Persistent oral ulcers in a woman with thymoma

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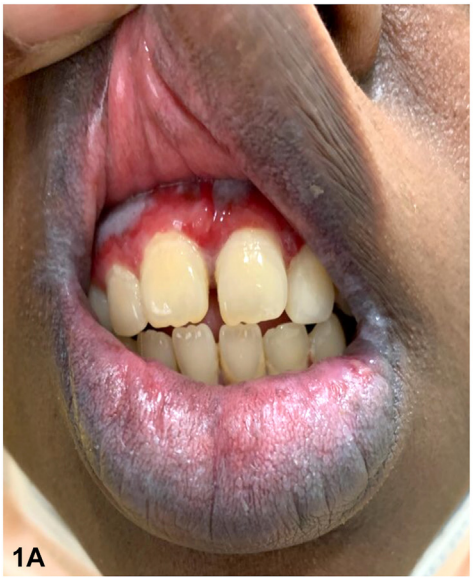
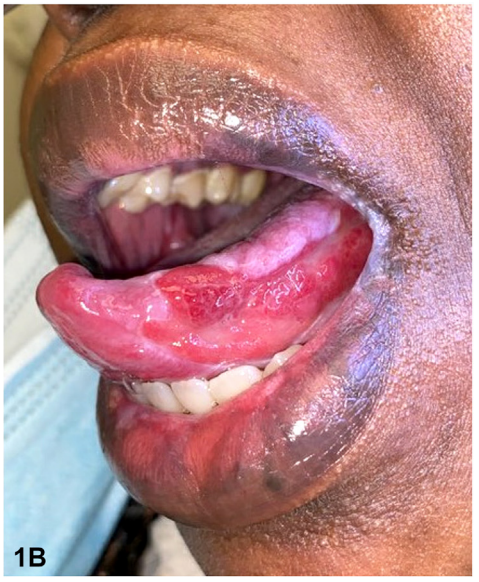
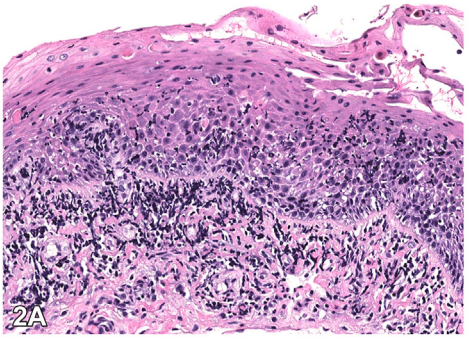
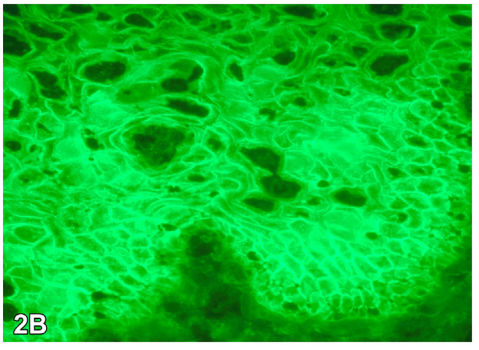
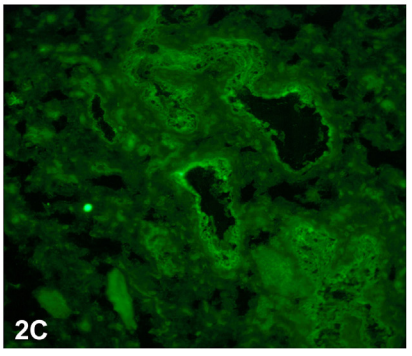
Key words: autoimmunity; immunofluorescence; paraneoplastic; pemphigus; thymoma.











CASE DESCRIPTION

A 37-year-old woman with metastatic thymoma was referred for painful oral sores refractory to multiple treatments including topical and oral steroid courses. Examination demonstrated desquamative gingivitis and punched out tongue, lip, and bilateral buccal mucosal ulcerations (Fig 1, *A* and *B*). An oral mucosal biopsy was obtained for hematoxylin and eosin, and direct and indirect immunofluorescence (DIF and IIF) studies.

