained by chromosome studies on bone-marrow cells and blood lymphocytes and by the micronucleus test. Mutat Res 1979;64:339-43.

How to cite this article: Tejaswi C, Mohanan S, Murugaiyan R, Karthikeyan K. Double trouble: Cyclosporine-induced thrombocytosis in a patient with methotrexate toxicity: Are they related?. J Pharmacol Pharmacother 2015;6:160-2.

Source of Support: Nil, **Conflict of Interest:** None declared.