Correspondence

Metastatic prostate cancer presenting as paraneoplastic pemphigus: a favourable clinical response to combined androgen blockade and conventional immunosuppressive therapy

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SIR, Paraneoplastic pemphigus (PNP), first described in 1990, is an autoimmune mucocutaneous blistering disease which is associated with an underlying malignancy and is characterized by polymorphic clinical signs.[1] Pathogenesis is due to an aberrant autoimmune response against the proteins of the plakin family such as plectin, envoplakin, periplakin, desmoplakin I and II, and bullous pemphigoid antigen I (BP230),[2] although several cases of PNP with antibodies to desmoglein (Dsg) 1 and 3 have been described.[3]

A 77-year-old man was admitted to our Oral Medicine Unit because of recalcitrant severe oral bullous/erosive mucositis with crusting lesions of the lips (Fig. 1a), accompanied by marked conjunctivitis of both eyes (Fig. 1b), with cutaneous bullous lesions of the abdomen and bilaterally of the hip and inguinal area (Fig. 1c). Nikolsky's sign, performed on the oral mucosa and skin, was positive.

Oral biopsy revealed suprabasal epithelial detachment with an eosinophilic and neutrophilic infiltrate. Direct immunofluorescence showed positive fluorescence in the intercellular cement substance (ICS) of IgG and complement 3c, while IgA and IgM were negative. Indirect immunofluorescence, using normal human skin as substrate, showed an intercellular signal confined to the ICS with a titre of 1 : 360. Enzyme-linked immunosorbent assay gave a value of 54 U mL^{-1} for Dsg1 (normal 0–14) and a value of 162 U mL^{-1} for Dsg3 (normal 0–14), confirming a diagnosis of pemphigus vulgaris.

PNP was suspected due to the severe and polymorphic mucocutaneous involvement, in particular of the conjunctiva and labial mucosa, which resembled erythema multiforme-like lesions. Routine haematological tests, serum tumour markers [β_2-microglobulin, prostate-specific antigen (PSA), alpha-fetoprotein, carcinoembryonic antigen, Ca 19-9, Ca 72-4, Ca 125, acid phosphatase, Bence-Jones proteinuria], chest X-ray, echocardiogram, colonoscopy and oesophagogastroduodenoscopy were negative except for microhaematuria and an elevated level of PSA (49·1 ng mL^{-1}; normal 0–4). A total body computed tomography (CT) scan revealed enlargement of the prostate, while bone scintigraphy revealed multiple foci of increased uptake (L2–L3, D8–D10). An ultrasound-guided needle biopsy of the prostate revealed a diffuse infiltration of adenocarcinoma. The prostate cancer grading (Gleason scale) was 8 (4 + 4). Immunoblotting analysis revealed the presence of antibodies to 250-, 210-, 190-, 160- and 130-kDa proteins (Fig. 2). So, in line with the criteria previously proposed,[2] a diagnosis of PNP was confirmed. Investigations by an internist and an otorhinolaryngologist were negative. High-resolution CT scan and tests for pulmonary function ruled out bronchiolitis obliterans.

The patient received conventional immunosuppressive therapy (CIST) comprising prednisone 100 mg daily and azathioprine 150 mg daily, and, at the same time, was referred to a nearby urological unit where he received combined androgen blockade (CAB) therapy comprising bicalutamide 150 mg and tamsulosin chlorohydrate 0·4 mg daily, goserelin acetate 10·8 mg every 75 days, alendronic acid 70 mg once weekly, and calcium carbonate/cholecalciferol 500 mg/440 IU every other day.

After 6 months, he was in complete clinical (Fig. 1d–f) and immunological remission on therapy (prednisone 50 mg twice weekly and azathioprine 50 mg daily), although still taking CAB, alendronic acid and calcium carbonate/cholecalciferol. The PSA level was 0·446 ng mL^{-1} and bone scintigraphy revealed only two foci with weak hypercaptation (areas of increased uptake).

