

Recurrent amenorrhoea associated with disease-modifying anti-rheumatic drugs: a case report

Sirs,

The patient had passed through the menarche at the age of 13, and subsequently had a regular 28-day menstrual cycle. She had given birth to two children normally. She was a smoker. At the age of 8 she developed psoriatic arthritis, with back pain, dactylitis, and psoriasis associated to HLA B27 gene. She was treated with sulfasalazine and non-steroidal anti-inflammatory drugs until age 35 when her symptoms were assessed as requiring treatment with methotrexate. Five months later she developed hot flushes and amenorrhoea, and investigation revealed low oestradiol, raised FSH and LH and normal thyroid function (Fig. 1). The amenorrhoea lasted four cycles. Methotrexate was withdrawn and adalimumab introduced in March 2009. Two months later, the menses resumed. Over the subsequent nine years she was treated intermittently with adalimumab and in April 2013 at age 38 switched to etanercept. During this period she reported repeated episodes of amenorrhoea and of climacteric symptoms, with disturbed biological tests (Fig. 1). Although full menstrual data are incomplete the pattern suggests that methotrexate, adalimumab and etanercept all caused reversible ovarian failure.

Four aspects of this patient's "menopause-like" were unusual: i) the progesterone withdrawal test induced menses, suggesting a residual synthesis of oestrogens, ii) it was reversible after drugs withdrawal, iii) markers of ovarian reserve (antral follicular count

and Anti-Müllerian hormone (AMH)) were unusually conserved during symptoms, between 2011 and 2017, iv) amenorrhoea was short lasting.

The lack of other causes and the reversibility of symptoms after drug withdrawal suggest the drugs' responsibility (2). According to the Naranjo probability scale (3), etanercept-induced secondary amenorrhoea was probable with a score of 7 and with a score of 5 concerning methotrexate and adalimumab. Constant levels of AMH and antral follicular count, together with positive progesterone challenge suggest a disturbance of mature (*i.e.* antral) follicular physiology. The relatively persistence of amenorrhoea (2 months) after adalimumab withdrawal is consistent with its high half-life ($T_{1/2}$ 2 weeks). However, this rationale does not explain the two-month delay in return of menses after stopping etanercept, the half-life of which is shorter ($T_{1/2}$ 70 hours). Regarding methotrexate, it might be associated with amenorrhoea when given at high doses, in association with different chemotherapy regimens (4).

To our knowledge, no similar case has been reported. Kroft *et al.* (5) reported a 2-year history of secondary unexplained amenorrhoea in a 44-year-old woman, after 5 years of treatment with methotrexate for rheumatoid arthritis, but FSH, estradiol, and prolactin were in normal ranges. Endometrial inhibition induced by methotrexate was hypothesised (5). Recent animal studies have suggested that TNF- α exerts negative effects on ovarian follicular development, steroidogenesis, ovulation, luteolysis, and plays a role in follicular atresia (6). As previously shown *in vivo* (7), TNF inhibitors (TNFi) should suppress those negative ef-

fects, whereas in our case, they appeared to disrupt follicular physiology, while not affecting ovarian reserve. Methotrexate as well as TNFi may act directly on follicles and disable oestrogen synthesis. Furthermore, TNFi may paradoxically induced development of organ-specific autoantibodies targeting ovary and might have been a possible explanation for this secondary amenorrhoea, but it would not explain the reversibility of symptoms (8). A previous paper demonstrated reduced TNF- α levels in sera of infertile patients with premature ovarian failure (9). Although these data could confirm our findings, it is worth mentioning that the decrease in circulating TNF- α concentration might be due to the decrease in ovarian reserve. In addition, there is no evidence suggesting a biological effect of the concentration difference (about 80pg/mL). Clearly, further reports are needed to determine the specific role of TNF- α inhibition in the occurrence of ovarian failure.

