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Localized Atypical Pemphigoid on Lymphoedema Following Radiotherapy

A. CALLENS[1], L. VAILLANT[1], M. C. MACHET[2], B. ARBEILLE[3], L. MACHET[1], A. DE MURET[2], P. Y. SIZARET[3] and G. LORETTE[1]

[1]*Dermatology Department,* [2]*Pathology Department and* [3]*Electron microscopy Unit, Centre Hospitalier Universitaire de Tours, France*

Autoimmune bullous diseases have been reported associated with different causal factors: drugs, mechanical trauma and physical trauma, particularly ultraviolet light and radiotherapy. In these cases different hypotheses regarding the pathogenesis of blister formation can be supported. In this observation, we report a localized cicatricial pemphigoid with unusual clinical presentation. Moreover, it appeared 9 years after radiotherapy for breast carcinoma and it was preferentially localized on an upper limb lymphoedema. Because of the long time between the treatment of carcinoma with radiotherapy and the onset of pemphigoid, we assume that lymphoedema played a major etiological role in this particular cicatricial pemphigoid. ***Key words: Cicatricial pemphigoid; Bullous pemphigoid; Immunoelectron microscopy; Dapsone therapy; Topical corticotherapy; Breast carcinoma.***

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L. Vaillant, Service de Dermatologie Hôpital Trousseau, F-37044 Tours Cedex, France.

Cicatricial pemphigoid is an uncommon chronic vesiculobullous disease. Mucosal involvement is usual and skin involvement is present in only 25% of cases. An exclusive cutaneous form was described by Brunsting & Perry in 1957 (1). Recently, the localization of autoantibodies on the basement membrane zone in cicatricial pemphigoid has been demonstrated by immunoelectron microscopy, mostly in the lamina densa and occasionally in the lamina lucida (2). Recent studies with immunoblotting have identified the same target antigen as in bullous pemphigoid: a polypeptide of 240 Kd or 180 kD (2, 3). Autoimmune bullous diseases may be precipitated by systemic or topical drugs (4–6) or by different skin injuries which include mechanical trauma (scratching, burns, scars, stomata, amputations, split skin graftings) (7–12) or physical trauma (ultraviolet light, radiotherapy) (13–28). The present study led us to consider the role of radiotherapy, cancer and lymphoedema in inducing a cicatricial pemphigoid and it puts forward some hypotheses on blister formation in this disease.

CASE REPORT

A 76-year-old woman was admitted in March 1991 with a 1-month history of bullous and pruritic eruption. She had been treated with isosorbide dinitrate (Risordan®), fenofibrate (Lipanthyl®), captopril-hydrochlorothiazide (Captea®), labetalol (Trandate®) and betahistine (Serc®) for many years. The bullous eruption had begun in her left armpit. Ten tense blisters containing clear fluid were confined to the axillary area on normal skin. Some macular lesions were present on the posterior and lateral surfaces of her left arm and there was one blister on the flexor surface. There were two erosions, one under the right breast and one near the umbilicus. Mucous membranes (ocular, genital, buccal) were not involved. She continued to develop two or three new blisters a day and the erythematous lesions extended rapidly to the lateral surface of her left upper arm (Fig. 1). The lesions were initially strictly localized in the left armpit, an area previously treated with radiotherapy for breast carcinoma, and then spread to the left arm, the site of secondary lymphoedema.

Histologic examination of one lesion revealed a subepidermal blister with a moderately dense upper dermal infiltrate composed of neutrophils, eosinophils and some mononuclear cells. The overlying epidermis was almost intact. Some eosinophils were present in the blister fluid. Direct immunofluorescent study of perilesional skin showed a linear and continuous band of C_3, IgG and IgA along the basement membrane zone. Indirect immunofluorescence findings were negative. Blood count showed no eosinophilia and a normochromic and normocytic anaemia (erythrocytes = 4×10^{12}/l, hemoglobin = 100 g/l). Immunoelectron microscopy revealed clusters of discontinuous deposits of C_3 and IgG in the lamina lucida and lamina densa (Fig. 2). Immunoblotting study of the serum of the patient did not detect any polypeptides on two separate occasions.

Left mastectomy with axillary lymphadenectomy for an infiltrating duct carcinoma of the left breast (stage T_{2A} N_{1A} M_0 Pev_0) had been performed 9 years previously. Postoperatively, she had received radiotherapy with cobalt. The dose given was 45 Gy on her left hemithorax and subclavicular area, 50 Gy on the axillary area and the internal mammary lymph node chain. Radiodermatitis lesions consisted of a few telangiectasia on her left hemithorax. Six years after surgery and radiotherapy, left upperlimb lymphoedema appeared and progressively increased. It was painless and the discomfort for the patient was minimal. Lymphoscintigraphy demonstrated slow lymphatic drainage of the left arm. Two small lymphadenopathies were detected without any blockage. Clinical examination, right mastography, thoracoabdominal scan and tumoral markers (ACE, CA 15-3) did not reveal any sign of local relapse or distant metastases.

