

Brief Research Report

Aromatase inhibitor-induced musculoskeletal symptoms in foot and ankle surgery

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ABSTRACT

INTRODUCTION. Third-generation aromatase inhibitors (AIs) are the cornerstone of the management of hormone receptor-positive breast cancer. Annually, approximately 4,700 Danish women are diagnosed with breast cancer. A large number of patients treated with long-term AI experience arthralgias and myalgias, described in the literature as AI-induced musculoskeletal symptoms (AIMSS). This report aims to summarise the existing knowledge on the syndrome and present cases of AIMSS referred with refractory foot pain to raise awareness of the syndrome as a diagnostic pitfall.

METHODS. In this study, the electronic patient journals of five potential cases of AIMSS were examined. The patients were all Caucasian females with breast cancer receiving treatment with anti-oestrogenic medication.

RESULTS. AIMSS was found to be the most probable explanation in all five cases. AI-associated musculoskeletal syndrome is reported in 30-70% of patients in AI treatment. Among the five summarised cases, no clinically relevant additional information was gained from extensive imaging. The symptoms led to surgery at our department, in one case with no effect.

CONCLUSIONS. AIMSS may affect all joints, including the ankles and feet. Lack of patient information regarding AIMSS can lead to unnecessary, time-consuming, costly and potentially harmful diagnostic procedures and treatment.

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Approximately 4,700 Danish women are diagnosed with breast cancer annually [1]. In the majority, either oestrogen receptor or progesterone receptor is overexpressed, promoting the development of breast cancer [2]. Thus, various hormone receptor-targeted therapies such as aromatase inhibitors (AI), e.g., anastrozole and letrozole, have been developed [3]. In postmenopausal women, AIs are the cornerstone for managing hormone receptor-positive breast cancer [4].

With the continually improving long-term prognosis for breast cancer patients, there is a growing focus on survivorship and quality of life for breast cancer survivors undergoing up to five years of antihormone treatment. AI treatment increases overall survival and is generally considered to have a well-tolerated side effect profile [5]. However, even third-generation AIs have been recognised to cause significant musculoskeletal symptoms affecting patients' quality of life and consequently causing frequent discontinuation of therapy [4, 6, 7].

Described musculoskeletal symptoms of AIs include arthralgias, myalgias, joint stiffness and tendinopathy - and approximately 70% of the patients treated with AIs in oestrogen receptor-positive and/or progesterone receptor-positive breast cancer presented arthralgias or myalgias [6]. The constellation of these musculoskeletal symptoms has been termed the AI-associated musculoskeletal syndrome (AIMSS). Recent studies suggest that abrupt oestrogen withdrawal is a key factor in its mechanism of development [4, 6]. Similar symptoms are described for postmenopausal patients with sudden withdrawal of menopausal hormone therapy [8].

Among the three types of AI, letrozole is the most commonly used in Europe, followed by anastrozole and exemestane [9]. Patient-reported outcomes confirm similar safety profiles for these treatments, although exemestane is linked to more side effects. For letrozole, the second most frequently reported adverse event was arthralgia [10]. Up to 70% of patients with arthralgias and myalgias reported a maximum pain intensity between 5 and 7 on a scale ranging from 1 to 10 [6]. Furthermore, 17-51% of patients report AIMSS-related pain localised in the ankles/feet [7, 11].

In this report, we describe illustrative cases of AIMSS referred to the Section of Foot and Ankle Surgery at Bispebjerg and Frederiksberg Hospital and Bornholm Hospital, Denmark to raise awareness of the syndrome as a diagnostic pitfall.

Methods

Five cases of suspected AIMSS were referred and evaluated by a foot and ankle surgeon in our outpatient clinics at Bispebjerg Hospital and Bornholm Hospital over a 40-month period. The exact location of complaints varied, but presentations were overall comparable. Informed consent was obtained for all potential cases, and electronic patient journals of all potential cases of AIMSS were examined.

Trial registration: not relevant.

Results

See **Table 1** for anamnesis, objective findings and paraclinical tests, along with treatment and outcome of the five cases.

TABLE 1 Case series A-E.

