

Single Case

Localized Cutaneous Adverse Event Induced by Anastrozole as Adjuvant Treatment for Breast Cancer: A Case Report

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Keywords

Adverse drug reaction · Aromatase inhibitor · Breast cancer · Vascular proliferation

Abstract

Cutaneous adverse events caused by aromatase inhibitors have been reported to be rare. We describe a rare case of a cutaneous adverse event that developed in a cancer-affected breast after aromatase inhibitor treatment. A 72-year-old postmenopausal female patient who was diagnosed with stage IA breast cancer received anastrozole as adjuvant treatment. Six months after the initiation of anastrozole, she developed an irregularly shaped purpuric plaque with several purpuric papules surrounding the postoperative scar on her left breast. Histological findings revealed capillary vessel proliferation and expansion, with hemorrhage in the superficial dermis. Immunohistochemistry of the skin biopsy specimen revealed hormone receptor expression limited to the vascular endothelial cells of the proliferating and expanding vessels. We believe that anastrozole induced a change in the local estrogen level, which affected the hormone receptor-positive endothelial cells in the dermis near the primary lesion of the breast cancer and caused a cutaneous adverse event only in the aforementioned area.

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Introduction

Aromatase inhibitors (AIs) are commonly used for hormone receptor-positive breast cancer both in the early stage, as adjuvant treatment, and in the advanced stage. Three AIs (anastrozole, letrozole, and exemestane) suppress the plasma estrogen level by inhibiting or inactivating aromatase. Although cutaneous adverse events caused by these AIs have been reported to be rare [1], we experienced a very rare case of a cutaneous adverse event due to anastrozole that was localized to the area around the postoperative scar from mastectomy.

Case Report

A 72-year-old, postmenopausal female patient who was diagnosed with breast cancer underwent left breast mastectomy and sentinel lymph node biopsy. The postoperative diagnosis was invasive ductal carcinoma, and no metastases were found in the sentinel lymph nodes (T1N0M0, stage IA). The tumor cells were positive for the estrogen receptor (ER) and progesterone receptor (PR), but negative for the human epidermal growth factor receptor 2 (HER2). She was started on 1 mg of anastrozole daily as adjuvant treatment and did not receive radiotherapy.

Six months after the initiation of anastrozole, she developed a hard, irregularly shaped erythema surrounding the postoperative scar on the left breast. Results of the skin biopsy revealed no evidence of skin metastasis of the breast cancer. She was referred to us because the erythema gradually expanded and changed to an indurated purpuric plaque. Fixed drug eruption was considered as the differential diagnosis; however, topical steroid and anti-allergy medicine did not improve the symptom. Additionally, several purpuric papules developed in the purpura (Fig. 1a); thus, another skin biopsy that included the new papule was performed.

Histological findings of the second biopsy specimens showed the proliferation and expansion of capillary vessels with hemorrhage in the superficial dermis (Fig. 2a–c). There was no obvious change to suggest drug eruption, vasculitis, or evidence of skin metastasis of the breast cancer. A few days after the cessation of anastrozole, the purpura rapidly disappeared (Fig. 1b). As the grade of the cutaneous change was not severe, anastrozole was readministered to the patient after a month of interruption. Eighteen months after readministration, there was no evidence of another cutaneous adverse event related to anastrozole treatment or the recurrence or metastasis of breast cancer.

Discussion/Conclusion

The molecular subtypes of breast cancer are determined using the hormone receptor status and HER2 status of the tumor cells. Treatment decisions are made with consideration of the tumor stage, tumor grade, and molecular subtype. Our patient was postmenopausal, had hormone receptor-positive breast cancer, and received anastrozole as adjuvant treatment.

The growth and metastasis of hormone receptor-positive breast cancer is stimulated by estrogen. The aromatase enzyme is responsible for estrogen biosynthesis from androgen in postmenopausal women. AIs suppress the plasma and intratumoral estrogen level by blocking the aromatase enzyme and exhibit an antitumor effect in the treatment of postmenopausal, hormone receptor-positive breast cancer.

