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CASE REPORT

Koki Abe · Takeshi Mitsuka · Shigeo Kanamori
Keishi Yamashita · Akiyoshi Yamaoka

Gynecomastia associated with low-dose methotrexate therapy for rheumatoid arthritis

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Abstract A 68-year-old man with a 3-year history of rheumatoid arthritis (RA) developed gynecomastia 3 months after beginning oral low-dose methotrexate (MTX) therapy. Four months after MTX therapy was discontinued, the gynecomastia symptoms improved. Only eight cases of gynecomastia resulting from low-dose MTX administration have been reported worldwide, and no cases have previously been reported in Japan. Although it occurs infrequently, gynecomastia resulting from low-dose MTX therapy should be considered in male patients with RA.

Key words Adverse effect · Gynecomastia · Methotrexate (MTX) · Rheumatoid arthritis (RA)

Introduction

Low-dose methotrexate (MTX) therapy is known to be an effective treatment for rheumatoid arthritis (RA). Methotrexate has immunosuppressant and anti-inflammatory properties. Although MTX is generally well tolerated, it has some side effects, commonly affecting the liver, lung, bone marrow, and oral mucosa. Several cases of sexual dysfunction and gynecomastia in men undergoing MTX treatment have been reported.[1–5] We report a patient with RA in whom gynecomastia developed within a few months of beginning of oral low-dose MTX therapy.

K. Abe · S. Kanamori
Department of Orthopaedic Surgery, Chiba-Tokushukai Hospital, Funabashi, Japan

K. Abe (✉) · T. Mitsuka · K. Yamashita · A. Yamaoka
Department of Orthopaedic Surgery, Social Insurance Funabashi Central Hospital, 6-13-10 Kaijin, Funabashi 273-8556, Japan
Tel. +81-47-433-2111; Fax +81-47-435-2658
e-mail: abeabeabe04@yahoo.co.jp

Case report

A 65-year-old man with a 3-year history of seropositive RA (Steinbrocker Stage II and Class 2) was treated with 200 mg/day bucillamine and 2 mg/day prednisolone (PSL) for 12 months (Fig. 1). The patient had no history of liver malfunction or alcoholism.

The bucillamine treatment was subsequently discontinued because of a cutaneous allergy. Salazosulfapyridine (SASP) at a dose of 1 g/day was substituted for bucillamine; however, SASP was also discontinued 7 months later because of cutaneous intolerance. After that the RA inflammation worsened, so MTX (4 mg/week) was administered and the dose of PSL was increased to 3 mg/day. Two months later the dose of MTX was increased to 6 mg/week because of persistent RA inflammation. One month after the increase in MTX dose the patient complained of tenderness in the right breast. On examination, a painful discoid nodule without nipple discharge was found (Fig. 2). A complete blood count and biochemical analysis at onset of gynecomastia did not show macrocytic anemia. Renal and hepatic function were within the normal ranges (Table 1). The patient denied having noticed obvious changes in libido, facial hair, or testicle size. We thought it was likely that MTX was causing this gynecomastia, and so discontinued MTX treatment. After cessation of the MTX treatment, the breast pain improved gradually, and 4 months later the gynecomastia symptoms had resolved completely. After discontinuation of MTX treatment, the RA inflammation worsened, so tacrolimus treatment was initiated. At the time of writing, tacrolimus seemed to be effective in controlling the patient's RA symptoms. The clinical course of the patient is illustrated in Fig. 3. Meloxicam, rebamipide, and lansoprazole were administered throughout. No folic acid preparation was used.

Discussion

Ten to 20 percent of cases of gynecomastia are drug-induced.[6] Although gynecomastia can be caused by various

