# Renal cell carcinoma-induced paraneoplastic pemphigus

Sir,

Paraneoplastic pemphigus (PNP) or more recently termed "paraneoplastic autoimmune multiorgan syndrome (PAMS)" by Czernik *et al*.[1] is a rare immunobullous paraneoplastic dermatosis. Intractable painful stomatitis is the most consistent clinical finding with varied cutaneous manifestations ranging from lichenoid eruptions, erythema multiforme-like lesions to frank blisters. PNP most commonly occurs in association with lymphoproliferative neoplasms (non-Hodgkin's lymphoma, Castleman disease, thymoma, and Waldenström macroglobulinemia) in addition to epithelial origin carcinomas, mesenchymal origin-sarcomas, malignant melanoma, other solid organ malignancy and rarely with difficult to classify, poorly differentiated neoplasms.[2] PNP in association with renal cell carcinoma (RCC) is extremely rare with only two cases reported so far [Table 1].[3,4] Herein, we report a case of PNP associated with RCC in a 45-year-old male.

A 45-year-old male presented to dermatology OPD with painful oral erosions for 7 months and cutaneous lesions for 2 months. The patient was a chronic smoker and had suffered weight loss of more than 10 kgs in the last 6 months. Mucocutaneous examination revealed erosions of the oral mucosa, lips [Figure 1a], conjunctiva and genitalia together with violaceous papules and plaques over palms, soles and dorsal aspect of bilateral foot [Figure 1b]. Abdominal examination revealed a 3 cm × 3 cm lump palpable in the left lumbar region. There was no regional or generalized lymphadenopathy. Contrast-enhanced computed tomography (CECT) abdomen scan revealed a round to oval well-defined heterogeneously enhancing exophytic mass measuring 1.7 × 2.3 × 2.1 cm (AP × TR × CC) arising from interpolar region of left renal cortex [Figure 2a and 2b]. Oral mucosal biopsy revealed focal suprabasilar acantholytic cleft with acantholytic cells and interface dermatitis with many apoptotic cells, basal layer damage, and dermal lymphocytic infiltrate [Figure 3a]. Direct immunofluorescence (DIF) from dorsum of right foot revealed intercellular suprabasal deposition of immunoglobulin Ig G and IgA in a fishnet pattern and linear deposition of IgG, IgA, and C3 along dermoepidermal junction, consistent with PNP [Figure 3b]. An ultrasound-guided core needle renal biopsy was consistent with renal cell carcinoma of clear cell subtype [Figure 3c].

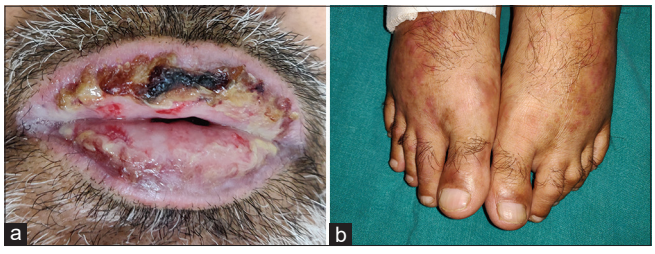


**Figure 1: (a): Erosions involving the upper and lower lips. (b): Erythematous to violaceous papules over dorsum of bilateral feet**

Based on history, examination and investigations, the patient was diagnosed as a case of PNP secondary to renal cell carcinoma (Stage I, T1a N0 M0). However, immunoprecipitation or indirect IF staining on rat bladder epithelium could not be done due to resource constraints. The cutaneous lesions subsided within 2 weeks following initiation of oral prednisolone (1.0 mg/kg) with marginal improvement in stomatitis which resolved completely within 2 months following nephrectomy.