Common adverse events associated with AIs are an increased risk of bone fracture, arthralgia, myalgia, and other musculoskeletal disorders. Complaints related to the skin such as rash, pruritus, dry skin, and acne appear less frequently [2]. However, rare cutaneous adverse events such as cutaneous vasculitis [1, 3–5], erythema nodosum [6], subacute cutaneous lupus erythematosus [7], lichen sclerosus vulvae [8], erythema multiforme [9], and erythema multiforme-like eruption [10] have been reported. A previous report suggested that inhibition of the estrogen effect, which prevents the pathogenesis of vasculitis, may paradoxically induce vasculitis [4]. The mechanism leading to other cutaneous adverse events has not been clearly explained. In our case, the cutaneous lesion was localized to the area around the mastectomy scar. There have only been two reports of a cutaneous adverse event limited to the cancer-affected breast [5, 10].

The local onset of a cutaneous disorder was supposedly explained by the concept of the immunocompromised district of skin [11]. The immunocompromised district is a skin area more vulnerable than the rest of the body due to the local dysregulation of immune control and is thought to be caused by several factors such as chronic lymphatic stasis, herpetic infection, ionizing or ultraviolet radiations, and various types of trauma. In two previously reported cases of a limited cutaneous adverse event related to anastrozole treatment, both patients had undergone radiation therapy and one experienced lymphedema [11]. Our patient did not undergo radiation therapy or lymph node dissection; therefore, the local condition of her left breast that caused the limited cutaneous lesion was not likely explained by the concept of the immunocompromised district of skin.

In postmenopausal women, extragonadal sites such as mesenchymal cells of the adipose tissue and skin, bone, and brain express aromatase and become the main source of estrogen. The estrogen produced by breast adipose tissue is strongly implicated in promoting the development and growth of ER-positive breast cancer [12]. Shibahara et al. [13] reported that the aromatase status of a primary tumor generally represents the status of metastatic lymph nodes, and aromatase immunoreactivity was detected in the adipose tissue surrounding the lymph node. The endocrine environment of an ER-positive tumor remains stable during the metastatic process. In our case, we considered the possibility that this endocrine environment, which was related to the development of a cutaneous adverse event, was limited to the cancer-affected breast.

Immunohistochemistry of the skin biopsy specimen was performed, and ER/PR expression was observed in the vascular endothelial cells of the proliferating and expanding vessels in the superficial dermis (Fig. 3a–d). Extravasation of erythrocytes was also observed around the proliferating vessels with hormone receptor-positive endothelial cells, which reflects the clinical manifestation of purpura. There was no ER/PR expression in the other vessels in the dermis without proliferation. In a postmenopausal, non-breast cancer patient, ER/PR expression was not observed in the skin of the breast or adipose tissue (Fig. 3e, f). We believe that AIs induced a change in the local estrogen level, which affected the proliferating ER/PR-positive endothelial cells in the dermis near the primary lesion of the breast cancer and caused a cutaneous adverse event only in the aforementioned area.

We initially considered whether therapeutic alteration was necessary because the cutaneous change in our patient seemed to be skin metastasis of the breast cancer based on its appearance or drug eruption due to anastrozole. However, if her cutaneous lesion was caused by the change in the local estrogen level induced by anastrozole, like we thought, it might indicate the effect of the treatment against tumor progression. In that case, continuation of the anastrozole treatment will be preferable.

On the other hand, AIs are supposed to affect the vascular endothelial growth factor and endostatin levels, and lead to angiogenic balance, which decreases intratumoral microvessel density in patients with breast cancer [14]. In our patient, AIs may have caused cutaneous vascular change through these proangiogenic and antiangiogenic proteins.

