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Case Report

Dermatology Section

Anything Rare is Possible: Letrozole Induced Eczematous Skin Eruption

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ABSTRACT

Letrozole is used as first line drug in postmenopausal women with early-stage or advanced hormone-sensitive breast cancer. Letrozole has favourable tolerability profile when administered once daily and significant adverse reactions occur rarely. The objective of this report is to describe a case of eczematous skin eruption that occurred during letrozole treatment. A 61-year-old female patient was admitted with lump in the left breast. FNAC, HPE were done and the patient was diagnosed to have invasive ductal breast carcinoma. After a month of completing CT and EBRT, the patient was given 2.5 mg OD tab. letrozole at night. She developed itchy skin lesions over the right thigh that later generalised, at 6- weeks of treatment. The lesion has been defined as eczematous moderate to severe drug eruption. These lesions were attributed to letrozole therapy and recurred within 24h after rechallenge. Drug eruption is associated with many drugs but this is the first such report with letrozole. We suggest of being aware of such reactions during letrozole usage.

Keywords: Breast carcinoma, Old age, Rechallenge

CASE REPORT

We report a rare case with eczematous moderate severe drug eruption associated with the use of letrozole for breast cancer.

A 61-year-old female came to the hospital, Manipal, India with complaint of lump in the left breast in December 2012. The lump measured 4cm x 3cm, borders were well-defined, margins negative and two left pectoral and one left subclavicular, 3/16 (18%) lymph nodes were involved. Right breast was completely normal. Following ultrasonography and Fine Needle Aspiration Cytology (FNAC) the lump was diagnosed to be carcinoma of the left breast. Modified Radical Mastectomy was done 15d later and the sample was sent for histopathological examination (HPE). HPE showed invasive ductal breast carcinoma. On the basis of HPE report the patient was diagnosed to have luminal A molecular subtype (ER+ and low grade) Carcinoma of left breast, Stage IIB and T2N1M0.

Immunohistochemistry studies of left breast tissue revealed Estrogen Receptor (ER) positive, Progesterone receptor (PR) negative, Her2/neu was 1+ and Ki-67 <14%. The line of treatment decided for this patient included 4 cycles of chemotherapy (adriamycin + cyclophosphamide) followed by 5wks of External Beam Radiotherapy (EBRT) and finally letrozole based hormonal therapy. The first cycle of chemotherapy (CT) was started in April 2013 with adriamycin 80mg i.v. and cyclophosphamide 800mg i.v. Three weeks later in May 2013 the second cycle of CT was administered wherein adriamycin was replaced by epirubicin 100mg i.v. because of intractable nausea. Further, third cycle of CT was administered three weeks later and the fourth, final cycle was given in June 2013. The patient responded well to all four cycles and blood counts were within normal range.

One month later, the patient was treated with EBRT at 50 Gy for five wks starting from July 2013 to August 2013. After a month's gap i.e. in September 2013, tab. letrozole 2.5mg was started, once daily at night and therapy was advised for a total period of three months.

At six weeks of letrozole therapy, the patient complained of localized itchy skin lesions over the right thigh which later progressed onto waist, groin, back and both buttocks, arms and forearms. She was non diabetic, no past or present history of renal or thyroid disease, iron deficiency, jaundice or any other allergic skin reactions. On clinical examination, there were multiple hyperpigmented scaly plaques over right axilla and waist. Erythematous plaques were seen bilaterally over the forearms, cubital fossae, elbows, thighs and right side of the groin. Diffuse pigmentation was clearly visible over left side of chest. However, no signs of fever, hepatic involvement, eosinophilia, and lymphadenopathy were present. Ultimately, the diagnosis was made as drug induced eczematous eruption by unit dermatologist. Betamethasone lotion 0.1% for local application, tab. cetirizine 5mg and tab. hydroxyzine 25 mg were prescribed daily, for a period of one month and the patient continued with letrozole therapy. Meanwhile, the patient reported back to the hospital within 2 weeks with worsening of generalized itching and more number of lesions all over the body. Eventually, tab. letrozole was stopped and betamethasone lotion was changed to tab. prednisolone 24 mg per day for 3 days and the patient was asked to consult again. Three days later, there was 50-60% improvement in the skin lesions. Thence, prednisolone dosage was tapered from 24 mg/day to 16 mg/day for next five days followed by 8 mg for another five days. Tab. cetirizine 10 mg, tab. rabeprazole 20 mg, betamethasone lotion were prescribed as adjuvant therapy for 10 days and an antibiotic tab. co-amoxiclav 625 mg TID, daily for five days. One month later when tab. letrozole 2.5 mg was restarted, the patient started developing itching similar to the previous episode over the arms and legs within 24h. On examination hyperpigmented plaques were seen over the arms, legs and tab. letrozole was stopped again. The patient was prescribed tab. cetirizine 10 mg and halobetasol propionate cream 0.05% for a period of one month. After a gap of one week tab. anastrozole 1 mg was started instead of letrozole and after one month of treatment there were no further complains of itching or lesions.

