Radiation-induced bullous pemphigoid

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Systematic review

Radiation-induced bullous pemphigoid: A systematic review of an unusual radiation side effect

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Abstract

***Background*: Percutaneous radiotherapy (RT) may cause a range of acute and late side effects of the skin within the irradiated area. In rare cases radiotherapy can cause bullous pemphigoid (BP). BP is reported to occur mainly within irradiated fields following radiation treatment. Exceptionally, BP may arise during RT. It is unclear which mechanism exactly triggers BP following megavoltage irradiation and whether there is a potential association with hormonal anticancer treatment.**

***Methods*: A systematic literature based review was performed. Publications reporting histologically confirmed BP and a treatment with RT were retrieved based on a standardized query using electronic databases. A standardized quality assessment was applied.**

***Results*: Out of 306 potentially relevant publications 21 were identified to be relevant and included in this review. An association between RT and BP was reported in 27 patients. The majority developed BP after RT and a median dose of 50 Gy. Four patients developed BP during RT after a minimal dose of 20 Gy.**

***Conclusions*: BP induced by RT was observed predominantly in patients with breast cancer. In all reported cases, there is a clear relationship with RT. Therefore, BP may be considered as RT-induced side effect. RT can induce a BP following a minimal dose of 20 Gy. New biological agents may play a role in the future treatment of BP.**

Keywords: Bullous pemphigoid; Parapemphigus; Breast cancer; Radiotherapy

A range of acute and late side effects of the irradiated skin may be caused by percutaneous radiotherapy (RT). In patients irradiated for breast cancer, usually only a slight erythema is observed which is sometimes accompanied by a local epidermolysis. However, it has been reported that in rare cases RT can cause the eruption of skin conditions such as bullous pemphigoid (BP), pemphigus vulgaris, lupus erythematosus or epidermolysis bullosa acquisita [12,21,28,33,41]. A leading symptom for the diagnosis of BP is a severe pruritus in combination with a bullous eruption. In the context of RT, it has so far been described as occurring mostly within irradiated fields following and, only in a few cases, during radiation treatment [14,15,19]. It is unclear which mechanism exactly triggers blistering diseases such as BP following megavoltage irradiation and whether there is a potential association with hormonal anticancer treatment such as tamoxifen. BP is not only seen in combination with megavoltage irradiation, but also with certain medication, trauma, ultraviolet and infrared (laser) irradiation [20,24,26,30,37]. Here, we performed a systematic literature review in order to get more insight into the mechanisms and risk factors in relation to development of BP, in particular with regard to RT.

Methods

Search strategy and selection criteria review

We performed a review based on published literature based on a standardized query using the following electronic databases (until April 30, 2006): CINAHL, EMBASE and MEDLINE. There was no limit applied by publication year, language or study design. Search terms (using free text words as well as MESH terms) alone or in combination, related to radiotherapy treatment, cancer and blistering diseases,

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were used. This included the following terms: neoplasm, cancer, carcinoma, breast cancer, radiotherapy, radiation effects, radiation sickness, complications, adverse effects, side effect, bullous pemphigoid and blister.

Further studies were identified through scanning reference lists or relevant articles and hand searches of specialist journals (e.g. Radiother Oncol, Int J Radiat Oncol Biol Phys). After identifying search results, only studies that were published in the Dutch, English, French, Italian or German language, concerning patients with a histological confirmed bullous pemphigoid and a treatment with RT, were included. Studies with patients suffering from a pemphigus vulgaris and other forms of pemphigus, as well as bullous diseases not based on a pathohistologic diagnosis, were excluded.

Key outcomes and quality assessment

Two independent reviewers assessed the literature searches, both for the quality of the methods and for the results of key outcomes, which were identified and tabulated (Table 1). Since all included studies concerned case reports, no specific scientific quality assessment was performed. Two reviewers (VM, BB) extracted data independently to ensure validity, while a third reviewer (JJ) was responsible for resolving discrepancies.

