

Case Report

Aromatase Inhibitor-Associated Tendinopathy and Muscle Tendon Rupture: Report of Three Cases of This Exceedingly Rare Adverse Event

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Keywords

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Abstract

Aromatase inhibitors (AIs) are a commonly used antihormonal therapy in the treatment of breast cancer in postmenopausal women, specifically in the treatment of hormone receptor-positive breast cancer. AI-associated tendinopathy and muscle tendon rupture is exceedingly rare. Until now, only one case with AI-associated severe tendinopathy has been reported in the medical literature, and there are no recorded cases of AI-associated muscle tendon rupture. We report three cases of postmenopausal women with hormone receptor-positive breast cancer, who experienced tendinopathy or muscle tendon rupture under antihormonal treatment with letrozole. All of the three women were in the adjuvant setting, and the treatment of tendinopathy or tendon rupture consisted of AI discontinuation, initiation of corticosteroids, or surgical treatment. Diagnosis was made via MRI. Furthermore, in our cases, there were no signs of underlying systemic disease, there was no abnormal physical activity preceding the complaints, and there was no use of other drugs beside letrozole. AIs are one of the most commonly used drugs in antihormonal therapy for hormone receptor-positive breast cancer. In every case of a female patient with hormone receptor-positive breast cancer under treatment with AIs and arthralgia, an MRI should be performed in order to exclude the presence of tendinopathy or muscle tendon rupture.

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Introduction

Aromatase inhibitors (AIs) are an antihormonal therapy, which is commonly used in the treatment of breast cancer in postmenopausal women, specifically in the treatment of hormone receptor-positive breast cancer. They are considered as part of adjuvant therapy after mastectomy or breast conservation therapy. Moreover, they can be used as first-line therapy in metastatic hormone receptor-positive breast cancer.

The 3 third-generation AIs in routine clinical practice are anastrozole, letrozole, and exemestane. They all have a similar toxicity and efficacy profile. The most common adverse events induced by AIs include menopausal symptoms, vaginal dryness, musculoskeletal symptoms, and sexual dysfunction. The most commonly recorded musculoskeletal symptoms consist of pain in bones and muscles (myalgias and arthralgias), bone fracture, and increased risk for osteoporosis. Tendinopathy and muscle tendon rupture are rarely recorded in the medical literature. We report 3 cases of postmenopausal women with severe tendinopathy or muscle tendon rupture, while they were treated with AIs in the adjuvant setting.

Case Presentations

Case 1

A 74-year-old female patient was diagnosed with luminal B (ER+, PR+, Her2–, Ki67 25%) invasive ductal adenocarcinoma in the left breast, stage IIB (pT3 pN0 cM0). The patient underwent mastectomy, followed by adjuvant chemotherapy and radiotherapy. Thereafter, we initiated antihormonal therapy with letrozole. One year after the initiation of letrozole treatment, the patient complained of persistent pain in her left shoulder. We performed an MRI of the left shoulder, which revealed a partial rupture of the tendon of the supraspinatus muscle. Furthermore, we excluded local recurrence in the chest wall or neck by performing staging with a CT scan of the chest and neck. There were no signs of underlying systemic disease, there was no abnormal physical activity preceding the complaints, and there was no use of other drugs beside letrozole. We discontinued the AI, and the patient was referred to the Orthopedic Clinic of our hospital for surgical treatment.

Case 2

A 62-year-old female patient was diagnosed with luminal B (ER+, PR+, Her2–, Ki67 30%) invasive ductal adenocarcinoma in the left breast, stage I (pT1c pN0 cM0). The patient underwent lumpectomy, followed by adjuvant chemotherapy and radiotherapy. We initiated antihormonal therapy with letrozole. Eleven months after initiation, the patient complained of persistent pain in her left shoulder. We performed an MRI of the left shoulder, which revealed severe tendinopathy of the supraspinatus tendon. There were no signs of underlying systemic disease, and there was no abnormal physical activity preceding the complaints. We excluded local recurrence in the chest wall or neck by performing staging with a CT scan of the chest and neck. We discontinued the treatment with letrozole, and the patient was started on conservative management with corticosteroids. One month after replacing her drug, a complete withdrawal of symptoms was observed.

Case 3

A 71-year-old female patient underwent lumpectomy of the left breast and was diagnosed with luminal A (ER+, PR+, Her2–, Ki67 15%) invasive ductal adenocarcinoma, stage IIA (pT2

pN0 cM0). She received radiotherapy, and then we initiated antihormonal therapy with letrozole. Eighteen months after letrozole initiation, the patient suffered from a persistent arthralgia in the right shoulder. An MRI of the right shoulder revealed a complete rupture of the tendons of the supraspinatus muscle and the subscapularis muscle and a partial rupture of the tendon of the infraspinatus muscle. We had previously excluded local recurrence by performing a CT scan of the chest and neck. Any signs of underlying systemic disease and any abnormal physical activity preceding the complaints were excluded. There was no use of other drugs beside letrozole. The patient discontinued letrozole and was referred to the Orthopedic Clinic of our hospital for surgical treatment.

