

Paraneoplastic pemphigus secondary to neuroendocrine carcinoma



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INTRODUCTION

Paraneoplastic pemphigus (PNP) is a rare, multi-organ autoimmune syndrome with severe mucocutaneous disease that develops in the setting of a past or current history of malignancy.¹ The most frequent underlying neoplasms are hematologic malignancies, whereas a small fraction are nonhematologic malignancies.¹ Here, we present a case of PNP secondary to neuroendocrine carcinoma (NEC) as a novel association.

CASE REPORT

A 59-year-old man with a history of hepatitis C presented with a 1-month history of painful mouth and genital erosions and a 2-day history of a new diffuse pruritic eruption. The patient reported an approximately 18 kg weight loss over the preceding 4 months. One week prior to presentation, his primary care physician palpated an abdominal mass on physical examination. An abdominal computed tomography scan showed a large intrahepatic mass, lymphadenopathy, and retroperitoneal lesions. On physical examination, there were innumerable red papules and thin plaques with targetoid macules on his palms and extensive intraoral erosions (Fig 1, A and B).

A punch biopsy demonstrated suprabasal acantholysis and a brisk lichenoid infiltrate composed of lymphocytes, histiocytes, and scattered eosinophils at the dermoepidermal junction (Fig 2, A). Direct immunofluorescence was IgG⁺ and C3⁺ in the intercellular spaces (Fig 2, B). Indirect immunofluorescence on rat bladder epithelium was 2+ with a 1:10 titer (Fig 2, C), and indirect immunofluorescence on monkey esophagus was weakly positive with a titer of 1:20 (not shown). Desmoglein 1 enzyme-linked immunosorbent assay was negative,

Abbreviations used:

NEC: neuroendocrine carcinoma
PNP: paraneoplastic pemphigus

and desmoglein 3 enzyme-linked immunosorbent assay was indeterminate. Based on the combination of clinical, histopathologic, and immunofluorescence findings, the patient was diagnosed with PNP. The patient underwent an ultrasound-guided left hepatic mass biopsy and was diagnosed with well-differentiated, World Health Organization grade 2 NEC.

DISCUSSION

PNP is a rare pemphigus subtype with roughly 500 cases reported in the literature since first described in 1990.²⁻⁴ The potential for severe multiorgan involvement and 90% mortality without treatment make an early diagnosis of PNP critical.⁵ PNP is most frequently associated with hematologic neoplasms, with non-Hodgkin lymphoma being the most frequently reported (52.78%), followed by chronic lymphocytic leukemia (22.92%), Castleman disease (18.60%), and other underlying hematologic malignancies (5.70%).⁶ Although the majority of associated malignancies are lymphoproliferative, there is a lower prevalence seen in association with solid tumors, including thymoma, liposarcoma, carcinoma of epithelial origin, sarcoma of mesenchymal origin such as leiomyosarcoma, and malignant melanoma.^{1,5,7} To our knowledge, the association of PNP with a solid organ NEC is unusual and novel.

Several theories regarding PNP pathogenesis exist; however, it is thought that the underlying neoplasm can impact both humoral and cell-mediated

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Fig 1. Clinical features of paraneoplastic pemphigus. **A**, Thin plaques with targetoid macules on palms. **B**, Extensive mucosal and intraoral ulcerations.

immunity, which may impact the clinical and histopathologic findings. Antibody production by the tumor or tumor-induced immune abnormalities may result in autoantibody production or epitope spreading. Cell-mediated immunity with features of lichenoid dermatitis on histopathology has been supported by high levels of cytokines that result in a cytotoxic immune response. This cell-mediated immune reaction also may predispose to the stimulation of the humoral immune system.³