Dapsone treatment (Disulone®) 100 mg/day was started. Pruritus rapidly disappeared and the blisters healed without scar formation or milia. During treatment, one blister developed every 5 days. After 2 months' treatment, blood count revealed an accentuated regenerative

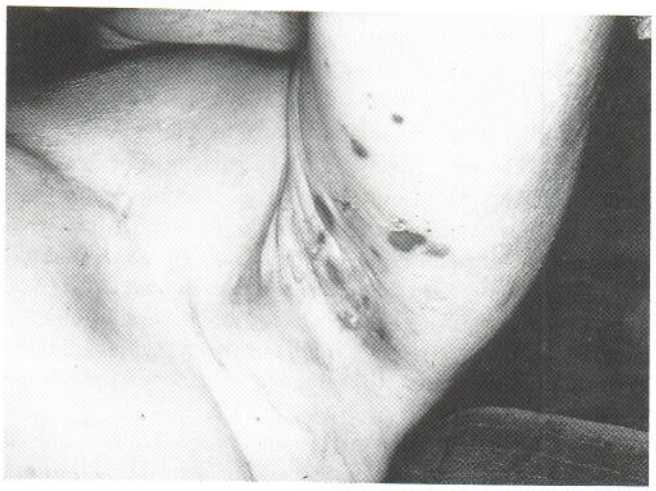

Fig. 1. Eruption of blisters on the left upper arm, the site of secondary lymphoedema.

Fig. 2. Immunoelectron microscopy study showed discontinuous deposits of C_3 and IgG in both lamina lucida and lamina densa.

anaemia (hemoglobin = 80 g/l, reticulocytes = 100×10^9/l) and dapsone was stopped. Local corticotherapy with betamethasone dipropionate (Diprolene®) twice a day was initiated. Lesions cleared in a few weeks. Nine months later, no pruritus or bullae had appeared; the tumour had not recurred.

DISCUSSION

In this observation we diagnosed atypical localized pemphigoid. The findings of direct immunoelectron microscopy were consistent with cicatricial pemphigoid. It appeared 9 years after irradiation for breast carcinoma and 3 years after the development of lymphoedema. Localization of blisters in this case suggests that radiotherapy, neoplasm or lymphoedema may have been causal factors of this bullous disease.

This atypical localized pemphigoid had an uncommon presentation. Clinical manifestations, including tense blisters, pruritus, absence of mucous involvement and healing without scarring, were consistent with the diagnosis of bullous pemphigoid. Moreover bullous pemphigoid starts as a localized eruption in 15 to 30% of patients and it may remain localized (29). The majority of patients with localized bullous pemphigoid have lesions on the lower extremities and particularly on the pretibial areas. However, it has been demonstrated that there is a regional variation in the expression of the bullous pemphigoid antigen (30). The flexor areas of arms and the armpits have a high density of antigen which could explain the onset of bullous pemphigoid in this area in our patient. However, the absence of circulating antibody, as in our case, is more frequent in cicatricial pemphigoid than in bullous pemphigoid (80% and 30%, respectively) (29). The diagnosis of cicatricial pemphigoid was based on the results of immunoelectron microscopy. Discontinuous thick deposits of C_3 and IgG were observed in both lamina lucida and lamina densa. This has previously been reported in cicatricial pemphigoid (2, 31, 32). In bullous pemphigoid the deposits are strictly localized in the lamina lucida (32, 33). Our case of cicatricial pemphigoid had some unusual features: the absence of mucous membrane involvement is rare in cicatricial pemphigoid and the non-scarring lesions of the skin are usually observed in generalized forms (34). Our case was not consistent with the Brunsting-Perry type or chronic localized pemphigoid (1). Recent reports have demonstrated that, in this form, immunoelectron microscopy may be similar to cicatricial pemphigoid (35). Our case is difficult to classify. Because of the immunoelectron microscopy it may be classified as a localized cicatricial pemphigoid, although the patient had no scarring or atrophy, nor chronic evolution. Nowadays it seems that there are different target antigens in cicatricial pemphigoid: 160–180 kD antigens (33), epilligrin or nicein antigenes. Therefore, it is possible that cicatricial pemphigoid is a syndrome and not a single disease. Thus our case may be a variant of the so-called cicatricial pemphigoid syndrome which affects the lamina densa.

