Oral Paraneoplastic Pemphigus Associated with Renal Malignancy

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Sir,

We present a case of oral ulcerative lesion that was dependent on the presence of a hidden renal malignancy and proved to be paraneoplastic pemphigus (PNP). This disorder led to the diagnosis of the neoplasm and, to our knowledge, PNP has not yet been described in association with renal cell carcinoma.

CASE REPORT

A 72-year-old woman was admitted to our hospital owing to respiratory tract infection and derangement of diabetes mellitus. Three days previously, she had developed fever (38–39°C) accompanied by cough and headache. The symptoms persisted for the next few days; on the day of admission, dizziness and weakness also developed. Her medical history included diabetes mellitus for 15 years, controlled with oral hypoglycaemic agents, arterial hypertension for 20 years that was responding well to oral medications, and stable angina pectoris treated medically for the past 5 years. Six months previously she had developed a painful oral lesion that had been characterized clinically by a dermatologist as lichen planus and had been treated during the last 6 months with prednisolone, intralesionally and orally, with a gradually decreasing dose (5 mg daily the week before her admission). Despite this prolonged treatment, the ulceration showed only a slight improvement.

On physical examination, her temperature was 38.5°C. Lung auscultation revealed rhonchi at the base of the right side. Heart sounds were normal and no murmurs were heard. The rest of the physical examination showed no pathologic findings, except for the oral lesion that involved particularly the buccal region and the tongue and was characterized by erosion and ulceration (Fig. 1).

On admission, the patient had neutrophil leucocytosis (white blood cell count 20.2×10^9/l, neutrophils 80%), anaemia (haemoglobin 11.2 g/dl), hyperglycaemia (24.7 mmol/l) and glycosuria. Erythrocyte sedimentation rate was 105 mm at the first hour and C-reactive protein 364 mg/l. Immunological tests showed slightly decreased IgG and IgM (5.3 g/l and 280 mg/l, respectively) and increased C3 (1.73 g/l). A chest radiogram revealed small patchy infiltrates on the lower right side. Blood, urine and sputum cultures as well as viral tests for cytomegalovirus and Epstein-Barr virus were negative. Indirect immunofluorescence (IIF) performed on mouse oesophagus was negative for antibodies against pemphigus antigen, but antibodies against PNP were not tested since the required substrate (rat bladder epithelium) was not available in our country.

The patient was treated empirically with amoxycillin-clavulanate (1.2 g × 3/day) for the pulmonary infection and intravenous insulin for the diabetes mellitus. On the sixth hospital day, the fever had subsided, the auscultation of the lungs was clear and the chest radiogram became normal. Blood glucose was regulated and the patient returned to her previous treatment.

Biopsies were obtained from the persistent oral ulceration. In the centre these showed lichenoid dermatitis with ulceration of mucous epithelium, adjacent to which there was spongiosis, vacuolar alteration of basal layer and dermoepidermal cleft formation, as well as intensive plasma cell infiltration with few eosinophils and necrosis in the dermis. In the periphery, there was intraepidermal bulla formation filled with acantholytic cells suggestive of pemphigus (Fig. 2). The direct immunofluorescence taken from the periphery of the lesion was positive, revealing deposition of IgG and C3 intercellularly and along the basement membrane zone (Fig. 3). Radiologic examination with barium of the stomach and colon was normal. Chest computed tomography (CT) scan was also normal, but the abdominal CT scan revealed a mass of 4 cm in diameter on the upper pole of the right kidney. The mass had an inhomogeneous density and was consistent with renal carcinoma. The patient was operated on in an attempt to save as much renal tissue as possible and, because of the small size of the neoplasm, the surgeon preferred partial renal excision. There was no infiltration of the local lymph nodes. Pathology revealed renal carcinoma of clear cell type with nuclear atypia grade 1. The tumour invaded the renal capsule but was confined within Gerota's fascia. The case was evaluated as TNM stage II and did not receive chemotherapy. Two months later the oral lesion had disappeared and erythrocyte sedimentation rate and gammaglobulin values had returned to normal. Fourteen months postoperatively, re-evaluation of the patient was negative.

DISCUSSION

In 1990, Anhalt et al. described PNP, a mucocutaneous disease associated with neoplasia (1). Subsequently, more than 150 cases have been reported, usually in association with a previously diagnosed lymphoreticular malignancy (2, 3). A characteristic antibody profile has affirmed its autoimmune origin and it appears as a model autoimmune paraneoplastic disorder (2, 4, 5).

PNP consists of a polymorphous mucocutaneous eruption; involvement of the oral mucosa is the rule, while skin manifestations may coexist. The diagnosis is based on the presence of seven criteria according to Anhalt et al. (2); at least four of them are necessary to establish the diagnosis. Our case fulfilled the following four criteria: (i) a clinical picture associating signs of pemphigus vulgaris, erythema multiforme and/or bullous pemphigoid; (ii) an association with neoplasia and disappearance of the lesion after surgical removal of the tumour; (iii) histologic findings associating suprabasal acantholysis, keratinocyte necrosis and/or

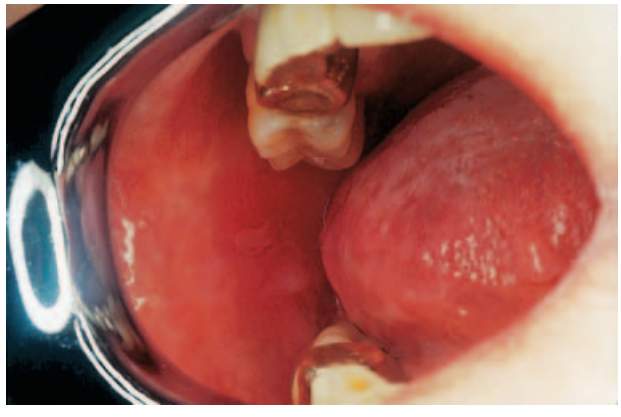

Fig. 1. Erosion and ulceration of the buccal mucosa and tongue at admission of the patient.

