Localized pemphigus exacerbation associated with underlying breast cancer

Localized pemphigus exacerbation associated with underlying breast cancer

Roberto Maglie, MD, Francesca Montefusco, MD, Stefano Senatore, MD, Angelo Massimiliano D'Erme, MD, Giovanni Bagnoni, Emiliano Antiga, MD, PhD

PII: S2352-5126(20)30752-9

DOI: https://doi.org/10.1016/j.jdcr.2020.10.018

Reference: JDCR 1618

To appear in: *JAAD Case Reports*

Received Date: 14 September 2020

Revised Date: 13 October 2020

Accepted Date: 13 October 2020

Please cite this article as: Maglie R, Montefusco F, Senatore S, D'Erme AM, Bagnoni G, Antiga E, Localized pemphigus exacerbation associated with underlying breast cancer, *JAAD Case Reports* (2020), doi: https://doi.org/10.1016/j.jdcr.2020.10.018.

Article type: Case reports

Title: Localized pemphigus exacerbation associated with underlying breast cancer

Author: Roberto Maglie MD,[1] Francesca Montefusco MD,[1] Stefano Senatore MD,[1] Angelo Massimiliano D'Erme MD,[2] Giovanni Bagnoni,[2] Emiliano Antiga MD, PhD[1].

[1]Department of Health Sciences, Section of Dermatology, University of Florence, Florence, Italy

[2]Melanoma and Skin Cancer Unit, AVNO (Area Vasta Nord Ovest) and Unit of Dermatology, Livorno Hospital, Livorno, Italy.

Corresponding author:

Dr. Roberto Maglie
Department of Health Sciences
Section of Dermatology
University of Florence
Viale Michelangiolo 41
50125 Florence, Italy
Email: robertomaglie.med@libero.it

Funding sources: none

Conflicts of Interest: None declared.

Reprint requests: Roberto Maglie

Manuscript word count: 858
References: 9
Figures: 3
Supplementary figures: 0
Tables: 0
Supplementary tables: 0

Keywords: pemphigus vulgaris; malignancy-exacerbated pemphigus; breast cancer; desmoglein 3; desmoglein 1.

Introduction

Pemphigus is a rare, autoantibody-mediated, mucocutaneous disease characterized by loss of the 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]. 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 underlying ductal carcinoma.

Case report

A 54-year-old woman presented to our department because of a 3-month history of a skin rash localized to her right breast. Six months before presentation, she was diagnosed with oral pemphigus vulgaris (PV). An enzyme- linked immunosorbent assay at this time point showed elevation of both anti-Desmoglein (Dsg) 3 (150 UI/mL) and Dsg1 (100 UI/mL) IgG antibodies. The disease was managed with a short-course of oral and topical corticosteroids, with complete remission on low dose systemic corticosteroids (prednisone 7.5 mg/day) without the need of 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; initial hardening and retraction of her right breast had appeared since about 18 months, but the patient did not consult her physician until the manifestation of the skin rash. The skin overlying her right breast was covered with multiple confluent erosions, hyperkeratotic scales and crusts (Figure 1). The morphological anatomy and the skin of the contralateral breast appeared normal. Some erythematous-scaling plaques were also noted across the back. Examination of the oral mucosa, conjunctivae and genital mucosa appeared normal. Histopathology examination obtained from an erosion of the right breast's skin showed suprabasal epidermal acantholysis. Direct immunofluorescence from the perilesional skin showed intercellular deposition of IgG and C3 in the epidermis, while ELISA showed high level of IgG autoantibodies against Dsg1 (101.3 UI/mL) and Dsg3 (148.8 UI/mL). Indirect immunofluorescence (IIF) on monkey oesophagus as a substrate showed intercellular IgG deposition; while IIF on the rat bladder epithelium gave negative results. The above findings were consistent with a relapse of her PV. A computed tomography scan and a 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 (Figure 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 immunopathological 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 removal of the tumor, PNP intrinsically runs a more severe and possibly life-threatening clinical course. Hence, making a differential diagnosis between those entities is crucial [7].

