Invasive breast cancer found in a patient with new-onset pemphigus foliaceus

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INTRODUCTION

Pemphigus disorders are a class of rare autoimmune blistering dermatoses caused by antibody-mediated disruption of intraepithelial junctions. An association between pemphigus disorders and malignancy has primarily been established in the paraneoplastic pemphigus (PNP) subtype.[1] Emerging evidence suggests that pemphigus vulgaris (PV) and pemphigus foliaceus (PF), the 2 most common types of pemphigus, may also be associated with an increased incidence of certain malignancies.[2-5] Here, we report a patient with no known medical history who presented with new-onset PF and was subsequently diagnosed with an invasive mammary carcinoma from investigation of a possible paraneoplastic etiology. This case provides supportive evidence for potential paraneoplastic associations of PF and highlights the clinical importance of screening for malignancy in patients with pemphigus.

CASE REPORT

A 64-year-old Asian woman with no significant medical history presented with a 6-month history of a progressively worsening blistering rash. The rash started on her neck and upper portion of the chest as small pruritic blisters, which readily eroded into painful sores. Within months, it became widespread throughout her body surface. The patient was not taking any medications, and she denied any travel history or exposure to new skin products before onset of the rash. Physical examination revealed numerous superficial crusted erosions throughout her scalp, face, ears, chest, abdomen, back, and all 4 extremities (Fig 1). Flaccid vesicles were noted on her left breast, abdomen, arms, and legs. The conjunctival, oral, and genital mucosa was spared.

Punch biopsy showed superficial epidermal acantholysis (Fig 2, *A* and *B*). Direct immunofluorescence staining was positive for pericellular IgG and C3 deposition in the epidermis and negative for IgA and immunoglobulin M deposition (Fig 2, *C* and *D*). Serologic study was positive for anti-desmoglein 1 (Dsg1) IgG (>200 IU/mL) and negative for anti-Dsg3 IgG (<2 IU/mL). Indirect immunofluorescence staining was positive on monkey esophageal epithelium and negative on rat bladder epithelium substrate. Collectively, these findings confirmed a diagnosis of PF, with a pemphigus disease activity index score of 35.[6]

The patient was started on a prednisone taper course, with rapid improvement, and was transitioned to mycophenolate mofetil. Meanwhile, she underwent laboratory workup and age-appropriate cancer screening to rule out underlying autoimmune and paraneoplastic etiologies. Although her blood tests were unremarkable, a mammogram and subsequent breast biopsy detected an invasive ductal carcinoma (ER/PR+/HER2−) of the left breast. Upon diagnosis, both mycophenolate mofetil and prednisone were discontinued immediately. Lumpectomy and sentinel lymph node (LN) biopsy revealed a 1.7-cm grade 1 invasive ductal carcinoma, metastasized in 2 of 2 sentinel LNs with extranodal extension; subsequent left-sided axillary LN dissection with lymphovenous bypass demonstrated micrometastatic carcinoma involving 1 of 16 LNs. While the patient underwent