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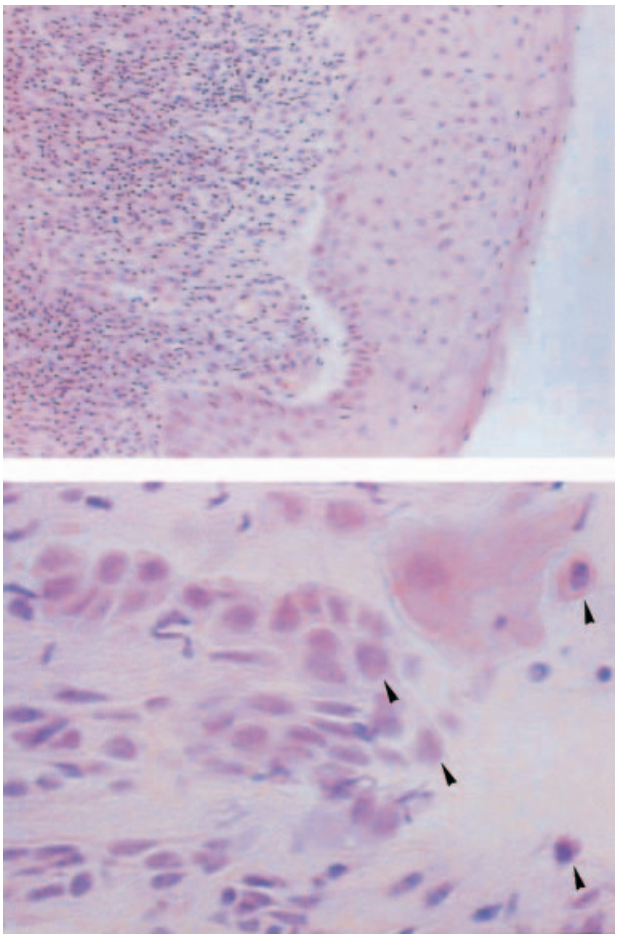

Fig. 2. Upper panel: Lichenoid reaction: hydropic degeneration of basal cell layer with cleft formation and dyskeratotic cells in the epidermis (H/E ×100). Lower panel: Pemphigus vulgaris: acantholytic cells above the basal layer (arrows). (H/E ×400).

vacuolar interface dermatitis; and (iv) positive staining on direct immunofluorescence (6). The IIF on rat bladder epithelium and on normal human skin and the immunoprecipitation constitute the remaining three of the seven criteria, which were not performed because they are not available in our laboratories. The

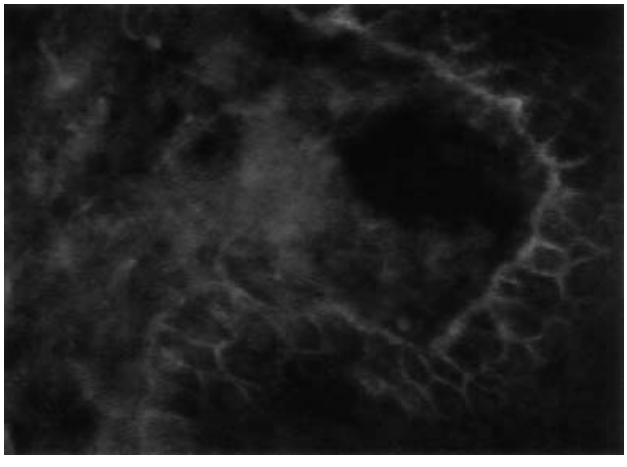

Fig. 3. Direct immunofluorescence technique showing deposition of C3 intercellularly and along the basement membrane zone.

IIF performed on monkey oesophagus was negative but in cases of PNP the use of this substrate can give negative or weakly positive staining (4).

Regarding the pathogenesis of PNP, it is believed that the tumour antigens evoke an autoimmune response that is humoral (4). This immune reaction is directed against the neoplasm, potentially providing a level of protection against progression or dissemination of the tumour, but also cross-reacting with the host epithelial tissues. Surface proteins of the neoplastic cell provide the antigenic stimulation that leads to pemphigus-like antibody production, which causes the blistering eruption with stomatitis or conjunctivitis. This current theory does have some experimental support (4, 7).

Paraneoplastic pemphigus has a generally poor prognosis (3–5, 8). Mortality is high, reaching 90% in a series of 84 patients followed at several academic centres (9). This grave prognosis is due either to the presence of the underlying neoplasia and the side effects of the potent medications required to treat the disease or to PNP itself in cases in which the respiratory mucosa is involved (10). Remission of pemphigus can only be achieved by successful treatment of the underlying malignancy (9). In our patient, the oral ulceration disappeared at the beginning of the second postoperative month; 14 months after tumour excision, the CT examination was negative for relapsing neoplasia and the haematologic and biochemical profile was normal.

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