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**Gynecomastia associated with low-dose methotrexate therapy for
rheumatoid arthritis ameliorated by folate supplement**

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Abstract

A 62-year-old male with a 10-year history of seropositive rheumatoid arthritis (RA) developed gynecomastia 8 month after beginning oral low-dose methotrexate (MTX) therapy. Two month after folate supplementation, the gynecomastia symptoms improved. Gynecomastia associated with low-dose MTX is a rare occurrence, with only nine cases previously reported in the literature. This is the first report showing folate supplementation to be effective against gynecomastia following low-dose MTX. Although it occurs infrequently, gynecomastia associated with low-dose MTX therapy should be considered in male patients with RA.

Keywords

rheumatoid arthritis, methotrexate, gynecomastia, folate

Introduction

Although low-dose methotrexate (MTX) therapy for rheumatoid arthritis (RA) is generally well tolerated, it has some side effects, primarily on the gastrointestinal, hepatic, and hematologic systems. In contrast,

gonadal side effects are rare and only a few cases of sexual dysfunction or gynecomastia have been reported. We herein report a patient with RA who demonstrated gynecomastia following treatment with MTX. Treatment with folate supplement ameliorated the gynecomastia within weeks.

Case report

A 62-year-old male with a 10-year history of seropositive RA had been treated with bucillamine (200mg/day) and prednisolone (10mg/day). Bucillamine treatment was discontinued due to poor control of disease activity (DAS28:3.70) and oral MTX (4mg/week) was started.

Two months later, the dose of MTX was increased to 8 mg/week and the patient's RA symptoms thereafter significantly improved (DAS28:2.67). Eight months after MTX treatment was started, the patient complained of tenderness in his left breast. Evaluations revealed an enlarged breast without discrete nodules or surface changes. A CT scan of the left breast revealed a 3 cm x 2 cm irregular mass without calcification or any other signs of malignancy (Fig. 1). Fine needle aspiration cytology from the breast lump confirmed presence of glandular tissue without features of atypia,

compatible with the diagnosis of gynecomastia. We considered MTX to be an inducer of gynecomastia, and began folate supplementation at the rate of 5mg/day. The breast tenderness improved gradually after folate supplementation was started and the gynecomastia symptoms completely resolved within two months (Fig.1).

Because the gynecomastia subsided shortly after starting folate supplementation, we believe this symptom was secondary to the MTX administration. The patient was also taking lansoprazole, a potent “gynecomastia inducer”. Although lansoprazole was administered throughout the follow up period, the patient’s gynecomastia disappeared following folate supplementation, which suggests that lansoprazole was not responsible for the gynecomastia in this patient.

Gynecomastia associated with low-dose MTX is a rare occurrence, with only nine cases previously reported in the literature [1-7]. A survey of these reports shows that symptoms appeared between two weeks to two years after MTX was started, and weekly MTX doses ranged from 5 to 20 mg. Folate supplementation was administered in two cases before gynecomastia appeared. A surgical resection was performed in two cases, and in the

remaining cases, withdrawal or reduction of MTX resulted in the resolution of gynecomastia within one week to four months. This is the first report showing folate supplementation to be effective against gynecomastia following low-dose MTX.

The mechanism of MTX-related gynecomastia remains speculative. In rabbits, MTX induces oligospermia, decreased serum testosterone and elevated serum follicle-stimulating hormone (FSH) [8]. A similar result has been reported in humans following high-dose MTX chemotherapy, with multiple patients developing oligospermia and elevated serum FSH levels in the presence of normal serum testosterone and luteinizing hormone levels [9]. Among the nine cases of MTX-related gynecomastia previously reported in the literature, hormonal changes indicating testicular failure were found in only two [1,3], thus suggesting that a subtle increase in the serum estrogen/androgen ratio may be responsible for the gynecomastia in the remaining cases. We postulate that this may result from an increased aromatization of androgen, an enhanced synthesis of androgenic carriers or an increased bioavailability of estrogen resulting from the removal of estrogen from its carrier proteins [5,10].

Although gynecomastia is primarily a cosmetic problem, it can also be psychologically disabling. Because MTX is widely used in rheumatology practice, physicians should be aware of this iatrogenic side effect. If no other cause of gynecomastia is found following extensive screening, then MTX should be withdrawn or folate supplementation should be considered to induce regression. The case presented herein indicates the potential effectiveness of folate supplementation to resolve gynecomastia related to low-dose MTX treatment.

Conflict of interest

The authors declare that they have no conflict of interests.

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Figure legend

Figure 1. (Upper) A CT scan of the left breast showed a 3 cm x 2 cm mass without calcification (arrow). (Lower) The clinical course of this case. BUC, bucillamine; MTX, methotrexate; PSL, prednisolone.