Discussion

AIs are used in the adjuvant setting in postmenopausal women with hormone receptor-positive breast cancer and as first-line treatment in the metastatic setting of hormone receptor-positive breast cancer. Prior to menopause, estrogen is mainly produced in the ovaries. After menopause, estrogen production mainly occurs in the peripheral tissues like the skin, fat, muscle, and benign and malignant breast tissue through the conversion of androgen to estrogen by the P450 cytochrome enzyme aromatase. AIs suppress plasma estrogen levels by inhibiting or inactivating aromatase, the enzyme responsible for the peripheral conversion of androgens to estrogens [1]. The non-steroidal AIs (letrozole and anastrozole) competitively inhibit aromatase. Exemestane (a steroidal AI) irreversibly inhibits aromatase. Nevertheless, both types suppress plasma and tissue concentrations of estrone, which is the main estrogen in postmenopausal women [2–4].

Adjuvant endocrine therapy reduces breast cancer recurrence and breast cancer mortality in postmenopausal women with non-metastatic hormone receptor-positive breast cancer. When compared with tamoxifen, AIs result in a more substantial reduction in recurrence during treatment and in a lower breast cancer mortality both during and after treatment [5]. Furthermore, postmenopausal women who progress at least 12 months after the end of adjuvant endocrine therapy or who present with de novo metastatic hormone receptor-positive breast cancer and with low metastatic burden are eligible for endocrine therapy. The preferred choices in these patients are a combination of CDK4 inhibitors with AIs or AIs as single therapy.

In postmenopausal women with hormone receptor-positive breast cancer (metastatic or not), it has been demonstrated that AIs have a more favorable toxicity profile in comparison to tamoxifen. In large randomized trials, it was demonstrated that in comparison to tamoxifen, AIs were correlated with fewer thromboembolic events, cardiovascular events, and cases of endometrial cancer [6].

Despite the most favorable toxicity profile in comparison to tamoxifen, AIs still remain drugs which can induce some side effects. The most common adverse events induced by AIs are musculoskeletal symptoms, sexual dysfunction, menopausal symptoms, vaginal dryness, and, rarely, fatigue, forgetfulness, and poor sleep hygiene [7]. Sexual dysfunction consists of reduced sexual interest, reduced vaginal lubrication, and higher rates of dyspareunia [8]. Musculoskeletal symptoms induced by AIs include arthralgia, joint stiffness, bone pain, bone fracture, and an increased risk of osteoporosis [9]. These symptoms can be severe in a third of the patients. Carpal tunnel syndrome [10], tenosynovitis [11], and tendinopathy [12] are less frequently recorded. There is a clear association between postmenopausal estrogen deficiency

and the development of osteoporosis, correlated with the regulative role of estrogen in bone remodeling.

Despite the absence of an obvious pathophysiological mechanism, there is a correlation between the intake of AIs and tendinopathy or muscle tendon rupture. Possible causes of tendinopathy include inherited disorders, endocrine and metabolic disorders, and rheumatologic diseases [13]. Furthermore, intrinsic factors, like age and joint laxity, and extrinsic factors, like occupation and sport, can be high-risk features for developing tendinopathy [12]. Beside these factors, the intake of AIs can be correlated with severe tendinopathy or tendon rupture. Till now, there has only one case been recorded in the medical literature with AI-induced severe tendinopathy. In our cases, there were no signs of underlying systemic disease, there was no abnormal physical activity preceding the complaints, and there was no use of other drugs beside letrozole. In addition, in all cases, local recurrence in the chest wall or in the neck was excluded. In two of three patients, muscle tendon rupture was recorded. These are, to our knowledge, the first two cases of muscle tendon rupture correlated with the intake of AIs recorded in the medical literature.

In our cases, diagnosis was performed using an MRI. Characteristic changes in tendon appearance on ultrasound or MRI studies can be used to confirm the diagnosis of tendinosis, identify macroscopic tears, and identify the involvement of associated structures. In similar cases with patients receiving AIs and suffering from arthralgia or myalgia, MRI or ultrasound can reveal or exclude tendinopathy or muscle tendon rupture.

In the treatment of tendinopathy, discontinuation of AIs and the use of corticosteroids seem to be the treatment of choice. In the case of muscle tendon rupture, surgical treatment in combination with discontinuation of AIs seems to be the more favorable choice. In every case, we should take this side effect of AIs seriously into consideration, when we have a patient with severe and permanent arthralgia or myalgia.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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