

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

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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.

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

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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/mm³; platelet count- 5×10^5 /mm³) 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/mm³). 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/mm³; platelet count - 4.11×10^5 /mm³). 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 (9.0×10^5 /mm³) when tested, on multiple occasions. Cyclosporine was stopped due to suspicion of drug-induced thrombocytosis. The platelet count dropped to a high normal value (5×10^5 /mm³) 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.



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

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 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-1 β 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.

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