It has been postulated that the autoimmune response in PNP may be twofold: (i) humoral, via cross-reaction of foreign tumour antigens to epidermal antigens, or production of plakin proteins induced by the tumour, or an epitope spreading phenomenon,[4] and (ii) cell mediated, via activation of CD8+ cytotoxic T lymphocytes, CD56+ natural killer cells and CD68+ monocytes/macrophages.[4,5] In addition, cytokine dysregulation was found: in particular, interleukin (IL)-6 seems to play a fundamental role in the pathogenesis of clinical manifestations of PNP.[6] Dysregulation of IL-6 might promote B-cell differentiation and then drive the synthesis of anti-Dsg3 IgG antibodies, damaging the cell membranes via the acantholytic process.[7] Following the damage to membranes, an epitope spreading phenomenon might occur, fostering the production of antiplakin autoantibodies, which target specific autoantigens in the cell.[8] This mechanism might also occur in prostate cancer, which may variably express proteins belonging to the plakin family.[9]

Our patient was diagnosed with a diffuse infiltration of prostate adenocarcinoma and bone metastasis. Over time, he developed mucocutaneous manifestations of PNP with a high

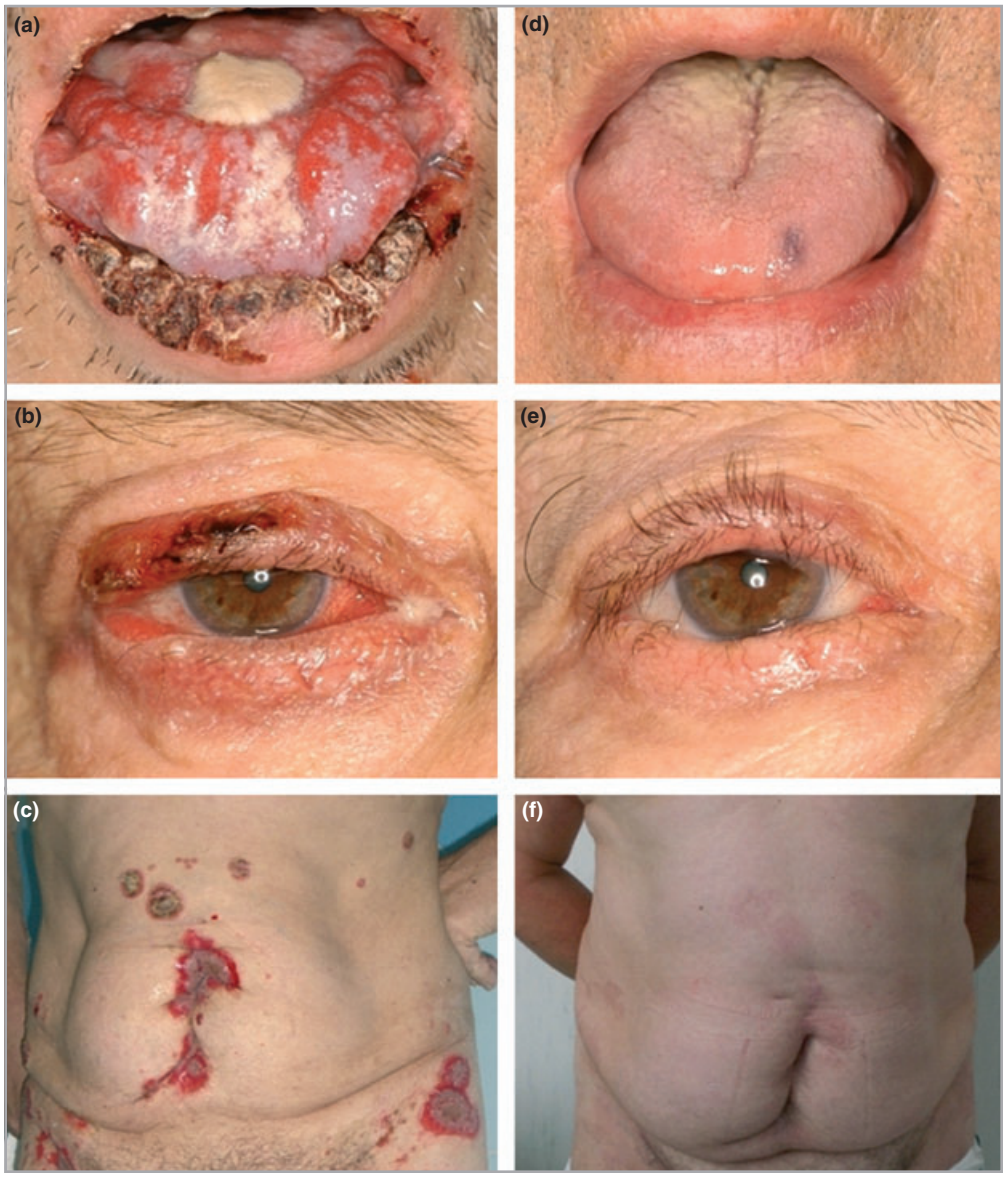

Fig 1. (a) Bullous/erosive oropharyngeal mucositis with crusting lesions of the lips, (b) erosive and erythematous lesions of the right eye, and (c) cutaneous involvement of abdomen and bilateral hip and inguinal area, prior to commencing therapy with combined androgen blockade and conventional immunosuppressive therapy. Complete clinical remission of the (d) oral, (e) ocular and (f) cutaneous lesions following therapy.

