Volume 24 Number 2| February 2018
24(2): 4

Paraneoplastic pemphigus without antibodies to desmoglein 1 and 3

Kelsey Flood[1] MD, Christopher Stroud[2] MD, Zelmira Lazarova[3] MD, Nadarajah Vigneswaran[4] BDS DMD, Sylvia Hsu[2] MD

Affiliations:: [1]Feinberg School of Medicine, Northwestern University, Chicago, Illinois, [2]Department of Dermatology, Baylor College of Medicine, Houston, Texas, [3]Department of Dermatology, Medical College of Wisconsin, Milwaukee, Wisconsin , [4]Department of Pathology, The University of Texas Health School of Medicine at Houston, Houston, Texas

Corresponding Author: Kelsey Flood, Northwestern University Feinberg School of Medicine, 420 East Superior Street, Chicago, IL 60611, Email: kelsey.flood@northwestern.edu

Abstract

Paraneoplastic pemphigus is a severe autoimmune blistering disease presenting in the setting of underlying malignancy. Paraneoplastic pemphigus is associated with diffuse painful stomatitis throughout the oral cavity with extension to the lips. The cutaneous findings are varied and have been described as lichenoid, pemphigoid, and targetoid lesions. Herein, we report a patient with paraneoplastic pemphigus whose routine testing led to a diagnosis of pemphigus vulgaris. However, further testing was pursued revealing an antibody profile consistent with paraneoplastic pemphigus. Subsequent neoplastic workup revealed an intra-abdominal mass. Our case represents a subtle, non-classic presentation of paraneoplastic pemphigus and suggests the importance of a comprehensive investigative work-up in atypical cases of pemphigus.

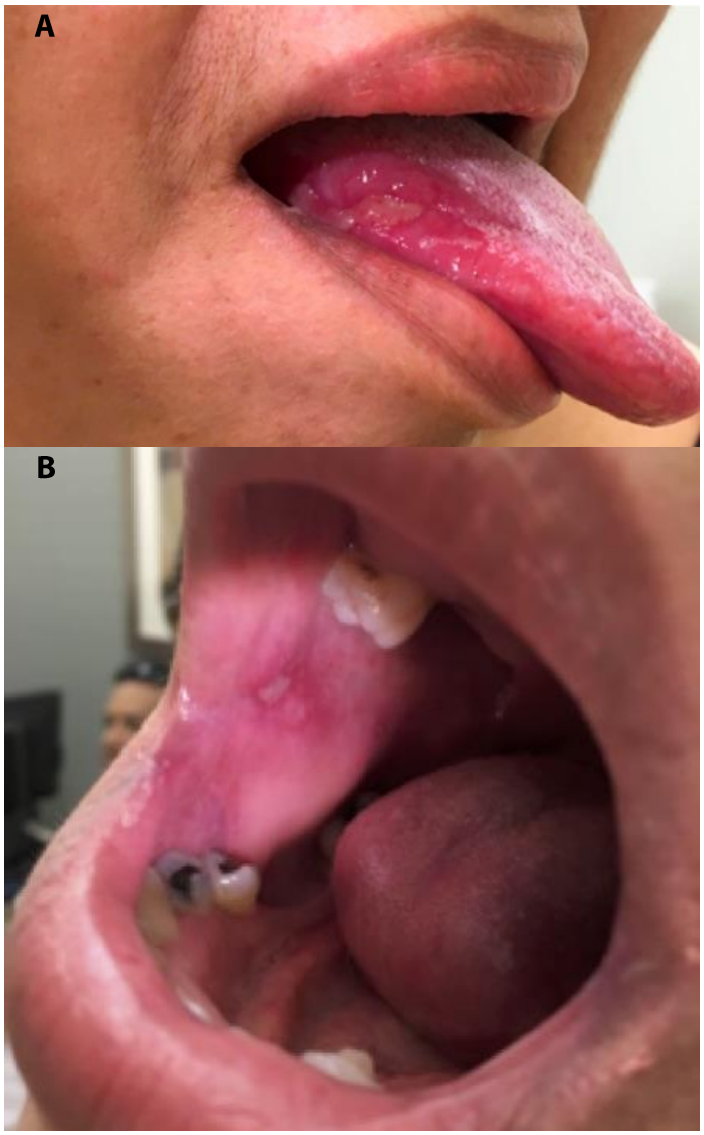
Keywords: paraneoplastic pemphigus, stomatitis, desmoglein, desmoglein compensation theory

Case Synopsis

A 50-year-old diabetic woman with no known history of malignancy presented to her primary care physician in December 2015 with tongue ulcerations and secondary dysphagia. After initial symptomatic management failed, she was referred to the dentistry department where a biopsy was performed. Hematoxylin and eosin staining revealed stratified squamous epithelium with parakeratosis, acantholysis, and suprabasilar clefting. The underlying inflammatory cell infiltrate was comprised of plasma cells, macrophages, lymphocytes, and focal neutrophilic aggregates. Direct immunofluorescence staining demonstrated intercellular positivity for IgG. These findings suggested a diagnosis of pemphigus vulgaris. She was started on dexamethasone oral solution and prednisone 20 mg PO with minimal improvement.

