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A Sinister Disease Hides Behind Recalcitrant Mucocutaneous Disorder: A Case Report

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Abstract

Paraneoplastic pemphigus (PNP) is a rare autoimmune disorder associated with underlying benign or malignant neoplasia. Its signs and symptoms may be the first presentation of a concealed malignancy. Due to late diagnosis, the prognosis of PNP is not good, so early diagnosis and treatment are of paramount importance. Herein, we present a case of 22 years old female who presented to our outpatient department (OPD) with a history of recurrent, severe, recalcitrant, painful oral ulcers; lichenoid lesions over the hands, and feet; widespread blistering and erosions involving the soles. Histopathological examination was consistent with paraneoplastic pemphigus and demonstrated features of lichenoid dermatitis. Computed Tomography scan revealed retroperitoneal mass suggestive of Castleman disease. We referred the patient to the surgical team for further management.

Key words: *Castleman disease; lichenoid dermatitis; paraneoplastic pemphigus*

Introduction

Paraneoplastic pemphigus (PNP) is a rare autoimmune blistering disease associated with underlying benign or malignant neoplasia.[1] It is also known as a paraneoplastic autoimmune multisystem syndrome, as its involvement is not only limited to the skin and mucosae.[2] PNP can have varied clinical presentations and resemble pemphigus, bullous pemphigoid, erythema multiformae, graft-versus-host disease, lichen planus (LP), and acute lupus erythematosus.[1,3] It is mostly associated with hematological neoplasia. PNP can be associated with Castleman disease (CD). CD is a lymphoproliferative disorder that results in autoantibodies production, which can cross-react with desmosomal and hemidesmosomal components of the skin.[1,4,5]

Case report

We report a case of 22 years old unmarried female who presented with painful oral ulcers for 3-4 years, rashes over both hands and feet for 4-5 months, and non-healing ulcers over feet for 2-3 months. She also gave a history of significant weight loss for one year. There was no involvement of eyes or genitalia. She did not give any history of intake of any drug before the onset of symptoms. She denied any history of sexual contact, chronic medical condition, or prior surgical intervention. Dermatological examination revealed multiple ulcers and erosions over the tongue (Figure 1), buccal mucosa, and palate. She had mild scaly plaques with violaceous pigmentation over her lips. Multiple erythematous to violaceous papules and plaques were present over both palms on thenar and hypothenar eminences, extending distally from

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metacarpophalangeal joints (Figure 2). She had well-defined erythematous plaques with whitish adherent scales distributed symmetrically over the dorsal aspect of the fingers and toes, mostly involving the proximal interphalangeal joints and extending distally (Figure 3). There were erythematous plaques on bilateral soles, with multiple ulcers and extensive erosions with overlying yellowish slough and crusts (Figure 4). She also had clubbing of fingers.

The differential diagnoses of PNP and lichenoid dermatitis were made based on the clinical findings. Skin biopsies were taken from a lesion over the palm and a lesion on the sole for histopathological examination (HPE). HPE of palm showed subepidermal bullae with a dense band-like lymphocytic infiltrate in the dermis below the bulla (Figure 5). HPE of sole showed a dense band of lymphocytic infiltrate over the upper dermis (Figure 6). HPE findings were consistent with bullous LP and PNP. Her baseline investigations, including liver function test, renal function test, and complete blood counts, were within normal limits, except 15% eosinophils. Direct immunofluorescence (DIF) was not done due to financial constraints. Ultrasonography of abdomen and pelvis showed large heteroechoic mass (10.3 x 7.5 cm) containing hyperechoic focus (14 cm) in Morrison's pouch closely abutting surrounding structures. Contrast-enhanced computed tomography (CECT) of the abdomen was advised, which revealed a large well defined soft tissue mass of approximately 11.4 x 7.8 x 7.5 cm in the right retroperitoneal region. The lesion showed intense enhancement in the post-contrast study. The lesion also noted a tiny focus of calcification. The lesion was pushing the duodenum and pancreas anteriorly and inferior vena cava posteriorly (Figure 7). Based on HPE and radiological findings, a diagnosis of PNP due to CD was made. The patient was then referred to the surgical team for further management. After surgery, the patient was referred to the cancer hospital.