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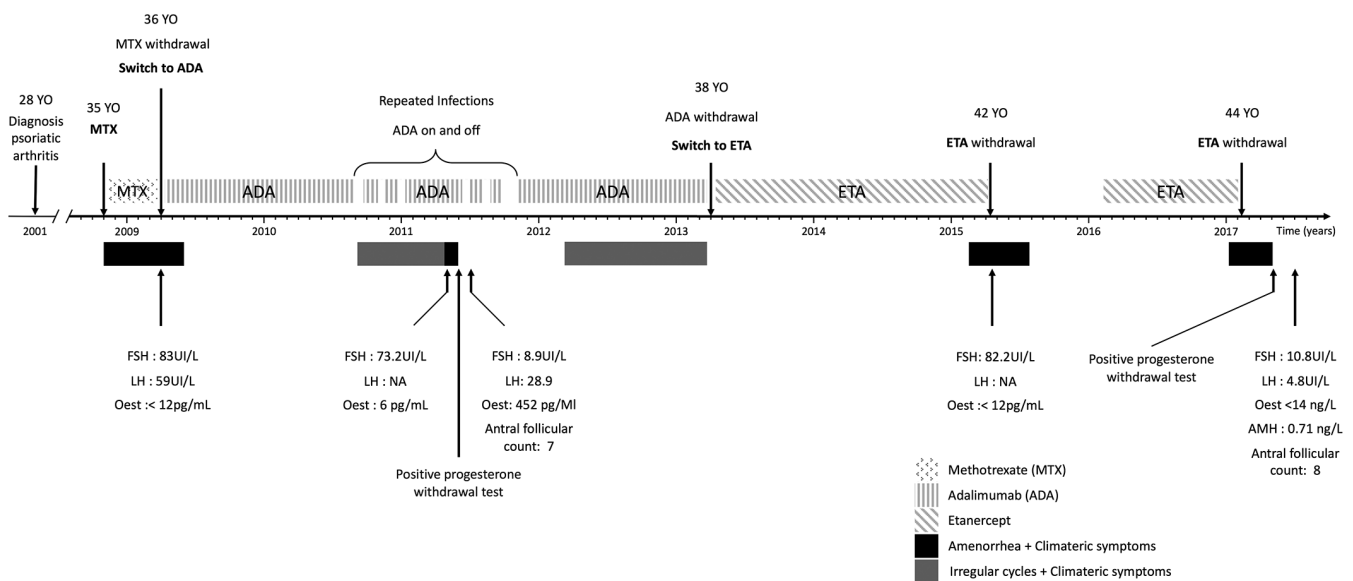


Fig. 1. Historical timeline of treatments, with biological and ultrasound assessments.

Follicle Stimulating Hormone (FSH) (UI/L): N 25.8 to 134.8 in menopause, luteinising hormone (LH): N 7.7 to 59 UI/L in menopause, Oestradiol (pg/mL): (n: >12.5), Anti-Müllerian hormone (AMH): 0.7 to 2.3 ng/L. YO: year-old, NA: not available, MTX: methotrexate, ADA: adalimumab, ETN: etanercept, D3: Day 3.

Letters to the Editors

References

1. NELSON LM: Clinical practice. Primary ovarian insufficiency. *N Engl J Med* 2009; 360: 606-14.
2. KLEIN DA, POTH MA: Amenorrhea: an approach to diagnosis and management. *Am Fam Physician* 2013; 87: 781-8.
3. NARANJO CA, BUSTO U, SELLERS EM *et al.*: A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239-45.
4. MINTON SE, MUNSTER PN: Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. *Cancer Control* 2002; 9: 466-72.
5. KROFT J, SABRA S, ARTHUR R, WOLFMAN W: Unexplained amenorrhea in a patient taking methotrexate for the treatment of rheumatoid arthritis. *Gynecol Endocrinol* 2010; 26: 179-80.
6. MORRISON LJ, MARCINKIEWICZ JL: Tumor necrosis factor alpha enhances oocyte/follicle apoptosis in the neonatal rat ovary. *Biol Reprod* 2002; 66: 450-7.
7. NAYLOR AJ, DESANTI G, SAGHIR AN, HARDY RS: TNFalpha depleting therapy improves fertility and animal welfare in TNFalpha-driven transgenic models of polyarthritis when administered in their routine breeding. *Lab Anim* 2018; 52: 59-68.
8. RAMOS-CASALS M, PEREZ-ALVAREZ R, DIAZ-LAGARES C, CUADRADO M-J, KHAMASHTA MA: Autoimmune diseases induced by biological agents: a double-edged sword? *Autoimmun Rev* 2010; 9: 188-93.
9. NAZ RK, THURSTON D, SANTORO N: Circulating tumor necrosis factor (TNF)-alpha in normally cycling women and patients with premature ovarian failure and polycystic ovaries. *Am J Reprod Immunol* 1995; 34: 170-5.