Table 1
Literature overview of cases with BP in combination with RT

Publication year reference	Gender	Age (ys)	HT	Total dose RT (Gy)	Onset of symptoms	
					Dose onset (Gy)	Localisation during/after RT. Time interval after RT
BP and breast cancer						
1998 [21]	F	58	No	n.m.		n.m. in-field
1989 [3]	F	n.m.	No	n.m.		Weeks in-field
1998 [10]	F	58	No	n.m.		2 ms in-field
1996 [11]	F	55	Yes	n.m.		1 yr in-field, lymphoedema
2005 [5]	F	n.m.	No	n.m.		ys in-field
1982 [16]	F	79	No	40 (e^-)		5 ms in-field
1996 [11]	F	56	No	46		15 ys in-field (10 ys after radionecrosis and lymphoedema axilla)
1997 [32]	F	65	No	45		5 ms in-field
1993 [13]	F	78	No	50		1 yr in-field
1993 [9]	F	76	No	50		9 ys in-field, later extension along lymphoedematous arm
1996 [11]	F	78	No	50		4 ys in-field
1997 [32]	F	76	Yes	50		1.4 ys in-field
1999 [23]	F	78	No	50		3 ys in-field, 7 ms later extension to trunk/leg
2005 [30]	F	75	No	50		6 ms in-field, 2 weeks later generalization
2007 [31]	F	66	Yes	50	20	in-field
2007 [31]	F	88	Yes	50	32	outside field exacerbation
1994 [38]	F	57	No	55 (e^-)		3 weeks in-field
1995 [17]	F	59	No	60		3 weeks in-field, ms later generalization
2000 [29]	F	66	No	60		16 ys in-field
2002 [8]	F	94	No	60		4 ms in-field, 2 weeks later generalization
1998 [27]	F	66	Yes	66.4		1 ms in-field
BP and gynaecological cancer						
1989 [18] Cervix ca.	F	86	No	29		2 weeks left thigh, later generalization
2001 [34] Vulvar ca.	F	78	No	59.4		3 weeks in-field, later extension to trunk/breast
PB and cancer of the thoracic region (lung and oesophagus)						
1967 [15] NSCLC	M	53	No	n.m.		n.m. generalized outside field
1981 [19] Oesophagus ca.	M	77	No	80	20	Outside field, 3 ms generalization
BP and other cancers						
1988 [14] Squamous cell ca. inguina	M	75	No	n.m. (e^-)	20	In-field inguina; 1 week later generalization
2005 [5] NHL	n.m.	n.m	No	n.m.		7 ys in-field

Each reference represents one reported case.
Abbreviations: yr, year; ys, years; ms, months; n.m., not mentioned; RT, radiotherapy; e^-, irradiation with electrons; HT, hormonal treatment; NHL, Non-Hodgkin-Lymphoma; ca., cancer; NSCLC, non-small cell lung cancer; BP, bullous pemphigoid; F, female; M, male.

Results

Search results

From the 306 search hits, 17 duplicates were removed. Out of the remaining 289 potentially relevant publications we excluded clearly irrelevant references and identified 45 relevant papers regarding different types of cancer. Through manual searches of the reference list, and specialist journals, two additional references were identified. On the remaining 47 studies we applied the above-mentioned restrictions and selected only studies dealing with histologically proven bullous pemphigoid in association with irradiation. Overall, 21 references were retrieved for the present review.

Relation of BP and RT in the literature

A reported association of BP with RT was found in 27 patients, with a median age of 75 years, of whom the majority experienced blistering confined to the irradiated area (24 out of 27, 89%). The majority had a breast carcinoma (21 out of 27; 78%). In most cases, onset of BP occurred at more than 1 year following RT. Only 5 patients developed BP within weeks and 6 patients after 1–6 months post-radiation. The median dose for these patients was 50 Gy (range: 29–66.4 Gy). Four patients developed BP during RT at a dose of 20 Gy (3 patients) or 32 Gy (1 patient). Only 3 out of 27 patients had BP outside the irradiated field. For 3 patients BP was described in the lymphoedematous area [9,11]. In five cases, the use of hormonal therapy is reported (Table 1).

Discussion

BP or parapemphigus is a very common pruritic bullous skin disease in older patients, but is rarely reported in combination with RT. Remarkably, most reported cases of BP in combination with RT had a breast carcinoma. It has been speculated that BP occurring subsequent to irradiation and in conjunction with an invasive breast carcinoma may represent a distinct sub-entity within the heterogeneous group of diseases of ''initially localized BP'' [23]. The authors' reasoning is based on the knowledge that primary human malignant breast cells in culture exhibit a mixture of hemidesmosome phenotypes and that BP antigens consist of these very hemidesmosome proteins [1]. The fact that BP is predominantly observed in female patients with breast cancer might suggest that hormonal therapy may be involved. In that context, it was interesting that the two patients seen in our institute were indeed treated with hormonal therapies for breast cancer [31]. For only three other cases, the use of tamoxifen or other hormonal therapy is reported (Table 1). A potential association between anticancer hormonal treatment and BP is therefore unclear.

