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Letrozole-induced necrotising leukocytoclastic small vessel vasculitis: First report of a case in the UK

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ABSTRACT

INTRODUCTION: Letrozole, an aromatase inhibitor, is a commonly used neo-adjuvant drug to treat hormone-sensitive breast cancer. There have been a few cases of aromatase inhibitor induced vasculitis but the first case of letrozole-induced vasculitis was reported from Switzerland in 2014 (Digklia et al.) [1].

PRESENTATION OF CASE: We report the case of a 72-year-old woman with a small breast cancer. She was started on pre-operative letrozole (2.5 mg/d) whilst awaiting surgery. Ten days later she presented with burning pain and purpuric skin lesions which progressed to extensive ischaemic superficial necrosis of the lower limb skin, resolving over 3–4 months after local and systemic steroids. Histologically, it showed leucocytoclasis with evidence of eosinophilia consistent with a diagnosis of cutaneous leukocytoclastic small vessel vasculitis.

DISCUSSION: The initial clinical presentation was severe burning pain around the ankles and a spreading violaceous rash. Letrozole was stopped. Wide local excision (lumpectomy) and sentinel node biopsy were postponed because of the accompanying pneumonitis and gastrointestinal upset, and were carried out 3.5 months later. Fortunately, the tumour size did not increase, but appeared to reduce, and axillary lymph nodes remained negative, i.e., this patient's cancer outcome does not seem to have been jeopardized.

CONCLUSION: Leukocytoclastic vasculitis is a hypersensitivity reaction that is usually self-resolving, though our case needed systemic steroid treatment. Letrozole is a commonly used drug in clinical practice and prescribers should be aware of this rare side effect, which in our case delayed treatment without any apparent harm and possibly reduced tumour size.

1. Introduction

Aromatase inhibitors have replaced tamoxifen as the preferred adjuvant endocrine treatment in the majority of postmenopausal breast cancer patients. They inhibit or inactivate the aromatase enzyme and therefore inhibit oestrogen synthesis in peripheral fat, the main source of oestrogen after menopause. Generally, they are well-tolerated and common side effects include nausea, vomiting, alopecia, dry skin and osteoporosis. Cutaneous manifestations are rare, with few documented cases of erythema nodosum, cutaneous vasculitis, toxic epidermal necrolysis, Henoch-Schönlein purpura, and cutaneous lupus erythematosus [2–8].

A vasculitis secondary to letrozole has been reported in Switzerland [1] but to the best of our knowledge, this is the only other case reported in the world.

2. Presentation of case

A 72 year old woman with left-sided invasive lobular carcinoma of the breast (18 × 8 × 7 mm on ultrasound, Grade 2, ER positive, PR positive, HER2 negative, Mib-1/Ki67 proliferation index 15%) was scheduled to have a wide local excision of the cancer (lumpectomy) and sentinel node biopsy. However, due to her wish to visit

Abbreviations: PCR, protein creatinine ratio; ANCA, anti-neutrophil cytoplasmic antibody; CLSVV, cutaneous leukocytoclastic small vessel vasculitis; HE, hematoxylin and eosin stain.

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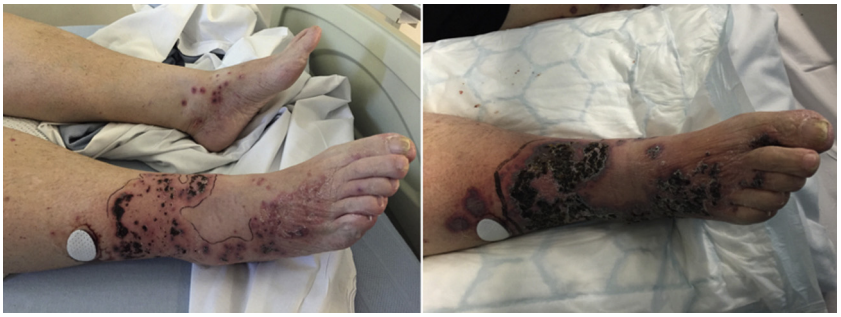

Fig. 1. Images taken on the first day and a week later showing palpable purpura and violaceous macules becoming confluent with superficial skin necrosis: Left 17th Feb 2015, Right 24th Feb 2015.

her elderly husband in Ireland, the surgery was postponed and letrozole was started in the meantime. She was taking amlodipine and bendroflumethiazide for hypertension, digoxin and aspirin for atrial fibrillation, simvastatin, occasionally a salbutamol inhaler for asthma, and co-codamol for knee pain. She has no known drug allergies.

