LETTERS

Will steroidal aromatase inhibitors induce rheumatoid arthritis?

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Aromatase inhibitors are used in advanced breast cancer treatment to cause an oestrogen deprivation. Such treatment can induce benign arthralgias.^{1 2} We describe a case of rheumatoid arthritis after treatment with aromatase inhibitors. A 64-year-old Caucasian woman, with a 3-year history of advanced right breast cancer (infiltrative ductal carcinoma classified as oestrogen-receptor positive; progesterone-receptor negative with positive lymph nodes; pT2pN1bM0) received treatment with tamoxifen (20 mg/day) for about 3 years. Cancer follow-up was normal and no side effects were reported. In November 2004, tamoxifen was switched to exemestane (25 mg/day) in accordance with studies showing better efficacy and good safety. A few days later, she developed arthralgias affecting the hips, shoulders, knees, wrists and hands associated with morning joint stiffness for 2 h. Treatment with non-steroidal anti-inflammatory drugs did not improve her condition. About 4 weeks later, she developed symmetric and active arthritis, with swelling affecting the wrists, metacarpophalangeal joints and proximal interphalangeal joints. Erythrocyte sedimentation rate and C reactive protein concentration were raised (30 mm/h and 15 mg/l, respectively). After 4 months, exemestane treatment was stopped and tamoxifen restarted. However, this switch did not induce a regression of joint symptoms. At this stage, we examined the patient. She had active and symmetric

arthritis with synovitis affecting both wrists, metacarpophalangeal joints and proximal interphalangeal joints. In addition, she had flexor tenosynovitis and ulnar deviation of fingers. Erythrocyte sedimentation rate was 14 mm/h and C reactive protein concentration 13.2 mg/l. Tests for rheumatoid factor and anti-anticyclic citrullinated peptide antibodies were negative. The shared epitope was present with the human leucocyte antigen DRB1*0101 allele. *x* Rays already showed erosions of the first and second metacarpophalangeal joints and joint space narrowing of other metacarpophalangeal joints. A magnetic resonance image of the right hand showed synovitis and erosions affecting the wrists and metacarpophalangeal joints (fig 1). The patient fulfilled the American College of Rheumatology criteria for rheumatoid arthritis and had an active disease with a Disease Activity Score including 28-joint count of 4.77. Methotrexate was started at 15 mg/week, inducing an improvement of the Disease Activity Score, including 28-joint count at 2.30 after 4 months.

This case suggests the role of aromatase inhibitors in the induction of rheumatoid arthritis. Many arguments favour the role of hormones in the induction and expression of rheumatoid arthritis. Its highest incidence and prevalence are observed in women after menopause. Moreover, symptoms are reduced during pregnancy and increased in the postpartum period,³ as observed in the case of a 36-year-old woman who developed

Figure 1 (A) Coronal T1-weighted magnetic resonance imaging (MRI) scan of the right wrist and metacarpophalangeal joints showing small erosions of the first metacarpal head near the proximal synovial insertion as well as defined areas of decreased signal (arrow). (B) Coronal contrast-enhanced T1-weighted MRI scan of the right wrist and metacarpophalangeal joints showing synovitis on the first metacarpal head near the proximal synovial insertion and on the carpus, as well as defined areas of increased signal (arrow). (C) Axial contrast-enhanced T1-weighted MRI scan of the right carpus showing synovitis of the carpus and defined areas of increased signal (arrow).

both rheumatoid arthritis and ulcerative colitis 2 weeks after a normal delivery.⁴

Accordingly, this case suggests the contribution of the anti-aromatase treatment. In this case, additional factors such as the presence of the shared epitope could explain the switch from common benign arthralgias to active destructive rheumatoid arthritis. At the late stage, cessation of treatment had no effect on arthritis. The presence of erosions suggests that the patient had rheumatoid arthritis with low disease activity, which became worse when aromatase inhibitors were used. Accordingly, arthralgias in women receiving aromatase inhibitors should be better evaluated to estimate the incidence of rheumatoid arthritis.

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Improved insulin sensitivity by anti-TNF α antibody treatment in patients with rheumatic diseases

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Insulin resistance is a key factor in the pathogenesis of the metabolic syndrome and type 2 diabetes, but the underlying mechanisms remain poorly understood. Adipocytokines, including tumour necrosis factor α (TNF α), interleukin 6, leptin and adiponectin,^{1,2} are increasingly recognised as important regulators of both insulin sensitivity, as well as inflammation, and a dysregulation of their levels and/or functions has been shown in both obesity and rheumatoid arthritis.³ Further investigations have substantiated the important negative effects of TNF α on insulin-mediated glucose uptake and the development of insulin resistance.⁴ In this study, the influence of therapeutic TNF α blockade on insulin

sensitivity was investigated in regularly treated patients with rheumatic diseases.

A group of eight patients who were non-diabetic and having various chronic inflammatory disorders (table 1) were investigated in an open prospective study design. Patients were attending the outpatient clinic of the Sint Maartenskliniek in Nijmegen and entered the study after giving their written informed consent. The regional medical ethical committee approved the study. Patients started the treatment with infliximab (3 mg/kg) and were followed up over a period of 6 weeks. During this interval, the additional antirheumatic drugs remained unchanged. Table 1 gives the patient characteristics.

Table 1 Characteristics of study participants

Patient number	1	2	3	4	5	6	7	8	Mean (SEM)
Age (years)	65	38	70	57	54	34	61	43	53 (5)
Sex	M	M	M	M	M	F	M	M	M:F=7:1
Diagnosis	RA	RA	RA	RA	Wd	RA	AS	AS	
Disease duration (years)	7	4	14	10	3	8	26	22	
RF	+	–	+	+	NA	+	NA	NA	
DAS28 I	5.26	4.28	7.65	3.75	4.25	3	NA	NA	4.7 (0.7)
DAS28 II	2.75	1.09	5.40	2.68	4.43	2.25	NA	NA	3.1 (0.6)
ESR I (mm/h)	36	14	43	37	38	10	67	14	32 (7)
ESR II (mm/h)	26	3	25	18	56	6	15	5	19 (6)
Prednisone	Yes	No	Yes	No	Yes	Yes	No	Yes	
DM2 in family	No	Yes	No	No	No	Yes	No	Yes	
Glucose (mmol/l)	7.5	5.2	4.9	4.3	4.6	5.7	4.9	4.8	5.2 (0.4)
BMI (kg/m ²)	27	25	24.3	22	28.1	22.4	26	24.5	24.6 (0.7)
Δ M(mg/kg/min)	0.12	2.79	1.33	4.28	0.06	3.46	–1.13	0.17	0.75 (5.41)

AS, ankylosing spondylitis; BMI, body mass index; DAS28 I/II, disease activity score at baseline (I) and after 6 weeks (II); DM2, type2 diabetes mellitus; ESR I/II, erythrocytes sedimentation rate at baseline (I) and after 6 weeks (II); F, female; M, male; Δ M, variation of insulin sensitivity, as assessed by M value; –, minus; NA, not available; +, plus; RA, rheumatoid arthritis; RF, rheumatoid factor; Wd, Whipple's disease.

Results are expressed as mean (SEM), except for Δ M where they are presented as median (range).