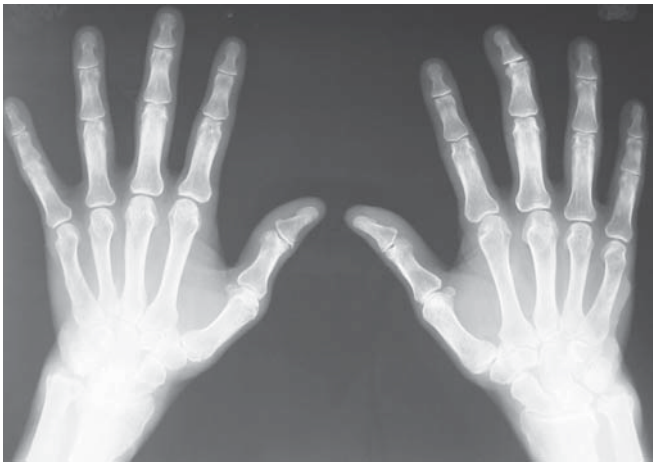

Fig. 1. Radiograph of the hands showing stage 2 rheumatoid change

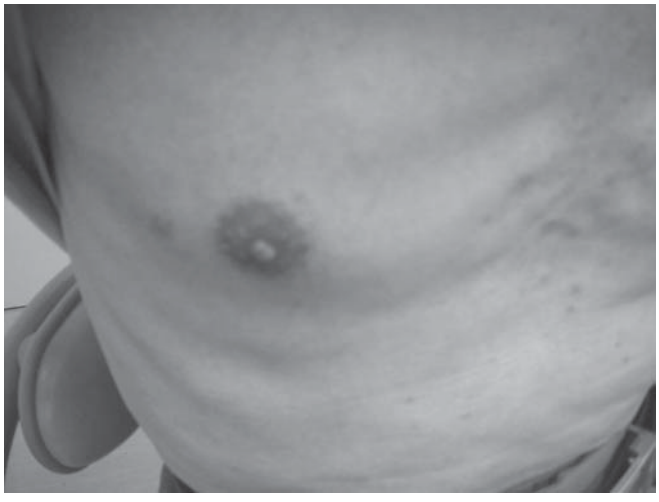

Fig. 2. Unilateral gynecomastia in a patient with rheumatoid arthritis being treated with methotrexate. The patient complained of tenderness in the right breast, and on examination, a painful discoid nodule was found in the right breast

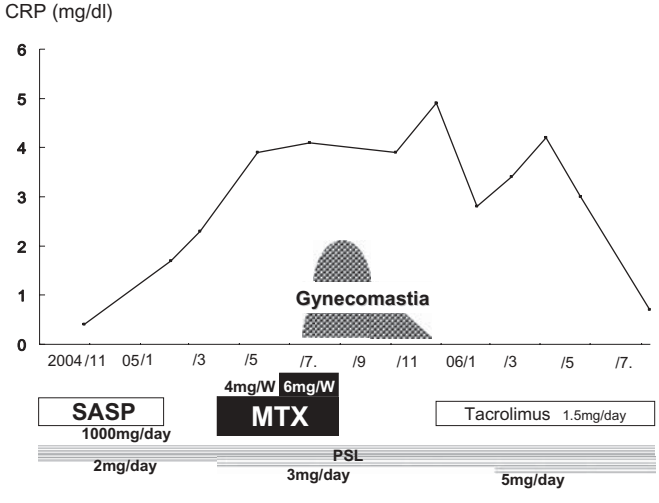

Fig. 3. Clinical course. *SASP*, salazosulfapyridine; *MTX*, methotrexate; *PSL*, prednisolone

Table 1. Laboratory findings at onset of gynecomastia

CBC		**Blood chemistry**	
WBC	9000/μl	TP	6.9 g/dl
RBC	407×10^4	BUN	12.3 mg/dl
Hb	12.9 g/dl64.4	CRE	0.7 mg/dl
Ht	39.2%	T-bil.	0.4 mg/dl
MCV	$96.3 \times 10\,\mu m^3$	AST	17 IU/ml
MCH	31.7×10 pq	ALT	11 IU/ml
MCHC	$32.9 \times 100\%$	LDH	455 IU/l
Platelet	30.8×10^4/l	ALP	201 IU/l
Serology		**ESR**	62 mm/h
CRP	4.1 mg/dl		
RF	162 IU/ml		

CBC, complete blood cell count; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TP, total protein; BUN, blood urea nitrogen; CRE, creatinine; T-bil., total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CRP, C-reactive protein; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate

drugs, cases associated with MTX treatment are rare. We studied the case of a patient with RA who was being treated with low-dose MTX, who presented with gynecomastia.

