Sjögren's syndrome and aromatase inhibitors treatment: is there a link?

Sirs,

Postmenopausal hormone receptor-positive breast cancer accounts for 70% of breast cancer cases and the introduction of aromatase inhibitors (AIs) has been a major therapeutic advance in its management (1).

For many years, tamoxifen was the cornerstone of endocrine therapy, with a substantial body of evidence showing benefits in overall survival (2).

However, more recently the third generation of AIs, including anastrozole, letrozole, and exemestane, have proven to be superior to tamoxifen (2).

Major trials established that they improve disease-free survival (DFS) when used either as initial adjuvant therapy or as a switch/sequential option for patients completing two or more years of prior tamoxifen treatment (2, 3).

With many patients taking these drugs worldwide, adverse events are being investigated; the two main adverse effects of AIs were identified as a reduction in bone mineral density (BMD) and the development of musculoskeletal symptoms, which were recently given the term AIMSS (AI-induced musculoskeletal symptoms) (4). Although much has been published, the mechanisms behind AIMSS are not clearly understood. Some authors also reported the development of rheumatological diseases such as rheumatoid arthritis (5), spondyloarthropathy (6) and Sjögren's syndrome (SS) (7).

Here, we briefly report three cases of postmenopausal women who developed primary SS according to the 2002 European criteria (8) during the first year of adjuvant therapy with AIs.

The first was a 71-year-old female treated with anastrozole for 2 years, the second a 60-year-old female treated with anastrozole for 3 years, and the third a 75-year-old female treated with letrozole for 3 years. All of them complained of diffuse arthralgias, with no evidence of joint effusion and also developed a sensation of dryness of the oral cavity impeaching phonation and mastication and inducing a state of thirst, associated with similar symptoms of eye dryness including burns, itching, and sensation of foreign body. These symptoms appeared after 3 (patient 1 and 3) and 5 months (patient 2) from the beginning of AI therapy.

The sicca syndrome was confirmed by a Schirmer test, showing 4 mm of bilateral tearing in the first patient and 2 mm in the second and third ones.

Laboratory evaluation, including acute phase reactants and serology for autoimmunity, were reported in Table I.

Table I. Clinical features and laboratory data of the patients mentioned.

Patient	Age (yrs)	Age at breast cancer diagnosis (yrs)	Aromatase inhibitor	Laboratory findings	Chisholm stage
1	71	68	Anastrozole	ESR: 42 (0-35 mm/h); CRP: 0.9 (<0.5 mg/dl); gamma-globulins: 20.7 (0-18%); RF: 32 (<20 U/ml); ANA: 1:320; anti-Ro/SS-A: 57 (<7 U/ml); anti-CCP: negative	4 (Focus score >1)
2	60	56	Anastrozole	RF: 41 (<20 U/ml); ANA: 1:320; anti-CCP: negative	4 (Focus score >1)
3	75	71	Letrozole	ESR: 55 (0-35 mm/h); CRP: 1.2 (<0.5 mg/dl); gamma-globulins: 24 (0-18%); anti-Ro/SS-A: 155 (<7 U/ml); anti-CCP: negative	4 (Focus score >1)

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ANA: antinuclear antibodies; anti-CCP: anti-cyclic citrullinated peptide; anti-Ro/SS-A: anti-Sjögren's syndrome A antibodies.

In the three patients, a labial salivary gland biopsy was performed, exhibiting similar histopathologic findings such as a moderate lymphoplasmacytic infiltrate (>1 focus in 4 mm^2), a severe ductal ectasia, a mild interstitial fibrosis, and a Chisholm and Mason stage of 4.

All the three patients fulfilled the SS diagnostic criteria after one year of adjuvant therapy with AIs (8).

SS is a chronic, slowly progressive, inflammatory autoimmune disorder, characterised by lymphocytic infiltration of the exocrine glands, leading to decrease in glandular secretion. The disease may occur alone (primary SS) or in association with other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and scleroderma (secondary SS).

Only Laroche *et al*. (7) reported the development of 1 definite SS and 7 probable SS in a group of 24 women under AI treatment. In an animal model, Shim *et al*. (9) demonstrated how aromatase-knockout (ArKO) mice develop severe autoimmune exocrinopathy resembling SS, associated with renal involvement. Moreover, as is typically found in human SS, there were proteolytic fragments of α-fodrin in the salivary glands and anti-α-fodrin antibodies in the serum of both male and female ArKO mice.

This animal model, associated with the cases described, suggests that oestrogen deficiency, as determined by AI therapy, may play a role in the development and maintenance of SS. When androgen concentrations are low, as in women, oestrogens seem to specifically protect secretory glandular acinar cells against apoptosis, whereas lack of oestrogens specifically leads to increased apoptosis of the exocrine secretory cells (10). Apoptotic cells release microparticles and later apoptotic bodies, which via self-ssRNA, activate immature plasmacytoid dendritic cells (pDC) via Toll-like receptors (TLR7) to produce interferon-α/β (IFN-α/β) and Th0 polarising cytokines. pDC mature to antigen-presenting cells expressing co-stimulatory molecules and major histocompatibility complex class II (MHC II) molecules, which presents antigenic epitopes to T-cell receptors (TCRs). The ensuing pDC activation can have two alternative consequences: it can lead to an auto-inflammatory/autoimmune attack against the epithelial target cells, which already suffer from the hormonally induced apoptosis, or it can activate a tolerogenic negative feedback loop (10).

In conclusion, the cases reported here suggest a possible relationship between AI therapy and SS. Clinicians should consider this hypothesis, when patients undergoing AI therapy develop AIMSS and sicca symptoms.

More studies with bigger samples are needed to establish the real incidence of SS in patients treated with AIs, and to assess the possible reversibility of SS after discontinuation of this therapy.

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Competing interests: none declared.

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