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Localized pemphigus exacerbation associated with underlying breast cancer

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39 **Introduction**

40

41 Pemphigus is a rare, autoantibody-mediated, mucocutaneous disease characterized by  
42 loss of the adhesion between keratinocytes and intraepidermal blistering [1]. Although idiopathic  
43 in most cases, epidemiologic studies suggest an association between pemphigus and

44 malignancies, including in particular lymphoproliferative disorders and gastrointestinal tumors  
45 [2,3]. Pathophysiologic mechanisms behind this association remain elusive.  
46 In the literature, pemphigus occurrence in patients with underlying breast cancer has been  
47 reported as a particularly rare association, with most of the published cases occurring after  
48 radiation therapy [4]. Here, we describe a patient with a history of oral pemphigus vulgaris (PV)  
49 experiencing a severe disease flare predominantly affecting her right breast skin in the setting of  
50 underlying ductal carcinoma.  
51

## 52 **Case report**

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

63 Physical examination showed a significant retraction of the right breast and nipple; initial  
64 hardening and retraction of her right breast had appeared since about 18 months, but the  
65 patient did not consult her physician until the manifestation of the skin rash. The skin overlying  
66 her right breast was covered with multiple confluent erosions, hyperkeratotic scales and crusts  
67 (Figure 1). The morphological anatomy and the skin of the contralateral breast appeared  
68 normal. Some erythematous-scaling plaques were also noted across the back. Examination of  
69 the oral mucosa, conjunctivae and genital mucosa appeared normal. Histopathology  
70 examination obtained from an erosion of the right breast's skin showed suprabasal epidermal  
71 acantholysis. Direct immunofluorescence from the perilesional skin showed intercellular  
72 deposition of IgG and C3 in the epidermis, while ELISA showed high level of IgG autoantibodies  
73 against Dsg1 (101.3 UI/mL) and Dsg3 (148.8 UI/mL). Indirect immunofluorescence (IIF) on  
74 monkey oesophagus as a substrate showed intercellular IgG deposition; while IIF on the rat  
75 bladder epithelium gave negative results. The above findings were consistent with a relapse of  
76 her PV. A computed tomography scan and a subsequent breast biopsy confirmed the presence  
77 of an invasive triple negative ductal carcinoma. Surgical removal of the tumor resulted in a  
78 marked improvement of the pemphigus flare, with complete resolution of the lesions on the  
79 breast skin and persistence of a few residual lesions on the trunk (Figure 2), which did not  
80 require an increase in her daily prednisone dose.

81

## 82 **Discussion**

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

92

93 Both PNP and malignancy-associated pemphigus have been rarely reported in the  
94 setting of underlying breast tumors. In our patient, clinical examination and immunopathological  
95 findings suggested a diagnosis of breast-cancer exacerbated PV. PNP was ruled out due to i)  
96 the absence of severe mucosal involvement and internal complications at time of pemphigus  
97 relapse, ii) negative results of IIF using rat bladder as a substrate, and iii) no evidence of  
98 interface dermatitis at the skin biopsy [8]. Although the breast cancer was likely present before  
99 the onset of the first pemphigus manifestation, the causal relationship between the presence of  
100 the tumor and the localized pemphigus flare was strengthened by the prompt disease  
101 improvement following the surgical removal of the tumor and the lack of recurrence of  
102 pemphigus lesions on the post-operative skin.  
103

104 Indeed, an unusual, and to our knowledge previously unreported, finding of this case  
105 was the localization of most pemphigus lesions in close proximity to the underlying tumor. There  
106 may be different factors that have possibly contributed to this phenomenon. First, cancer cells of  
107 triple negative ductal carcinoma have been shown to over-express Dsg3 [9]; second, the  
108 malignancy-induced alteration of the vascular supply and lymphatic drainage, as well as the  
109 abundance of antigens produced by neoplastic cells, may have favoured the accumulation of  
110 Dsg3 specific-B cells in the contiguous skin. The excision of the affected skin area might have  
111 presumably removed those autoreactive B-cells, explaining the significant reduction of  
112 pemphigus activity. Local production of anti Dsg-antibodies by skin-resident B-cells is a recently  
113 recognized phenomenon in pemphigus, possibly accounting for local pemphigus exacerbation  
114 or resistance to immunosuppressive therapies [10].  
115

115

## 116 Conclusion

117 This case provides further evidence for the pathogenetic link between pemphigus and  
118 solid tumors. Clinicians should be aware about the possibility of underlying malignancies in  
119 pemphigus patients experiencing localized flares.  
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#### 169 **Figure legend**

170 **Figure 1:** Breast-cancer exacerbated pemphigus vulgaris: morphological alteration of right breast  
171 anatomy with nipple retraction. The skin of the right breast was covered with multiple erosions, scales  
172 and crusts.

174 **Figure 2:** complete resolution of the cutaneous lesion of the breast skin following the surgical removal of  
175 the tumor.

176



