Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Inflammatory osteoarthritis which was precipitated by Arimidex and resolved with tamoxifen

Stella Williams,¹ Benedict Michael,² Devesh Mewar,³ Edward Tunn³

¹ Department of General Medicine, Whiston Hospital, Liverpool, UK

² Walton Centre for Neurology and Neurosurgery, Liverpool, UK

³ Department of Rheumatology, Royal Liverpool University Hospital, NHS Trust, Liverpool, UK

Correspondence to Benedict Michael, stella.Williams@shkht.nhs.uk

Summary

We report the case of a 51-year-old woman who presented with an inflammatory flare of osteoarthritis of the small joints of her hands occurring in a temporal relationship with the commencement of Arimidex, prescribed to reduce systemic oestrogen levels to treat breast cancer. Following the cessation of Arimidex and the initiation of tamoxifen, a specific oestrogen receptor antagonist, this flare resolved. It has long been observed that during the menopause, as oestrogen levels decline, many women develop osteoarthritis or experience progression of the disease. However, this theory of oestrogen-dependent osteoarthritis has not been consistently demonstrated in animal models. As far as the authors are aware, this is the first case in which systemic oestrogen reduction has resulted in a severe osteoarthritis flare but targeted oestrogen receptor blockade led to a resolution of symptoms. These findings may inform the pathophysiological process underlying oestrogen-dependent osteoarthritis, although further series are needed.

BACKGROUND

Osteoarthritis is the most common cause of joint disease and yet often remains difficult to prevent and treat. Although the development of osteoarthritis is multifactorial, one significant aetiological component which has been identified is oestrogen, as a marked increase in the incidence of osteoarthritis is observed in women around the menopause as oestrogen levels decline. Despite many studies which have attempted to investigate this, no direct mechanisms have been consistently demonstrated.

This case highlights some of the effects of oestrogen depletion on osteoarthritis, and demonstrates that certain oestrogen receptors may be implicated to a greater degree than others in the pathogenesis of oestrogen-dependent osteoarthritis. These findings may support a role for targeted oestrogen receptor activity and direct future research in this field.

CASE PRESENTATION

We report the case of a 51-year-old woman who was referred to the rheumatology clinic from primary care with an acute history of intense swelling and pain affecting the small joints of her hands. Prior to this inflammatory flare she had relatively stable osteoarthritis of her hands, confirmed with plain radiographs taken before this episode.

She presented with hot, swollen and tender metacarpophalangeal and interphalangeal joints (figure 1) which significantly impacted on her activities of daily living and hence independence.

This flare occurred within 2 weeks of commencing Arimidex therapy which the patient was receiving for breast cancer, diagnosed a year previously and managed

with surgery, radiotherapy and chemotherapy. There was no evidence of metastases or recurrence. Arimidex was changed to tamoxifen by the breast team due to the patient's osteoarthritis flare; by the time of the clinic appointment the flare had stopped progressing (the change in medication prevented further symptoms within 1–2 weeks). When reviewed just over 5 months later, when the patient was still undergoing tamoxifen therapy, the inflammation had settled significantly.

The patient had a past medical history of a hemicolectomy 2 years previously for a diverticular abscess.

Of interest, it was also noted retrospectively that the patient had had a significant flare of her osteoarthritis in the perimenopausal period 4 years previously.

INVESTIGATIONS

At presentation it was important to exclude the onset of a de novo inflammatory arthritis. Therefore, the patient underwent the following investigations:

1. inflammatory markers (erythrocyte sedimentation rate and C reactive protein); normal, likely due to the lack of active synovitis by the time of clinic appointment
2. full blood count, urea and electrolytes, and liver function tests; normal
3. immunology: rheumatoid factor; negative
 - ▶ anti-cyclic citrullinated peptide antibody; not raised
 - ▶ anti-nuclear antibody, double-stranded DNA, and extractable nuclear antigen antibodies; all negative.

Plain radiographs of the hands confirmed osteoarthritic changes with erosive osteoarthritis affecting multiple interphalangeal joints of both hands, and further osteoarthritic changes in both 4th and 5th metacarpophalangeal joints (figure 2).

Figure 1 Photographs of the hands of a patient with a flare of inflammatory osteoarthritis.

Figure 2 Plain radiographs of the hands of patient with a flare of inflammatory osteoarthritis.

DIFFERENTIAL DIAGNOSIS

Inflammatory arthritides including rheumatoid arthritis were excluded by the clinical phenotype, blood tests and plain radiographs of the patient's hands.

TREATMENT

Celecoxib 200 mg daily with proton-pump inhibitor cover (lansoprazole 30 mg) was prescribed in primary care prior to rheumatology review. The patient's regular medications were tamoxifen, alendronic acid and calcium supplementation.

Once a new inflammatory arthritis was excluded, the patient was reassured and referred to occupational therapy and physiotherapy to optimise hand function. She was advised to take simple analgesics and anti-inflammatories as required.

