Generalized granuloma annulare in association with breast carcinoma

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Conflict of interest: None to declare

Received: 23 August 2016
Accepted: 25 October 2016

The association of granuloma annulare and some neoplasms is controversial. However, there is an increase in the number of case reports and relevant studies supporting the concept of granuloma annulare being associated with certain types of hematologic neoplasms and solid tumors.

Herein, we describe a 54-year-old woman with a 20-month history of generalized annular lesions that did not respond to conventional treatment and was followed by breast cancer. Only two cases of granuloma annulare and breast cancer have been reported so far in the literature. We believe that these cases emphasize on considering granuloma annulare as a possible paraneoplastic dermatoses.

Keywords: breast cancer, granuloma annulare, neoplasm

Iran J Dermatol 2016; 19: 136-138

INTRODUCTION

Granuloma annulare (GA) has been reported to be associated with different neoplasms but to the best of our knowledge, only two cases of GA and breast cancer have been published in the literature so far [1,2].

CASE PRESENTATION

A 54-year-old woman presented with a relatively annular pruritic eruption comprising erythematous papules and plaques that were symmetrically distributed on her back, chest, and upper extremities (Figure 1). The patient had a history of hypothyroidism since 10 years ago. Other laboratory tests were normal. Histopathological

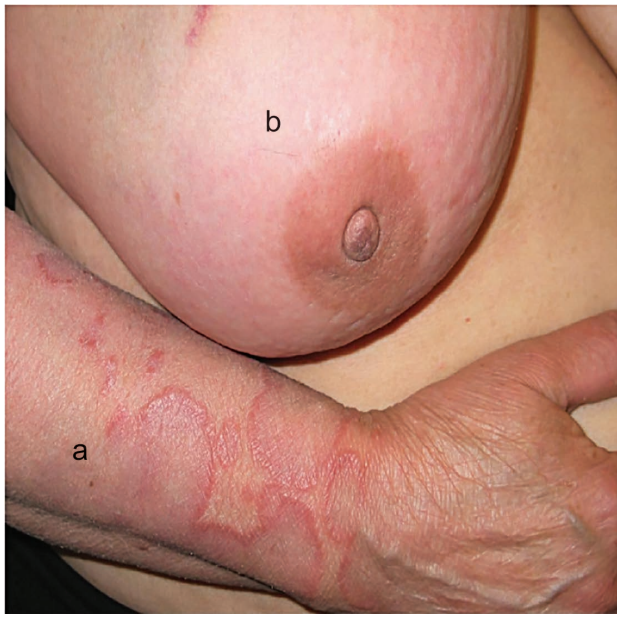

Figure 1. Typical lesion of GA **(1.a)** and breast lesions including nipple retraction and erythema of the adjacent skin **(1.b)**.

examination did not show any significant changes in the epidermis. The dermis showed perivascular infiltrates, interstitial lymphocyte track, and some histiocytes. A clinical diagnosis of GA was confirmed (Figure 2). She did not have any improvement with systemic glucocorticoids, pentoxifylline and dapsone but reported some improvement in pruritus with a potent topical steroid (clobetasol propionate cream 0.05%) but no lesion reduction after 20 months. On her follow up evaluations, a mass was found on her right breast, which was later proved breast cancer. It was an invasive ductal carcinoma grade 2, with negative *HER2/neu* on immunohistochemistry staining. Progesterone receptors were strongly positive in 40% of the tumor cells and estrogen receptors positivity was demonstrated in 35% of the tumor cells. Mastectomy, chemotherapy, and radiotherapy were performed and the patient received tamoxifen therapy afterwards. Skin lesions cleared after successful treatment of breast cancer.

DISCUSSION

GA is a common inflammatory disorder with various clinical features and a benign course. The generalized variant of GA is rare and has been reported in association with solid organ tumors, Hodgkin's disease, non-Hodgkin lymphoma, granulomatous mycosis fungoides, and toxic thyroid adenoma [2-8]. There is controversy regarding the association of GA and neoplasm. Harman *et al.* reported an association between GA and malignancy in 1977 [9].

The exact pathogenesis of GA associated with malignancy is still not fully understood. The expression of tumor antigen and secretion of cytokines by tumor cells are considered triggering factors to advance it to a malignant state. Some evidence suggests that it is an immunologic disease [6,10,11]. In these patients, the clinical pattern is frequently atypical, and the lesions are in unusual locations, including the palms and soles. Pain and pruritus may be a prominent complaint in generalized lesions [11].

