# A Case Report of Paraneoplastic Pemphigus Associated With Retroperitoneal Inflammatory Myofibroblastic Tumor

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**Abstract-** Paraneoplastic pemphigus (PNP) is an autoimmune bullous disease associated with underlying neoplasms, both malignant and benign. The most constant clinical presentation of PNP is the presence of intractable stomatitis. Herein we present a 25-year-old male with a 3-month history of refractory stomatitis especially involving the lips and widespread vesiculobullous eruption on his trunk and extremities. The diagnosis of PNP was confirmed based on histological and serological results. Investigation for the underlying neoplasm revealed a retroperitoneal tumorous mass which was biopsied and diagnosed as the inflammatory myofibroblastic tumor (IMT). The tumor was surgically excised, and different treatment regimens were used to treat the mucocutaneous lesions. Skin lesions responded favorably to treatment, but oral stomatitis still persists which is the case in most PNP patients. This combination of PNP and IMT has rarely been reported in the literature. Treatment started with corticosteroid and rituximab then tumor excised.

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**Keywords:** Paraneoplastic pemphigus; Myofibroblastic tumor; Stomatitis

## Introduction

Paraneoplastic pemphigus (PNP) is a rare, life-threatening, autoimmune mucocutaneous blistering disease determined by the presence of intractable mucositis and polymorphous skin eruptions mimicking Pemphigus vulgaris (PV), pemphigus foliaceous (PF), bullous pemphigoid (BP), erythema multiforme (EM) and lichen planus (LP) (1,2). Most neoplasms associated with PNP are hematological malignancies, and it is rarely seen in other tumors such as inflammatory myofibroblastic tumor (IMT) (3). The prognosis of PNP depends on the nature of the underlying neoplasm. The tumor should have surgically excised in patients with benign neoplasm, and in most cases, improvement occurs substantially. Although steroids, radiotherapy, and chemotherapy may be used for cases that complete surgical resection cannot be done (4).

## Case Report

A 25-year-old man presented to our outpatient department with a 3 months history of erosive oral lesions, flaccid and tense vesiculobullous lesions over his extremities and trunk. Oral erosions had gradually progressed to widespread ulcers during the course of the disease. He had later developed conjunctivitis in both his eyes. In physical examination, he had crusted erosions on upper and lower lips and multiple painful oral erosions on the buccal and palatine mucosa. He also had moderate conjunctivitis. Generalized flaccid and tense blisters were observed on the anterior and posterior aspects of his trunk and abdomen and also on upper and lower extremities. He also had multiple dusky targetoid lesions on his palms and soles (Figure 1,2).

The patient reported 8 kg weight loss 2 months prior to his first visit. Skin biopsy for histological examination, direct and indirect immunofluorescence (DIF and IIF) were done for definite diagnosis. Histological examination revealed many apoptotic cells, basal layer damage, lymphocyte infiltration in the upper dermis, suprabasal acantholysis with characteristic thumbstoning along the basement membrane leading to the subepidermal cleft formation (figure 3). DIF staining showed intercellular deposition of IgG and focal granular deposition of C3 in basement membrane suggestive of paraneoplastic pemphigus. IIF staining detected circulating auto-antibodies against the epithelia of a rat bladder with a titer of 1/160. Elevated levels of anti-desmoglein 1 and 3 antibodies were noted by

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enzyme-linked immunosorbent assay. Laboratory investigation showed normochromic -normocytic anemia with normal leukocyte counts, and other laboratory results including urea and creatinine, electrolytes, liver function tests, LDH and serum protein electrophoresis were within normal limits. Chest, Abdomen and pelvic computed tomography (CT) scans were performed to detect any underlying neoplasm and revealed a 65x47 mm heterogeneous retroperitoneal mass on the anterior of Inferior Vena Cava (IVC) and adjacent to duodenum that caused pancreas deviation to the anterior and left side of the abdominal cavity. Tumor biopsy showed inflammation and spindle cell proliferation suggesting the differential diagnosis of inflammatory myofibroblastic tumor, low-grade inflammatory fibrosarcoma, and low-grade spindle cell sarcoma.