PNP occurs in 5% of patients with internal malignancy.[5] The original diagnostic criteria were proposed by Anhalt *et al*.,[6] which were subsequently modified by Camisa and Helm. They proposed three major and three minor diagnostic criteria with three major criteria, or two major and two minor criteria required for diagnosis. The major criteria include polymorphic mucocutaneous eruptions, concomitant internal neoplasm, and serum antibodies with a specific immunoprecipitation pattern, whereas the minor criteria include histological evidence of acantholysis, intercellular and basement membrane fluorescence on DIF and demonstration of autoantibodies in patient's serum by indirect IF staining on rat bladder epithelium.[7] Clinical variants of PAMS include pemphigus-like, pemphigoid-like, erythema multiforme-like, graft-versus-host disease-like, and lichen planus-like, with erythema multiforme-like presentation being the most common.[8] It can affect both stratified and non-stratified epithelia including the eyes, lungs, gastrointestinal tract, thyroid, and kidneys. Respiratory involvement in the form of bronchiolitis obliterans is a poor prognostic sign.[9] The differential diagnosis of PNP includes lichen planus, erythema multiforme, bullous

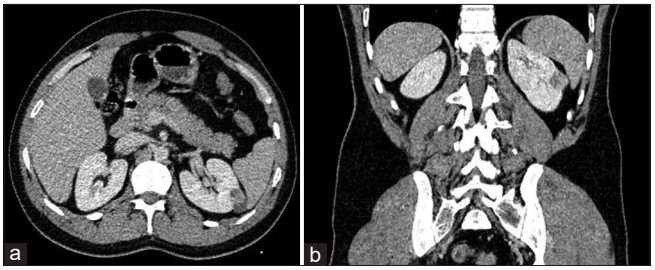


**Figure 2: CECT abdomen (a) axial image and (b) coronal image demonstrating a round to oval well-defined heterogeneously enhancing exophytic mass measuring 1.7 × 2.3 × 2.1 cm (AP × TR × CC) arising from interpolar region of left renal cortex without any evidence of internal calcification, fat or air density which is laterally abutting the spleen with loss of fat planes without any obvious features of parenchymal infiltration**

**Table 1: Summary of clinical, investigational, histological features, and treatment response in reported cases with RCC associated PNP**

| Disease characteristics | Aessopos *et al.*[3] | Gupta *et al.*[4] | Present case |
|---|---|---|---|
| Age (in years) | 72 | 64 | 45 |
| Sex | Female | Female | Male |
| **Clinical features** | | | |
| Oral lesions | Present | Present | Present |
| Cutaneous lesions | Absent | Present | Present |
| Duration of symptoms | 6 months | 6 months | 7 months |
| **Laboratory investigations** | Leucocytosis | Leucocytosis | Within normal limits |
| **CECT abdomen** | | | |
| Diseased kidney | Right | Right | Left |
| Size of tumor | 4 cm | 20 cm | 2.3 cm |
| **Histology** | | | |
| Biopsy site | Oral mucosa | Skin | Oral mucosa |
| Interface dermatitis | Present | - | Present |
| Spongiosis | Present | - | Present |
| Basal cell vacuolar degeneration | Present | - | Present |
| Supra-basilar cleft | Present | Present | Present |
| Acantholytic cells | Present | Present | Present |
| Dermal infiltrate | Plasma cells and eosinophils | - | Lymphocytes |
| **Renal biopsy** | Clear cell RCC | Clear cell RCC with sarcomatoid change | Clear cell RCC |
| **DIF** | | | |
| Immunoreactants | IgG and C3 | Not reported | IgG, IgA and C3 |
| Intercellularly | Fish-net pattern | - | Fish-net pattern |
| DEJ | Linear | - | Linear |
| **Metastasis** | Absent | Present | Absent |
| **TNM** | T1b N0 M0 | T3a N0 M1 | T1a N0 M0 |
| Staging | I | IV | I |
| **Treatment response** | | | |
| Oral corticosteroids | | | |
| Cutaneous lesions | - | Good response | Good response |
| Oral lesions | Poor response | Poor response | Poor response |
| Nephrectomy | Complete resolution after 2 months | Poor response | Complete resolution after 2 months |
| Oral lesions | | | |