Diagnosis of PNP can be aided by the minimum criteria proposed by Anhalt⁸ that included the following: (1) painful, progressive mucositis with preferential involvement of the tongue, (2) histologic features of acantholysis or lichenoid or interface dermatitis, (3) demonstration of antiplakin autoantibodies, and (4) demonstration of underlying lymphoproliferative neoplasm. Immunofluorescence plays a crucial role in diagnosis. For instance, direct immunofluorescence that demonstrates IgG autoantibodies and/or complement deposition in the intercellular spaces and/or along the basement membrane of the epidermis is diagnostic of PNP along with indirect immunofluorescence using rat bladder to detect circulating autoantibodies.³ The use of rat bladder has a high specificity (98%) and is particularly helpful in differentiating PNP from other pemphigoid diseases that do not have antiplakin autoantibodies.³ The cutaneous findings of PNP can include diffuse erythema, vesiculobullous lesions, papules, scaly plaques, exfoliative erythroderma,

erosions, or ulcerations. The erythema can also vary from macular to urticarial to targetoid to polymorphous.⁵

Successful treatment of the underlying malignancy is the primary factor related to the improvement of PNP. Solid tumor malignancies, such as benign thymomas or localized Castleman disease, have a high chance of remission with surgical resection, whereas cases associated with non-Hodgkin lymphoma and chronic lymphocytic leukemia are more difficult to treat and have poor outcomes.⁸ Reducing the tumor burden does not necessarily stop autoimmune disease progression, and the resolution of cutaneous disease is variable, with oral mucositis generally being more refractory to treatment.⁸ Treating the dermatologic manifestations of PNP is complex and requires coordination with oncology in order to ensure that there is no interference with the treatment of the associated malignancy. In this case, the patient was treated topically with triamcinolone 0.1% ointment for his cutaneous lesions; dexamethasone oral solution, nystatin, and magic mouthwash (lidocaine 2%, Maalox, and diphenhydramine) for intraoral erosions; and oral prednisone 80 mg daily. He had a dramatic improvement in his cutaneous and oral manifestations with this regimen. The oral prednisone was gradually tapered to 20 mg daily over 3 months with continued disease control and a plan to transition to a longer-term immunomodulating agent. He also started chemotherapy with