The immunohistochemical staining was positive for vimentin and smooth muscle actin and negative for anaplastic lymphoid kinase (ALK), CD 34 and desmin. According to these evaluations, a diagnosis of IMT was made.

The patient was first treated with 100 mg/day prednisolone plus 150 mg/day azathioprine for one month. Due to lack of response to this treatment, azathioprine was discontinued, prednisolone was tapered to 75 mg/day, and four weekly infusions of 500 mg rituximab were added to his treatment regimen. Two months after receiving rituximab significant improvement was observed in cutaneous lesions, but oral mucosa was still involved. At this stage, prednisolone was tapered to 60 mg/day, and the patient was referred to oncology service for tumor excision. The whole retroperitoneal mass was excised with laparotomy and sent for histological examination, which was compatible with the inflammatory myofibroblastic tumor. On his follow-up visit after tumor excision, skin lesions were improved, but oral lesions persisted. Six weeks after surgery he was treatment with Intravenous immunoglobulin (IVIG) was initiated but was discontinued due to deep vein thrombosis formation.

A course of plasmapheresis was also performed for the patient with relative improvement of oral lesions. He is currently being treated for oral erosions with 2 gr/day mycophenolate mofetil, 12.5 mg/week methotrexate, and 30 mg/day prednisolone. Our patient didn't develop bronchiolitis obliterans that can be a major cause of death in paraneoplastic pemphigus patients. It may be due to early diagnosis and total excision of the tumor before respiratory involvement.

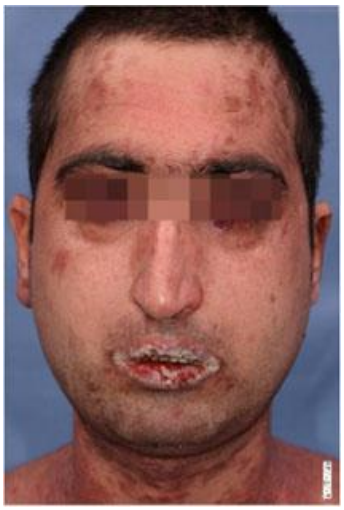

**Figure 1.** Clinical manifestations: Crusted erosions on upper and lower lips

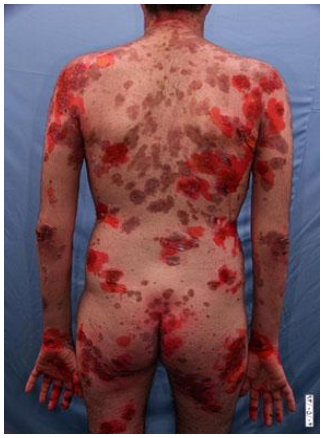

**Figure 2.** Clinical manifestations: Flaccid and tense blisters with PIH of old lesions all over the body

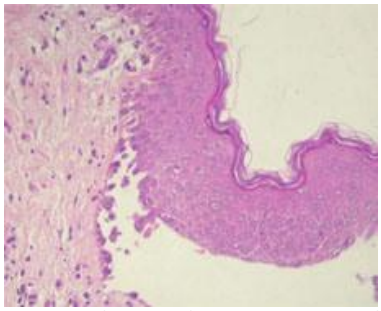

**Figure 3.** Histopathologic findings of the skin: Bullous cleft formation and acantholytic cells in the suprabasal layer

## Discussion

Paraneoplastic pemphigus (PNP) was first described by Anhalt *et al*., in 1990(1).