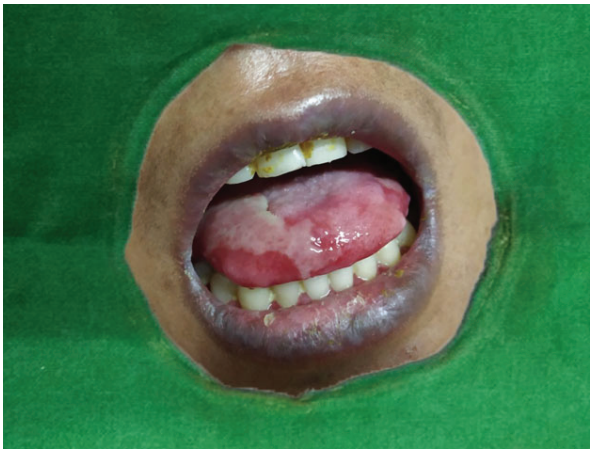

Figure 1: Ulcers over tongue, mostly localized to the lateral border. Mild scaly plaque over lower lip with violaceous pigmentation.

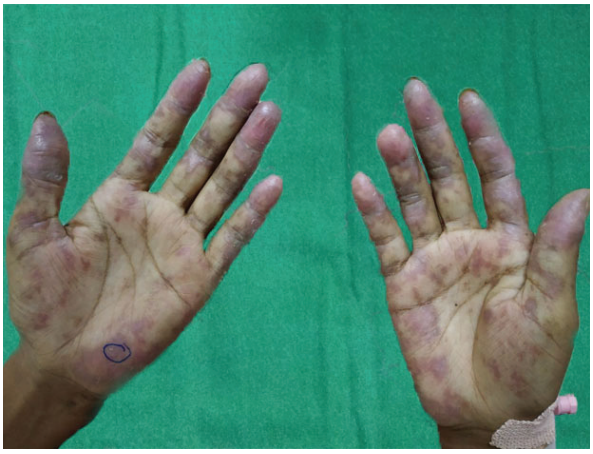

Figure 2: Multiple erythematous to violaceous plaques over bilateral palms over thenar and hypothenar eminences and extending distally to involve interphalangeal joints and fingertips.

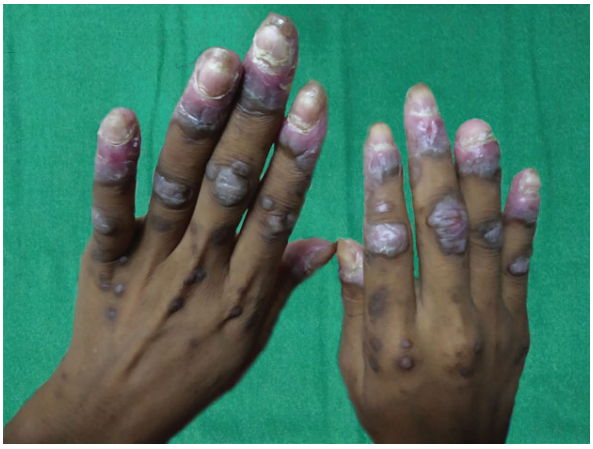

Figure 3: Well defined erythematous to violaceous plaques over dorsal aspect of bilateral hands mostly over proximal interphalangeal joints and extending distally from distal interphalangeal joints.

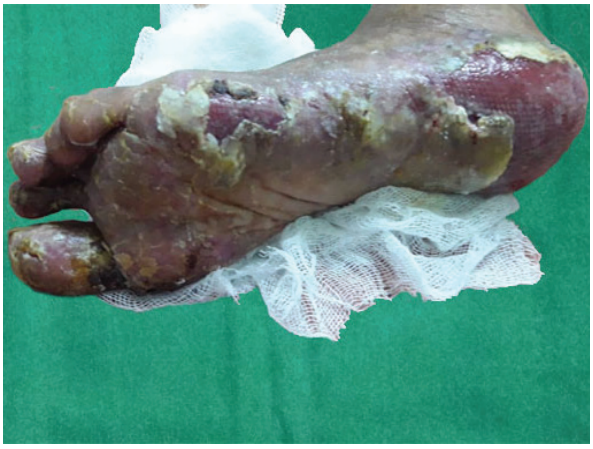

Figure 4: Extensive erosion over heel of left foot, with areas of ulceration, yellowish crusts, and desquamation over sole and even extending to involve volar aspect of toes.