The localization of blisters in our case could be attributed to radiotherapy, cancer or lymphoedema. Initially blisters were confined to an area of radiotherapy, which had been irradiated 9 years before. This particular localization suggests that irradiation may have been a causal factor. In the literature several cases of autoimmune diseases (bullous pemphigoid, cicatricial pemphigoid and pemphigus) have been reported after irradiation with cobalt (18, 24), radium (20), x-ray (19, 26, 27) and electron therapy (18, 21, 23, 28). In most cases the eruption was confined to the irradiated areas at the beginning and extended thereafter. Different mechanisms have been proposed. Some authors have proposed an increase in the permeability of blood vessels, leading to an increase of deposition of antibodies on the basement membrane zone (23). They have also suggested that the alterations in the basement membrane zone following irradiation (23) may have unmasked the antigen, or modified their antigenicity and triggered antibody formation. Remy et al. (18) demonstrated that x-ray irradiation applied to human skin biopsy specimens results in an increase in basement membrane zone antibody-binding of two to three titer dilution for a dose of 70 Gy. A local modification of the immune system induced by radiotherapy must also be considered, since radiotherapy has been found to depress circulating T-lymphocyte levels and certain T-cell functions for more than a year (36). Others have speculated that degenerated products of neoplastic cells due to irradiation may have etiologic effects, perhaps due to a common antigen between the tumour and the basement membrane zone (24).The responsibility of radiotherapy in our case was questionable in view of the time lapse between radiotherapy and development of the blisters (9 years). In the literature blisters appear during irradiation or a few months later. In bullous pemphigoid they appeared during radiotherapy in two cases (23, 24), a few days after in one case (18), 13 days after in another (19), 5 months after in another (21) and 3 years after in the most delayed case (20). In two cases the delay was not known (22, 25). A case of cicatricial pemphigoid has been reported after radiotherapy for a buccal lesion. It appeared after 4 Gy (18). Moreover, in our patient lesions occurred initially only in the left armpit, although other areas such as the left hemithorax and the subclavicular area had also been irradiated. Some lesions were seen in non-irradiated areas: umbilicus, right breast and lymphoedema.

This encouraged us to formulate other hypotheses. The history of the patient led us to consider a possible local or metastatic relapse of her cancer (37). In our case, clinical and complementary examinations did not show a recurrence of the breast cancer, and 1 year after the occurrence of cicatricial

pemphigoid no relapse has been detected. However, some authors have demonstrated positive direct immunofluorescence in tumours of patients with bullous pemphigoid and disappearance of deposits of C_3 in unaffected skin after surgical removal of the cancer (38).

The localization of blisters on the lymphoedema was also striking. Blisters occurred principally on the lymphoedema and this area had not been irradiated. Only two blisters were in other areas (umbilicus, right breast). The slow local and disturbed circulation in the lymphatic vessels of the upper limb may explain an increased permeability of the capillaries and the preferential deposits of antibodies in this area. This mechanism has been suggested by Demitsu in two cases of Sweet's syndrome arising on postmastectomy lymphoedema (39). A mechanical factor may be postulated. The accentuation of hydrostatic pressure in the site of lymphoedema and the cleavage of the epidermal junction, secondary to lymphatic incompetence or lymphatic obstruction, may favour blister formation by the alteration of the basement membrane zone. This fact has also been suggested in pretibial bullous pemphigoid (40–42). A local modification of the immune system caused by the slow lymphatic flux can be proposed. This modification can alter the immune balance and may explain a local secretion of antibodies. In our case, this local immune deficiency, secondary to lymphoedema, may have been added to the immune deficiency induced by radiotherapy and lymphadenectomy, which suppressed the immunological afferent pathways.

Thus it seems that a combination of different local factors may provoke autoimmune bullous disease. The role of local factors in the pathogenesis of localized cutaneous cicatricial pemphigoid is supported by Ahmed's study (43): in one patient he transplanted normal skin into a cicatricial plaque. A biopsy on the graft site which demonstrated deposits of IgG components on the basement membrane zone was performed. The patient then developed sub-epidermal bullae at the graft donor site, suggesting that trauma induced their formation. The fact that only a few people develop cicatricial pemphigoid or other bullous disease after radiotherapy suggests a possible genetic susceptibility to the development of this disease or the preexistence of a subclinical bullous disease in certain patients. Once the antigen has been unmasked locally, the bullous disease can generalize by natural progression or by the acceleration of local antibody production.

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