A Case Report of Erythema Nodosum Following Letrozole Administration in a 44-Year-Old Iranian Female Patient With Breast Cancer

Farshad Abedi[1], Negin Allahyari[2], Abolghasem Allahyari[3], Ahmad Reza Taheri[4], Omid Arasteh[1*]

[1]Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

[2]School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

[3]Department of Hematology and Oncology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

[4]Department of Dermatology, Cutaneous Leishmaniasis Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

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Abstract

Letrozole, a nonsteroidal aromatase inhibitor, is the adjuvant endocrine treatment for postmenopausal women with estrogen receptor-positive breast cancer. Erythema nodosum (EN) is a rare skin adverse effect of letrozole which has been previously reported in a few case reports. We report a new case of EN-induced by letrozole in a 63-year-old Iranian woman with left breast cancer who was estrogen receptor-positive. Physical examination and laboratory findings were consistent with EN. Manifestations resolved following discontinuation of letrozole and treatment with oral prednisolone. This case highlights EN as a potential adverse effect of letrozole. Clinicians should be aware of this rare but significant reaction, as early recognition and discontinuation of the offending agent can lead to complete resolution of symptoms.

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Introduction

Erythema nodosum (EN) is a delayed-type hypersensitivity reaction with septal panniculitis without vasculitis. It mainly presents as acute erythematous lesions and tender nodules on the extensor area of the lower legs. Histologically, EN is characterized by septal panniculitis (inflammation of the septae) in the subcutaneous fat. There is a thickening of the septae and a predominant lymphohistiocytic infiltration along with sparse eosinophils (1). EN is triggered by infection, pregnancy, malignancy, and inflammatory conditions, such as sarcoidosis or gastrointestinal disorders. The trigger might also be idiopathic or even caused by drugs, such as oral contraceptives, penicillin, sulfonamides, and tumor necrosis factor-alpha (TNF-α) inhibitors (2).

Letrozole, a nonsteroidal competitive aromatase inhibitor, suppresses plasma estrogen levels by inhibiting or inactivating aromatase, the enzyme responsible for the peripheral conversion of androgens to estrogens. It is the preferred adjuvant endocrine treatment for postmenopausal women with estrogen receptor-positive breast cancer (3). Common side effects associated with letrozole include osteoporosis, ischemic heart disease, and musculoskeletal disorders, such as arthralgia, ostealgia, tenosynovitis, and carpal tunnel syndrome (4).

Dermatologic adverse effects, including cutaneous vasculitis, toxic epidermal necrolysis, urticaria, xeroderma, skin rash, and erythema multiforme have also been reported with letrozole in postmarketing (1, 5-8). Also, there have been a few cases of aromatase inhibitor-induced EN (9, 10). Herein, we report a case of postmenopausal breast cancer who developed EN after initiation of letrozole.

Case Report

A 63-year-old Iranian woman with the past medical history of hypothyroidism and present illness of left breast cancer (invasive ductal carcinoma) underwent a partial mastectomy. She received chemotherapy with docetaxel and cyclophosphamide, every three weeks for four cycles. In drug history, she also received dicyclomine and oxycodone as needed, as well as granulocyte colony-stimulating factor (GCSF). The immunohistochemical analysis of her tumor was estrogen receptor-positive but progesterone and HER-2 receptor-negative, and she was

Corresponding Author: Omid Arasteh
Address: Department of Clinical pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985131801760
E-mail: ArastehO@mums.ac.ir

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administered letrozole 2.5 mg/day after the completion of surgery and chemotherapy.

The patient presented with tender, erythematous, subcutaneous nodules on the anterior aspects of both lower extremities approximately 3 weeks after initiating letrozole therapy. The nodules were firm, measured 1–3 cm in diameter, and were accompanied by mild localized warmth and tenderness to palpation. The overlying skin was erythematous but intact, with no evidence of ulceration or discharge (Figure 1, A). The lesions were consistent with the classic presentation of EN. The patient had no prior history of similar skin lesions or recent infections, and no other medications were introduced around the time of symptom onset. She had a normal blood pressure (122/79 mmHg) with a mild increase in C-reactive protein (CRP) 24 mg/dL, and erythrocyte sedimentation rate (ESR) 35 mm/hour. Primary laboratory investigations revealed white blood cell (WBC) 6.3×109/L (neutrophils 55.5%), hemoglobin 11 g/dL, platelets 432×109/L, as well as normal liver, kidney, thyroid, and lipid profile function. Moreover, components of the complement (C3 and C4) and antinuclear antibodies were at normal ranges.