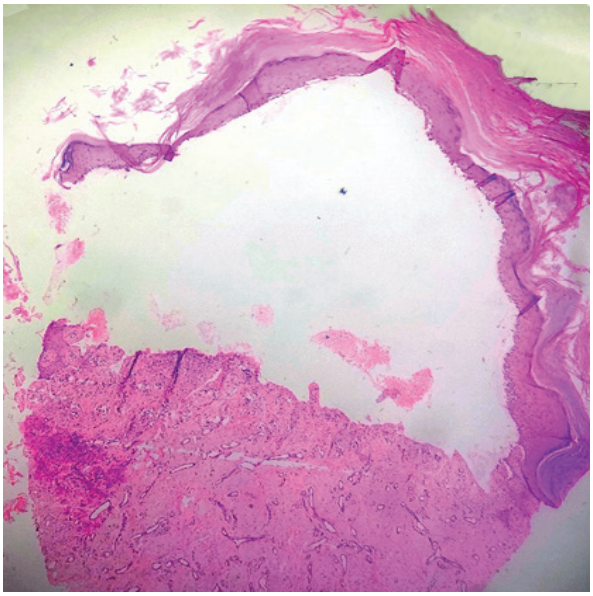

Figure 5: Hematoxylin and eosin stain, 40X. Histopathology of palmar lesion shows subepidermal bullae with lichenoid infiltrate in the dermis

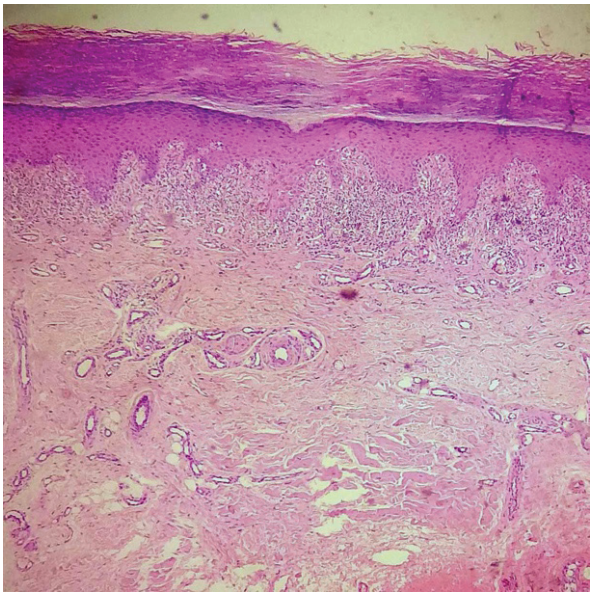

Figure 6: Hematoxylin and eosin stain, 100X. Histopathology of lesion from sole shows dense lichenoid infiltrate in the dermis.

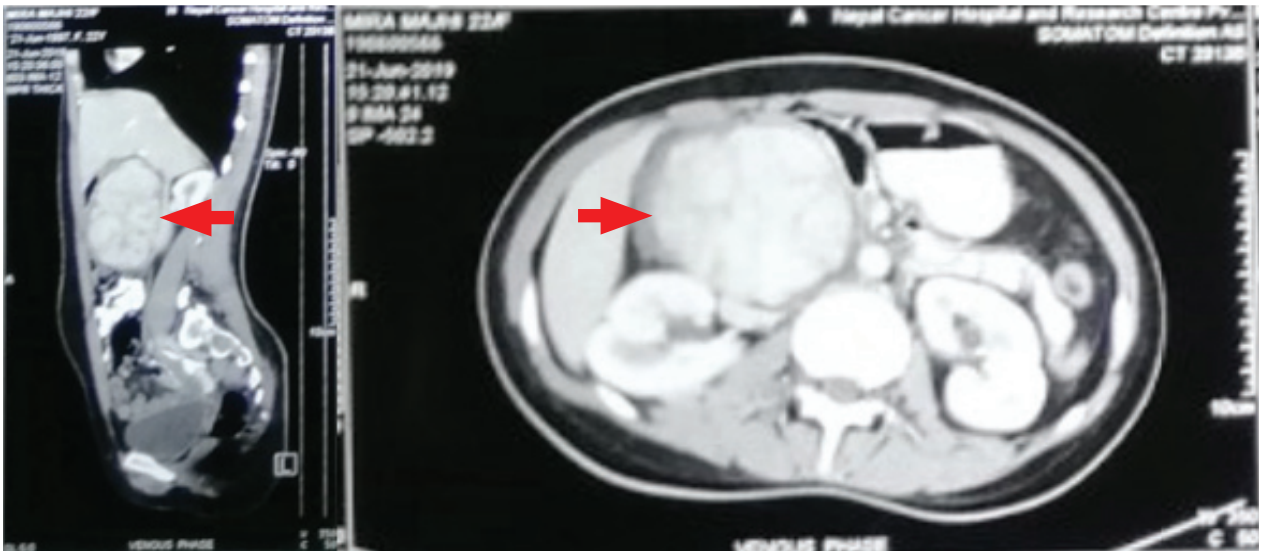

Figure 7: CECT (both sagittal and axial planes), showing intensely enhanced retroperitoneal mass (red arrow) suggestive of CD, compressing and abutting surrounding structures.