Statement of Ethics

Informed consent was obtained orally from the patient to publish her case; however, a signed document was not obtained because she stopped visiting us.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Aya Tanaka conducted the work. Chigusa Yamashita, Haruna Hinogami, and Hirohiko Shirai contributed to the dermatological analysis. Jun Yamamura took charge of the treatment of the breast cancer. Ryota Itoh contributed to the histopathological analysis. All authors helped in drafting the work or revising it critically for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

- 1 Pathmarajah P, Shah K, Taghipour K, Ramachandra S, Thorat MA, Chaudhry Z, et al. Letrozole-induced necrotising leukocytoclastic small vessel vasculitis: first report of a case in the UK. *Int J Surg Case Rep*. 2015;16:77–80.
- 2 Cristofanilli M, Valero V, Mangalik A, Royce M, Rabinowitz I, Arena FP, et al. Phase II, randomized trial to compare anastrozole combined with gefitinib or placebo in postmenopausal women with hormone receptor-positive metastatic breast cancer. *Clin Cancer Res*. 2010 Mar;16(6):1904–14.
- 3 Santoro S, Santini M, Pepe C, Tognetti E, Cortelazzi C, Ficarelli E, et al. Aromatase inhibitor-induced skin adverse reactions: exemestane-related cutaneous vasculitis. *J Eur Acad Dermatol Venereol*. 2011 May;25(5):596–8.
- 4 Shoda H, Inokuma S, Yajima N, Tanaka Y, Setoguchi K. Cutaneous vasculitis developed in a patient with breast cancer undergoing aromatase inhibitor treatment. *Ann Rheum Dis*. 2005 Apr;64(4):651–2.
- 5 Bock VL, Friedlander M, Waring D, Kossard S, Wood GK. Cutaneous adverse effects of hormonal adjuvant therapy for breast cancer: a case of localised urticarial vasculitis following anastrozole therapy and a review of the literature. *Australas J Dermatol*. 2014 Nov;55(4):282–5.
- 6 Jhaveri K, Halperin P, Shin SJ, Vahdat L. Erythema nodosum secondary to aromatase inhibitor use in breast cancer patients: case reports and review of the literature. *Breast Cancer Res Treat*. 2007 Dec;106(3):315–8.
- 7 Zarkavelis G, Kollas A, Kampletsas E, Vasiliou V, Kaltsonoudis E, Drosos A, et al. Aromatase inhibitors induced autoimmune disorders in patients with breast cancer: A review. *J Adv Res*. 2016 Sep;7(5):719–26.

- 8 Potter JE, Moore KA. Lichen sclerosus in a breast cancer survivor on an aromatase inhibitor: a case report. *J Gen Intern Med*. 2013 Apr;28(4):592–5.
- 9 Nakatani K, Matsumoto M, Ue H, Nishioka A, Tanaka Y, Kodama H, et al. Erythema multiforme after radiotherapy with aromatase inhibitor administration in breast-conservation treatment for breast cancer. *Breast Cancer*. 2008;15(4):321–3.
- 10 Wollina U, Schönlebe J, Heinig B, Tchernev G, França K, Lotti T. Segmental erythema multiforme-like drug eruption by aromatase inhibitor anastrozole - first case report and another example of an immunocompromised district. *Open Access Maced J Med Sci*. 2018 Jan;6(1):79–81.
- 11 Ruocco V, Ruocco E, Piccolo V, Brunetti G, Guerrera LP, Wolf R. The immunocompromised district in dermatology: A unifying pathogenic view of the regional immune dysregulation. *Clin Dermatol*. 2014 Sep-Oct;32(5):569–76.
- 12 Mukhopadhyay KD, Liu Z, Bandyopadhyay A, Kirma NB, Tekmal RR, Wang S, et al. Aromatase expression increases the survival and malignancy of estrogen receptor positive breast cancer cells. *PLoS One*. 2015 Apr;10(4):e0121136.
- 13 Shibahara Y, Miki Y, Ishida T, Nakamura Y, Suzuki T, Ohuchi N, et al. Immunohistochemical analysis of aromatase in metastatic lymph nodes of breast cancer. *Pathol Int*. 2013 Jan;63(1):20–8.
- 14 Holmes CE, Huang JC, Pace TR, Howard AB, Muss HB. Tamoxifen and aromatase inhibitors differentially affect vascular endothelial growth factor and endostatin levels in women with breast cancer. *Clin Cancer Res*. 2008 May;14(10):3070–6.