In May 2016, the patient presented to the dermatology department where physical exam demonstrated no ulcerations or erosions of the oropharyngeal mucosa or lips. However, given persistent odynophagia and oral pain, a pemphigus panel was ordered to assess antibody titers and disease activity. ELISA testing for Dsg1 and Dsg3 was negative. However, indirect immunofluorescence (IIF) to monkey esophagus, ordered as part of a routine pemphigus panel, was positive, suggesting the presence of other IgG antibodies. Subsequent work-up revealed a positive indirect immunofluorescence to transitional rat bladder epithelium (**Figure 1A**) and positive ELISA for envoplakin and periplakin antibodies. Additionally, a Western blot was completed using cultured human keratinocyte extract as an antigenic substrate, which was remarkable for envoplakin and periplakin, confirming the diagnosis of paraneoplastic

pemphigus (**Figure 2B**). At follow-up visits in June and July 2016, physical exam demonstrated shallow ulcerations of the right lateral tongue and buccal mucosa with sparing of the majority of the oropharynx and the entirety of the labial mucosa (**Figure 1A, B**). A cancer work-up was initiated including a PET scan demonstrating a 13×11×9 cm soft tissue mass in the uterine position, although the patient was post hysterectomy. The mass was heterogenously hypermetabolic, SUV max 5.72 and suspicious for neoplasm. Biopsy yielded the diagnosis of an extranodal follicular dendritic cell sarcoma.



Figures 1. *Patient presented with oral erosions involving the right lateral tongue* **(A)** *and buccal mucosa* **(B)**.

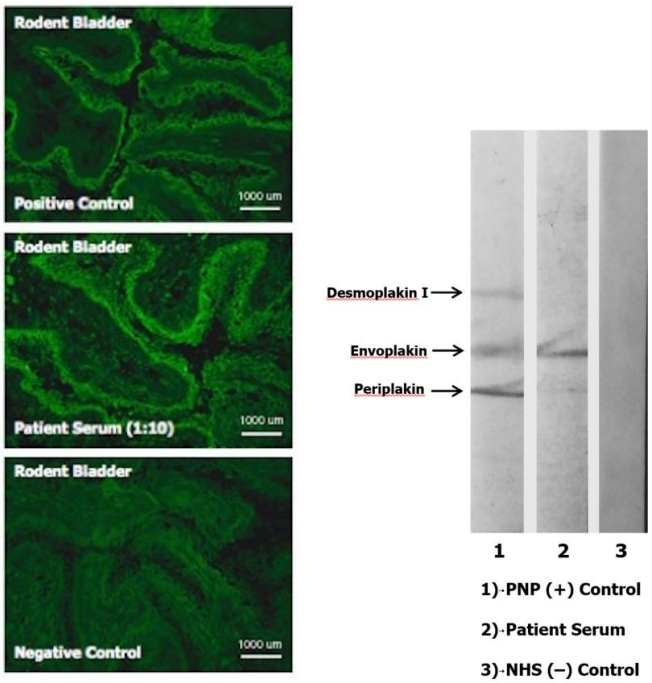


Figure 2. *Indirect immunofluorescence (IIF) and immunoblot of the patient's serum. (A) Autoantibody in the patient's serum reacted with the transitional epithelium of rat bladder at dilution of 1:10 using specific anti-human IgG conjugate. (B) Immunoblot studies were performed using cultured human epidermal keratinocyte extract as an antigenic substrate. The patient's serum demonstrated strong immunoreactivity with envoplakin and faint immunoreactivity with periplakin bands as it is shown in the lane 2. Lane 1 was developed with a sample of paraneoplastic pemphigus serum, while lane 3 shows normal human serum.*

Case Discussion

Our patient's initial clinical presentation and routine histopathological findings suggested a diagnosis of pemphigus vulgaris. Additional work-up ultimately led to a diagnosis of paraneoplastic pemphigus. Had additional testing not been pursued, her otherwise asymptomatic sarcoma may have remained undiagnosed. Our patient is not the only case in which a presentation of paraneoplastic pemphigus overlapped with pemphigus vulgaris. A recent report detailed a case of cutaneous blistering initially diagnosed as pemphigus vulgaris. When a chest X-ray obtained during a TB work-up revealed a mediastinal mass, more extensive testing was pursued including ELISA that proved to be negative for anti-desmoglein 1 and 3 antibodies, but positive anti-envoplakin antibodies. This mass was later resected and pathology was consistent with

Castleman disease [1]. Further, in a study of 88 patients with paraneoplastic pemphigus, 27% initially presented with mucosal only lesions, thus highlighting the importance of distinguishing between these two entities [2]. Although the exact number of paraneoplastic pemphigus cases initially diagnosed as pemphigus vulgaris is unclear, there may be value in performing a more thorough work-up, including ELISA and IIF staining, in difficult to treat cases of PV or in cases where diagnostic testing results in inconclusive data. Indeed, diagnostic proficiency in paraneoplastic pemphigus is paramount as morality rates exceed 90% [3].

