Case Report

Recurrence of Pemphigus Vulgaris after Bilateral Breast Irradiation: A Case Report and Review of the Literature

Camille Invernizzi^a Victor Gaultier^b Philippe Guilbert^a
Christelle Jouannaud^c Anne-Laure Labrousse^d Charles Marchand Crety^a

^aDepartment of Radiation Therapy, Institut Godinot, Reims, France; ^bDepartment of Gynecology Obstetrics, Centre Hospitalier Universitaire Robert Debré, Reims, France;

^cDepartment of Medical Oncology, Institut Godinot, Reims, France; ^dDepartment of Dermatology, Polyclinique Courlancy, Reims, France

Keywords

Pemphigus · Radiotherapy · Breast cancer

Abstract

Pemphigus is a serious and rare chronic bullous autoimmune disease. It is characterized by mucocutaneous erosions secondary to autoantibodies directed against desmogleins 1 and 3, proteins involved in intercellular adhesion mechanisms. The occurrence of pemphigus is based on the triggering of genetic and external environmental factors such as drugs, infection, and more rarely radiotherapy. To date, only 16 cases of radiation-induced pemphigus are described in the context of breast cancer treatment. We present the case of a 76-year-old woman who had a recurrence of pemphigus vulgaris limited to the irradiation field after exposure to an adjuvant radiotherapy treatment for a bilateral triple-negative breast cancer. The onset was bilateral limited to the irradiation area and was treated effectively with local and systemic corticosteroids. After a rigorous review of the literature, only 16 cases of breast cancer radiation-induced pemphigus appeared. In contrast to several cases, the rash was limited to the irradiated area and improved with systemic corticosteroids. For more than three-quarters of the described cases in the literature, pemphigus occurs within 3 months following the end of treatment. After systemic immunosuppressive treatment, this disease disappears in the vast majority of the reported cases.

© 2021 The Author(s).

Published by S. Karger AG, Basel

Correspondence to:
Charles Marchand Crety, charles.marchandcretty@gmail.com

Background

Pemphigus is a chronic epithelial bullous disease presenting 3 major subtypes: pemphigus vulgaris (PV) or deep pemphigus, pemphigus foliaceus or superficial pemphigus, and paraneoplastic pemphigus [1]. It is a rare disease with an estimated incidence in non-Jewish and Jewish populations of 0.5–10 and 16–32 cases per million per year, respectively [2]. The vulgaris subtype is the most common form of the pathology diagnosed in more than two-thirds of patients with this disease [2]. Typically, pemphigus has common characteristics: flabby blisters, erosions, and unlike pemphigoid diseases, a positive Nikolsky sign. These phenotypes can be explained by the presence of immunoglobulin G (IgG) autoantibodies directed against desmosome proteins (anti-desmoglein 1 and 3 antibodies) [1, 2]. These autoantibodies can be demonstrated in serum by indirect immunofluorescence (anti-intercellular substance autoantibodies leading to “chicken-wire” or “fish-net” staining aspect) or on the skin surface by direct immunofluorescence IgG deposits, complement C3, or both [3]. In addition, the occurrence of pemphigus requires genetic factors (mostly) and external environmental triggering factors such as thiol-based drugs, infection (simple herpes viruses), and much more rarely exposure to radiotherapy.

To date, only a few cases of radio-induced pemphigus have been described in the context of breast cancer treatment. In this study, we present the interesting case of a 76-year-old woman with a recurrence of PV in the context of bilateral breast cancer as well as the first review of the literature concerning radio-induced pemphigus in breast cancer.

