INTRODUCTION

Over the years, low-dose methotrexate (MTX) therapy has become an important way of psoriasis management with a relatively safe side effect profile. However, occasionally in practice, a few cases of idiosyncratic reactions to the drug are witnessed where complications of the drug clearly outweigh the concentration of the drug being administered.

Here, we report one such case of a patient of guttate psoriasis who developed acute-onset anagen effluvium following the administration of only two doses of MTX 7.5 mg once per week.

Explanation of such bizarre reactions lies in the polymorphisms in the genes for MTX regulating intracellular uptake and enzyme inhibition which are known to render individuals susceptible to toxicity. Prior testing for such polymorphisms may have a role in preventing such events.

CASE REPORT

A 22-year-old woman, a recently diagnosed case of guttate psoriasis, was started on tablet MTX 7.5 mg/week. Three weeks after starting the drug, the patient presented with a complaint of acute-onset diffuse loss of about 30%–40% hair from the scalp over the past 4 days [Figures 1 and 2]. She denied the use of any other medication, any change in cosmetic, and a history of any other illness in the past 6 months.

Her general and systemic examination was normal. Dermatological examination revealed diffuse involvement

How to cite this article: Sinha P, Bhatt S, Radhakrishnan S, Neema S, Sinha A. Anagen effluvium after methotrexate: An idiosyncratic reaction. Int J Trichol 2020;12:93-6.
Sinha, et al.: Anagen effluvium after methotrexate: An idiosyncratic reaction

of the complete scalp in the form of hair loss and empty follicles. No scarring was seen. Hair pull test was positive.

Dermoscopy revealed a few black dots, yellow dots, and few miniaturized hair [Figure 3]. Light microscopy revealed dystrophic anagen hair bulbs [Figure 4].

Her hematological and biochemical parameters were within normal limits. Thyroid profile and antinuclear antibodies were normal. Scalp biopsy revealed no significant findings and only mild perivascular lymphocytic inflammatory infiltrate. No foamy histiocytes or granuloma was noted, and no evidence of dysplasia or malignancy was noted.

Based on the above clinical, trichoscopic, light microscopic, and histopathological findings, a diagnosis of anagen effluvium was given likely due to the drug MTX.

MTX was stopped, and the patient was managed with counseling, multivitamins, and advice to eat a healthy diet. The hair loss gradually stopped over the next 3 months [Figure 5]. For psoriasis, she was managed with topical steroids and emollients with regression of skin lesions.
DISCUSSION

Anagen effluvium refers to abrupt loss of hair in their growing phase due to any event which causes sudden stoppage of the metabolic or mitotic activity of the hair follicle. As the anagen phase of the hair follicle is longest around 2–6 years and, at any point of time, about 85%–90% of hair follicles in the scalp are in the anagen phase, hence anagen effluvium is associated with sudden massive loss of hair in contrast to the slow insidious onset hair loss in case of telogen effluvium.[10]

The hairs in anagen effluvium are broken rather than shed as compared to telogen effluvium, so semantically anagen effluvium is a misnomer as effluvium means to shed.[10]

Anagen effluvium is of two types, namely dystrophic anagen effluvium and loose anagen syndrome. Loose anagen hair syndrome is characterized by loosely anchored anagen hairs that can be easily and painlessly pulled from the scalp which results from hereditary keratin defects in the inner root sheath and/or the opposed companion layer.[2]

Dystrophic anagen effluvium occurs commonly due to chemotherapeutic agents but can also occur in case of protein–energy malnutrition, pemphigus, alopecia areata, and various heavy metal poisoning. The common causative agents with frequency of occurrence of anagen effluvium are 80% for antimicrotubule agents (e.g., paclitaxel), 60%–100% for topoisomerase inhibitors (e.g., doxorubicin), more than 60% for alkylating agents (e.g., cyclophosphamide), and 10%–20% for antimetabolites (e.g., 5-fluorouracil).[1]

MTX is known to cause anagen effluvium but only at high doses (>1 g/m²) used in cancer chemotherapy. This occurs as the mechanism of action of MTX at higher doses is primarily cytotoxic and antiproliferative. At high extracellular concentrations, MTX also enters cells through high-capacity, low-affinity processes such as passive diffusion in addition to being transported intracellularly through reduced folate carrier (RFC) giving its higher intracellular concentration. At higher doses (>30 mg/m²), MTX primarily acts by inhibiting DNA and RNA synthesis during the S phase of the cell cycle in the rapidly dividing cells.[10] In contrast the mechanism of action of MTX at lower doses is primarily by inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase domain of the bifunctional enzyme AICAR transformylase/inosine monophosphate cyclohydrolase (ATIC). Inhibition of this metabolic pathway results in increased levels of extracellular adenosine. Increased adenosine has diverse actions that downregulate inflammation.[9]

A possible explanation to variable side effect profile of MTX in different individuals may lie in the pharmacogenetic diversity of the various aspects of its metabolism and action.