OUTCOME AND FOLLOW-UP

Since the Arimidex was substituted with tamoxifen the patient's osteoarthritis showed a marked improvement, with decreased pain and swelling. There has been some reduction in the functional capability of the patient's manual dexterity as a result of this flare. However, through close follow-up with our physiotherapy and occupational therapy team we anticipate that she will achieve increasing function with time.

DISCUSSION

Variations in the incidence of osteoarthritis occur according to local and systemic factors. In addition to local factors such as joint injury, obesity and occupation, the most significant increase is seen in older women who are three times more likely to be affected than men of a similar age.¹

Epidemiological studies investigating the link between osteoarthritis and oestrogen have reported two main findings, first that onset of the menopause is associated with increased osteoarthritis incidence and severity, and second that hormone replacement therapy may reduce this effect. Oestrogen receptors α and β have been found in chondrocytes from both healthy and osteoarthritic joints. Two in vitro studies have demonstrated in a model of oxidative stress that cultured chondrocytes are protected by physiological doses of 17β -oestradiol in a dose-dependent relationship.^{2 3}

A recent systematic review of 11 animal studies attempted to summarise the effect of ovariectomy and oestrogen therapy on cartilage.⁴ However, the authors found the evidence inconclusive. A number of the studies used immature animals and a more convincing relationship between ovariectomy and cartilage changes was seen when these experiments were excluded. Animal studies are extremely limited in their application to humans, especially as ovariectomy will cause a change in several hormones and does not directly reflect the physiological changes during the menopause.

The involvement of oestrogen in the homeostasis of joint tissues has been widely described, and it has been inferred that such protective effects will be reduced or lost as a result of the menopause. However, the most recent published in vivo research in humans remains inconclusive. The most recent systematic review found no clear evidence for an association between hand, hip and knee osteoarthritis and female serum hormonal levels, specifically assessing the duration of the fertile period, endogenous hormones, age at menarche/menopause, menopausal status, years since menopause and surgical menopause.⁵ A similar review by the same authors studied the link between exogenous

hormone use and osteoarthritis of the hand, hip and knee, and again no evidence of any association was identified. However, this paper did identify that women using unopposed oestrogen therapy had a lower incidence of total hip replacements, and the authors described this as a possible protective effect in hip osteoarthritis.⁶

A recent study assessed the potential association between radiographic evidence of hand osteoarthritis and single-nucleotide polymorphisms in oestrogen receptors α and β , which have been associated with osteoarthritis in other joints. However, no significant relationship was identified.⁷

Here we report a case in which the global systemic reduction in oestrogen as a consequence of anastrozole therapy was associated with a profound inflammatory exacerbation of osteoarthritis but specific oestrogen receptor antagonism controlled the flare. This finding suggests that the osteoarthritis flare in this patient may have been due to the effect of reduced levels of oestrogen activity through non-tamoxifen dependent pathways. This supports the link between oestrogen and osteoarthritis, which has been so widely described in epidemiological studies but remains difficult to demonstrate in controlled studies.

Arimidex (anastrozole) is an aromatase inhibitor which acts by inhibiting the biosynthesis of oestrogens from androgens, as oestrogens have a proliferative effect on oestrogen-dependent breast tumours.⁸ Both arthralgia and osteoporosis are reported side-effects of anastrozole therapy, although further research into the pathophysiological mechanisms involved is required.

Tamoxifen is a selective oestrogen receptor modulator (SERM) used as an alternative adjuvant therapy for oestrogen receptor positive breast cancer. It has two major metabolites, N-desmethyldamoxifen and trans 4-hydroxydamoxifen. Trans 4-hydroxydamoxifen has been found to show oestrogenic activity, while its side-chain is antioestrogenic.⁹ Additionally, it is well demonstrated that SERMs reduce cartilage damage in ovariectomised animals.¹⁰

It is noteworthy that tamoxifen has been found in studies to increase bone mineral density and reduce numbers of fractures, thought due to its oestrogen-agonist effects.¹¹ Arimidex showed the opposite effect with a reduction in bone mineral density.¹²

As far as the authors are aware, this is the first case in the literature to describe inflammatory osteoarthritis precipitated by Arimidex but resolved with tamoxifen. Improved understanding of the pathophysiological mechanisms involved in osteoarthritis in patients on treatment with oestrogen modifying agents may improve our understanding of the mechanisms involved in peri- and postmenopausal osteoarthritis. This could potentially lead to specific therapeutic targets to reduce disease progression in postmenopausal women who are burdened with osteoarthritis.

Learning points

- Osteoarthritis is a significant cause of morbidity, affects three times as many women as men and currently has limited treatment options to alter disease progression.
- It has long been described that many women experience a flare of their osteoarthritis during the postmenopausal period, as oestrogen levels fall; however, the pathophysiological mechanisms remain poorly understood.
- We report a case where global systemic reduction in oestrogen due to Arimidex caused a flare in osteoarthritis, but tamoxifen, a specific oestrogen receptor antagonist, controlled the flare.
- Although further case series are needed, this case highlights the potential role of oestrogen modulation in the exacerbation of osteoarthritis and, if demonstrated in larger series, may direct future research towards specific oestrogen receptors rather than simply assessing systemic oestrogen levels.

Competing interests None

Patient consent Obtained.

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