

BRIEF REPORTS

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

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ABSTRACT

Hormonal therapy with either tamoxifen or aromatase inhibitors is commonly used to treat women with breast cancer in both the adjuvant and recurrent disease setting. Cutaneous adverse reactions to these drugs have been rarely reported in the literature. We report an unusual case of urticarial vasculitis following the aromatase inhibitor anastrozole that localised to the unilateral trunk and mastectomy scar, and review the literature on the cutaneous adverse effects of hormonal therapy for breast cancer.

Key words: adjuvant hormonal therapy, anastrozole, aromatase inhibitor, breast carcinoma, leukocytoclastic vasculitis, urticarial vasculitis.

Aromatase inhibitors (anastrozole, letrozole and exemestane) are widely used to treat postmenopausal women with oestrogen receptor-positive breast cancer in both the adjuvant and recurrent disease setting. Cutaneous adverse reactions associated with aromatase inhibitors have been rarely reported in the literature. We report an unusual case of urticarial vasculitis following anastrozole that localised to the unilateral trunk and mastectomy scar, and review the literature on cutaneous adverse effects of hormonal therapy for breast cancer.

A 69-year-old woman underwent a right mastectomy for a grade II lobular breast cancer which was strongly oestrogen and progesterone-receptor positive and node negative. She was commenced on adjuvant anastrozole 1 mg daily orally and within 2 days of commencing treatment complained of headaches, sweating and arthralgias. The patient ceased anastrozole after a total of 7 days of treatment with the prompt resolution of her symptoms. She was then prescribed tamoxifen 20 mg daily orally as adjuvant therapy. She remained on tamoxifen for 1 year but during this time had a number of intermittent adverse effects of headaches, hot flushes and sweating. The tamoxifen was discontinued and she restarted anastrozole 1 mg daily in the hope that she would have fewer adverse effects compared to those on tamoxifen.

She experienced no recurrence of headaches, sweating or arthralgias on anastrozole. However, 9 days after commencing anastrozole she developed a unilateral tender and erythematous urticarial plaque over the mastectomy scar extending to the abdomen, axilla and back (Fig. 1). Given the localised nature of the eruption, a cutaneous recurrence of her breast cancer in the form of carcinoma erysipeloides was suspected and a skin biopsy was obtained for histology.

The skin biopsy revealed leukocytoclastic vasculitis with dermal oedema, swollen endothelial cells with surrounding nuclear debris and a superficial and deep perivascular inflammatory infiltrate consisting of lymphocytes and neutrophils (Fig. 2). Further investigation including urinalysis and blood tests revealed no evidence of a systemic vasculitis.

Anastrozole was discontinued after a total of 10 days treatment and oral prednisone 25 mg daily was commenced, weaning over 1 week. The eruption resolved rapidly within 4 days of commencing oral prednisone without residual purpura or pigmentation. She was not rechallenged with

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Abbreviation:

SCLE subacute cutaneous lupus erythematosus



Figure 1 Unilateral urticarial and erythematous plaque over the trunk.

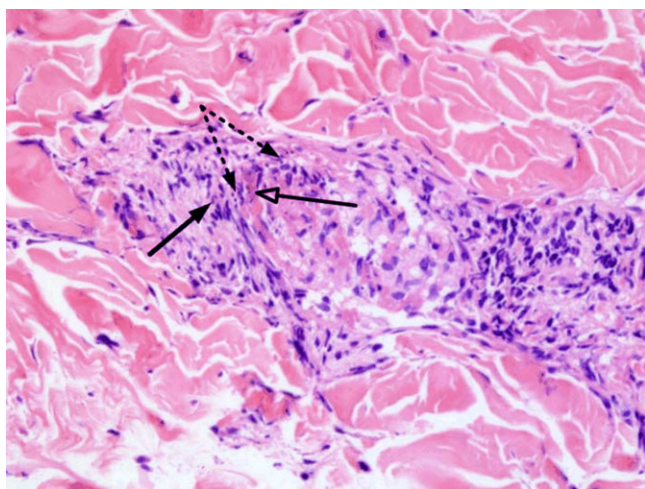


Figure 2 Histopathology from the cutaneous eruption revealing leukocytoclastic vasculitis with neutrophils (solid arrow), leukocytoclasia (dashed arrows) and fibrinoid necrosis (open arrow) (H&E).

anastrozole or any other aromatase inhibitor in view of the adverse side effects. A visual timeline of her drug administration and adverse effects is presented in Figure 3.

Breast cancer is the most common malignancy in women, accounting for 27% of all new cancers and 15% of all cancer deaths in Australian women, excluding non-melanoma skin cancers.¹ Since the year 2000 aromatase inhibitors have largely superseded tamoxifen as the gold standard for the first-line treatment of postmenopausal women with early and advanced oestrogen-receptor positive breast cancer with regard to disease-free survival and incidence of contralateral breast cancer. In addition, anastrozole has been shown to be significantly better tolerated than tamoxifen with respect to endometrial cancer, ischaemic cerebrovascular events, thromboembolic events and hot flushes. However, anastrozole has significantly more side-effects of musculoskeletal disorders and fractures than tamoxifen.^{2,5}

Aromatase inhibitors act via the inhibition of the enzyme aromatase, which catalyses the conversion of adrenal androgen substrates to oestrogens (the main source of oestrogen in postmenopausal women). First-generation and second-generation aromatase inhibitors are not used due to their toxicity and extensive first-pass metabolism, respectively.⁴ The new third-generation aromatase inhibitors currently in use in Australia include anastrozole, letrozole and exemestane. Anastrozole and letrozole are both reversible non-steroidal inhibitors that are highly selective for the aromatase enzyme.^{5,6} Exemestane is an irreversible steroidal inhibitor of aromatase. All three drugs have been shown to reduce aromatase activity by at least 98%.⁷

