A Case of Radiation-Induced Pemphigus

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Radiation induced pemphigus, as an example of induced pemphigus, is a rare disease which occurs in patients receiving radiotherapy.

A 56-year-old male patient with nasopharyngeal cancer received 3 cycles of chemotherapy and radiotherapy on the neck and anterior chest areas. One month after completion of radiotherapy, eroded and crusted areas developed within the irradiation site. In spite of systemic antibiotic treatment, the skin lesions persisted and spread further to the trunk and upper extremities with new crops of bullae. He was treated with a high dose of prednisolone and the skin lesions cleared. We discuss the suggestive pathogenesis of radiation-induced pemphigus with the comparative results of immunoblotting in various variants of pemphigus.

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Key Words : Radiation-induced pemphigus, Immunoblot

Since the first case of radiation-induced pemphigus was reported in 1973[1], 8 or more cases of pemphigus associated with radiation have been reported in the literature. Basically, radiation-induced pemphigus is much similar to true pemphigus cytohistologically and immunologically except that a prodromal non-specific eruption may be often misinterpreted as radiation dermatitis and that a variable duration of latency may be followed by vesicobullous eruptions at irradiation sites. The disease has a good clinical course as it responds well to systemic steroid therapy.

We present here a patient with nasopharyngeal cancer who developed a pemphigus vulgaris 3 months after the end of radiotherapy.

CASE REPORT

A 56-year-old male patient was referred to the Department of Dermatology on December 18, 1995 from the Otolaryngology Department because of the skin lesions which had developed as large erosive areas on the anterior chest and neck in the exact fields of previous radiotherapy(Fig. 1).

The patient had been treated with 3 cycles of chemotherapy and radiotherapy (7020 cGy in total) for a nasopharyngeal cancer(lymphoepithelioma). One month after completion of radiotherapy, erosions developed within the previous irradiation site. Two months later, the lesions spread further to the trunk and new flaccid bullae developed there, on the upper extremities and also in the oral mucosa as erosions(Fig. 2). Histopathological findings in the upper extremities revealed a suprabasilar intraepidermal vesicle with eosinophilic spongiosis and typical acantholytic cells. Direct immunofluorescence showed deposition of IgG and C3 in the intercellular space ; indirect immunofluorescence was positive at a titer of 1:20 in an intercellular staining pattern. In an immunoblotting analysis using normal human foreskin keratinocytes, the patient's serum showed a reactivity with a single 130KD protein band which was considered as cadherin(Fig. 3). On HLA typing, HLA DRw6 showed positivity.

An Oral systemic steroid was instituted with an initial dose of prednisolone 90mg/day. This was tapered off with a gradual improvement to

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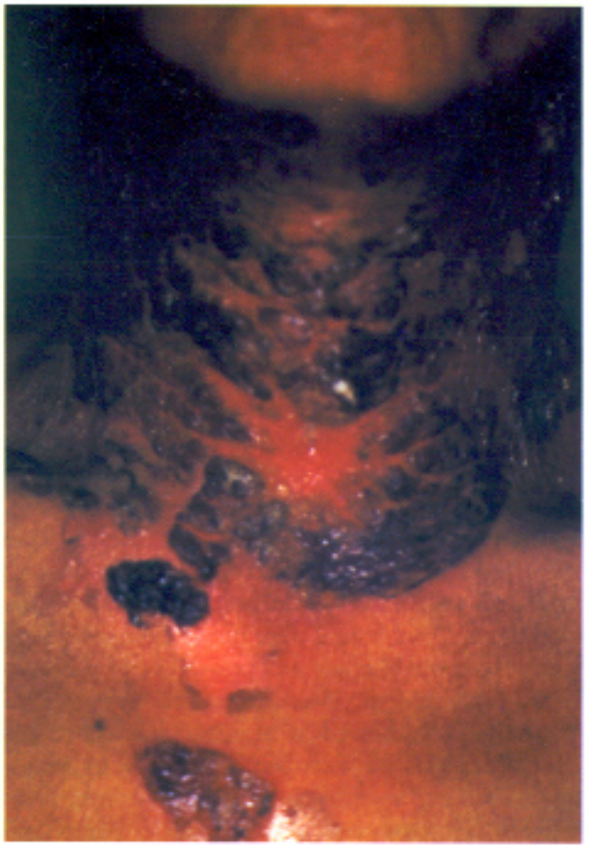

Fig. 1. Large erosive areas on the anterior aspects of the neck exactly outlining the exact fields of previous radiotherapy.