DISCUSSION

A morbilliform pattern cutaneous reaction is the most common hypersensitivity drug reaction, comprising 95% of all drug-induced skin eruptions [1]. Eczematous reactions can often be caused by allopathic, herbal or homeopathic medications. Geriatric population is more prone to develop these reactions probably because of

concomitant medications or changes in drug metabolism and /or excretion with age. A 2006 study by Yalcin and colleagues found the prevalence of cutaneous Adverse drug reaction (ADR) to be 1.4% during a five year period when analysing 4099 geriatric patients [2]. The rate of hospitalisation for adverse drug reactions in the elderly has been reported to be as high as 16.6% to 24% compared with 4.1% in younger patients [3]. A large study of hospitalized adults found that ADRs occurred at a rate of 5.5% per drug exposure, of which 2.2% were cutaneous ADRs [4]. The rates of drug reactions are higher in patients who are immunosuppressed, such as those with HIV, systemic lupus erythematosus, and lymphoma. The severity of the reaction can be correlated with the stage of the disease. Patients with AIDS are at least 8.7 times more likely to develop cutaneous drug reaction compared with the average population [5]. The treatment is prompt cessation of the causative drug, following which the lesions normally resolve within over 1–2 weeks. Certain drugs like aminopenicillins, sulfonamides, cephalosporins, anti-epileptics, blood and blood products and allopurinol are more likely to evoke a morbilliform eruption in more than 3% of users [6,7].

Breast cancer is the leading cause of cancer deaths among women in both developed and in developing countries. Letrozole, a third-generation, nonsteroidal aromatase inhibitor, is approved for first- and second-line treatment of advanced breast cancer in postmenopausal women. The efficacy, cost effectiveness and favourable tolerability profile of letrozole are reflected in current treatment guidelines recommending the drug as a first-line therapy [8]. However, in accordance with the notion “no drug is safe” the most common drug related adverse events with letrozole are hot flushes 5–20%, back pain 15%, headache 7–11%, nausea 5–11%, dyspnoea 10%, peripheral oedema 6% and fatigue 5%. Other common adverse effects are thinning of hair, myalgia and arthralgia. Abnormal liver test results, unrelated to liver metastases, were recorded in ≈3% of patients taking letrozole therapy and in a few patients reported to affect bone mineral density causing osteoporosis.

Thus, considering potential survival benefits and cost-effectiveness, it appears that letrozole may be preferable to anastrozole. However, present case is about skin reaction (eczema) due to letrozole and therapy was replaced by tab. anastrozole 1 mg. In view of exploring the reasons other than letrozole, we found that many extrinsic causative factors which could have triggered eczema like general health changes or chronic illness (e.g. diabetes, renal failure, thyroid disease, anaemia, or jaundice), poor dietary and fluid intake, allergies, urinary or faecal incontinence, low mental state and personal hygiene. Possibility of these co-morbid conditions causing eczema was ruled out because none were present at the time of presentation. As we know discontinuation of the drug is the ultimate litmus test to confirm diagnosis of drug eruption. In our case scenario, we did confirm letrozole induced moderate to severe eczematous scaly eruptions by de-challenge, wherein these reactions started abating after three days of withdrawal. With the letrozole re-challenge, however, the skin eruption presented within much shorter time i.e. 24h.

Older people’s skin changes as they age. Intrinsic skin changes include a reduction in epidermal cell replacement and collagen formation, resulting in wrinkles as well as thin and fragile skin (which is susceptible to breakdown and ulceration). The stratum corneum is the outer layer of skin; older people have impairment or removal of barrier lipids, resulting in reduced formation of natural moisturising factors [1]. These changes reduce the skin’s barrier function, resulting in water loss, causing dry, scaly, and itchy skin, and a reduction in defence against bacterial, fungal and chemical irritants.

Limitation of the case study

No skin biopsy, no specific dermal patch test and no photographs of the reaction were taken.

CONCLUSION

Herewith, we can speculate that the letrozole induced skin eruption may be due to many reasons. It may be related to the old age of this patient or her immunocompromised status or it could be a drug induced hypersensitivity syndrome or some idiosyncratic skin reaction or nonspecific allergic skin eruption. Indeed, it needs further similar case reports and scientific investigations to elucidate in detail.

REFERENCES

[1] Onselen JV. Eczema: A common skin condition in older people. *Nurse Prescribing*. 2013; 11(4): 165-73.
[2] Yalcin B, Tamer E, Toy GG, et al. The prevalence of skin disease in the elderly; analysis of 4099 geriatric patients. *Int J Dermatol*. 2006; 45: 672-6.
[3] Ahmed AM, Pritchard S, Reichenberg J. A Review of Cutaneous Drug Eruptions. *Clin Geriatr Med*. 2013; 29: 527–45.
[4] Segal RA, Doherty KM, Leggott J, Zlotoff B. Cutaneous reactions to drugs in children. *Pediatrics*. 2007; 120 (4): 1082-96.
[5] Hernandez SA, Rosales SP, Rangel FS, et al. Epidemiology of adverse cutaneous drug reactions. A prospective study in hospitalized patients. *Arch Med Res*. 2006; 37: 899–902.
[6] Bibgy M. Rates of cutaneous reactions to drugs. *Arch Dermatol*. 2001; 137: 765–70.
[7] Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology.* 2005; 209: 123-9.
[8] Scott LJ and Keam SJ. Letrozole In Postmenopausal Hormone-Responsive Early-Stage Breast Cancer. *Drugs*. 2006; 66 (3): 353-62.

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