

CASE REPORT

Generalized granuloma annulare in a case of breast cancer: A case report and review of the literature

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Abstract

Generalized granuloma annulare can be associated with breast cancer. Atypical granuloma annulare especially in older patients should alert physicians to the possibility of an occult malignancy.

KEYWORDS

breast cancer, granuloma annulare, neoplasm, paraneoplastic

1 | INTRODUCTION

Association between granuloma annulare and malignancy has long been an area of debate. However, there is an increasing number of studies supporting the concept of generalized granuloma annulare can be associated with breast cancer.

Granuloma annulare (GA) is an uncommon cutaneous disease characterized by popular primary lesions and a tendency to annular grouping. Generalized variants can potentially involve any area of the skin.¹ GA is a benign condition that usually occurs as an idiopathic condition. The relationship between generalized GA (GGA) and malignant neoplasms is uncertain, although several reports supporting the association with malignancy. Among these, some studies have shown its association with breast cancer.² Herein, we present a patient with GGA who had a history of breast cancer 4 years ago. Then, we review literature that show the association of GGA with breast cancer.

2 | CASE REPORT

A 51-year-old woman was referred to our clinic presented with a 1-month history of annular eruption comprising erythematous papules and plaques that were distributed on her both flanks and pubis areas (Figure 1). Four years before presentation, she was diagnosed with breast cancer (invasive ductal carcinoma grade 2) and had been in complete remission after undergoing mastectomy, chemotherapy, and radiotherapy, and was on oral tamoxifen 20 mg/day.

Her laboratory studies, including complete blood count, fasting blood glucose, metabolic profile, lipid profile, serum vitamin D, thyroid hormone, and urinalysis were within normal limits. Microscopic examination of the hematoxylin-eosin-stained section from a lesional biopsy showed areas of necrobiosis surrounded by lymphohistiocytic infiltration in the dermis. The epidermis was not remarkable except for mild acanthosis. Histopathology findings were compatible with the diagnosis of GA (Figure 2).

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Gynecological and surgical consultation did not provide any evidence of a relapse of breast carcinoma.

The patient received topical potent corticosteroid for 1 month without significant results. Due to lack of improvement, 2 session injections of triamcinolone acetonide 1 month apart led to an incomplete regression of several preexisting skin lesions on her flanks but did not prevent the de novo development of additional skin lesions on her extremities. Then, we initiated a therapeutic trial with oral isotretinoin 20 mg daily. The patient discontinued isotretinoin because of intolerable side effects. As she was asymptomatic, she decided not to treat her skin lesions.

3 | DISCUSSION

Granuloma annulare is a benign inflammatory skin disorder characterized by multiple clinical morphologies. It is a chronic granulomatous dermatosis presenting as annular grouped papules that most commonly seen on the distal extremities of young adults.³ Generalized GA is defined by the presence of ≥ 10 cutaneous lesions or disseminated annular plaques affecting the trunk or extremities.⁴ It differs from the localized form by the later age of onset, protracted course, and poor response to therapy.¹

Association between GA especially generalized form and some neoplasms is controversial. However, increasing number of studies are supporting the concept of association of GA with a certain type of hematological and solid organ neoplasm.^{2,5,6} In this regard, some cases reported to be a paraneoplastic manifestation which is more reasonable to accept this concept.^{3,7}

In the current study, we describe a patient with GGA who was known case of breast cancer. Although several reports have addressed this issue, no previous articles have summarized those reported cases.

There were 17 cases, including the current case, with GGA associated with breast cancer that has been reported in the medical literature since 1989 (Table 1).^{1,3,4,7-13} In addition, there are some reports of localized variants of GA in patients with a history of breast cancer that is not around the topic of this article.³⁻¹⁴ The mean age of onset of GA was 59 years as compared with classic GA onset, which occurs during the 3rd to 5th decades of life.³

The duration between the onset of cutaneous lesions and diagnosis of breast cancer varied widely ranging from 14 years before to 17 years after the diagnosis of carcinoma. In 4 (23.52%) instances breast cancer preceded and in 8 (47.05%) it followed the onset of GGA. Based on a wide variation in the period between two disorders, some experts rejected a causative relationship between them.^{1,4}

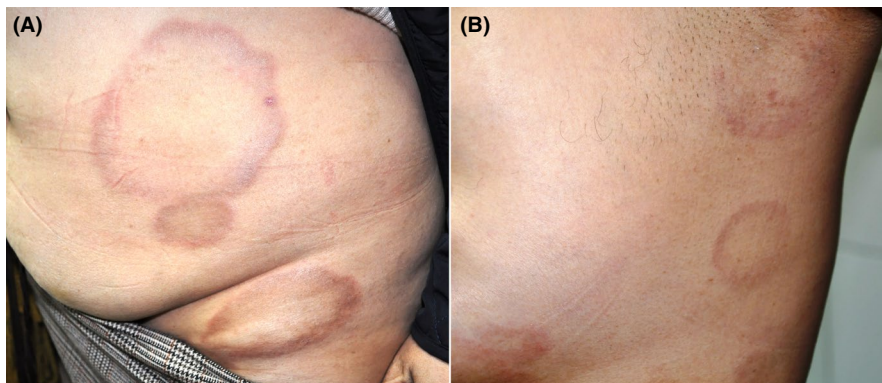


FIGURE 1 (A) Multiple annular plaques involving patient's abdomen and thigh. (B) Annular lesions on the breast and axilla.