A day before the surgery (i.e 14 days after starting letrozole) the patient gave a four-day history of a severe burning sensation around both ankles. The overlying skin had an erythematous and violaceous rash with blisters and was tender on palpation (Fig. 1). She gave a two-day history of vomiting and diarrhoea as well as a productive cough and wheeze, but no haematemesis and no haemoptysis.

Urine dipstick showed mild proteinuria and Protein Creatinine Ratio (PCR) of 48 (normal range: <45 mg/mmol), but no haematuria. Her observations including blood pressure (131/81 mmHg) were all normal and blood cultures did not show any growth. Anti-Nuclear Antibody was negative, Anti-Neutrophil Cytoplasmic Antibody (ANCA) was negative but complement C4 was raised to 51 mg/dL (normal range: 20–40 mg/dL). A diagnosis of vasculitis, possibly related to letrozole use, was considered and a skin punch biopsy of the rash on the right leg was taken (Fig. 1).

Letrozole was stopped and the patient was started on topical steroid, clobetasol propionate 0.05% (Dermovate). The pneumonitis and gastrointestinal upset meant that the scheduled lumpectomy had to be cancelled. Amoxicillin was started.

Five days later there was increased burning sensation around both ankles and lower legs (Fig 1, right). There was circumferential necrosis on the right leg and multiple non-exudative violaceous small lesions extending to both upper thighs and lower back. There was breakdown of the skin with crusting of coalescent areas. The right leg was warm to touch and pedal oedema extended to the mid-shin. She was unable to tolerate clobetasol propionate due to intense pain when applying it and instead was started on analgesia and 40 mg of oral Prednisolone. She was admitted for observation and pain relief.

By this time, the histopathology of the punch biopsy was available and showed extensive ischaemic necrosis of the epidermis and the papillary dermis, with the formation of a sub-epidermal blister. There was interstitial haemorrhage with scattered nuclear dust and karyorrhectic debris (leucocytoclasis). Neutrophils and eosinophils surrounded the blood vessels and there was infiltration of vessel walls with fibrinoid necrosis, consistent with a diagnosis of cutaneous leukocytoclastic small vessel vasculitis (Fig. 2).

Renal function improved quickly, ruling out significant renal involvement. Three days later the legs were still painful but the erythematous area had decreased in size. The following week there were no new lesions but there was extensive superficial skin necrosis. The prednisolone dose was tapered off. Letrozole was not re-introduced. The lesions healed over the next 10–12 weeks (Fig. 3).

Three and a half months after the initial scheduled surgery (17th February 2015), the patient underwent wire guided wide local excision of the tumour and sentinel node biopsy on 2nd June 2015. The final pathology report confirmed a 12 mm invasive lobular carcinoma excised with clear margins. Lymphovascular invasion was absent and the sentinel lymph node was free of metastasis. She received postoperative breast radiotherapy with tumour bed boost and is currently on tamoxifen (20 mg/d), a selective oestrogen receptor modulator (SERM), rather than an aromatase inhibitor for adjuvant systemic therapy.

3. Discussion

Leukocytoclastic vasculitis is an immune complex-mediated reactive transient small-vessel vasculitis. It causes 10–20% of all small-vessel vasculitides [9]. Cutaneous leukocytoclastic small vessel vasculitis (CLSVV) is a diagnosis of exclusion, and infection and

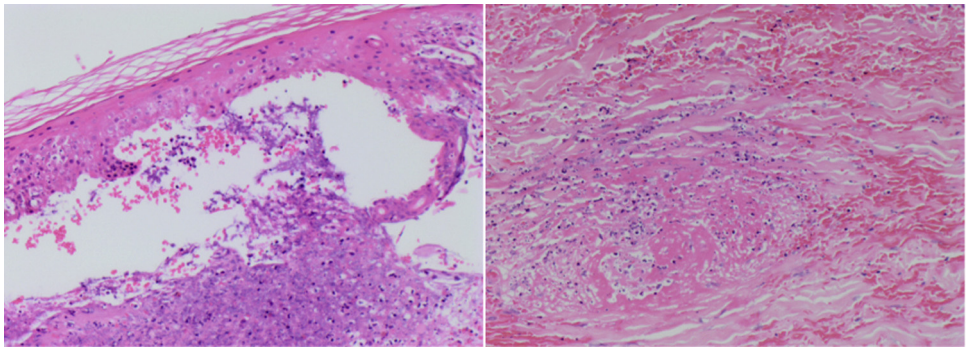

Fig. 2. Left HE; ×100 magnification: Necrotic epidermis lies partly detached from the underlying dermis to form a subepidermal blister. Right HE; ×200 magnification: Dermal changes of fibrinoid necrosis involving small vessels, karyorrhectic debris (leucocytoclasis) and red blood cell extravasation.