Hormonal adjuvant therapy for breast cancer is generally well-tolerated apart from menopausal side-effects, and cutaneous adverse effects other than flushing are uncommon. A review of the literature identified published case reports of cutaneous adverse events due to adjuvant hormonal therapy for breast cancer (see Table 1). In total, 21 cases, including the present patient, were identified. Vasculitis was the most common reported adverse cutaneous event for both tamoxifen and aromatase inhibitors, with four cases of vasculitis reported for both drug classes^{8–11,17,18,22} Other reactions to tamoxifen included subacute cutaneous lupus erythematosus (SCLE), radiation recall dermatitis, eccrine squamous syringometaplasia and a maculopapular eruption.^{12–16} Of the five cases involving anastrozole, three cases presented with vasculitis (including our patient)^{17,18} and one case each with SCLE¹⁹ and a micropapular eruption.²⁰ Three cases of erythema nodosum were reported for letrozole²¹ one of vasculitis²² and two of unspecified eruptions²³ to exemestane. Only one other case of cutaneous vasculitis with an unusual distribution was identified.⁸ The distribution in that patient was similar to our patient and involved the mastectomy scar, unilateral chest and axilla following oral tamoxifen therapy.

The reason for the peculiar localisation to the mastectomy scar area, unilateral axilla and upper back in this case is unknown. The patient did not receive any radiotherapy to the area, which excludes a radiation recall phenomenon. It is possible that prior breast surgery may have led to an anatomical disruption of vessels and poorer circulation locally. This may have predisposed the area to the development of vasculitis. Alternatively, it is possible that some interruption to the normal innervation as a result of surgery may have predisposed the skin to vasculitis.

Adjuvant hormonal therapy is commonly used to treat women with breast cancer. Although cutaneous adverse events are uncommon, when they occur they are often clinically significant. We have reported this case because of its unusual presentation. To our knowledge this is the first report of urticarial vasculitis in response to anastrozole therapy and the first report of vasculitis localised to the unilateral trunk with an aromatase inhibitor. We have also reviewed the literature and summarised reported cutaneous adverse events to this class of drugs.

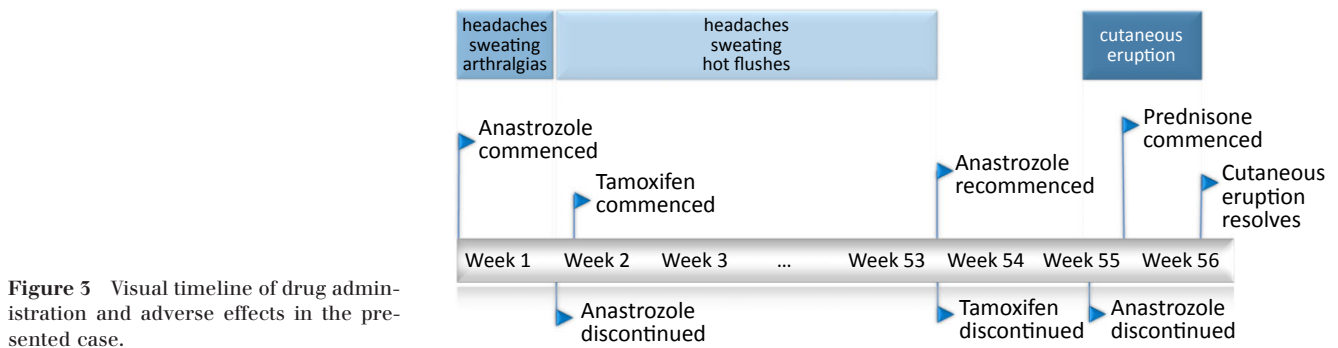


Figure 3 Visual timeline of drug administration and adverse effects in the presented case.

Table 1 Published case reports of cutaneous adverse effects of hormonal adjuvant therapy for breast cancer

Hormonal drug class	Drug name	Cutaneous adverse reaction	Number of cases	Reference
Non-steroidal anti-oestrogen	Tamoxifen	Localised vasculitis	1	Betto <i>et al.</i> ⁸
		Vasculitis	3	Drago <i>et al.</i> ⁹
				Baptista <i>et al.</i> ¹⁰
				Candelaria <i>et al.</i> ¹¹
				Fumal <i>et al.</i> ¹²
				Teoh <i>et al.</i> ¹³
Aromatase inhibitor	Anastrozole	Radiation recall dermatitis	2	Bostrom <i>et al.</i> ¹⁴
				Parry ¹⁵
		Delayed maculopapular eruption	1	Descamps <i>et al.</i> ¹⁶
		Localised urticarial vasculitis	1	This case
		Vasculitis	1	Shoda <i>et al.</i> ¹⁷
		HSP	1	Conti-Beltraminelli <i>et al.</i> ¹⁸
	Letrozole	SCLE	1	Trancart <i>et al.</i> ¹⁹
		Micropapular eruption	1	Bremec <i>et al.</i> ²⁰
		EN	3	Jhaveri <i>et al.</i> ²¹
				Santoro <i>et al.</i> ²²
	Exemestane	Vasculitis	1	
		'Rash'	2	Gennatas <i>et al.</i> ²³

EN, erythema nodosum; HSP, Henoch-Schonlein purpura; SCLE, subacute cutaneous lupus erythematosus.

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