positive titre of anti-Dsg1 and Dsg3. To our knowledge, despite the wide variety of haematological (Hodgkin and non-Hodgkin lymphoma, Castleman disease, thymoma)[4] and non-haematological malignancies (pancreas, colon, breast)[2] related to PNP, it appears that this is the first case of PNP with metastatic prostate cancer. The only previous patient with PNP and prostate cancer also had chronic lymphoid leukaemia,[10] so in that case the role of prostate cancer appears to be unlikely, although it might have contributed, as the most common malignancies related to PNP are nonhaematological. Another paraneoplastic case with prostate cancer has been described, but this was paraneoplastic bullous pemphigoid, associated with breast cancer.[11]

Our observation broadens the spectrum of nonhaematological neoplasms underlying PNP and confirms the potential of prostate cancer to induce a paraneoplastic syndrome and also describes the first case of PNP induced by metastatic prostate cancer alone, with an apparently favourable outcome, without surgery or radiotherapy. None the less, the effectiveness of CIST and CAB therapy alone in the treatment of PNP related to metastatic prostate cancer needs to be confirmed by wider investigations.

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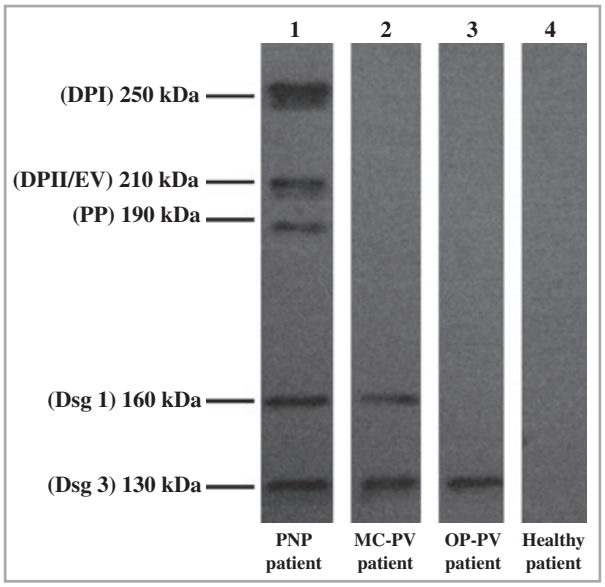

Fig 2. Immunoblotting analysis of the sera of various patients. Lane 1 shows serum of our patient with paraneoplastic pemphigus (PNP) reacting with 250-, 210-, 190-, 160- and 130-kDa antigens; lane 2 shows serum of a control patient with mucocutaneous pemphigus vulgaris (MC-PV) reacting with 160- and 130-kDa antigens; lane 3 shows serum of a control patient with oropharyngeal pemphigus vulgaris (OP-PV) reacting with a 130-kDa antigen; lane 4 shows serum of a control healthy individual reacting with no antigens. DPI, desmoplakin I; DPII, desmoplakin II; EV, envoplakin; PP, periplakin; Dsg, desmoglein.

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Conflicts of interest: none declared.