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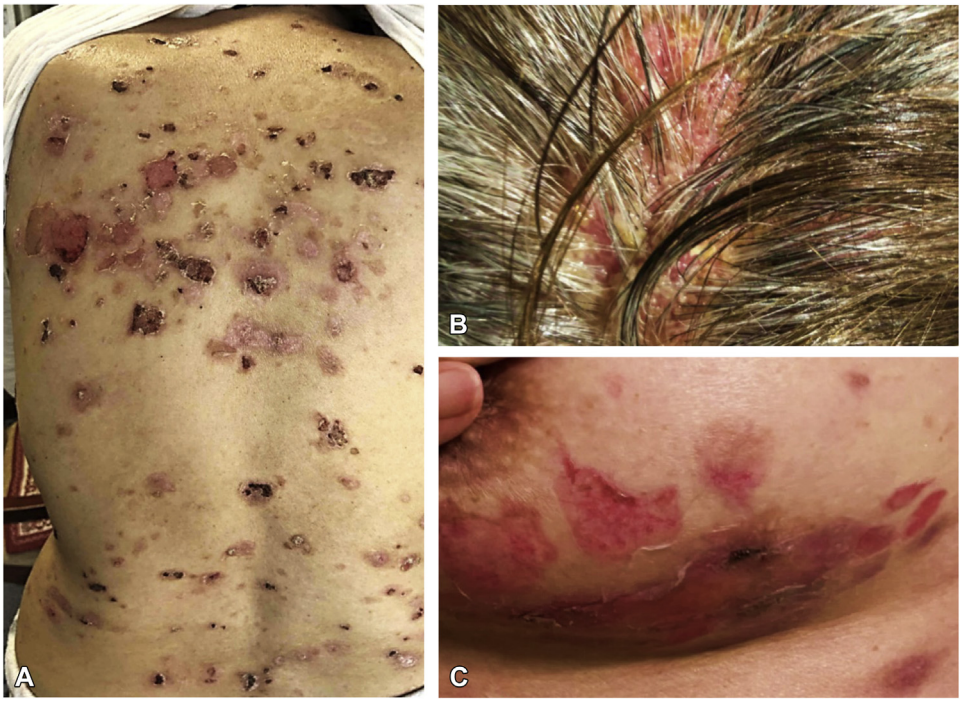

Fig 1. Numerous erythematous eroded papules and plaques on the back (**A**), vertex of the scalp (**B**), and left breast (**C**).

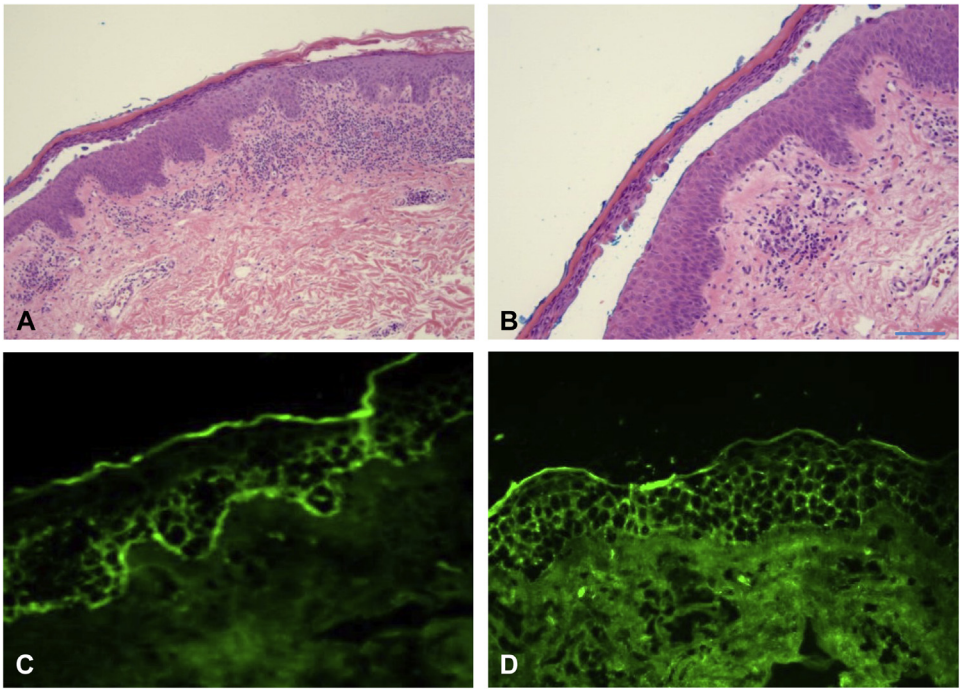

Fig 2. Punch biopsy of a vesicular lesion on the left thigh (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×10; **B**, ×20.); Low-power magnification of direct immunofluorescence staining for IgG (**C**) and C3 (**D**).

surgeries for breast cancer and immunosuppressive therapies had been suspended, she had an exacerbation of PF. She was treated with high-dose intravenous immunoglobulin infusions (2 g/kg divided into 4 doses) and started on minocycline orally as a nonimmunosuppressive therapy. At her most recent visit 2 months after intravenous immunoglobulin infusion, the patient showed

remarkable clinical improvement, with fewer than 10 residual active lesions.