Case Presentation

The case we report is a 76-year-old female patient who presented with a recurrence of unilateral PV 1 month after adjuvant irradiation for bilateral triple-negative breast cancer. The patient had a history of PV of the scalp, neck, and face, shingles in adolescence, and allergies to kiwi and hazelnuts. Five years before the diagnosis of breast cancer, the patient had an initial bubble-like injury to the neck. Crusty, erosive, oozing, and itchy lesions of the scalp, neck, and face then occurred in flare-ups. No mucosal lesion had been objectified. A PV had been confirmed after a histological examination which showed blister-like lesions by intraepidermal cleavage associated with acantholysis and a discrete exocytosis containing eosinophils (Fig. 1). Intercellular deposits of IgG and C3 were found throughout the epidermis. Anti-intercellular substance autoantibodies were positive (1:160) by indirect immunofluorescence. The lesions eventually resolved after treatment with local and oral corticosteroids.

Fig. 1. Microscopy. **a** Intraepidermal bulla (arrow) on histological picture (HES, ×100). **b** Suprabasal cleft (arrow) and acantholytic cells dense cytoplasm (HES, ×400).

Fig. 2. Skin lesion pictures. **a** The current case 2 months after completion of the breast irradiation course, right breast with typical aspect of pemphigus vulgaris with erosive bubbles predominant on the previous radiation field. **b** Current case 6 months later acquired healing after 3 months of systemic corticosteroids.

Five years later, the patient was treated for a bilateral triple-negative cancer with a positive axillary node on the left. After bilateral lumpectomy surgery with left axillary dissection and a sentinel lymph node procedure on the right, adjuvant treatment with sequential chemotherapy (4 cycles of doxorubicin/cyclophosphamide followed by 12 weekly courses of paclitaxel) and then radiotherapy was carried out. Thirty-three fractions were delivered for a total dose of 66 Gy according to the scheme of bilateral breast irradiation (50 Gy for each breast), a boost on the tumor beds (16 Gy for each breast), and a dose of 46 Gy for the left supraclavicular node area. Concurrently with the radiation, a grade 1 radiodermatitis covered all the irradiated areas. One month after the end of adjuvant radiotherapy, a rash appeared limited to the irradiation area. The lesions were characterized by centimetric flaccid bubbles with positive Nikolsky sign originating from the submammary sulcus of the right breast with a characteristic appearance of PV (Fig. 2a). No biopsy was performed given the certainty of the clinical diagnosis provided by an experienced dermatologist who previously diagnosed the first flare-up of PV. After resistance to topical treatment with corticosteroids (clobetasol propionate, 0.05%), the lesions disappeared with systemic steroid therapy within 3 months (Fig. 2b). Moreover, barely 2 months after the end of radiotherapy, herpes zoster appeared in the left laterothoracic region. Our patient received oral valacyclovir, and it resolved quickly within 8 days. A thoracic-abdominal-pelvic CT scan and a follow-up mammogram were performed, respectively, at 3 and 6 months after the end of the radiotherapy, both showing no cancer recurrence. Also, no clinical recurrence of pemphigus or herpes was found at 3-, 6-, and 9-month follow-up after the completion of radiotherapy.

Discussion and Conclusions

Here, we report the case of a patient presenting a bilateral recurrence of PV following adjuvant radiotherapy treatment for a bilateral breast cancer. To date, after a careful review of the literature, we report 17 cases of radio-induced pemphigus in the context of breast cancer, including ours [4–9]. These cases are described in Table 1. Five presented with