HISTOPATHOLOGICAL FINDINGS

Histopathology demonstrated evidence of lichenoid interface dermatitis with necrotic keratinocytes and pseudoepitheliomatous hyperplasia without epidermal acantholysis (Fig 2, *A*). DIF was negative. Serum IIF demonstrated intercellular depositions of IgG on monkey esophagus (Fig 2, *B*) and rat bladder epithelium (Fig 2, *C*).

CLINICAL OUTCOME

The patient was started on intravenous immunoglobulin (IVIG) and tacrolimus swishes with improvement.

Question 1: What is the diagnosis?

A. Erythema multiforme

B. Lichen planus

C. Paraneoplastic pemphigus (PNP)

D. Pemphigus vulgaris

E. Bullous pemphigoid

Answers:

A. Erythema multiforme — Incorrect. While erythema multiforme shares many clinical features with PNP including targetoid lesions, histopathology does not support this diagnosis taking into account the positive IIF studies.

B. Lichen planus — Incorrect. While PNP can present as lichenoid papules or plaques with lichenoid changes on histopathology, the positive IIF results do not support the diagnosis of lichen planus.

C. PNP — Correct. The diagnosis is PNP secondary to thymoma. PNP is a rare autoimmune disease with poorly understood pathophysiology that involves both humoral and cellular autoimmune responses.[1,2] It is characterized by painful stomatitis and oral lesions that may resemble erosive lichen planus, erythema multiforme, or graft versus host disease. Clinical presentation varies, making the diagnosis challenging. The diagnosis can be confirmed by serum IIF, which typically shows intercellular depositions of IgG on rat bladder epithelium as well as monkey esophagus (Fig 2, *B*).[3]

D. Pemphigus vulgaris — Incorrect. Both PNP and pemphigus vulgaris demonstrate intercellular depositions of IgG on monkey esophagus, but only PNP demonstrates this finding on rat bladder epithelium, with identification of autoantibodies directed against plakins, among which autoantibodies to envoplakin and periplakin are the most specific.[3,4]

E. Bullous pemphigoid — Incorrect. IIF shows the presence of intercellular IgG deposits which are not found in bullous pemphigoid.

Question 2: Which of the following is least likely to result in successful treatment of this condition?

A. Immunosuppressants

B. Antivirals

C. Plasmapheresis

D. IVIG

E. Systemic glucocorticoids

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Answers:

A. Immunosuppressants — Incorrect. With a mortality rate of up to 90%, early diagnosis and treatment are critical.[4-6] First-line therapy involves treating the underlying neoplasm. High-dose corticosteroids and immunosuppressants such as cyclosporine, cyclophosphamide, azathioprine, and mycophenolate mofetil are often used in combination with steroids for management.[7] It has been reported that PNP may persist after surgical resection of tumors such as thymoma.[2]

B. Antivirals — Correct. The pathogenesis of PNP is not clearly understood but involves both humoral and cellular autoimmune responses; the pathogenesis is not driven by a virus and thus antivirals are not recommended.

C. Plasmapheresis — Incorrect. Plasmapheresis has been used to treat PNP, particularly in cases which are recalcitrant to other medical therapies.[8]

D. IVIG — Incorrect. IVIG has demonstrated efficacy in treating PNP associated with underlying neoplasms.[8] As described here, we report that IVIG is a promising treatment of thymoma-associated PNP.

E. Systemic glucocorticoids — Incorrect. Systemic glucocorticoids are used in combination with immunosuppressants for management of the underlying neoplasm in cases on PNP.[7]

Question 3: Which of the following findings is not true about this condition?

A. Histologic features include epidermal acantholysis, clefting, necrotic keratinocytes, and lymphocytic inflammation

B. DIF must be positive in order to diagnose PNP

C. Thymomas are associated with both lichen planus and PNP

D. PNP is associated with both benign and malignant neoplasms

E. The most common underlying neoplasms associated with PNP are lymphoproliferative disorders

Answers:

A. Histologic features include epidermal acantholysis, clefting, necrotic keratinocytes, and lymphocytic inflammation — Incorrect. This statement is true. However, as described in this case, these histopathologic features are not present in all patients. This case highlights that pathology may demonstrate lichenoid interface dermatitis without classical acantholysis.[3]

B. DIF must be positive in order to diagnose PNP — Correct. This statement is not true. DIF findings include IgG and complement deposition intercellularly and linear deposition along the epidermal basement zone. Some PNP cases, including the case described in this study, have a negative DIF.[4] This emphasizes the importance of obtaining serum IIF to confirm the diagnosis. IIF allows identification of autoantibodies directed against plakins, among which autoantibodies to envoplakin and periplakin are the most specific.