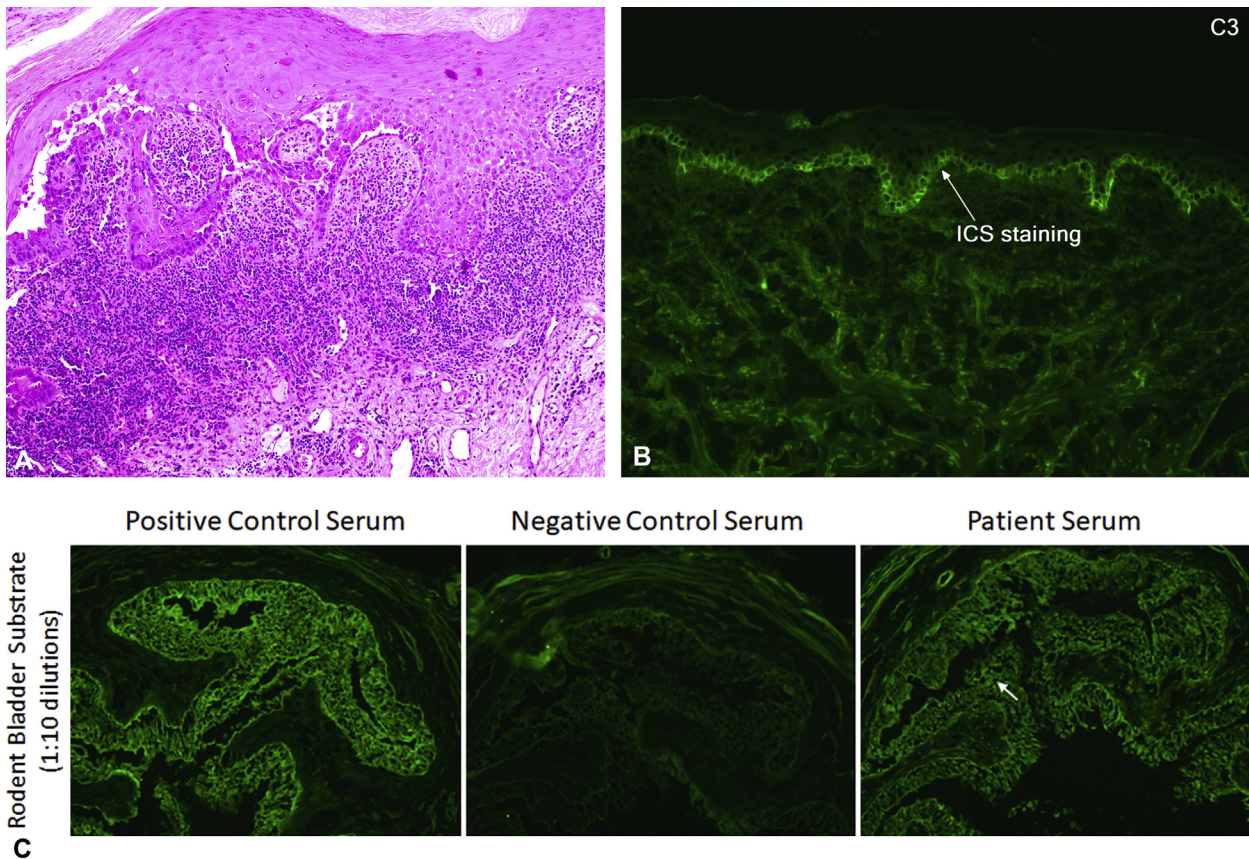


Fig 2. Histopathology and immunofluorescence of paraneoplastic pemphigus. **A**, Suprabasal acantholysis with brisk lichenoid infiltrate composed of lymphocytes, histiocytes, and scattered eosinophils at the dermoepidermal junction. **B**, Direct immunofluorescence was C3⁺ (arrow) and IgG⁺ (not shown) in the intercellular spaces, which is limited to the basal layer of the epidermis. **C**, Indirect immunofluorescence was 2+ (arrow) with a 1:10 titer on rat bladder epithelium. ICS, Intracellular staining. (A, Hematoxylin-eosin stain; original magnification: A, ×10.)

capecitabine and temozolomide for the treatment of his underlying malignancy. Although rituximab and intravenous immunoglobulins were considered, they were not started due to the patient's preference and improvement on the abovementioned regimen. Unfortunately, the patient succumbed to his NEC 8 months after diagnosis. This case demonstrates a novel association of PNP with NEC and highlights potential treatment considerations.

Conflicts of interest

None disclosed.

REFERENCES

- Anhalt GJ, Kim SC, Stanley JR, et al. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. *N Engl J Med*. 1990;323(25):1729-1735. <https://doi.org/10.1056/NEJM199012203232503>
- Kaplan I, Hodak E, Ackerman L, Mimouni D, Anhalt GJ, Calderon S. Neoplasms associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. *Oral Oncol*. 2004;40(6):553-562. <https://doi.org/10.1016/j.oraloncology.2003.09.020>
- Kim JH, Kim SC. Paraneoplastic pemphigus: paraneoplastic autoimmune disease of the skin and mucosa. *Front Immunol*. 2019;10:1259. <https://doi.org/10.3389/fimmu.2019.01259>
- Tirado-Sánchez A, Bonifaz A. Paraneoplastic pemphigus. A life-threatening autoimmune blistering disease. Article in Spanish. *Actas Dermosifiliogr*. 2017;108(10):902-910. <https://doi.org/10.1016/j.adengl.2017.04.011>
- 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. <https://doi.org/10.3390/ijms18122532>
- Ouedraogo E, Gottlieb J, de Masson A, et al. Risk factors for death and survival in paraneoplastic pemphigus associated with hematologic malignancies in adults. *J Am Acad Dermatol*. 2019;80(6):1544-1549. <https://doi.org/10.1016/j.jaad.2018.03.043>

7. Vassileva S, Drenovska K, Manuelyan K. Autoimmune blistering dermatoses as systemic diseases. *Clin Dermatol*. 2014;32(3):364-375. <https://doi.org/10.1016/j.clindermatol.2013.11.003>
8. Anhalt GJ. Paraneoplastic pemphigus. *J Invest Dermatol Symp Proc*. 2004;9(1):29-33. <https://doi.org/10.1111/j.1087-0024.2004.00832.x>