Many polymorphisms to such effect have been detected: (i) MTX is transported intracellularly by the RFC. A polymorphism leading to substitution of arginine for histidine at codon 27 of the RFC protein has been identified (RFC G80A), and studies suggest that this polymorphism had higher plasma MTX levels and higher intracellular polylglutamated MTX levels than patients with other genotypes.[10] (ii) A tandem repeat sequence within 5'-untranslated region of the TYMS gene, containing a variable number of 28 base-pair repeats, has been identified which function as enhancers, and with increased number of repeat sequences, both mRNA expression and enzyme activity are increased.[11] (iii) Methyltetrahydrofolate dehydrogenase, an enzyme is a central regulatory enzyme in the folate pathway which catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. It is the most studied gene with respect to genetic polymorphism of the drug, and at least 15 polymorphisms of the drug have been detected, out of which single-nucleotide polymorphisms (SNPs) in C677T and A1298C have been associated with toxicity of the drug.

Toxicogenic index for MTX is a sum of homozygous variant genotype for four SNPs (MTHFR C677T, ATIC C347G, the TYMS 28-bp tandem repeat, and a SNP within serine hydroxymethyltransferase, C1420T). For each unit increase of the index, there is a 1.9-fold increase in the likelihood of side effects.[10]

Despite MTX being a relatively safe drug in long-term management of psoriasis, idiosyncratic reactions such as the one being reported are occasionally witnessed during the clinical practice. Sudden hair fall of such magnitude can be a devastating complication leading to serious mental and life quality implications, especially in young females.

Therefore, wherever possible, prior genetic testing for polymorphisms must be undertaken to identify individuals who are at higher risk of developing such complications. Due to financial constraints, we could not get genetic testing done for our patient.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have
given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kanwar AJ, Narang T. Anagen effluvium. Indian J Dermatol Venereol Leprol 2013;79:604.
2. Price VH, Gummer CL. Loose anagen syndrome. J Am Acad Dermatol 1989;20:249-56.
3. Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's Textbook of Dermatology. Chichester, West Sussex: John Wiley & Sons; 2016.
4. Malaviya AN, Sharma A, Agarwal D, Kapoor S, Gang S, Sawhney S. Low-dose and high-dose methotrexate are two different drugs in practical terms. Int J Rheum Dis 2010;13:288-93.
5. Laverdiere C, Chiasson S, Costea I, Moghrabi A, Krajnovic M. Polymorphism G80A in the reduced folate carrier gene and its relationship to methotrexate plasma levels and outcome of childhood acute lymphoblastic leukemia. Blood 2002;100:3832-4.
6. Dervieux T, Kremer J, Lein DO, Capps R, Barham R, Meyer G, et al. Contribution of common polymorphisms in reduced folate carrier and γ-glutamylhydrodrolase to methotrexate polyglutamate levels in patients with rheumatoid arthritis. Pharmacogenetics 2004;14:733-9.
7. Pullarkat ST, Stoehlmacher J, Ghaderi V, Xiong YP, Ingles SA, Sherrod A, et al. Thymidylate synthase gene polymorphism determines response and toxicity of 5-FU chemotherapy. Pharmacogenomics J 2004;1:65-70.
8. van Ede AE, Laan RF, Roel MJ, Huizinga TW, van de Laar MA, Denderen CJ, et al. Effect of folic or folic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: A forty-eight-week, multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2001;44:1515-24.
9. Berkun Y, Levartovsky D, Rubinow A, Orbach H, Aamar S, Grenader T, et al. Methotrexate-related adverse effects in patients with rheumatoid arthritis are associated with the A1298C polymorphism of the MTHFR gene. Ann Rheum Dis 2004;63:1227-31.
10. Weisman MH, Furst DE, Park GS, Kremer JM, Smith KM, Wallace DJ, et al. Risk genotypes in folate-dependent enzymes and their association with methotrexate-related side effects in rheumatoid arthritis. Arthritis Rheum 2006;54:607-12.