Discussion

Paraneoplastic pemphigus is a rare and often fatal autoimmune blistering disease associated with benign and malignant neoplasia. The prognosis of this condition depends on the associated tumor. Sometimes, excision of the tumor might cure PNP.[1] Malignancies commonly associated are Non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia, Castleman disease, thymoma, Waldenström's macroglobulinemia, Hodgkin lymphoma, monoclonal gammopathy, and melanoma.[6]

CD is a non-clonal neoplasm of lymphatic origin, which most commonly develops in retroperitoneal spaces or the chest. It is associated with a number of autoimmune conditions like autoimmune cytopenias, peripheral neuropathy, systemic lupus erythematosus, Sjogren's syndrome, and PNP.[4]

The pathophysiology of PNP is speculative. Tumor may produce abnormal epithelial proteins. Normal epithelial cells may thus cross-react with antibodies developed against tumor cells.[5] There may be markedly increased interleukin 6 (IL-6). CD cells secrete a

large amount of IL-6, which in turn promotes B-cell differentiation.[5,7]

Clinically, the first symptom of PNP is mostly severe painful oral erosions that spread to affect the entire vermilion and tongue. Cutaneous lesions follow mucosal lesions and mostly involve the upper body, though any site can be involved. PNP can have various presentations and classified as pemphigus like, bullous pemphigoid-like, erythema multiforme (EM)-like graft-versus-host-like, lichen planus-like, and acute lupus erythematous-like.[1,3]

The histologic features of PNP are variable. It depends upon the clinical features. Histologically PNP can mimic different conditions in the same individual. The usual findings include acantholysis, with basal cells apoptosis with vacuolar interface dermatitis with or without lichenoid inflammation. Other findings include dermoepidermal cleft and dyskeratotic keratinocytes.[8,9] DIF shows intercellular deposits of IgG and C3, but these deposits can also occur over the dermoepidermal junction. In addition to all desmosomal proteins, antibodies are also directed towards BP180 and BP230.[1,10,11]

PNP can be treated by treating the underlying neoplasm. In operable cases, surgical excision of the tumor might result in the remission of PNP. In a study by Fang et al., surgical excision of localized CD led to a decline in autoantibodies to normal or almost normal level, and mucocutaneous lesions of PNP also resolved almost completely within six months. There was no recurrence.[12] Unicentric, unresectable and recurrent CD can be treated with radiotherapy. In cases of multicentric CD, chemotherapy, immunomodulators, and IL-6 antibodies like tocilizumab and siltuximab can be used.[7,13]

Prednisolone (0.5-1.0 mg/kg) is the first-line treatment of PNP. Cutaneous lesions heal faster than mucosal lesions. Prednisolone can be combined with cyclosporin, cyclophosphamide, azathioprine, and mycophenolate mofetil.[1,14] Rituximab has been used to treat PNP. It seems to be more effective and is less tumorgenic.[15] In unresponsive patients, rituximab can be combined with intravenous immunoglobulins (IVIG).[16] However, IVIG does not seem to be a good option in a developing country like Nepal.

The prognosis of PNP is not good. Despite treatment, mortality ranges from 75-90%. The most common cause of death is respiratory failure. In a study by Nikolskaia et al.,[4] 22 of 28 patients presenting with features suggestive of PNP, who were later diagnosed as CD, died over a period of two years secondary to respiratory failure. PNP associated with NHL carries the worst prognosis. Among the varied clinical presentations, EM-like lesions have a poorer prognosis. Histologically presence of necrotic keratinocytes in a patient having the severe disease has a poorer prognosis.[4,17]

In Nepal, only a few cases of PNP have been reported. Shah et al. had reported a case of PNP, which presented with severe recalcitrant stomatitis. Unlike our case, the patient also had involvement of genitalia, and eyes, with targetoid lesions, and multiple vesicles and bullae over body. The computed tomography scan had revealed a solid ovarian tumor, which was excised as part of the multi-disciplinary approach needed for the management of PNP.[18]

Conclusion

PNP is a rare autoimmune disease associated with underlying malignancy. The mucocutaneous symptoms occurring in PNP may be the first presenting complaints. The symptoms are mostly recalcitrant to treatment unless the underlying malignancy is discovered and treated. One of the causes of PNP is CD. Sometimes tumor removal of tumor may improve dermatological manifestations but still, the condition may be fatal. So, a multidisciplinary approach is needed for early detection and proper management of PNP, including dermatologists, radiologists, surgeons, and oncologists.

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