The neoplasms associated with PNP are mostly lymphoproliferative tumors, including non-Hodgkin's

lymphoma (42%), chronic lymphocytic leukemia (29%), Castleman's disease (10%), thymoma (6%), retroperitoneal sarcomas (6%) and Waldenstrom macroglobulinemia (6%) (5). the diagnosis of PNP is based on clinical manifestations, histological features and direct. Immunofluorescence (DIF), indirect immunofluorescence (IIF) on rat bladder epithelium, and immunoprecipitation tests may aid in confirmation of the diagnosis. Camisa and Helm (6) revised diagnostic criteria of PNP and reported major signs as polymorphic mucocutaneous eruption, concurrent internal neoplasia, and serum immunoprecipitation with a complex of four proteins (desmoplakin I, BP Ag, envoplakin and desmoplakin II, and periplakin) and minor signs of histological evidence of acantholysis, DIF showing intercellular and basement membrane deposition of autoantibodies and IIF staining with rat bladder epithelium. Three major signs or two major plus two minor signs are required to confirm the diagnosis of PNP. Our case fulfills these diagnostic criteria for PNP. To the best of the authors' knowledge six cases of PNP associated with inflammatory myofibroblastic tumor (IMT) have been reported so far (Table 1). All but one (10) of these reports have been described in young adults and most recently in a 7-year-old girl (7). Therefore despite the low occurrence of PNP in childhood and adolescent, it should be included in the differential diagnosis of oral erosive lesions, and thorough examination for underlying neoplasm should be performed.

**Table 1. Paraneoplastic pemphigus patients with underlying inflammatory myofibroblastic tumor**

| Authors | Age/Sex | Location of the tumor/tumor size | Features of paraneoplastic pemphigus | Death due to bronchiolitis obliterans |
|---|---|---|---|---|
| **Halpert *et al.*,**[7] | 7/F | Right flank/ 55mm | Oral ulcers, denuded lips, vesiculobullous eruption of the face, extremities, and lower back (40% of body surface) | No |
| **Ghandi *et al.*,**[8] | 30/F | Anterior and superior mediastinum/- | Persistent and painful oral ulcers, irritated eyes and dusky eroded lesions on the limbs and palms and soles which progressed to tense bullae | No |
| **Schols *et al.*,**[9] | 18/M | Left hemiabdomen/20×9×11cm$^3$ | Painful oral ulcers leading to 10kg weight loss | No |
| **Lee *et al.*,**[10] | 48/F | Paraspinal mass in right costodiaphragmatic recess/5×3×4cm$^3$ | Chronic relapsing oral ulcers, blisters and erythematous papules on trunk | Yes |
| **Kahawita *et al.*,**[11] | 23/F | Retroperitoneal mass/7.5×7cm | Extensive stomatitis especially on the lips, flaccid blisters and target lesions of the trunk and target lesions on the palms and soles which later progressed to tense blisters | Yes |
| **Mar *et al.*,**[12] | 11/F | Retroperitoneal | Erosive lesions of oral and genital mucosa | Yes |

. In a small case series in 2014, four cases of IMT-associated PNP were reported. In two patients the tumor was located in retroperitoneum similar to our patient, and in the two other patients, the tumor was located in the anterior mediastinum and costophrenic angle (7).

Inflammatory myofibroblastic tumors are rare, benign pseudotumor lesions of unknown etiology that can be located at different anatomical sites. These tumors are more common among children and adolescents. IMT`s are also known as plasma cell granuloma, xanthogranuloma, inflammatory pseudotumor, and fibrous histiocytoma (13).

Although IMT is a benign tumor it is recognized to show partially invasive behavior and a tendency to recur. In recent years most cases of IMT have been found in the lung, orbit, mesentery, omentum, gastrointestinal and genitourinary tract (14). Who classification of tumors of soft tissue and bone currently defines IMT as a distinctive neoplasm composed of myofibroblastic spindle cells with inflammatory infiltration of plasma cells, lymphocytes, and/or eosinophils (15).

As mentioned before the treatment of choice is radical resection.

Oral erosions of our patient persisted after treatment of the underlying tumor. Paraneoplastic pemphigus usually remits after treatment of underlying neoplasm, but this is not always the case as observed in our case.

Skin lesions have a better prognosis compared to refractory stomatitis. Because local and distant recurrence and sarcomatous degeneration have been reported in IMT, long term follows up is suggested (16).

Although hematological malignancies are the more common neoplasms associated with PNP, IMT which is a rare tumor has been reported underlying this disease. The association of this rare tumor with an even more rare autoimmune disease is noteworthy.

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