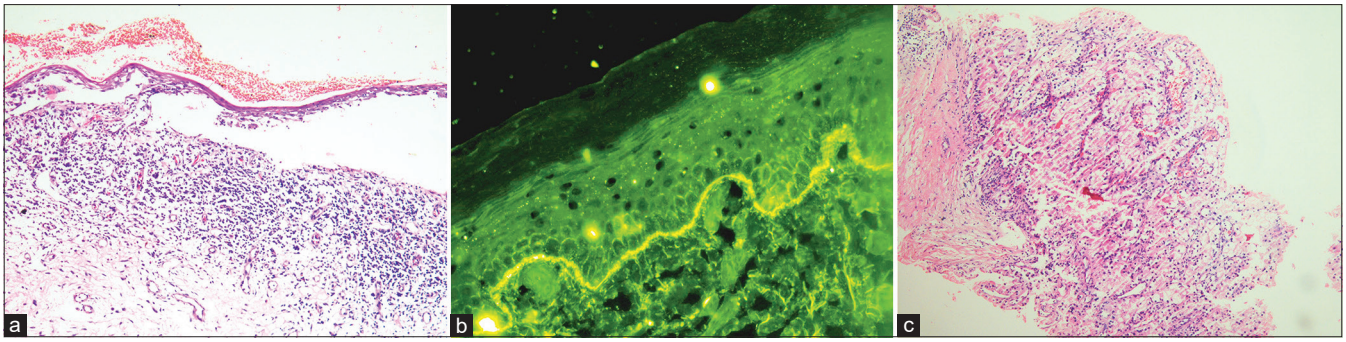


**Figure 3: (a): Biopsy (oral mucosa) revealing focal suprabasilar acantholytic cleft and interface dermatitis with many apoptotic cells, basal layer damage, infiltration of dermal lymphocytes, and pigment incontinence (H&E 10×). (b): Direct immunofluorescence evaluation of perilesional specimen from dorsum of right foot revealing intercellular suprabasal deposition of IgG and IgA in a fishnet pattern and linear deposition of IgG, IgA, and C3 along dermoepidermal junction (40×). (c): Ultrasound-guided core needle renal biopsy showing compact nests and sheets of cells with clear cytoplasm and distinct membrane consistent with renal cell carcinoma of clear cell subtype (H&E 10×)**

pemphigoid, pemphigus vulgaris, graft-versus-host disease, and Stevens-Johnson syndrome.

PNP is characterized by the presence of autoantibodies to a range of protein components of desmosomes and hemidesmosomes of basement membrane zone. The target antigens include desmoglein 1 (160 kD) and 3 (130 kD), desmoplakin 1 (250 kD) and 2 (210 kD), bullous pemphigoid antigen 1 (230 kD), envoplakin (210 kD), epiplakin (>700 kD), periplakin (190 kD), and alpha-2-macroglobulin-like-1 antigen (170 kD). Autoantibodies to plakin proteins are most specific to PNP.[8] The pathogenesis of PNP is not completely understood. Various theories which have been proposed include, antitumor immune response that cross-reacts with constitutively or anomalously expressed epithelial proteins by tumor cells and normal constitutive epithelial proteins of the host skin, and dysregulated cytokine production (elevated levels of IL-6). Autoantibodies can also be derived from B-cells of tumor origin as in Castleman disease.[10]

There are no guidelines for the management of PNP; hence, early diagnosis and management of underlying neoplasm is of paramount importance. The tumor should be minimally manipulated during surgery to avoid hematogenous dissemination of autoantibodies. Alternatively, intravenous immunoglobulins (IVIg) can be used before surgery. Medical management options include, corticosteroids, biologics (rituximab, alemtuzumab, daclizumab, and basiliximab), IVIg and conventional steroid sparing agents including cyclophosphamide, mycophenolate mofetil, and cyclosporine, though they have not been found to be much useful.[11]

Herein we report a case of PNP secondary to renal cell carcinoma (stage I) presenting with recalcitrant stomatitis and lichen planus like cutaneous lesions. This report serves to reiterate the fact that recalcitrant stomatitis is the earliest and most common manifestation of PNP and subtle cutaneous sings in the form of lichenoid papules limited to extremities without any obvious vesicles or bulla can occur in PNP. Unlike cutaneous lesions, stomatitis may not respond well to corticosteroid therapy but improves dramatically following tumor removal. Hence, PNP should be suspected in such cases to detect and manage malignancy at an early stage.

## *Declaration of patient consent*

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patients understands that his name and initial will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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## *Conflicts of interest*

There are no conflicts of interest.

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