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Editor Letter

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DOES METHOTREXATE CAUSE MENORRHAGIA? A CASE REPORT OF MENORRHAGIA IN A PATIENT WITH PSORIATIC ARTHRITIS

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Dear Editor, besides cancer chemotherapy and tumor arena, methotrexate (MTX), an anti-metabolite drug has been used for the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA) and psoriasis since 1980s and has become the cornerstone of RA therapy.[1,2,3] Methotrexate acts on folate metabolism. It inhibits dihydrofolate reductase and prevents the synthesis of tetra hydro folate from dihydrofolate. As a result, the synthesis of timidilate, purine and ultimately DNA is blocked. Induction of apoptosis is, in part, responsible for its therapeutic effects,[4,5,6,7] so patient having this medication is closely monitored for possible side effects on liver but also for other organs.[8,9] To our knowledge, there is no information regarding interaction between heavy menorrhagia, endometrial hyperplasia, and MTX use in a woman at reproductive age. We here presented a patient who was admitted to our hospital because of a continued and heavy menorrhagia for 11 days.

The patient was 43 year-old, G5, P2, living 2 (l7 yo F and l4 yo M) with normal labor and delivery. She works as a nurse in the hospital. Her past medical history was remarkable for ovarian cystectomy and appendectomy 23 years ago; extra uterine pregnancy operation, hemorrhoidectomy and rectal polypectomy 11 years ago; and lumbar disc operation 8 years ago. She has been diagnosed as having psoriasis for 20 years and as having psoriatic arthritis for the last 5 years. Her first line therapy was corticosteroids, meloxicam, and acemetazine. These medications were found not useful and she started MTX two years ago. She used 2.5 mg tablet every other day so 7.5 mg per week. During this two years period she had to discontinue the therapy once because of the elevation of liver enzymes. On laboratory examination, liver enzymes were found to be high at the time of the endometrial biopsy and were attributed to MTX. Enzymes were as follows: AST=275; ALT=442; AFP=2.79 (ranged 0-7); CEA=0.23 (ranged 0-3.4); CA125=16.5 (ranged 0-35); CA19-9=6.73 (ranged 0-39); CA15-3=13.64 (ranged 0-25); hemoglobin 12 g/dL; WBC=4500 $10^3/mm^3$; platelet= $24700010^3/mm^3$.

HBs Antigen and HCV were all negative on pelvic examination uterus was of normal size av/af deviated to the right. The adnexa and the parametrium were free. Because of her age, a D&C operation for treatment was planned and endometrial biopsy was performed. The tissue submitted to pathology laboratory consisted of hemorrhagic tissue in 1 cm^3 in diameter. Routine histopathological examination revealed simple endometrial hyperplasia with many apoptotic cells. After D/C and the discontinuation of MTX use, the bleeding ceased and the patient was symptom free. A repeat D&C was performed after 2 months and biopsy showed normal proliferative endometrium.

There has been a biologic continuum between proliferative endometrium, usual endometrial hyperplasia and endometrial carcinoma related to unopposed Estrogen influence. Recent studies have showed that molecular mechanisms such as apoptosis are involved in the development of proliferative lesions of the endometrium. Apoptosis is gradually increased in proliferative, secretory and menstrual endometria.[10,11,12] Under pathologic conditions, it was demonstrated that the apoptosis-related proteins increased progressively from proliferative endometrium, secretory endometrium, and neoplastic endometrium.[13,14,15] We postulated that menorrhagia and simple endometrial hyperplasia seen in our case could explain with the presence of apoptosis induced by methotrexate treatment. Monitoring the development of side effects of MTX in patients on MTX medication is recommended among rheumatologist.[16] We believe that it is also necessary to be aware of its possible impact on endometrium.

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