CASE REPORT

Treatment of estrogen-induced dermatitis with omalizumab

Jesus A. Ocana, MD, PhD,[a] Maria C. Bell, BMus,[a] Jordan B. Heskett, MD,[b] William H. Baker, MD,[c,d] Nico Mousdicas, MBBS,[d] and Matthew J. Turner, MD, PhD[b,d]
Indianapolis, Indiana

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INTRODUCTION

In 1945, Drs Bernhard Zondek and Yehuda Bromberg demonstrated intradermal treatment with estrone and estradiol benzoate induced urticarial lesions in some patients.[1] Fifty years later, Shelley et al,[2] who introduced the concept of progesterone dermatitis several decades prior, defined estrogen dermatitis based on studies of 7 women with premenstrual flares of skin eruptions including papulovesicular, urticarial, or eczematous lesions or generalized pruritus. Previously described therapies for estrogen dermatitis include estrogen desensitization, tamoxifen, leuprolide, and oophorectomy.[3] Here we report a case of estrogen-induced dermatitis successfully treated with omalizumab.

CASE REPORT

We previously described the case of a 37-year-old woman who presented with a longstanding history (>10 years) of a waxing and waning polymorphous eruption consisting of symmetrically distributed migratory pruritic and occasionally painful arcuate erythematous plaques involving the medial aspects of the breasts consistent with a gyrate erythema (Fig 1) as well as urticarial plaques scattered on the trunk and extremities.[3] Flares regularly began on or near day 2 of menses, and lasted for approximately 2 weeks.[3] Intradermal injections (0.1 mL) of conjugated estrogen (100 μg), medroxyprogesterone (100 μg), histamine, and normal saline were administered to the patient's forearm.[3] Estrogen and histamine injection sites were positive for wheal formation within 15 minutes, but no reaction was seen in the progesterone or saline injection sites.[3] Based on the clinical presentation and skin testing, estrogen dermatitis was diagnosed. This condition did not respond to an oral antihistamine regimen of 10 mg cetirizine daily and 10 to 20 mg of hydroxyzine nightly. Although significant improvement was seen with a 6-month course of leuprolide, (11.25-mg injections every 3 months), the response was incomplete, and leuprolide was subsequently discontinued when the patient underwent an elective hysterectomy and bilateral oophorectomy for symptomatic uterine fibroids.[3] Despite this surgery, the patient's estrogen dermatitis persisted. Given lack of or insufficient control provided by the therapies mentioned above, the patient, at 41 years of age (body mass index, 34 kg/m^2), elected to begin treatment with omalizumab, 150 mg subcutaneously every 4 weeks. Treatment with omalizumab rapidly cleared the patient's estrogen dermatitis, which has now been well controlled with monthly omalizumab infusions for 2 years. In asthma, use and dosing of omalizumab are determined by body weight and total serum IgE; however, total serum IgE and body weight are not used to guide use or dosing of omalizumab for chronic idiopathic urticaria, for which dosing options are 150 mg or 300 mg every 4 weeks. Based on this finding, baseline IgE measurements were not obtained in our patients, and the lower dose (150 mg) was chosen with the plan to increase if needed.

From The Departments of Dermatology[b] and Medicine,[c] Indiana University School of Medicine[a]; and Richard L. Roudebush Veterans Affairs Medical Center.[d]

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Some clinical aspects (ie, the diagnosis of estrogen dermatitis) of this patient's presentation were previously published in Perdue et al.[3] The patient's response to omalizumab has not been published and is the focus of this manuscript.

Correspondence to: Matthew J. Turner, MD, PhD, Indiana University School of Medicine, Department of Dermatology, 45 Barnhill Dr EH139, Indianapolis, IN 46202. E-mail: turner41@iu.edu.