Both PNP and malignancy-associated pemphigus have been rarely reported in the setting of underlying breast tumors. In our patient, clinical examination and immunopathological 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 time of pemphigus relapse, ii) negative results of IIF using rat bladder as a substrate, and iii) no evidence of interface dermatitis at 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 pemphigus lesions on the post-operative 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 have possibly contributed to this phenomenon. First, cancer cells of triple negative ductal carcinoma have been shown to over-express Dsg3 [9]; second, the malignancy-induced alteration of the vascular supply and lymphatic drainage, as well as the abundance of antigens produced by neoplastic cells, may have favoured the accumulation of Dsg3 specific-B cells in the contiguous skin. The excision of the affected skin area might have presumably 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 local pemphigus exacerbation or resistance to immunosuppressive therapies [10].

Conclusion

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

References

[1] Didona D, Maglie R, Eming R, Hertl M. Pemphigus: Current and Future Therapeutic Strategies. Front Immunol 2019;10:1418. https://doi.org/10.3389/fimmu.2019.01418.

[2] Kridin K, Zelber-Sagi S, Comaneshter D, Cohen AD. Coexistent Solid Malignancies in Pemphigus: A Population-Based Study. JAMA Dermatol 2018;154:435–40. https://doi.org/10.1001/jamadermatol.2017.6334.

[3] Kridin K, Zelber-Sagi S, Comaneshter D, Batat E, Cohen AD. Pemphigus and hematologic malignancies: A population-based study of 11,859 patients. J Am Acad Dermatol 2018;78:1084-1089.e1. https://doi.org/10.1016/j.jaad.2017.11.039.

[4] Schauer F, Ishii N, Mockenhaupt M, Bruckner-Tuderman L, Hashimoto T, Kiritsi D. Radiation-Associated Pemphigus Vulgaris in a Patient With Preceding Malignancy: Treatment With

Rituximab as a Valuable Option. Front Immunol 2019;10:3116. https://doi.org/10.3389/fimmu.2019.03116.

[5] Solimani F, Maglie R, Pollmann R, Schmidt T, Schmidt A, Ishii N, et al. Thymoma-Associated Paraneoplastic Autoimmune Multiorgan Syndrome-From Pemphigus to Lichenoid Dermatitis. Front Immunol 2019;10:1413. https://doi.org/10.3389/fimmu.2019.01413.

[6] Ohzono A, Sogame R, Li X, Teye K, Tsuchisaka A, Numata S, Koga H, Kawakami T, Tsuruta D, Ishii N, Hashimoto T. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. Br J Dermatol. 2015;173:1447-52. doi: 10.1111/bjd.14162.

[7] Streifel AM, Wessman LL, Schultz BJ, Miller D, Pearson DR. Refractory mucositis associated with underlying follicular dendritic cell sarcoma of the thymus: Paraneoplastic pemphigus versus malignancy-exacerbated pemphigus vulgaris. JAAD Case Rep 2019;5:933–6. https://doi.org/10.1016/j.jdcr.2019.09.009.

[8] Maglie R, Genovese G, Solimani F, Guglielmo A, Pileri A, Portelli F, et al. Immune-Mediated Dermatoses in Patients with Haematological Malignancies: A Comprehensive Review. Am J Clin Dermatol 2020. https://doi.org/10.1007/s40257-020-00553-9.

[9] Fei H, Chen S, Xu C. RNA-sequencing and microarray data mining revealing: the aberrantly expressed mRNAs were related with a poor outcome in the triple negative breast cancer patients. Ann Transl Med 2020;8:363. https://doi.org/10.21037/atm.2020.02.51.

[10] Yuan H, Zhou S, Liu Z, Cong W, Fei X, Zeng W, et al. Pivotal Role of Lesional and Perilesional T/B Lymphocytes in Pemphigus Pathogenesis. J Invest Dermatol 2017;137:2362–70. https://doi.org/10.1016/j.jid.2017.05.032.

Figure legend

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

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