In a retrospective study of GA patients with over 20 years of follow-up in Mayo Clinic, no definite relationship was found between GA and malignancy [12]. Li *et al.* reviewed 16 cases of GA related to neoplasms which were mostly hematologic neoplasm followed by solid tumors. In that review, skin lesions had histological features of GA, but often had atypical clinical features (painful lesions on the palms and sole). They concluded that there was no definite relationship between GA and malignancies, but they suggested

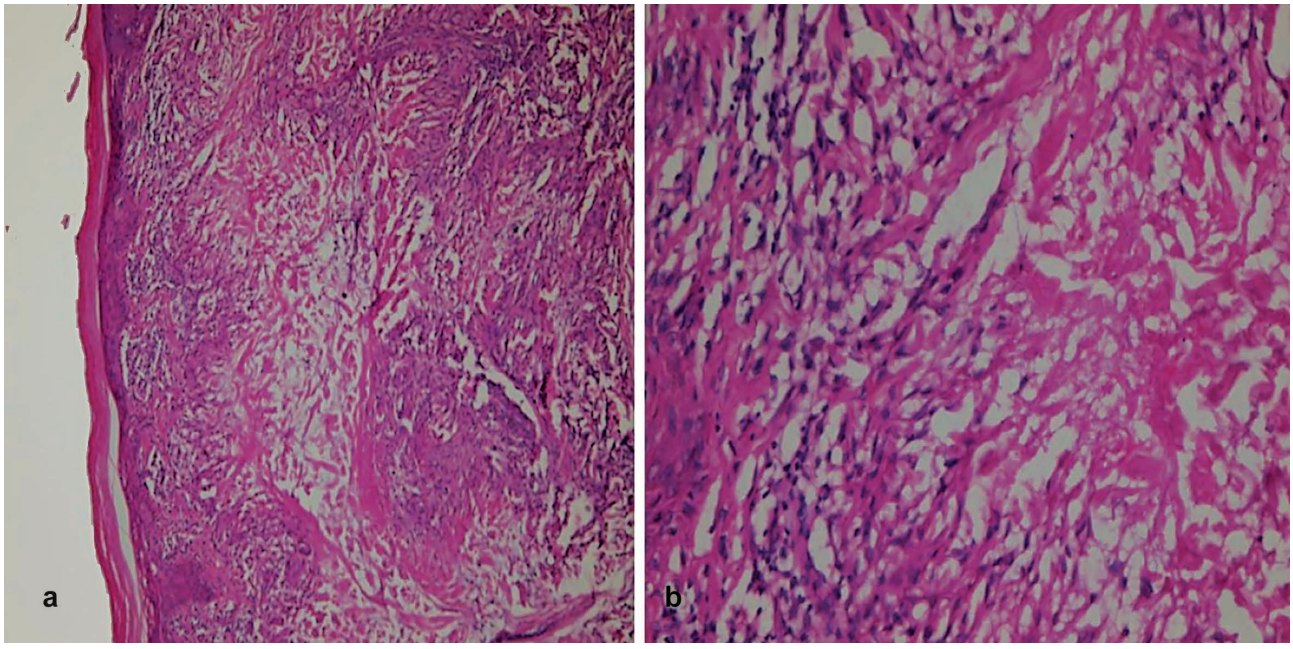

Figure 2. Histopathological examination did not show significant changes in the epidermis. The dermis showed perivascular infiltrate, palisades of histiocytes around degenerated collagen, and histiocytes interposed between collagen bundles **2.a.** (H & E, 100×), **2.b.** H & E, 400×).

underlying malignancies should be investigated, particularly in older patients with skin lesions that histologically, but not necessarily clinically, resemble GA. Among hematologic malignancies, malignant lymphoma has been commonly reported. The interval between a diagnosis of dermatosis and neoplasm is reported to be 5 months to 3 years [11].

There are only two reports of GGA with breast cancer in the literature [1,2]. In our case, generalized GA was preceded by breast cancer. It was resistant to routine treatments of GA and its resolution was associated with successful treatment of the neoplasm. We assume that this clearance was related to tumor removal itself and not to the immunosuppressive effects of chemotherapy because if it was the case, we would have seen the recurrence of skin lesions upon stopping of chemotherapy. Therefore, we agree with description of Cohen who used the term GA lesions coinciding with the discovery of a previously or simultaneously unsuspected visceral neoplasm [2].

Generalized GA can be a possible cutaneous paraneoplastic syndrome. We recommend that patients with generalized GA undergo age-appropriate screening tests for solid and hematologic malignancies, especially in the setting of atypical manifestations such as intractable itching, pain, or unusual location.

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