C. Thymomas are associated with both lichen planus and PNP — Incorrect. This statement is true. Thymomas, although not a frequent cause, have been reported in about 6% of patients with PNP. In addition to mucocutaneous disorders such as PNP and erosive lichen planus, thymomas are also associated with several paraneoplastic syndromes including myasthenia gravis, Lambert-Eaton, enteritis, paraneoplastic cerebellar degeneration, and acquired neuromyotonia, which may all fall within the spectrum of thymoma-associated multiorgan autoimmunity.[5,9]

D. PNP is associated with both benign and malignant neoplasms — Incorrect. This statement is true. PNP is a rare autoimmune disease associated with both benign and malignant neoplasms, most commonly lymphoproliferative disorders. PNP is most frequently associated with non-Hodgkin lymphoma, followed by chronic lymphocytic leukemia, Castleman disease, and rarely, thymoma.[1]

E. The most common underlying neoplasms associated with PNP are lymphoproliferative disorders — Incorrect. This statement is true. Lymphoproliferative neoplasms are the most commonly identified underlying disease in PNP, accounting for up to 84% of cases. Approximately 66% of cases are associated with non-Hodgkin lymphoma and chronic lymphocytic lymphoma.[10]

Abbreviations used:

DIF: direct immunofluorescence
IIF: indirect immunofluorescence
PNP: paraneoplastic pemphigus

Conflicts of interest

None disclosed.

REFERENCES

1. Paolino G, Didona D, Magliulo G, et al. Paraneoplastic pemphigus: Insight into the autoimmune pathogenesis, clinical features and therapy. *Int J Mol Sci*. 2017;18(12):2532.
2. Lim JM, Lee SE, Seo J, Kim DY, Hashimoto T, Kim SC. Paraneoplastic pemphigus associated with a malignant thymoma: a case of persistent and refractory oral ulcerations following thymectomy. *Ann Dermatol*. 2017;29(2):219-222.

3. Horn TD, Anhalt GJ. Histologic features of paraneoplastic pemphigus. *Arch Dermatol*. 1992;128(8):1091-1095.
4. Anhalt GJ. Paraneoplastic pemphigus. *J Investig Dermatol Symp Proc*. 2004;9(1):29-33.
5. Venuta F, Anile M, Diso D, et al. Thymoma and thymic carcinoma. *Eur J Cardio Thorac Surg*. 2010;37(1):13-25.
6. Sinha AA. Paraneoplastic pemphigus: autoimmune-cancer Nexus in the skin. *Anti Cancer Agents Med Chem*. 2015;15(10): 1215-1223.
7. Hertzberg MS, Schifter M, Sullivan J, Stapleton K. Paraneoplastic pemphigus in two patients with B-cell non-Hodgkin's lymphoma: significant responses to cyclophosphamide and prednisolone. *Am J Hematol*. 2000;63(2):105-106.
8. Nanda M, Nanda A, Al-Sabah H, Dvorak R, Alsaleh QA. Paraneoplastic pemphigus in association with B-cell lymphocytic leukemia and hepatitis C: favorable response to intravenous immunoglobulins and prednisolone. *Int J Dermatol*. 2007;46(7):767-769.
9. Czernik A, Camilleri M, Pittelkow MR, Grando SA. Paraneoplastic autoimmune multiorgan syndrome: 20 years after. *Int J Dermatol*. 2011;50(8):905-914.
10. Kartan S, Shi VY, Clark AK, Chan LS. Paraneoplastic pemphigus and autoimmune blistering diseases associated with neoplasm: characteristics, diagnosis, associated neoplasms, proposed pathogenesis, treatment. *Am J Clin Dermatol*. 2017;18(1): 105-126.