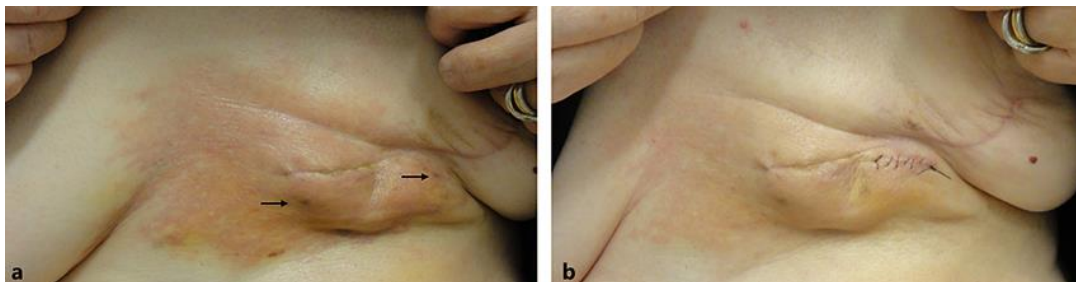


Fig. 1. **a** Clinical appearance. Indurated purpuric plaque with several purpuric papules (→) surrounding the postoperative scar on the left breast. **b** A few days after the cessation of anastrozole, the purpura has disappeared.