DISCUSSION

An association between pemphigus disorders and malignancy has primarily been established in PNP. PNP is a severe and progressive blistering dermatosis, thought to result from neoplasia-triggered autoimmunity against multiple self-antigens, such as Dsg3, Dsg1, desmoplakins, and bullous pemphigoid antigen-1.[1] In contrast, PF is considered a relatively benign and often idiopathic condition caused by autoantibodies against Dsg1 expressed in cutaneous epithelium. Unlike PNP, which has early and striking mucosal involvement, PF spares mucosal surfaces due to the absence of autoantibodies against Dsg3, which is primarily expressed in mucosal epithelium. PF is further distinguished from PNP by negative indirect immunofluorescence labeling of rat bladder epithelium.[1] The association of PF with underlying malignancy has not been well established.[1] Recent studies documented significantly higher incidences of lymphoproliferative malignancies and solid cancers (esophageal and laryngeal cancers, lung cancers, and nonmelanoma skin cancers) in patients with PV and PF, suggesting a paraneoplastic association in pemphigus disorders beyond PNP.[2-5] In light of these emerging findings, we recommended and coordinated age-appropriate cancer screenings for our patient. This led to the diagnosis of an otherwise asymptomatic and nonpalpable stage IIA breast cancer.

An association between breast cancer and pemphigus disorders in general, let alone PF, is unusual. A review of 104 patients with PNP reported only a single case of comorbid breast cancer.[7] Two cases have been reported of patients with breast cancer and a PF phenotype (eg, sparing of mucosal surfaces). However, unlike our patient, the diagnoses were biochemically consistent with PNP and PV.[8,9] Maglie et al[10] reported a patient with exacerbation of PV primarily localized to the right breast, where a ductal carcinoma was present. Right-sided mastectomy led to substantial clinical improvement; however, the investigators documented the persistence of residual extramammary lesions on the trunk.[10] Similarly, our patient's postsurgical course was notable for continued pemphigus activity and sustained presence of serum anti-Dsg1 IgG (>200 IU/mL 2 months after lumpectomy). This is not surprising, given the longevity of autoimmune memory lymphocytes and the long half-life of IgG. The long duration of autoimmune processes following various triggers has been observed in many autoimmune conditions, including PNP. The precise immunologic mechanisms and long-term prognosis of malignancy-associated pemphigus remain to be further elucidated.

Our case illustrates the importance of cancer screening in patients with pemphigus with no known precipitating factors. Early diagnosis of the associated malignancies not only improves the prognosis of cancer but also minimizes the risk of iatrogenic immunosuppression from pemphigus treatment. Pemphigus often requires inductive therapy with corticosteroids or rituximab, followed by long-term immunosuppressants such as cytotoxic immunomodulators (mycophenolate mofetil, azathioprine, methotrexate, cyclosporine) and antimalarial agents.[6] We encourage clinicians to conduct appropriate cancer screening in patients with pemphigus before initiating rituximab and long-term immunosuppressive therapies. Dapsone and tetracyclines have both shown efficacy in pemphigus and may be the preferred maintenance drugs in patients with uncertain cancer status.[6] For more severe cases, intravenous immunoglobulin is a nonimmunosuppressive and efficacious option.[6] A consensus on future guidelines on cancer screening in patients with pemphigus and treatment algorithms for those with concomitant malignancies is needed for safe and effective management of pemphigus.

Conflicts of interest

None disclosed.

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