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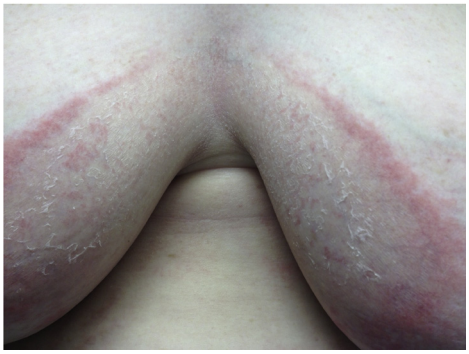

Fig 1. Estrogen dermatitis manifesting as arcuate erythematous plaques with trailing scale on medial aspects of the breasts.

DISCUSSION

The pathophysiology of estrogen-induced urticarial eruptions and dermatitis remains to be defined. In addition to demonstrating that intradermal estrogen administration could induce urticarial eruptions in patients, Zondek and Bromberg[1] reported that serum from estrogen-sensitive patients could induce similar skin reaction in naïve patients. These investigators also found that heating serum from estrogen-sensitive patients to 56°C prior to passive transfer reduced the severity of these urticarial eruptions, leading the investigators to suggest these eruptions were antibody dependent.[3] The cyclical course of our patient's skin eruption in relation to menses, coupled with positive intradermal testing to estrogen and the urticarial component to the eruption led us to hypothesize her estrogen dermatitis might represent a type of IgE-mediated hypersensitivity reaction, which was the basis for a therapeutic trial of omalizumab.

Omalizumab is a neutralizing IgG monoclonal antibody that binds free circulating IgE. This binding inhibits IgE from binding its high-affinity Fc receptor on the surface of mast cells and basophils. Currently, omalizumab is approved for the treatment of chronic idiopathic urticaria and asthma with some efficacy extending into other IgE-mediated diseases.[4] The fact that the patient's cutaneous manifestations improved after treatment with omalizumab suggests that this condition is mediated by a hypersensitivity reaction involving IgE. From the standpoint of a type I hypersensitivity reaction, the insufficiency of antihistamines to control our patient's skin eruption suggests other mediators could be involved in the pathogenesis of estrogen dermatitis. Preformed mast cell–derived mediators that could also contribute include granule-stored polyamines, proteoglycans, proteases, lysosomal enzymes, and cytokines.[5] Additionally, activation of the Fc receptor could stimulate mast cell de novo synthesis and release of other mediators including cytokines, prostaglandins, and reactive oxygen species. Although classically implicated in type I hypersensitivity reactions, IgE can also alter T-cell function through engagement of the high-affinity IgE receptor on dendritic cells suggesting a potential for IgE to contribute to type IV hypersensitivity reactions in some settings.[6] The ability of IgE to contribute to different types of hypersensitivity reactions (ie, immediate and delayed types) could explain the polymorphous nature of this patient's estrogen dermatitis (ie, gyrate erythema and urticaria).

Another notable aspect of this case was that the patient's estrogen dermatitis was refractory to oophorectomy. The persistence of the patient's estrogen dermatitis was surprising (as the ovaries are the primary producers of estrogen) and prompted us to consider other potential sources of this hormone.[2] Our patient's body mass index was 34 kg/m^2; considering the association of increased estrogen levels with greater adiposity, it is possible that her estrogen dermatitis persisted because of peripheral aromatases in the fat converting adrenal gland–derived androgens into estradiol.[7] If this is the case, reducing adiposity through weight reduction would also be a therapeutic consideration to manage estrogen dermatitis. Other possible sources of estrogens to consider in this case would include residual ovarian tissue present after oophorectomy or dietary or environmental exposures. Phytoestrogens, naturally present in soy and grains, and phthalates, commonly found in plastics associated with food storage and household items, are structurally similar to endogenous estrogen.[8]

We present a case of estrogen dermatitis responsive to omalizumab. The unique treatment approach and favorable response for this patient may shed light on the pathophysiology of this condition. More specifically, this case supports a role for IgE in pathogenesis and suggests that omalizumab should be considered in the therapeutic ladder for estrogen dermatitis.

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