Case	Anamnesis	Objective findings and paraclinical tests	Treatment	Outcome
A	A 68-year-old woman presented with a history of spontaneous pain for 3.5 years in the right medial malleolus, dorsal foot and 1st ray. After further inquiry, the patient described simultaneous worsening of joint pains and stiffness in her hands and legs. Onset of this pain was described as sudden and occurring approx. 1 month after initiation of treatment with adjuvant letrozol. The pain was constant, but varied in intensity, especially after long walks, which occasionally led to periods of difficulty in walking and a need for sudden breaks	Ankle ROM was found to be normal, and standard X-ray and MRI all turned out normal except for evidence of well-healed previous osteotomies on both 1st metatarsals performed 30 years ago	Prior to presentation, the patient had tried acupuncture, massage therapy, regular physiotherapy, and even intra-articular steroid injections, all without clear effects	The patient had regular outpatient follow-ups in both an oncological and rheumatological department. They had previously attempted breaks of up to 3 months. In AI medication without any effects. Alterations in her medication were also attempted by replacing letrozol with anastrozol and exemestane. However, this also produced no effect on her symptoms. The patient subsequently decided to stop her AI treatment after four years due to continued discomfort without any clear improvement
B	A 76-year-old woman, referred with a 3-year history of considerable pain in the left foot. Further inquiry also revealed simultaneous lower back pain. The patient had no history of prior trauma, and the onset of symptoms occurred shortly after initiation of treatment with letrozol	The feet were flexible and flat and had been largely asymptomatic. Metatarsal footpads and form-fitted footwear had been tried with no effect on the pain. The pain caused occasional limping. Ankle ROM was normal and standard X-rays showed osteoarthritis of the left 1st MTP joint. Initial treatment was conservative with rest and non-weight-bearing exercises; however, the patient was re-referred 1 year later due to progression of her pain, which was now mainly localised to the 1st-3rd MTP joint	Arthrodesis of the 1st MTP joint and Weil osteotomies of the 2nd and 3rd metatarsals were then performed	Despite surgery being uncomplicated, the patient still presented with unaltered pain compared with preoperative levels. All osteosynthesis material was removed surgically 1 year post-operatively, still without improvement in symptoms. The patient reported to later try neuro-cryotherapy, acupuncture, massage therapy and osteopathy, all without effect on the pain. The oncologists attempted to pause her letrozole treatment for 3 months, without any effect on symptoms. However, treatment with letrozol was subsequently terminated in consultation with the oncologists, before finishing the recommended 5-year period
C	A 79-year-old woman, referred with a history of pain localised to the medial side of her right ankle through 2.5 months. The patient reported having completed a 10-km walk and played tennis the day before pain onset. The patient had already been treated with two steroid injections without significant effect prior to referral. The patient was 4 years into her treatment with letrozol and had since initiation of AI treatment, previously reported periods of bilateral fluctuating ankle and knee joint pain, though without clearly affecting her normal levels of activity and function	Objective findings included swelling around the entire ankle and tenderness upon palpation of both the malleoli and distal Achilles tendon. There was slight ankle stiffness but no instability. The patient had a slight limp. Standard radiographs showed mild midfoot arthrosis corresponding to her age. Due to a history of cancer metastasis, a PET was performed, showing increased bone remodeling in the medial malleolus	A conservative approach was recommended with an ankle-stabilising bandage for 6 weeks	The patient reported considerable improvement of pain and reduced swelling after 3 months
D	A 62-year-old woman presented with multiple joint pain. The pain in her left hindfoot and arch was particularly exacerbated by walking. Onset of symptoms was spontaneous 3 weeks after initiation of letrozol therapy	Objective findings included a slight limp, swelling around the medial malleolus and palpation tenderness of the tibialis posterior tendon. Standard radiographs, MRI and a SPECT were performed without abnormal findings	Steroid injections	The patient experienced 2-3 months relief of symptoms after radiologically assisted subtalar steroid injection, which was therefore repeated after 4 months due to return of symptoms. No pauses of letrozol were tried
E	A 71-year-old woman was referred with widespread joint pain. Of particular concern was increasing plantar pain and discomfort in the left forefoot, which was worsened by weight bearing. Onset of symptoms occurred shortly after treatment with letrozole was initiated, which was subsequently changed to exemestan due to side effects	The patient had noticed increasing malalignment and altered sensation in her 2nd-4th toes. Other clinical findings included bilateral flexible flat feet and metatarsalgia. Standard radiographs gave no other signs of pathology	The patient was treated conservatively with an offloading regime	There was no further contact with the patient thereafter

AI = aromatase inhibitor; MRI = magnetic resonance imaging; MTP = metatarsophalangeal; ROM = range of motion; SPECT = single-photon emission computed tomography.