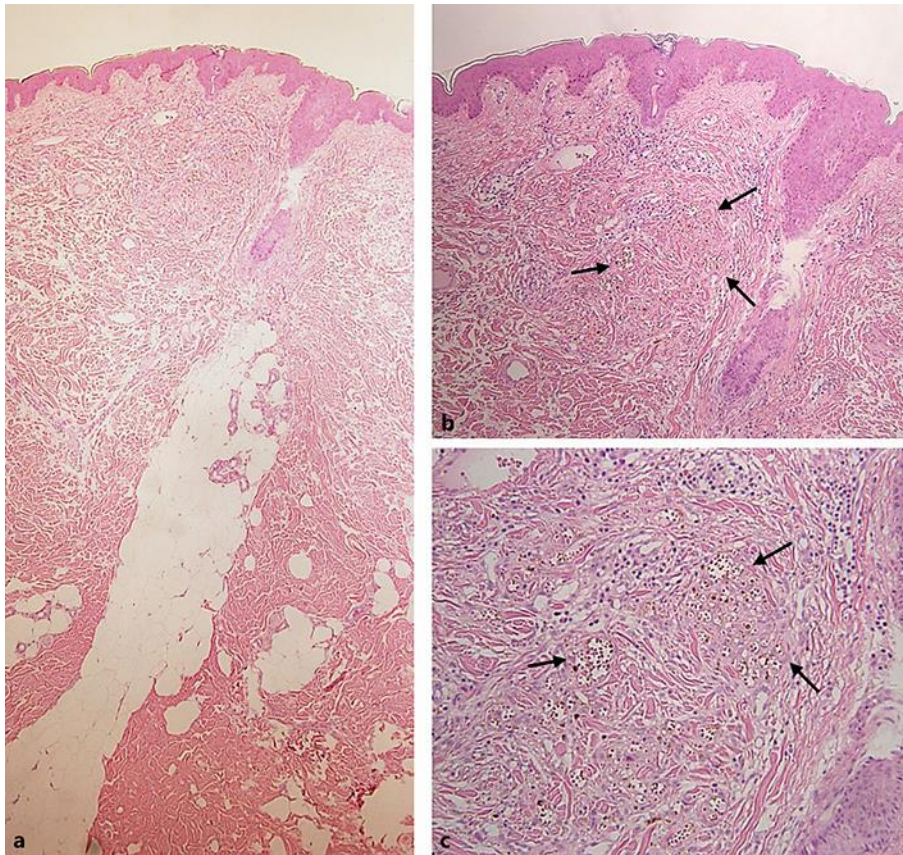


Fig. 2. Histological findings reveal proliferation and expansion of the capillary vessels with hemorrhage in the superficial dermis (arrows indicate the area with significant change). There is no evidence of skin metastasis of the breast cancer. Hematoxylin and eosin stain, magnification: $\times 40$ (a), $\times 100$ (b), $\times 200$ (c).

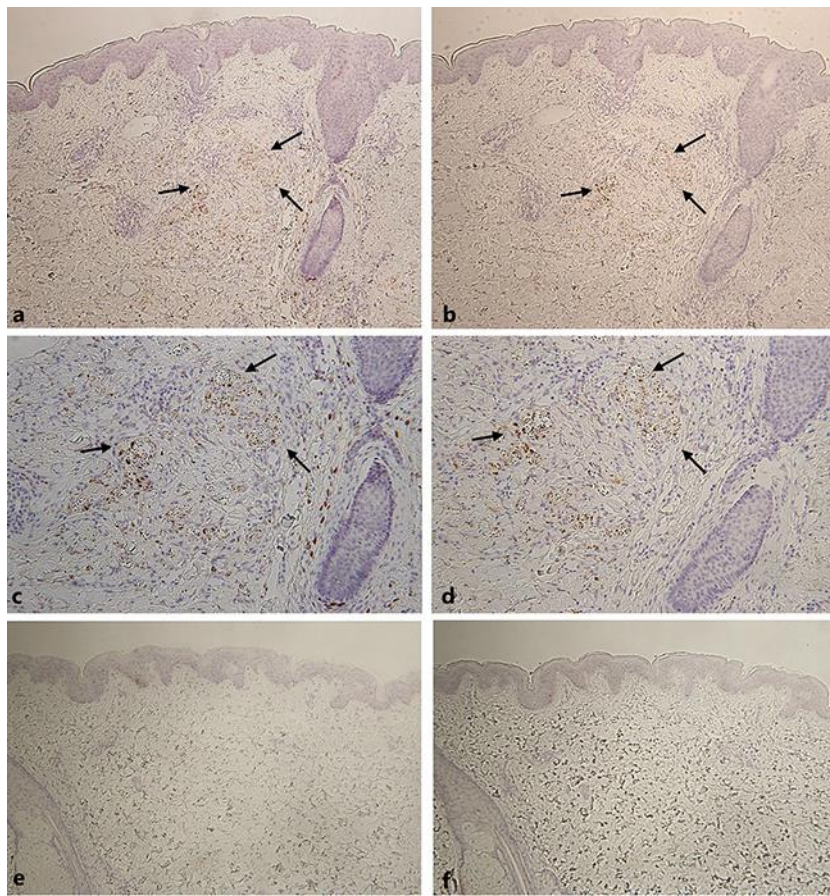


Fig. 3. Immunohistochemistry of the skin biopsy specimen indicates estrogen receptor (ER) and progesterone receptor (PR) expression in the vascular endothelial cells of the proliferating and expanding vessels in the superficial dermis. Arrows indicate the proliferated and expanded vessels with hormone receptor-positive endothelial cells at the same area as in Figure 2. Magnification: ER, $\times 100$ (a); PR, $\times 100$ (b); ER, $\times 200$ (c), PR, $\times 200$ (d). In a postmenopausal, non-breast cancer patient, ER/PR expression is not observed in the skin of the breast or adipose tissue. Magnification: ER, $\times 40$ (e), PR, $\times 40$ (f).