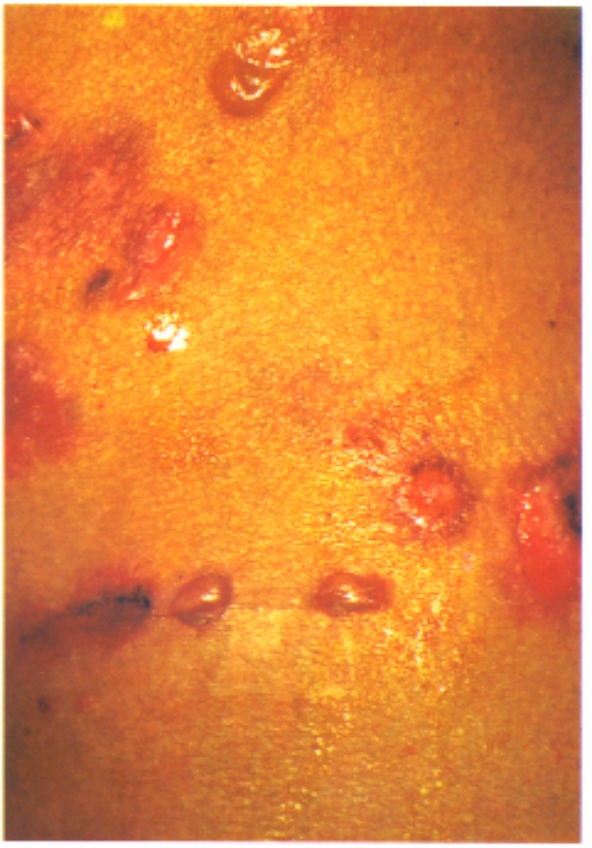

Fig. 2. At three months after completion of radiotherpy, flaccid bullae developed on the upper extremies.

7.5mg/day. He was completely free of any skin lesions when he was discharged on March 22, 1996. However, 1 month later, some erosive skin lesions recurred on the neck area showing wax and wane patterns. He died on December 6, 1996 after the appearance of secondary to nasopharyngeal adhesions.

DISCUSSION

Since a report for penicillamine-induced pemphigus by Degos et al[2], the concept of induced pemphigus has been introduced into diversified categories of pemphigus etiopathogenesis in that induced pemphigus is a unique entity provoked or favoured by heterogeneous factors which seemingly have no pathogenetic potential in clinical, cytohistologic and immunological aspects[3]. There are so many factors which are classifiable as drugs, physical agents, viruses, neoplasms and miscellaneous things. Burns, UV and ionizing radiation can be included into the physical agents.

Induced pemphigus is almost always preceded by prodromal lesions and its expression is correlated each time with an inducing factor. The prodromal manifestation is usually non-specific, as it may appear as pleomophic lesions or it does not have cytohistological(acantholysis) and immunological signs (intercellular antibodies) of pemphigus in the prodromal stage. Additionally, it is followed by a latency period of variable length averaging weeks to months and sometimes the interrelation between the inducing factor and pemphigus is difficult to be accepted if there is an extremely long incubation period[4]. In the full-blown disease, induced pemphigus presents features of foliaceus, erythematosus or herpetiformis variants and rarely of the vulgaris form.

Several distinctive clinical findings were demonstrated in every case of radiation-induced pemphigus. A prodromal skin eruption occurred during and/or af-