Only eight cases of gynecomastia related to low-dose MTX administration have been reported (Table 2). Four of these patients had RA, two had psoriatic arthritis, one had adult Still's disease, and another had pustular psoriasis. The longest duration of MTX therapy was 2 years and the shortest was 2 weeks. The weekly dose ranged from 2.5 to 20 mg. In two cases, surgical excision was performed, and for the other cases discontinuation of MTX caused symptoms to subside within a week to 4 months. In the case of the patient with pustular psoriasis, 6 weeks after the condition developed MTX was discontinued and the gynecomastia improved. However, because the pustular lesions recurred, MTX was readministered, after which the pustular lesions again subsided, and the patient's breast size increased. Only two of the eight patients had abnormal hormone levels, with the remainder being normal. One patient had low testosterone levels, and another had an elevated estrogen to androgen ratio. Regrettably, serum hormone levels, including levels of estrogen, testosterone, and thyroid hormone, were not measured for our present patient.

Physiologically, gynecomastia is caused by a hormone imbalance in the neonatal period, during puberty, and between the ages of 50 and 80.[6] The present patient fits into the third group, in which the condition is referred to as senile gynecomastia. However, this patient's gynecomastia symptoms appeared 3 months after MTX treatment began, and the symptoms resolved 4 months after the drug was discontinued. There was no alteration of renal or hepatic function in this patient. Therefore, we believe that this patient's gynecomastia was secondary to MTX treatment. Our patient was also treated with lansoprazole, which has also been reported to be a cause of gynecomastia.[7] Although lansoprazole was administered throughout the treatment period, the gynecomastia improved after discontinuation of MTX, so we consider that lansoprazole was not responsible for the gynecomastia in this case.

Table 2. Reported cases of gynecomastia associated with low-dose methotrexate treatment

Age (years)/ sex	Underlying disease	MTX dose per a week (duration)	Bilateral or unilateral mass	Convalescence time	Serum hormone levels	First author, year[Ref.]
19/M	AOSD	2.5 mg (2 weeks)	Bilateral	1 week	Testosterone ↓	Del Paine, 1983[1]
68/M	RA	10 mg (3 months) and 15 mg (3 months)	Unilateral	(Surgical excision)	Normal	Thomas, 1994[2]
47/M	RA	10 mg (2 months) and 15 mg (13 months)	Unilateral	(Surgical excision)	Normal	Thomas, 1994[2]
32/M	RA	10 mg (2 months)	Unilateral	3 months	Normal	Finger, 1995[3]
65/M	RA	10 mg (5 months)	Unilateral	NR	E/A ↑	Finger, 1995[3]
42/M	PsA	7.5 mg (1 year)	Unilateral	Several weeks	Normal	Aguirre, 2002[4]
30/M	PsA	7.5 mg (2 years)	Unilateral	A few weeks	Normal	Aguirre, 2002[4]
50/M	PP	20 mg (4 months)	Bilateral	6 weeks	Normal	Pandhi, 2005[5]
68/M	RA	4 mg (7 weeks) and 6 mg (5 weeks)	Unilateral	16 weeks	–	Present study

MTX, methotrexate; ASOD, adult Still's disease; RA, rheumatoid arthritis; PsA, psoriatic arthritis; PP, pustular psoriasis; NR, not recorded; E/A, estrogen to androgen ratio

Drugs that cause clinically significant gynecomastia can be classified into three groups on the basis of their mechanism of action: those that mimic or enhance estrogen, those that inhibit testosterone synthesis or activity, and those with unknown mechanisms. Estrogen in the body is produced from androgenic steroids by aromatization, and is metabolized by hydroxylation and glucuronate conjugation.[7] In previous reports it has been inferred that MTX disrupts the estrogen–testosterone balance, which is the origin of most cases of gynecomastia.[6] This might result from increased aromatization of androgenic agents. In other reports it has been suggested that MTX-induced gynecomastia is due to increased breast tissue sensitivity to estrogen.[4,5,8] Details of the mechanism by which MTX causes gynecomastia are not currently well understood. In a laboratory animal study, the toxic effects of parenteral MTX on rabbit testis reportedly include decreased serum testosterone levels, oligospermia, and elevated serum follicle-stimulating hormone (FSH) levels.[9,10] Also, humans who have been given high-dose MTX chemotherapy for the treatment of malignancy have been found to develop oligospermia and elevated FSH levels in association with normal serum testosterone and luteinizing hormone levels.[11]

Although it occurs infrequently, gynecomastia due to treatment with low doses of MTX should be considered in male patients. Low-dose MTX therapy is widely used for the treatment of RA today, so it would be beneficial to determine the mechanism underlying MTX-induced gynecomastia via a more detailed investigation.

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