Table 1. Review of 17 cases of breast irradiation-induced pemphigus

Cases, n	References	Patient age	breast cancer histology	immunologic history	Diagnosis of Pemphigus			Localization	Radiotherapy treatment			Treatment
					type	DIF	IIF		dose	acute toxicity	time from the end of RT to start eruption	
1	Krain et al. [4]	65	Scirrhous carcinoma	na	PV	na	na	Irradiated area with generalized progression	na	na	<1 month	OC, MTX, AZT
2	Low et al. (1990)	73	na	na	PV	+	+	Irradiated area with generalized progression	55 Gy	na	3 months	OC
3	Orion et al. (2004)	45	In situ ductal carcinoma	No	PV	+	na	Irradiated area	68 Gy	na	7 days	OC
4	Gianchini et al. (2006)	70	Adenocarcinoma	No	PF	+(IgG, C3)	+(IgG)	Irradiated area with generalized progression	60 Gy	na	12 months	LC
5	Ambay et al. (2006)	92	In situ ductal carcinoma	No	PF	+	na	Irradiated area with generalized progression	50.4 Gy	No	3 months	na
6	Bar-Sela et al. (2008)	49	Invasive carcinoma, HR+, HER2-	No	PV	+	na	Nonirradiated area (mouth, esophagus)	50 Gy	No	1 month	OC, MTX
7	Vigna- Taglianti et al. (2011)	48	In situ ductal carcinoma	PV 9 years before	PV	na	+	Irradiated area	50 Gy	Grade 2 dermatitis	6 months	OC, LC
8	Thimon et al. (2014)	58	Invasive ductal carcinoma stage I, HR+	na	PV	+(IgG, C3)	+	Irradiated area with generalized progression	65 Gy (B&TBB) 46 Gy (SCLN) 50 Gy (IMLN)	na	21 days	OC, MMF
9	Inadomi et al. (2015)	65	Invasive carcinoma	na	PF	+(IgG, C3)	na	Irradiated area	50 Gy	na	2 months	OC
10	Shon et al. (2016)	58	In situ ductal carcinoma	No	PV	+(IgG)	+	Irradiated area with generalized progression	na	na	14 months	OC, AZT

Table 1 (continued)

Cases, n	References	Patient age	breast cancer histology	immunologic history	Diagnosis of Pemphigus			Localization	Radiotherapy treatment			Treatment
					type	DIF	IIF		dose	acute toxicity	time from the end of RT to start eruption	
11	Liebman et al. [2016]	44	Invasive carcinoma, HR+	Myasthenia gravis	PF	*(IgG, C3, C3d, C4d)	na	Irradiated area with generalized progression	na	na	22 months	LC, OC
12	Tang et al. [5]	84	na	na	PV	*(IgG)	*(IgG)	Nonirradiated area	60 Gy	na	8 months	LC, OC, AZT
13	O'Leary et al. [6]	68	Bilateral, invasive carcinoma, HR+	na	PV	+	NA	Irradiated area with generalized progression	40 Gy	Grade 1 dermatitis	<1 month	OC, MMF
14	Criado et al. [7]	66	In situ ductal carcinoma	No	PF	*(IgG, C3)	na	Irradiated with generalized progression	50 Gy	na	10 days	OC
15	Radin et al. [8]	56	Invasive ductal carcinoma, HR+, HER2-	PV with oral lesion	PV	na	*(IgG, C3)	Nonirradiated area (mouth)	na	na	<7 days	OC, fSCIG
16	Crocker et al. [9]	72	Invasive ductal carcinoma stage II, HR+ HER2-	No	PV	-	*(IgG, C3)	Irradiated area with progression to oral cavity	40 Gy	Grade 2 dermatitis	1 month	OC, LC
17	Current case	72	Bilateral, invasive carcinoma, triple negative	PV 5 years before zoster in childhood	PV	na	na	Irradiated area	66 Gy (B&TBB) 46 Gy (SCLN)	Grade 1 dermatitis	1 month	LC, OC

na, not available; PV, pemphigus vulgaris; PF, pemphigus foliaceus; RT, radiotherapy; Gy, gray; HR+, hormone receptor positive; HER2, human epidermal growth factor receptor-2; MTX, methotrexate; AZT, azathioprine; MMF, mycophenolate mofetil; LC, local corticosteroids; OC, oral corticosteroids; fSCIG, facilitated subcutaneous immunoglobulin; DIF, direct immunofluorescence; IIF, indirect immunofluorescence; B&TBB, breast and tumor bed boost; SCLN, supraclavicular lymph node; IMLN, internal mammary lymph node.

