Recurrence of pemphigus vulgaris after bilateral breast irradiation: a case report and review of the literature

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Case report

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Abstract

Background

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 a context of breast cancer treatment.

Case presentation:

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.

Conclusions

Pemphigus is a very rare side effect of radiotherapy, notably in breast cancer. For more than three-quarters of the described cases in the literature, this condition occurs within three months following the end of treatment. After systemic immunosuppressive treatment, this disease disappears in the vast majority of the reported cases.

Background

Pemphigus is a chronic epithelial bullous disease presenting three major subtypes: pemphigus vulgaris (PV) or deep pemphigus, pemphigus foliaceus (PF) or superficial pemphigus, and paraneoplastic pemphigus (1). It is a rare disease with estimated incidence in non-Jewish and Jewish populations of 0.5 to 10 and 16 to 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) (1–4). 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 (5,6). 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 (7,8).

To date, only a few cases of radio-induced pemphigus have been described in a context of breast cancer treatment. In this study we present the interesting case of a 76-year-old woman with a recurrence of pemphigus vulgaris in a 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 pemphigus vulgaris one month after adjuvant irradiation for bilateral triple negative breast cancer. The patient had a history of pemphigus vulgaris 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 pemphigus vulgaris 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.

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 (four cycles of doxorubicin/cyclophosphamide followed by twelve weekly courses of paclitaxel) then radiotherapy was carried out. Thirty three fractions were delivered for a total dose of 66 Gray (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 pemphigus vulgaris (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 pemphigus vulgaris. After resistance to topical treatment with corticosteroids (clobetasol propionate, 0.05%), the lesions disappeared with systemic steroid therapy within three months (Fig. 2b). Moreover, barely two 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 months follow-up after the completion of radiotherapy.

**Discussion And Conclusions**

Here we report the case of a patient presenting a bilateral recurrence of pemphigus vulgaris 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 a context of breast cancer, including ours (9-24). These cases are described in Table 1. Five presented with pemphigus foliaceus (PF) and 12 with pemphigus vulgaris (PV). Four patients had an immunological history of which 3 presented a recurrence of pemphigus vulgaris during their treatment with radiotherapy. Patients ranged in age from 44 years to 92 years old 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 non-irradiated area (mouth and esophagus). The diagnosis was made by direct immunofluorescence (DIF) 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 Gray. All but two 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 four 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 towards the severity of these lesions with resistance to oral and general corticosteroids treatments in more than half of the cases (56%) as well as a tendency for the lesions progression in non-irradiated areas. Schauer et al. 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 (24). In three cases, rituximab, an anti-CD20 monoclonal antibody, had been used for rapid and complete lesions remission. In breast cancer, no corticosteroids resistant patients have been treated with rituximab. A clinical trial and two recent meta-analyses revealed high efficacy and safety of this systemic immunotherapy for the treatment of pemphigus (26-28). 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. had shown a
strong association between the development of autoimmune bullous disease (including pemphigus) and radiotherapy in breast cancer patients (29). 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) (29).

Several studies attempted to explain the physiopathology of pemphigus. Among these, Ruocco et al. hypothesized a modification of keratinocyte antigens by the trigger factor, these keratinocyte antigens being the target of intercellular pemphigus antibodies (30;31). A more recent study showed that an alteration of the skin condition was often found, preceding the appearance of pemphigus (32). 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 (33).

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 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 (34,34).

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 a 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.

**Declarations**

**Ethics approval and consent to participate**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the corresponding author on request. All investigators ensure that the conduct of this study is in accordance with the ethical standards of their respective institution as laid down in the 1964 Declaration of Helsinki.

**Availability of data and materials**

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

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

None.

**Authors contribution**

VG, CI, CMC wrote the manuscript. All performed the initial biopsies and made the clinical diagnosis of recurrent pemphigus. CJ is the patient's referring oncologist and performed adjuvant chemotherapy. PG performed radiation therapy. All authors read and approved the final manuscript.
Acknowledgments

Not applicable.

Abbreviations

IgG: Immunoglobulin G

Gy: Gray

PF: pemphigus foliaceus

PV: pemphigus vulgaris

References


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

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>References</th>
<th>Age</th>
<th>Breast Cancer Histology</th>
<th>Immunologic History</th>
<th>Diagnosis of Pemphigus Type</th>
<th>Localization</th>
<th>Radiotherapy treatment</th>
<th>Time from the end of RT to start eruption</th>
<th>Treatment</th>
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<td>Low Gj et al. (1990) [9]</td>
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<td>irradiated area</td>
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<td>+</td>
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<td>PV</td>
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<td>-</td>
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<td>PV</td>
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<td>17</td>
<td>Current case</td>
<td>72</td>
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<td>PV 5 years before zoster in childhood</td>
<td>PV</td>
<td>NA</td>
<td>NA</td>
<td>irradiated area but only right breast</td>
<td>66 Gy (B&amp;TBB)</td>
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Figures

**Figure 1**

Microscopy. a) Intraepidermal bulla (arrow) on histological picture (HES x 100). b) Suprabasal cleft (arrow) and acantholytic cells dense cytoplasm (HES x 400).
Figure 2

Skin lesion pictures. a) 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.

Supplementary Files

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