

Herpetiformis Pemphigus and Lung Carcinoma: A Case of Paraneoplastic Pemphigus

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Sir,

No unanimous assent has been reached yet on the definition of cutaneous paraneoplastic syndromes, but judging from the literature, it seems clear that at least three essential criteria must be satisfied (1): first, the dermatosis must arise after the development of malignant tumor (although cutaneous manifestations may or may not precede its diagnosis); second, both the dermatosis and the malignancy should follow a parallel course; third, the dermatosis must be uncommon, in order to exclude a casual association.

In accordance with these guidelines, we describe the case of a 57-year-old man with pulmonary squamous cell carcinoma who developed a bullous eruption with clinical features of dermatitis herpetiformis and an immunopathological profile of pemphigus. Since the appearance of the disease and its evolution were on a strictly parallel neoplastic course, a diagnosis of paraneoplastic pemphigus herpetiformis was proposed. The rarity of this clinical presentation and the opportunity to include our case in the broad spectrum of paraneoplastic pemphigus (PNP), as it is classically defined, are also discussed.

CASE REPORT

A 57-year-old man presented for evaluation and treatment of a bullous dermatosis of 2-months' duration. A family history of lung carcinoma (in a brother) was significant and the patient was taking fenitoin for a post-treatment complication of a previous intracranial aneurysm.

At the time of our observation, erythematoinfiltrated urticarial lesions with annular or otherwise figurate borders were seen on the anterior chest and back of the patient (Fig. 1). Tense serous vesicles were superimposed on the plaques peripherally together, with linear crusts caused by persistent rubbing. On the proximal aspects of the thighs and the flexor surfaces of the arms similar lesions, without a tendency to blistering, could also be observed. The oral mucosa was clear. The patient complained of intense itching.

Laboratory investigations did not reveal any abnormality, with the exception of mild anemia (Hb = 11.3 g/dl). Paraneoplastic markers (CEA, α -FP, CA-19.9), anti-endomysium and anti-tissue transglutaminase autoantibodies were within normal limits, too. On indirect immunofluorescence (IIF), IgG autoantibodies to the intercellular spaces with a titer of 1:320 were detected on monkey esophagus. Direct



Fig. 1. Erythematoinfiltrated plaques and vesicobullae located on the back.

immunofluorescence (DIF) showed an intraepidermal deposition of IgG and C3. Immunoblot assay demonstrated autoantibodies against 150 and 230 kDa antigens that bound to the epidermal side of normal split skin.

Histological examination of lesional skin of the back disclosed mild eosinophilic spongiosis in the epidermis and mononuclear infiltration of the upper dermis with neutrophils and eosinophils when the erythematoinfiltrated urticarial plaque was biopsied; in contrast, at the periphery of the lesions, intraepidermal acantholysis and suprabasal detachment could be seen, vesicobullae containing acantholytic cells, eosinophils and fibrin.

When a routine chest X-ray was performed, a 5-cm cavitated mass was detected in the left upper lung zone. A CT scan showed both direct extension to the scissural and parietal pleura and enlargement of the ipsilateral hilar nodes. Mucosal biopsy of the lung using bronchoscopy revealed squamous cell carcinoma, histologically. An abdominal and cranium CT failed to detect metastatic spreading of the neoplasm.

Based on the clinical, histological and immunopathological findings, a diagnosis of paraneoplastic pemphigus herpetiformis was established and the patient was started on treatment with methylprednisone, 50 mg daily.

Interestingly, coincidental surgical excision of the lung carcinoma (since the pleural and mediastinal involvement, only a partial resection was possible) promptly accelerated pemphigus healing, leading to complete remission in a few weeks.

The patient was later followed by a number of pneumologists. No relapse of the dermatosis was observed, but after the first year of follow-up the patient died of metastatic diffusion of the internal malignancy.

DISCUSSION

When first described by Anhalt et al. in 1990 (2), PNP was delineated as a rare autoimmune blistering disease with unique clinical, histological and immunopathological features occurring in association with underlying lymphoproliferative neoplasm. Five diagnostic criteria were originally used to define PNP: (a) a polymorphous eruption that affects skin and mucous membranes; (b) histopathological picture consisting of acantholysis and dyskeratosis, with basal layer vacuolar changes and lichenoid mononuclear infiltration; (c) intraepidermal and/or basement membrane zone deposition of IgG and C3 on DIF; (d) serum autoantibodies to multiple epithelia; and (e) immunoprecipitation of a unique complex of 250, 230, 210 and 150 kDa antigens. These proposed characteristics of the syndrome have proven to be accurate, although there has been clarification of some points: first, it has been demonstrated that PNP may display at least 5 different clinical and immunopathological mucocutaneous variants (pemphigus-like, pemphigoid-like, erythema multiforme-like, graft-vs-host disease-like and lichen planus-like) (3). Furthermore, although approximately 80% of PNP cases are linked to non-Hodgkin's lymphoma, chronic lymphocytic leukemia and Castleman's disease (4), it has recently become clear that retroperitoneal sarcomas, thymoma, Waldenstrom's disease (5), and even pancreatic (6), tongue (7) and lung (8, 9) cancer could also be associated with the dermatosis.

Therefore, it has been suggested that PNP should be considered a heterogeneous autoimmune syndrome involving several internal organs (Paraneoplastic Autoimmune Multiorgan Syndrome or PAMS) (3) in which multiple pathophysiological mechanisms can lead to cutaneous, mucosal and internal lesions.

From the time our patient was diagnosed as suffering from lung carcinoma, the question arose whether concomitant skin blistering could be considered as a paraneoplastic dermatosis or not.

In our case, the diagnosis of PNP as it is commonly defined (2–5) was excluded both clinically (lack of mucosal involvement, herpetiform distribution of the lesions) and histologically, and also because of the association with a solid carcinoma rather than a lymphoproliferative neoplastic disorder. However, in our case, the rarity of clinical presentation of pemphigus and the strictly parallel course between the dermatosis and the internal disease continued to suggest that a significant relationship could exist.

In fact, pemphigus herpetiformis represents a rare variant of pemphigus in which the atypical bullous eruption and histological picture do resemble dermatitis

herpetiformis (DH), whereas DIF shows antiepidermal intercellular antibodies and lacks the immunopathologic features of DH (10).

To the best of our knowledge, two cases of pemphigus herpetiformis in neoplastic patients have been reported (8, 11). Both patients were Japanese men in whom pulmonary squamous cell carcinoma and well-differentiated epidermoid carcinoma, respectively, were discovered at the time of the cutaneous disease. Even though a parallel course was not clear in these cases, as was the case in our patient, these previous observations suggest the hypothesis that in some cases pemphigus herpetiformis might be a tumor-related cutaneous disease, and support the existence of a wider spectrum of paraneoplastic pemphigus, including not only the "traditional" PNP according to Anhalt's definition, but also polymorphous clinical entities fulfilling the "paraneoplastic syndrome" criteria.

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