pemphigus foliaceus and 12 with PV. Four patients had an immunological history of which 3 presented a recurrence of PV during their treatment with radiotherapy. Patients ranged in age from 44 years to 92 years with a median of 65 years old. In 7 cases (41%), the disease appeared very early within 1 month after the end of radiotherapy. In the majority of cases (12 cases; 71%), it occurred within 3 months, and in 5 cases (29%) beyond 3 months with one very distant case at 22 months. Ten cases (59%) were initially limited to the irradiation area with secondary progression, 4 cases (23%) presented pemphigus limited to the irradiated area, and 3 cases (18%) presented lesions in a nonirradiated area (mouth and esophagus). The diagnosis was made by direct immunofluorescence in 13 cases (76%) supplemented in 6 cases by indirect immunofluorescence. Two cases were diagnosed by indirect immunofluorescence. The prescribed dose of breast radiotherapy treatment varied between 40 and 68 Gy. All but 2 of the patients were treated orally or intravenously with corticosteroids (prednisone or prednisolone) at medium to high doses. However, these treatments were not sufficient for the majority of patients (9 cases; 56%), as these patients required additional treatments such as methotrexate, dapsone, azathioprine, mycophenolate mofetil, and immunoglobulins (fSCIG). Finally, only 4 cases appeared (including our own) with acute toxicity documented on radiotherapy prior to the appearance of pemphigus lesions (grade 1 or 2 radiodermatitis).

In the light of these cases, we highlight a tendency toward the severity of these lesions with resistance to oral and general corticosteroid treatments in more than half of the cases (56%) as well as a tendency for the lesion progression in nonirradiated areas. Schauer et al. [10] had indeed shown that for one-third of documented cases of radio-induced pemphigus, it is necessary to add an immunosuppressant to control the disease. In 3 cases, rituximab, an anti-CD20 monoclonal antibody, had been used for rapid and complete lesion remission. In breast cancer, no corticosteroid-resistant patients have been treated with rituximab. A meta-analysis revealed high efficacy and safety of this systemic immunotherapy for the treatment of pemphigus [11]. Thus, rituximab could be an interesting treatment choice in patients resistant to corticosteroids with radio-induced pemphigus associated with breast cancer. Otherwise, Hung et al. [12] had shown a strong association between the development of autoimmune bullous disease (including pemphigus) and radiotherapy in breast cancer patients. Indeed, while breast cancer appears to be a risk factor for the development of these bullous diseases (OR: 1.5), the addition of radiotherapy leads to a substantial increase in the risk of appearance (OR: 2.9) [12].

Several studies attempted to explain the physiopathology of pemphigus. Among these, Ruocco et al. [13] hypothesized a modification of keratinocyte antigens by the trigger factor, and these keratinocyte antigens being the target of intercellular pemphigus antibodies. A more recent study showed that an alteration of the skin condition was often found, preceding the appearance of pemphigus [14]. In our case, we could identify this skin alteration by the acute dermatitis found during radiotherapy treatment. This could lead to the exposure of new antigens and the formation of pemphigus autoantibodies. It should be noted that in the era of immunotherapy, pemphigus is likely to be a disease that will be more and more encountered by oncologists and therefore should not be disregarded.

In our case, diagnosis of paraneoplastic pemphigus, which is caused by a solid tumor in 10% of cases, was ruled out for several reasons. First, the patient had no typical mucosal lesions of paraneoplastic pemphigus phenotype. Then, immunological findings were not in favor of paraneoplastic pemphigus (anti-intercellular substance antibodies but no anti-basement membrane and anti-plakin antibodies). Finally, paraneoplastic pemphigus is associated with poor prognosis, deep organs involvement, and most of the time a fatal outcome, whereas in our case, imaging at 3 and 6 months showed complete remission. Concerning the herpes zoster which presented 2 months later, we think that it was favored by immunosuppression

induced by the general steroid therapy. However, we cannot eliminate with certainty that it was not induced by radiotherapy as suggested in several articles [15].

In conclusion, radiotherapy appears to be a rare cause for the development of pemphigus in breast cancer with 17 cases (including ours) documented to date. Despite the rarity of this condition, the radiotherapist must be vigilant with regard to the occurrence of radio-induced pemphigus in the context of breast cancer in order to have the earliest treatment to limit the impact of this disease on the quality of life and prognosis of patients.