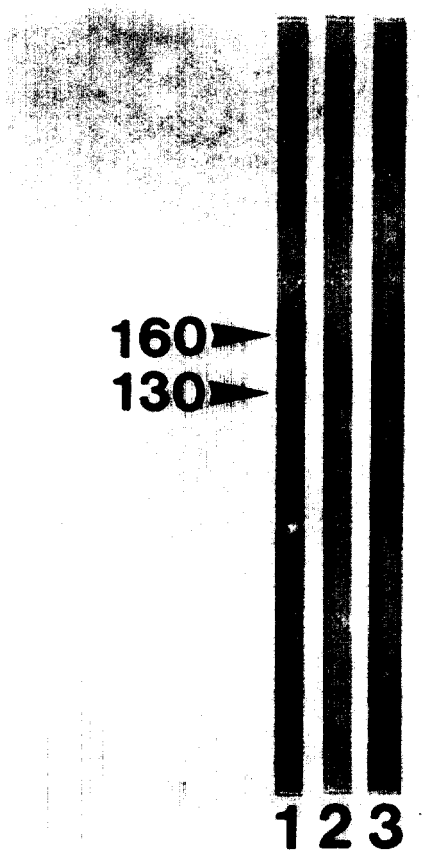

Fig. 3. Immunoblot analysis of the patient's serum showed a reactivity with a single a 130KD protein band which was considered as cadherin.
lane 1 : pemphigus vulgaris control
lane 2 : pemphigus foliaceus control
lane 3 : patient's serum

ter radiotherapy, which seemingly represented acute radiation dermatitis. There was a latency period of at least several weeks before the onset of the blistering eruptions. In addition, all skin lesions erupted initially within the area of irradiation, then subsequently extended to other skin areas[5]. Our patient also showed similar skin lesions to those of acute radiation dermatitis which was limited to the radiation field, and 2 months later distinctive bullae developed and spread to other body areas.

Radiation-induced pemphigus shows a pemphigus vulgaris pattern more commonly in contrast to other types of induced pemphigus including drug-induced pemphigus, in which the pemphigus foliaceus pattern is most commonly seen.

Although fixed antibodies of the intercellular type, like IgG with occasionally IgM class or C3 on the perilesional epidermis are constantly present, circulating intercellular antibodies are not demonstrated in a consistent pattern. They may be absent or their titer is often low and not related to the severity and prognosis of the disease even if they are present. This is in contrast to those of idiopathic pemphigus[6,7,8].

As in this case, most cases of radiation-induced pemphigus occur in cancer patients and so radiation-induced pemphigus must be differentiated from paraneoplastic pemphigus because the pathogenetic effect of ionizing radiation may obscure the paraneoplastic manifestation of concurrent malignant neoplasms. In this case, the skin lesions began first in the irradiated areas after 1 month of radiotherapy and subsequently spread to other skin sites beyond the initial site. As the skin lesions responded well to systemic corticosteroid therapy and the mucosal lesions were not so extensive or severe, we could exclude any possibility of paraneoplastic pemphigus. Moreover, the immunoblot analysis study showed a meaningful result to enable differentiation between both types. In an immunoblotting analysis, pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus sera showed specific reactivities with a 130KD, 150KD, and 210KD/190KD protein, respectively[9]. Our patient's sera showed specific reactivities with a 130KD protein, which is most likely cadherin, which is in contrast to those of paraneoplastic pemphigus.

As suggested previously about the pathogenesis of induced pemphigus, two possible mechanisms were suggested : (1) antigenic modification and (2) interference with immune surveillance[3].

The antigenic modification hypothesis suggests "pemphigus antigen(s)", which are known to contain sulfhydryl groups, are altered by pemphigus inducers, resulting in an antibody reaction against the nowaltered pemphigus antigen.

The theory of altered immune surveillance refers to depression of "forbidden clones", i.e., release of autoantibodies from normal down-regulation mechanisms. Penicillamine, propranolol, certain viruses, and sex hormones have been hypothesized to inhibit T-suppressor cell activity, thereby resulting in an unopposed T-helper cell activity and an increased production of autoantibodies from B-lymphocyte, some of which are directed against intercellular

antigens. This mechanism could apply to radiation-induced pemphigus, as T-suppressor cells are more sensitive to ionizing radiation than are T-helper cells[3,5].

Patients with pemphigus vulgaris have a markedly increased frequency in the class II major histocompatibility complex(MHC), serologically defined HLA DR4 and DRw6 haplotypes, compared to a matched population[10]. In addition, a specific HLA DQ-beta restriction fragment has been identified in nearly all patients with pemphigus, which may confer susceptibility to the disease[11].

As to the possible pathogenetic role of irradiation in pemphigus, it might be that it exposes masked epidermal antigens by altering the antigenicity of the epidermal cell surface, and that the impaired immunity associated with malignancy or X-ray irradiation itself plays a role[12].

We favor the theory of depression of "forbidden clones" by X-ray irradiation to the skin of a genetically susceptible person, who has susceptible HLA phenotypes like DRw6 in this case, and so we can regard X-ray irradiation as a triggering factor of clinical disease.

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