Discussion

AIMSS is a widely reported phenomenon, and suboptimal compliance with AI adjuvant therapy due to inadequately managed AIMSS remains a challenge and a major unmet need. To our knowledge, no specific literature on this topic exists, even though this diagnosis is very relevant for oncologists, rheumatologists, orthopaedic surgeons and general practitioners. In our opinion, significant improvements in patient treatment can be achieved with recognition of AIMSS as a possible differential diagnosis in cases of refractory pain after commencement of AI treatment.

Some studies refer to these symptoms as arthralgia syndrome and AI-induced arthralgia. However, more recently, the term AIMSS has been introduced to describe the constellation of joint pains [12-15].

The lack of a formally accepted definition for AIMSS remains a major challenge; however, there is agreement about the relation between the onset of symptoms and the start of AI therapy, as well as the relation between improvement in symptoms or spontaneous symptom resolution after cessation of AI treatment. Symptom onset

can range from a couple of weeks to more than ten months, with a median of 1.6 months [12-14, 16].

All five patients in this case series were referred to our foot and ankle surgeons by a general practitioner for severe foot and ankle pain consistent with AIMSS. In all cases, there was also a history of pain in other joints, and symptom onset consistently occurred after initiation of treatment with AI medication, which is also in line with the general definition of AIMSS. The five cases mentioned above, are - in our opinion - good examples that correspond with recent studies, which report the frequency of arthralgia associated with anti-oestrogen treatment to fall in the 30-70% range [4, 6].

In these cases, the suspicion of AIMSS as the most likely diagnosis was based on its temporal relationship to the initiation of antihormonal treatment. The variation in symptom relief after treatment breaks or termination could be attributed to insufficient duration of treatment breaks or premature referral to surgical evaluation before the effect of termination of treatment had been achieved. However, we acknowledge that there is no consensus in the existing literature on the necessary duration of treatment breaks for effective symptom relief. Niraveth et al. suggested that joint pain improves and may even resolve within as little as two weeks of stopping AI therapy. However, this was not found in any other published study [14].

It was also hypothesised that anti-oestrogen treatment might enhance the intensity of arthralgia already present or trigger other diseases, e.g., osteoarthritis, suddenly making it symptomatic at the time treatment was initiated. Furthermore, the secondary criteria, e.g., morning stiffness and improvement with use or exercise, were not described as related to foot and ankle pain in the charts of any of the reported cases.

Our series reports similar cases, which, in our opinion, were worsened by a lack of awareness and general knowledge. Even though our five cases cannot establish beyond a doubt that AIMSS was the cause of their symptoms, they illustrate typical clinical scenarios in which AIMSS could be suspected. One cannot draw firm conclusions from this material; however, it may increase awareness of AIMSS as a differential diagnosis in cases of spontaneous and/or worsening pain in the foot and ankle. Awareness may improve patient management and help avoid unnecessary or potentially harmful procedures and treatments.

It is important to note that this case series has several important limitations. One of the unavoidable drawbacks is that most patients with this condition are generally in an age bracket where it is common to encounter multiple concurrent degenerative musculoskeletal conditions. Similar symptoms are also described as a part of the musculoskeletal syndrome of menopause [8]. Hence, there is a risk that we may treat pre-existing conditions that are not necessarily the cause of the patient's actual symptoms.

We also wish to emphasise that AIMSS is not yet fully understood and further research into its mechanisms and treatment, as well as formal diagnostic criteria for this syndrome, is needed.

Conclusions

AIMSS affects the joints of the foot and ankle and may cause discomfort and pain near the start of AI therapy. All five cases reported debuted with severe foot or ankle pain after the patients initiated AI for breast cancer. Poor physician attention and subsequent lack of patient information of this known adverse effect of AI may result in redundant, time-consuming, costly and potentially harmful diagnostic procedures and treatments. We hope this report will raise awareness of AIs as a cause of spontaneous and refractory pain in the foot and ankle.

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