Blistering diseases are generally based on autoimmune mechanisms and this is also observed in relation with other diseases such as mycosis fungoides (MF). Two cases with MF are reported to have developed BP during treatment with PUVA, topical nitrogen mustard or UV-B [35]. The first was treated with methotrexate and prednisone for the BP and with a total body irradiation for MF. Interestingly the BP did not return during or after RT [35]. Paradoxically, in this case RT was not the trigger but the cure for the BP. The other patient developed BP at sites where the MF was decreasing [36]. Progression of the MF led to UV-B re-treatment 3 years later with almost complete remission. At that time, no BP developed [36]. Although it might be that one autoimmune mechanism eventually overrules the other, one would still expect the BP to develop when MF decreases. It must therefore mean that other currently unknown pathways are involved in the development of BP in patients with MF.

Possible mechanisms for triggering BP

Pathohistology

Histological assessment of skin biopsy specimen shows subepidermal blisters and, depending on the site of biopsy, eosinophilic granulocytes [36]. The blisters develop as a consequence of impairments in proteins within the cell-matrix-adhesion junctions of the epidermal basement membranes (Fig. 1).

Molecular mechanisms

Patients with BP have autoantibodies (IgG) against antigens BP230 and BP180, which can be measured in their serum. BP180 is also known as BPAG2. Both antigens are

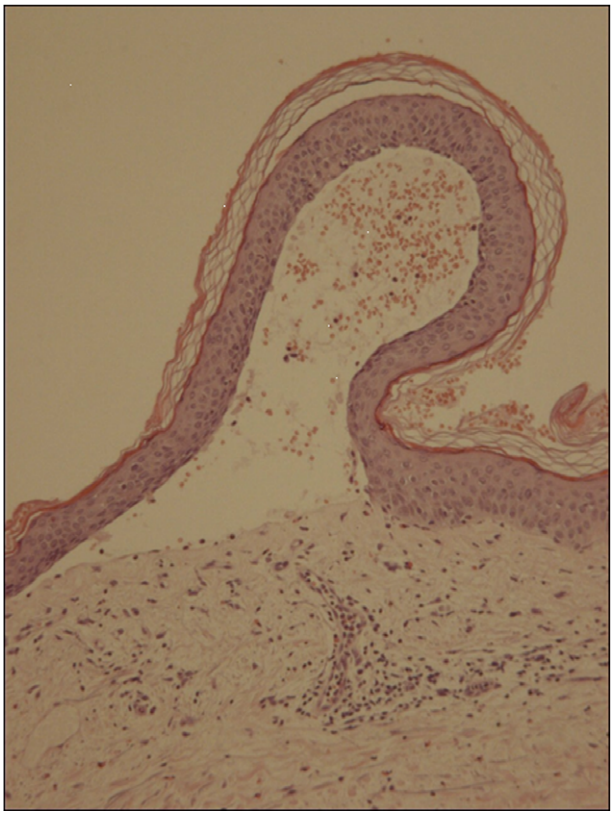

Fig. 1. Skin biopsy specimen with typical subepidermal bullae and an infiltrate of eosinophilic granulocytes.

key components of epidermal hemidesmosomes, adhesion structures that anchor the epidermal basal cells to the underlying basement membrane. Mainly BP180 is targeted by autoantibodies in patients with BP.

Although the mechanism of BP occurrence remains largely unclear, it has recently been reported that the plasminogen/plasmin signalling cascade synergizes with the neutrophile derived MMP-9 (matrix metalloproteinase 9) during the early onset of antibody-induced blister formation. MMP-9 is an enzyme involved in tissue remodelling processes and cell-matrix interactions and may thus eventually be a target for therapeutic intervention [41].

