Generalized granuloma annulare heralding relapse of non-Hodgkin lymphoma

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INTRODUCTION

Granuloma annulare (GA) is a benign dermatosis of unknown origin resulting in erythematous, brown, or skin-colored annular plaques usually found over boney surfaces on the extremities. Generalized GA, an uncommon variant of GA, is seen in middle age or older patients, presents with lesions on the trunk and extremities and has 3 main subtypes: (1) generalized annular, (2) disseminated papular, and (3) atypical.[1] GA has been reported in association with various hematologic, lymphoproliferative, and solid malignant neoplasms, but the underlying cause remains unknown. There are reported cases of GA occurring in relation to non-Hodgkin lymphoma (NHL), but GA associated with marginal zone lymphoma (MZL), a B-cell NHL, and arising within months before relapse is unusual. We describe a rare case of generalized GA preceding MZL relapse that resolved with the patient's second MZL remission, suggesting a paraneoplastic phenomenon.

Abbreviations used:

GA: granuloma annulare
MZL: marginal zone lymphoma
NHL: non-Hodgkin lymphoma

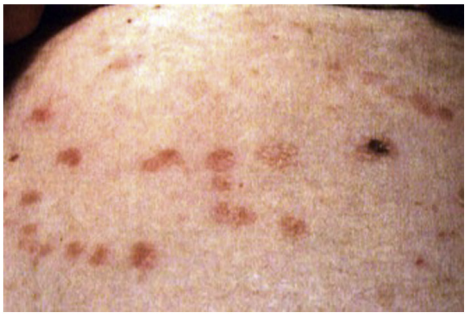

Fig 1. Generalized GA of the abdomen. Monomorphic, virtually identical, somewhat elongated multiple brownish-yellow, smooth papules.

CASE REPORT

A 72-year-old woman with stage IV MZL diagnosed 18 months prior, was in remission for 4 months after receiving 2 cycles of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) and 6 cycles of R-CVP (rituximab, cyclophosphamide, vincristine sulfate, and prednisone). She presented with a newly developed, asymptomatic eruption that began a month before on her brow and abdomen.

On examination, she had monomorphic, virtually identical, somewhat elongated, 2- to 3-mm, brownish-yellow, smooth papules, on the abdomen where they aggregated in a linear pattern along skin folds. There were numerous, discrete lesions on her mid-upper back and flanks. The papules were relatively featureless on epiluminescence microscopy, and none of them formed arcuate lesions (Fig 1).

A punch biopsy from a lesion on the left side of the abdomen found a normal epidermis. There were numerous dermal perivascular and interstitial non-caseating granulomas with multinucleated giant cells. The granulomas were loosely organized and associated with prominent lymphocytic infiltrate (Fig 2, *A* and *B*).

No organisms were seen with Grocott methenamine silver, periodic acid–Schiff, and acid-fast bacilli

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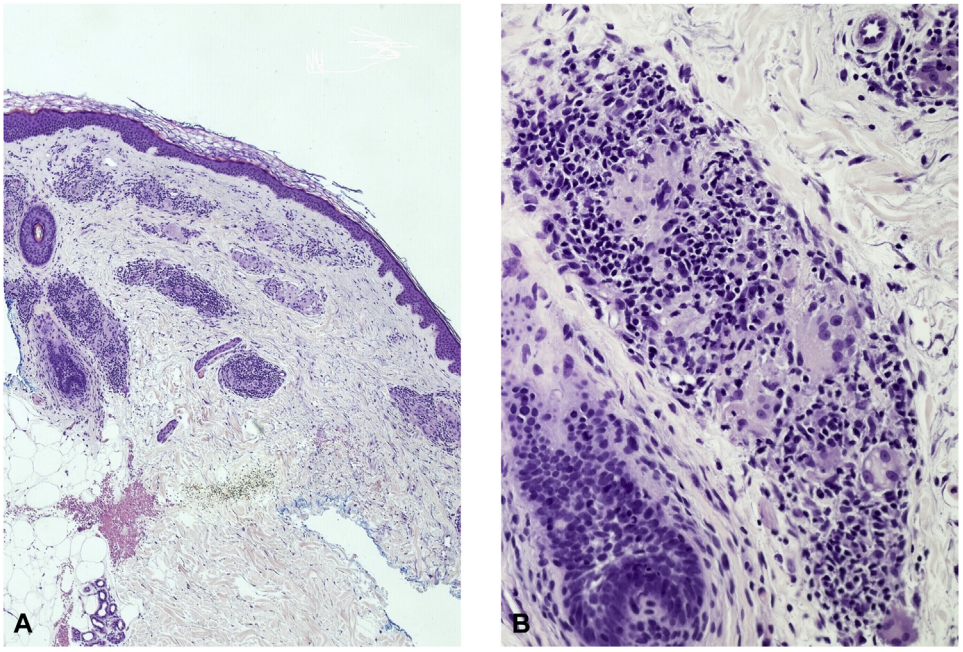

