Localized pemphigus exacerbation associated with underlying breast cancer

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INTRODUCTION

Pemphigus is a rare, autoantibody-mediated, mucocutaneous disease characterized by the loss of adhesion between keratinocytes and intraepidermal blistering.[1] Although idiopathic in most cases, epidemiologic studies suggest an association between pemphigus and malignancies, including, in particular, lymphoproliferative disorders and gastrointestinal tumors.[2,3] The pathophysiologic mechanisms behind this association remain elusive.

In the literature, pemphigus occurrence in patients with underlying breast cancer has been reported as a particularly rare association, with most of the published cases occurring after radiation therapy.[4] Here, we describe a patient with a history of oral pemphigus vulgaris (PV) experiencing a severe disease flare predominantly affecting her right breast skin in the setting of an underlying ductal carcinoma.

Abbreviations used:

PNP: paraneoplastic pemphigus
PV: pemphigus vulgaris

CASE REPORT

A 54-year-old woman presented to our department because of a 3-month history of a rash localized to her right breast. Six months before the presentation, she was diagnosed with oral PV. Enzyme- linked immunosorbent assay at this time point showed an elevation of both anti-desmoglein (Dsg) 3 (150 IU/mL) and Dsg1 (100 IU/mL) IgG antibodies. The disease was managed with a short course of oral and topical corticosteroids, with complete remission with low-dose systemic corticosteroids (prednisone 7.5 mg/day) without the need for other immunosuppressive medications. She was suffering from a major depressive disorder, for which she was on treatment with trazodone, sertraline, lamotrigine, and duloxetine.

Physical examination showed a significant retraction of the right breast and nipple; an initial hardening and retraction of her right breast had been present since approximately 18 months prior, but the patient did not consult her physician until the manifestation of the rash. The skin overlying her right breast was covered with multiple confluent erosions, hyperkeratotic scales, and crusts (Fig 1). The morphologic anatomy and the skin of the contralateral breast appeared normal. Some erythematous-scaling plaques were also noted across the back. Examination results of the oral mucosa, conjunctivae, and genital mucosa appeared normal. Histopathology examination performed on an erosion of the right breast's skin showed suprabasal epidermal acantholysis. A direct immunofluorescence test of the perilesional skin showed the intercellular deposition of IgG and C3 in the epidermis, while enzyme-linked immunosorbent assay showed a high level of IgG autoantibodies against Dsg1 (101.3 IU/mL) and Dsg3 (148.8 IU/mL). Indirect immunofluorescence test using monkey esophagus as a substrate showed intercellular IgG deposition; whereas indirect immunofluorescence test using rat bladder epithelium gave negative results. The above findings were consistent with a relapse of

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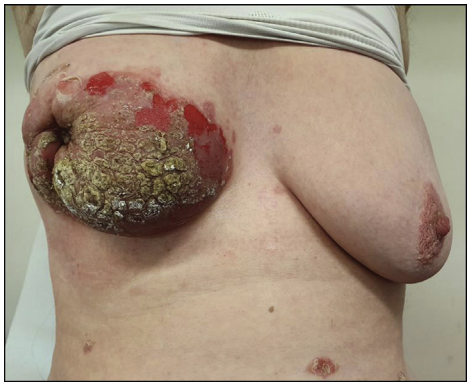

Fig 1. Breast cancer-exacerbated PV. A morphological alteration of the right breast anatomy with nipple retraction. The skin of the right breast was covered with multiple erosions, scales, and crusts. *PV*, Pemphigus vulgaris.

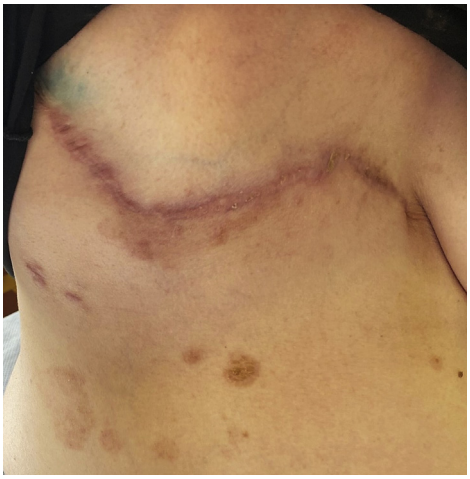

Fig 2. Complete resolution of the cutaneous lesion of the breast skin following surgical removal of the tumor.

her PV. A computed tomography scan and subsequent breast biopsy confirmed the presence of an invasive triple negative ductal carcinoma. Surgical removal of the tumor resulted in a marked improvement of the pemphigus flare, with complete resolution of the lesions on the breast skin and persistence of a few residual lesions on the trunk (Fig 2), which did not require an increase in her daily prednisone dose.

DISCUSSION

Malignancies can either induce or exacerbate pemphigus. Paraneoplastic pemphigus (PNP) is a rare pemphigus variant that also potentially occurs in patients with underlying malignancies. Unlike classical pemphigus variants, including PV and pemphigus foliaceus, PNP is characterized by distinct clinical and immunopathologic findings, including severe mucositis, internal complications such as bronchiolitis obliterans, and antibodies against other keratinocyte antigens in addition to Dsg3 and Dsg1.[5,6] While malignancy-induced or -exacerbated pemphigus often ameliorates, or even resolves, following the removal of the tumor, PNP intrinsically runs a more severe and possibly life-threatening clinical course. Hence, making a differential diagnosis between these entities is crucial.[7]

Both PNP and malignancy-associated pemphigus have rarely been reported in the setting of underlying breast tumors. In our patient, the clinical examination and immunopathologic findings suggested a diagnosis of breast cancer-exacerbated PV. PNP was ruled out due to i) the absence of severe mucosal involvement and internal complications at the time of pemphigus relapse, ii) negative results of the indirect immunofluorescence test using rat bladder as a substrate, and iii) lack of evidence of interface dermatitis in the skin biopsy.[8] Although the breast cancer was likely present before the onset of the first pemphigus manifestation, the causal relationship between the presence of the tumor and the localized pemphigus flare was strengthened by the prompt disease improvement following the surgical removal of the tumor and the lack of recurrence of the pemphigus lesions on the postoperative skin.

Indeed, an unusual and, to our knowledge, previously unreported finding of this case was the localization of most pemphigus lesions in close proximity to the underlying tumor. There may be different factors that possibly contributed to this phenomenon. First, the cancer cells of triple negative ductal carcinoma have been shown to overexpress Dsg3[9]; second, malignancy-induced alteration of the vascular supply and lymphatic drainage, as well as the abundance of antigens produced by neoplastic cells, may have favored the accumulation of Dsg3-specific B cells in the contiguous skin. The excision of the affected skin area might have removed those autoreactive B cells, explaining the significant reduction of pemphigus activity. Local production of anti-Dsg antibodies by skin-resident B cells is a recently recognized phenomenon in pemphigus, possibly accounting for the local pemphigus exacerbation or resistance to immunosuppressive therapies.[10]

This case provides further evidence for the pathogenetic link between pemphigus and solid tumors. Clinicians should be aware of the possibility of underlying malignancies in pemphigus patients experiencing localized flares.

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