Irradiation as triggering mechanism

How radiation therapy may alter the structures of the basement membrane zone is unclear: one theory is that RT itself changes antigenic properties and induces autoantibody formation through the very alteration of the basal membrane with unmasking of the antigen [11,17,38]. Binding of antibodies to BP antigens leads to complement activation and by means of chemotactic factors, it results in leukocyte-attraction. This might cause proteolytic cleavage of the lamina lucida and hence the formation of bullae [2].

In addition, because of the rarity of BP after irradiation, patients who develop BP may already have circulating low-titre anti-basement membrane antibodies and the tissue damage through RT may enhance the deposition of antibodies, for example through an alteration of permeability of blood vessels [3,11,38].

There are more hypotheses as to what the role of RT might be. RT influences the amount of MMP-9 and of growth factors as vascular endothelial growth factor (VEGF) (increase and decrease have been observed as a consequence of irradiation). VEGF not only plays an important role in angiogenesis during tumour development, but an increased expression of VEGF was also found in the lesional epidermis of BP and other bullous diseases [6]. In particular, high levels of VEGF were found in blister fluids of patients with a BP [6]. MMP-9 has a role in the development of blistering and may therefore be a direct trigger induced by irradiation. Furthermore, RT can induce local modifications of the immune system. Immune imbalance could lead to inhibition of T-cell suppressor activity, which might in turn result in overproduction of antibodies [11].

For patients, in whom the BP arises during RT, the theory of tissue damage through RT which in turn may enhance the deposition of antibodies (by e.g. an alteration of permeability of blood vessels) is preferable. The theory of immediately circulating antibodies before the start of irradiation may be true for those patients, who receive specific medication to be known for triggering a BP. A BP can develop later after radiotherapy or alternatively, progress outside of the irradiated area or even into a generalization. This fact may be explained by an immunological phenomenon termed epitope spreading, whereby a relatively restricted immune response spreads to involve different sites on the same autoantigen and to involve different autoantigens. In the literature, there are in total four cases reported with an eruption of BP during RT, which occurred after a minimal dose of 20 Gy [14,15,19]. In one of these cases, BP led to a withdrawal of RT [14].

Treatment of bullous pemphigoid

In general, BP shows a rapid response to therapy and the majority of patients respond well to therapy resulting in a complete remission. Therapeutic options are local corticosteroid cream, systemic prednisone [25], immunosuppressant like azathioprine [34], mycophenolate mofetil [23] or a combination of tetracycline and niacinamide. The latter two are thought to be involved in inhibiting the chemotaxis of eosinophils or other local factors. Indeed, despite disappearance of BP, the antibodies remain present in the patient's serum [22]. Mycophenolate mofetil acts as an inhibitor of the proliferation of lymphocytes and interferes with the production of lymphocytes [4,7,39]. Patients should be referred at an early stage to a dermatologist for treatment of the BP. Furthermore, there is no need to interrupt RT as the radiation dermatitis develops independently and parallel to the BP as observed by Mul et al. [31].

It has been recently reported that the use of new drugs like anti-CD25 medication can inhibit the secretion of antibodies against BP180 [40]. In this report, a case treated for B-pre-cursor ALL by total body irradiation and chemotherapy followed by stem cell transplantation was described. The patient subsequently developed Graft-Versus-Host-Disease and, 7 months later, BP. As he did not respond to standard treatment of BP, biological agents as anti-CD20 (rituximab, which binds to B cell receptors) and anti-CD25 (daclizumab) were given. The latter inhibits secretion of antibodies against BPAG2 or BP180 by blocking CD25(+)CD(4)+ T cell-helper function. Only to these combined regimens a complete response of the BP was seen [40]. Two months off anti-CD25 treatment, a new bulla developed. This responded to sole anti-CD25 medication as the patient was in remission of his B-pre-cursor ALL (no B-cell lymphocytosis).

Conclusion

In summary, RT can induce a BP following a minimal dose of 20 Gy. The BP is mostly confined to the radiation field but can occur outside of the irradiated area. Co-medication may modulate or induce the onset of BP. The triggering mechanisms remain unclear and the molecular cascades involved have not yet been clarified. New biological agents like anti-CD25, anti-CD20 medication to reduce the production of autoantibodies may play a role in treating BP. BP can appear during, early or late after RT and often generalizes after the first onset within the irradiated area. When induced by RT, BP was observed predominantly in patients with breast cancer (78%). As there was a clear relationship to RT in all cases, BP may be considered to be an early and late side effect of irradiation.

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