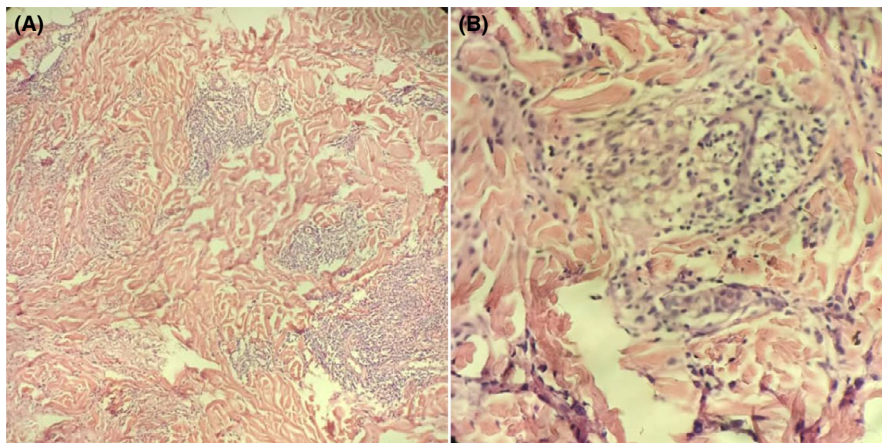


FIGURE 2 Lymphocytic and histiocytic infiltrate scattered and around degenerated collagen in the dermis. (A) (H&E, $\times 40$), (B) (H&E, $\times 100$)

TABLE 1 Breast cancer-associated generalized granuloma annulare

| Year of publication | Age ^a /Sex | Histology | Temporal relation to breast cancer diagnosis | Treatment | Paraneoplastic behavior ^b | Ref. no. |
|---------------------|-------------------------|-------------------------------|--|---|--|----------|
| 1989 | 5 patients 1 patient | - | 2 months – 17 year after 14 years before | - | 1 case whose skin lesions occur 2 months after breast cancer considered paraneoplastic | [1] |
| 1989 | 52/F | Infiltrating ductal carcinoma | 4 weeks before | Resolution 1 month after mastectomy | Yes | [7] |
| 2001 | 61/F | - | 3 years after | Clofazimine | No | [8] |
| 2005 | 59/F | - | 4 years after | Infliximab | No | [9] |
| 2008 | 50/F | Infiltrating ductal carcinoma | Coincident with breast cancer | Radical mastectomy | Yes | [10] |
| | 78/F | Infiltrating ductal carcinoma | Coincident with breast cancer | Chemotherapy | Yes | |
| 2008 | 81/F | Adenocarcinoma | 8 years after | Clobetasol | No | [11] |
| 2016 | 54/F | Invasive ductal carcinoma | 20 months before | Mastectomy, Chemotherapy Radiotherapy | No | [12] |
| 2018 | 1 patient | Adenocarcinoma | 2 years before recurrence | No treatment | No | [3] |
| 2019 | 45/F | Invasive papillary carcinoma | Coincident with breast cancer | Neoadjuvant Chemotherapy | Yes | [13] |
| 2019 | 1 patient | - | 72 months before | - | No | [4] |
| Present report | 51/F | invasive ductal carcinoma | 4 years after | Clobetasol Triamcinolone acetate Isotretinoin | No | - |

^aAge at diagnosis GGA.^bSkin lesions occurring within 6 months of the diagnosis of malignancy and/or persistent GA that resolved with cancer treatment.

On the contrary, skin lesions in 5 patients (29.41%) showed a paraneoplastic behavior defined as GA occurring within 6 months of the diagnosis of malignancy and/or persistent GA that resolved with cancer treatment.³

The pathogenesis of cancer-related GA remains to be determined. However, given that GA is a type IV delayed hypersensitivity reaction to a local or systemic stimulus, the expression of tumor antigens and secretion of cytokines by tumor cells are considered triggering factors. Besides, tumor-related alternation of cell-mediated immunity might be involved as can be seen in patients with human immunodeficiency virus infection or sarcoidosis.^{3,6}

Nevertheless, a recent study by Gabaldon et al. showed no association between generalized GA and malignancy. The average age of patients with generalized GA and cancer in their study was 74 years. They explained the relationship between two events (GGA and Cancer) is not supported by the fact that both GGA and cancer are more likely to occur at an advanced age.⁴

However, the average age of patients with GGA and breast cancer in this review was 59 years (among 9 cases whose data were available) which was much less compared with Gabaldon et al results. In addition, breast cancer is the second most common solid organ malignancy after lung cancer that is associated with GA.³ Considering these data and a paraneoplastic behavior in some cases, substantially suggest co-occurrence of GGA and breast cancer is not simply coincidental, although the sample is too small to draw any conclusion.

It is noteworthy, the dermatologists must be aware when facing a patient with an atypical presentation of GA including GGA. We advocate for age-appropriate screening in individuals who are nonresponsive to conventional treatments for an underlying neoplasm including breast cancer. In addition, in known cases of breast cancer and refractory GGA evaluation for possible cancer recurrence or metastasis should be considered.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

MS wrote and edited the manuscript. RK followed up the patients and wrote the manuscript. AA followed up and evaluated the patient.

ETHICAL APPROVAL

This study was performed according to the principles outlined by the World Medical Association's Declaration of Helsinki on experimentation involving human subjects

and has been approved by the ethics committee of the Isfahan University of Medical Sciences (IR.MUI.MED.REC.1400.104).

CONSENT

The authors confirm that a signed consent was obtained from the patient prior to publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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