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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

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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166

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.





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