Figure 1. (A) Painful and erythematous nodules of both legs in a patient treated with letrozole; (B) Resolve of erythematous nodules after treatment with prednisolone

A dermatology consultation suggested letrozole-induced EN. The diagnosis of EN was primarily clinical, supported by the characteristic presentation and temporal association with letrozole initiation. Laboratory tests, including complete blood count (CBC), ESR, and CRP, were within normal limits, ruling out infection or systemic inflammation. Doppler ultrasound of the lower extremities was performed to exclude deep vein thrombosis and superficial thrombophlebitis, which was negative. Although skin biopsy was not performed due to the classic presentation and patient preference, it would have provided definitive histopathological confirmation of septal panniculitis, consistent with EN. We also applied the adverse drug reaction probability scale (Naranjo score) to determine the causality between letrozole use and manifestations of EN (11). There were previous case reports on aromatase inhibitor-induced EN (+1 score); EN was manifested after starting letrozole (+2 score); and improved after discontinuation of letrozole and administration of systemic corticosteroid (+1 score). Accordingly, a possible causal relationship was found (total score of 4).

The letrozole was held and she was treated with oral prednisolone 25 mg/day for 10 days and then tapered

dose within two weeks. The EN completely resolved with this treatment (Figure 1, B).

Discussion

Aromatase inhibitors, such as letrozole, anastrozole, and exemestane, are the preferred hormonal treatment in postmenopausal estrogen receptor-positive breast cancer (3). However, there are a few case reports from the literature with EN induced by aromatase inhibitors.

For the first time in 2007, three cases of EN which developed in postmenopausal breast cancer patients on aromatase inhibitors were reported (9). The first patient was a 51-year-old female with breast cancer who enrolled in the MA 17 trial and received letrozole. However, three months later she developed painful, erythematous nodules compatible with EN. A follow-up evaluation six weeks later demonstrated persistent EN and rheumatology evaluation was normal. Then the steroid was started, and EN resolved well. She was rechallenged with anastrozole in a subsequent trial which caused an exacerbation of the EN. The anastrozole was discontinued but she continues to have periodic episodes of EN. The second patient was a 47-year-old female with breast cancer who developed EN after two months of beginning letrozole. Letrozole was discontinued and EN was resolved without any relapse. She has not been re-challenged with any other aromatase inhibitor. The third patient was a 50-year-old female with breast cancer who developed EN after three months of beginning letrozole. She was switched from letrozole to anastrozole, which decreased the number of nodules on the lower extremities, however, they were still present (9).

Another case report in 2019 described a 73-year-old woman with breast cancer who developed painful erythematous nodules located on the lower limbs and reactive synovitis of the ankles, a few weeks after initiation of letrozole. She was diagnosed with EN and received intravenous methylprednisolone (20 mg/day). A few days later, lesions were improved and methylprednisolone was tapered (10).

Cutaneous adverse reactions triggered by aromatase inhibitors are rare but reported with both steroidal (exemestane) and nonsteroidal (letrozole and anastrozole) aromatase inhibitors (12). Skin adverse reactions associated with aromatase inhibitors typically manifest anywhere and can appear from 2 days to 9 months after starting the medication, with a median onset of 2 months. These reactions may present as vasculitis, erythema nodosum, subacute cutaneous lupus erythematosus, or other skin conditions. In some cases, patients may develop skin lesions either at the original site of the breast cancer or in areas that were previously treated with surgery or radiotherapy (5, 13).

Case reports of skin adverse reactions by exemestane are fewer but this might be due to its limited administration compared with nonsteroidal aromatase inhibitors. Also, it is unclear if rechallenge with a different aromatase inhibitor is possible, in the case of drug-induced skin reactions. Interestingly, Kim, YJ et al. (2020) reported a case of anastrozole-induced dermatitis in a woman. She discontinued the drug and then the patient switched to exemestane without recurrence of skin dermatitis (5). However, in another case, a patient who experienced rash and pruritus with anastrozole and recurrence with exemestane was treated successfully with tamoxifen (14).

Several differential diagnoses were considered, including erythema multiforme, cellulitis, superficial thrombophlebitis, panniculitis, and cutaneous metastasis of breast cancer. The absence of target lesions, mucosal involvement, systemic symptoms, and unilateral distribution ruled out erythema multiforme and cellulitis. The nodular nature of the lesions and bilateral distribution made superficial thrombophlebitis and cutaneous metastasis unlikely. The clinical presentation and temporal association with letrozole initiation strongly supported the diagnosis of EN (15).

The pathogenesis of letrozole-induced EN is not fully demonstrated. However, EN is considered a delayed-type hypersensitivity reaction due to exposure to specific antigens. Deposition of immune complexes in the septal venules of the subcutaneous fat, neutrophil diapedesis, reactive oxygen species, and granuloma formation, as well as TNF-α production, are involved in the pathophysiology of EN (1).

We concluded that EN was associated with letrozole therapy, since quick resolution of EN after letrozole holding, no past medical history of EN, and no further relapses after drug discontinuation. EN should be considered as a possible side effect in breast cancer patients receiving aromatase inhibitors. In this case, we point out this side effect of letrozole as a causative drug among others inducing EN. The medicine was stopped and we started oral corticosteroid, which consequently caused the resolution of lesions. The patient will be followed up for a longer period in order to figure out more possible relapses of EN after discontinuation of letrozole.

Conflicts of interest

There are no conflicts of interest.

Acknowledgment

The authors confirm that all patient data in this case report has been thoroughly anonymized. Personally identifiable information has been removed or altered to protect the patient's privacy.

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