Furthermore, our patient is unique as she was negative for antibodies against both desmoglein 1 and 3 by ELISA. A key to understanding the role of autoantibodies in disease initiation and progression is to determine the binding sites, or epitopes, they recognize. Epitopes are generally divided in two categories, linear epitopes, in which a sequence of amino acids are sufficient for binding and conformational epitopes, in which key amino acid residues are brought together by protein folding. One of the possible explanations for negative ELISA results in this case is that the patient's circulating autoantibodies recognized only conformational epitopes on desmoglein 1 and 3, which are not present on recombinant proteins. Additionally, the role of anti-desmoglein antibodies in paraneoplastic pemphigus has been recently questioned. Previously, desmoglein 3 was thought to play a central role in the pathogenesis of paraneoplastic pemphigus [4]. However, not every case of paraneoplastic pemphigus is positive for desmoglein 3 antibodies. In one study of 104 patients with paraneoplastic pemphigus, 14.4% were negative for desmoglein 1 and 3 antibodies [2]. Further, in a study of 21 cases of paraneoplastic pemphigus, one patient lacked antibodies to both desmoglein 1 and 3. Only 12 of these 21 patients showed a link between the antibody profile and the clinical exam findings, suggesting that the desmoglein compensation theory may not always hold true in paraneoplastic pemphigus [5].

The desmoglein compensation theory has also been questioned in pemphigus vulgaris and foliaceus. The theory explains that desmoglein 3 can be isolated in sera of patients with mucosal-dominant pemphigus vulgaris, whereas in mucocutaneous pemphigus vulgaris antibodies against both desmoglein 1 and 3 can be isolated. These differences in antibody expression profiles have been correlated to the pathophysiology as well as to the variation in clinical manifestations between pemphigus vulgaris and pemphigus foliaceus [6]. However, others have reported a case of pemphigus foliaceus, which was positive for desmoglein-3 but negative for desmoglein-1 antibodies [7]. Additionally, there have been cases that clinically appeared consistent with pemphigus vulgaris yet lacked antibodies against desmoglein 3 and were positive for antibodies against desmoglein 1 [8]. These cases that digress from the desmoglein compensation theory require closer examination. Patients who present clinically as pemphigus vulgaris and ultimately lack antibodies to desmoglein 1 and 3 may have autoantibodies against different antigens present in the skin or may represent alternative pathologies, such as paraneoplastic pemphigus.

As these core tenets of our understanding of pemphigus are challenged, the utility of routine ELISA and IIF in pemphigus seems twofold. One, clarifying the antibody profile in cases that are not straightforward may help elucidate the diagnosis. Further, characterizing the antibody profile in these cases may provide opportunities to further our knowledge and provide a deeper understanding of pemphigus pathophysiology.

References

1. Lonowski S, Goldbach H, Holland V. Atypical laboratory presentation of paraneoplastic pemphigus associated with Castleman disease. *JAAD Case Rep.* 2017; 3(2):138-139. [PMID: 28367488].
2. Ozhono A, Sogame R, Li X, Teye K, Tsuchisaka A, Numata S, Koga H, Kawakami T, Tsuruta D, Ishii N, Hashimoto T. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. *Br J Dermatol.* 2015;173(6):1447-1452. [PMID: 26358412].
3. Nousari HC, Detrding R, Wojtczack H, Aho S, Uitto J, Hasimoto T, Anhalt G. The mechanism of respiratory failure in paraneoplastic pemphigus. *N Engl J Med.* 1999;340(18):1406-1410. [PMID: 10228191].

5. Amagai M, Nishikawa T, Nousari HC, Anhalt GJ, Hashimoto T. Antibodies against desmoglein 3 (pemphigus vulgaris antigen) are present in sear from patients with paraneoplastic pemphigus and cause acantholysis in vivo in neonatal mice. *J Clin Invest*. 1998;102(4):775-782. [PMID: 9710446].

6. Ohyama M, Amagai M, Hashimoto T, Nousari HC, Anhalt GJ, Nishikawa T. Clinical phenotypes and anti-desmoglein autoantibody profile in paraneoplastic pemphigus. *J Am Acad Dermatol*. 2001;44(4):593-598. [PMID: 11260531].

7. Mahoney MG, Wang Z, Rothenberger K, Koch P, Amagai M, Stanley JR. Explanations for the clinical and microscopic localization of lesions in pemphigus foliaceus and vulgaris. *J Clin Invest*. 1999;103(4):461-468. [PMID: 10021453].

8. Carew B, Wagner G. Cutaneous pemphigus vulgaris with absence of desmoglein 1 autoantibodies. An example of extended desmoglein compensation theory. *Australas J Dermatol*. 2014;55(4):292-295. [PMID: 25399788].

9. Koga H, Ohyama B, Tsuruta D, Ishii N, Hamada T, Dainichi T, Natsuaki Y, Sogame R, Fukuda S, Karashima T, Tada J, Yamashiro M, Uezato H, Chan PT, Hashimoto T. Five Japanese cases of antidesmoglein 1 antibody-positive and antidesmoglein 3 antibody-negative pemphigus with oral lesions. *Br J Dermatol*. 2012;166(5):976-980. [PMID: 22242828].