Fig 2. Loosely organized granulomas with prominent associated lymphocytic inflammation. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×4; **B**, ×20).

special stains, and no polarizable material was identified. The pathology was consistent with the rare sarcoidal variant of GA, in which the granulomas tend to be less well circumscribed and show more associated lymphocytic infiltrate versus the granulomas of sarcoidosis.[2] The lymphocytes and histiocytes did not show atypia, and no evidence of MZL or any other cutaneous malignant process was present. Posterioranterior and lateral chest radiographs were essentially normal, with a slightly elevated α I antitrypsin, indicative of atelectasis. Her angiotensin-converting enzyme level and Ca^{++} levels were within normal range, and there was no elevation of inflammatory parameters. Ophthalmologic evaluation was unremarkable with no evidence of granulomas. A diagnosis of generalized GA was made based on the clinicopathologic findings.

The patient was treated with 0.05% betamethasone cream applied to lesions 3 to 4 times a day. A month later, the lesions had flattened and slightly faded but subsequently became pruritic. Eight months after her lesions appeared and during treatment for her GA, the patient had relapse of MZL. She was treated with bendamustine and rituximab for 6 cycles. After her second cycle of chemotherapy, her GA lesions faded to barely visible pink macules and annular lesions on her abdomen, indicating near resolution of the lesions. Follow-up positron emission tomography/computed tomography scan after her fourth cycle of chemotherapy showed resolution of previously seen extensive lymphadenopathy and splenomegaly, and remission was achieved after the sixth cycle of chemotherapy.

DISCUSSION

GA has been associated with various systemic conditions, including viral infections, trauma, drug induction, thyroid disease, and malignancies.[3] Paraneoplastic GA has been predominantly reported in leukemias and lymphomas. Prior reports describe GA in both cutaneous and systemic lymphomas, with GA occurring anywhere from 5 years before malignancy to 27 years after.[4] In rare cases, GA was found during remission, preceding relapse of lymphoma.[1,3,4] Although a specific type of lymphoma has not been highly correlated with GA, increasing reports of association between the 2 diseases shows the potential of GA as a lymphoma indicator, especially in patients with an abnormal presentation or a history of lymphoma.[1]

Various treatments for generalized GA, both topical and systemic, are reported as successful, and in some cases, when GA is found in conjunction with lymphoma, the lesions resolved with successful remission.[4] In our patient, topical treatment of her GA lessened the severity but did not result in resolution. During chemotherapy, her GA resolved, and second remission was confirmed shortly thereafter.

The pathogenesis of GA remains unclear; however, the most widely accepted hypothesis is

that it is a granulomatous immunologic response to an antigen, resulting in the activation of immune mediators.[5] The occurrence of GA in relation to lymphomas further supports this hypothesis, as it alludes to GA being a result of an enhanced abnormal cellular response. B cells have been known to produce inflammatory cytokines, and MZL is a result of overproliferation of B cells. It is plausible that her GA resolved because of the resolution of her MZL, which subsequently caused a decrease in inflammatory cytokines.

Paraneoplastic syndromes result from an immune response to cancer. By definition, they are not the result of metastasis, direct tumor infiltration, or indirectly from toxicity, ectopic hormone secretion, or malignancy-induced coagulopathies.[6] They parallel the occurrence of cancer: symptoms will appear in conjunction with the occurrence of cancer and resolve as the cancer is treated and remission is achieved. Before her clinical diagnosis of MZL recurrence, our patient presented with generalized GA that did not resolve with standard topical treatment. However, after treatment of her MZL, the patient's GA improved. We cannot exclude the possibility that our patient's GA resolved because of a direct action of the chemotherapy. However, the age of the patient, the pattern of distribution, and the close temporal relationship of GA preceding her MZL relapse and resolution after her second remission would favor a paraneoplastic phenomenon. After thorough review of the literature, generalized GA preceding MZL relapse is a rare occurrence further supporting the necessity to consider relapse when GA lesions occur after remission. Generalized GA may indicate relapse of lymphoma and should be considered in patients with known malignancies in remission.

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