Statement of Ethics

This study was approved by the Ethics Review Committee of “the Jean Godinot Institute in Reims,” and informed consent was obtained from the subject prior to participation. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

This case report was fully funded by the Godinot Institute.

Author Contributions

C.I. and V.G. are co-first authors. V.G., C.I., C.M.C., and A.-L.L. wrote the manuscript. A.-L.L. performed the initial biopsies and made the clinical diagnosis of recurrent pemphigus. C.J. is the patient’s referring oncologist and performed adjuvant chemotherapy. P.G. performed radiation therapy. All authors read and approved the final manuscript.

Data Availability Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

References

- 1 Kasperkiewicz M, Ellebrecht CT, Takahashi H, Yamagami J, Zillikens D, Payne AS, et al. Pemphigus. *Nat Rev Dis Primers*. 2017 May 11;3(1):17026.
- 2 Alpsoy E, Akman-Karakas A, Uzun S. Geographic variations in epidemiology of two autoimmune bullous diseases: pemphigus and bullous pemphigoid. *Arch Dermatol Res*. 2015 May;307(4):291–8.
- 3 Hertl M, Jedlickova H, Karpati S, Marinovic B, Uzun S, Yayli S, et al. Pemphigus. S2 Guideline for diagnosis and treatment: guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). *J Eur Acad Dermatol Venereol*. 2015 Mar;29(3):405–14.
- 4 Krain LS, Bierman SM. Pemphigus vulgaris and internal malignancy. *Cancer*. 1974 Apr;33(4):1091–9.
- 5 Tang HKC, Lee DYH, Thompson I, Ingram JR, Stone N, Patel GK. Delayed and localized pemphigus vulgaris after breast cancer radiotherapy. *Breast J*. 2017 Nov;23(6):747–9.

- 6 O’Leary B, Alarcon L, Mallon E, Kirby A. Radiotherapy-associated pemphigus: a rare cause of grade 4 skin toxicity. *Clin Oncol (R Coll Radiol)*. 2017 Jan;29(1):e50.
- 7 Criado PR, Machado Filho CDA, Criado RFJ, Etcheverria ICR, Umeda LM, Landman G. Radiotherapy-induced pemphigus foliaceus: a rare adverse effect of breast cancer therapy. *Int J Dermatol*. 2018 Dec;57(12):e165–7.
- 8 Radin M, Roccatello D, Baldovino S, Sciascia S. Facilitated subcutaneous immunoglobulin treatment in pemphigus vulgaris. *BMJ Case Rep*. 2018 May 30;2018:2018.
- 9 Crocker C. Radiation-induced pemphigus in a patient with an invasive ductal carcinoma of the breast: a case report. *Oxf Med Case Reports*. 2020 Jan;2020(1):omaa001.
- 10 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.
- 11 Wang HH, Liu CW, Li YC, Huang YC. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. *Acta Derm Venereol*. 2015 Nov;95(8):928–32.
- 12 Hung TL, Chen YL, Lin KT, Chiang CP, Chung CH, Hung CT, et al. Risk of radiotherapy-associated autoimmune bullous disease among Taiwanese patients with breast cancer: a case-control study. *Arch Dermatol Res*. 2020 Jan;312(1):69–75.
- 13 Ruocco V, Vitale O, Astarita C. Transient pemphigus induced by sunburn. *J Cutan Pathol*. 1980 Dec;7(6):429–30.
- 14 Ruocco V, Ruocco E, Lo Schiavo A, Brunetti G, Guerrera LP, Wolf R. Pemphigus: etiology, pathogenesis, and inducing or triggering factors: facts and controversies. *Clin Dermatol*. 2013 Aug;31(4):374–81.
- 15 Lai YL, Su YC, Kao CH, Liang JA. Increased risk of varicella-zoster virus infection in patients with breast cancer after adjuvant radiotherapy: a population-based cohort study. *PLoS One*. 2019;14(1):e0209365.