BRIEF ARTICLES

Pemphigus Vulgaris Following Influenza: A Case Report

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ABSTRACT

Viruses have long been implicated as potential triggers of autoimmune disease. In the case of pemphigus vulgaris, members of the herpesviridae family are often associated with its development. There have also been reports of pemphigus being triggered by the influenza vaccine. We report a case of a 17-year-old male who developed mucous membrane-predominant pemphigus vulgaris after testing positive for the influenza virus and discuss proposed hypotheses for the association between viral infections and autoimmunity, such as molecular mimicry and epitope spreading.

INTRODUCTION

The association between viral infection and autoimmune disease is well-recognized in the literature.[1,2,3] In the case of pemphigus vulgaris, members of the herpesviridae family, including HSV, CMV, VZV, EBV, and HHV-8, have long been implicated. There are several hypotheses as to how viruses can react against keratinocyte proteins and induce autoimmune acantholysis seen in pemphigus. The association between viruses may be causal, may be due to molecular mimicry of viral and host proteins, or may be due to exposure of previously hidden host proteins after virus-induced tissue damage.[3]

CASE REPORT

We report a 17-year-old male who presented with a case of mucosal-predominant pemphigus vulgaris temporally associated with influenza virus infection. The patient initially presented with fever and a sore throat for three days duration. He tested negative for strep throat, but positive for influenza via a rapid influenza diagnostic test. He was prescribed oseltamivir; however, he did not take this or any other medications to treat the influenza. Over the next several weeks, he began to develop progressive oral ulcers until the entire oropharynx was involved with resultant poor oral intake and associated weight loss. He also developed waxing and waning conjunctival injection and ocular pain during this time. He denied any associated joint pains, genital ulcers, urinary changes, vision changes, or skin rash. There was no family history of autoimmune disease. He

also denied taking any medications prior to or during this time.

His symptoms progressed over a period of six weeks at which point he presented again to his primary care physician for further evaluation. The patient had a thorough yet unrevealing autoimmune and infectious workup (Table 1). He was then sent for direct admission to the hospital for consultation of dermatology, gastroenterology, ophthalmology, and allergy and immunology. On physical exam he had extensive coalescent ulcerations and erosions along the buccal mucosa, soft palate, and posterior oropharynx. In addition, the patient had hemorrhagic, crusted ulcerations on his upper and lower lip (Fig. 1). His conjunctivae were injected with no drainage or crusting. No intact vesicles or bullae were appreciated. There was no skin involvement noted. An infectious workup for CMV, HSV, and *Mycoplasma pneumoniae* was negative. The patient underwent EGD, which revealed extensive ulceration throughout the esophagus. Biopsies of both the mucosal lip (Fig. 2) and esophagus were obtained and revealed similar findings of full thickness and suprabasal acantholysis with maintenance of the attachment of the basal cell to the basement membrane, imparting a "tombstone" appearance. Significant dyskeratosis and cytopathic viral effect were absent. The subepithelial region showed a mixed infiltrate of lymphoid cells and eosinophils. Direct immunofluorescence taken from the lower lip showed weak deposits of IgG1 and IgG4 in the intercellular areas of the epithelium. Serologic testing revealed an elevation in desmoglein 3 (Table 1), consistent with pemphigus vulgaris with mucosal predominance.

After the diagnosis was confirmed, we placed the patient on 125mg/day of IV methylprednisolone. He experienced gradual improvement in his ulcers, conjunctival injection, and oral intake over the next few days. He was transitioned to oral prednisone prior to hospital discharge. At outpatient follow-up, he was started on dapsone in addition to systemic steroids, however after several weeks he did not demonstrate adequate improvement and thus the dapsone was discontinued and he was placed on azathioprine. Several attempts at tapering the steroid were made with worsening of disease. After an adequate trial of azathioprine, this medication was stopped, and he was started on mycophenolate mofetil, while still on high-dose systemic steroids, with plans to initiate rituximab.

Figure 1. Erosions and crusted ulcerations of the upper and lower mucosal lips.

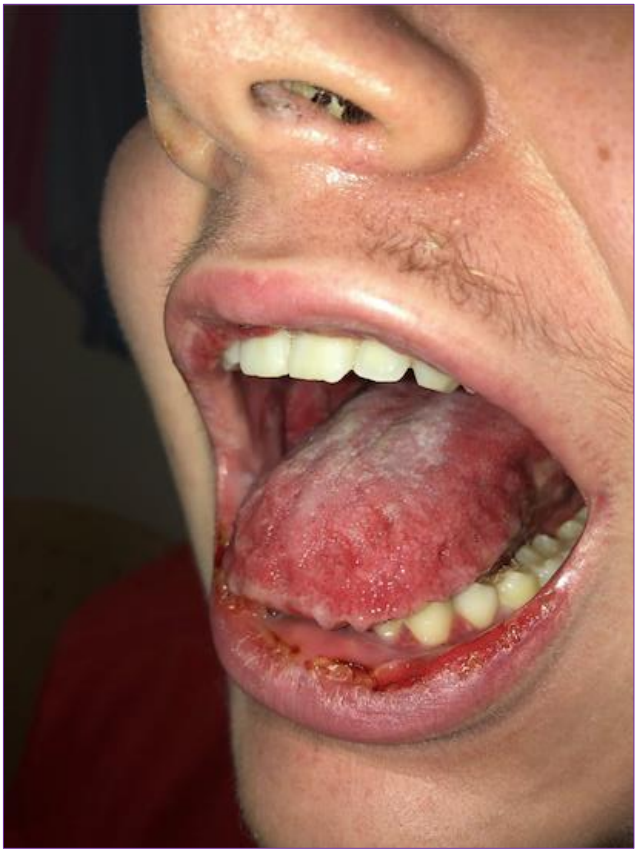

Figure 2. Punch biopsy from the mucosal lip showing suprabasilar acantholysis without dyskeratosis, creating a "row of tombstones" appearance (hematoxylin-eosin stain).

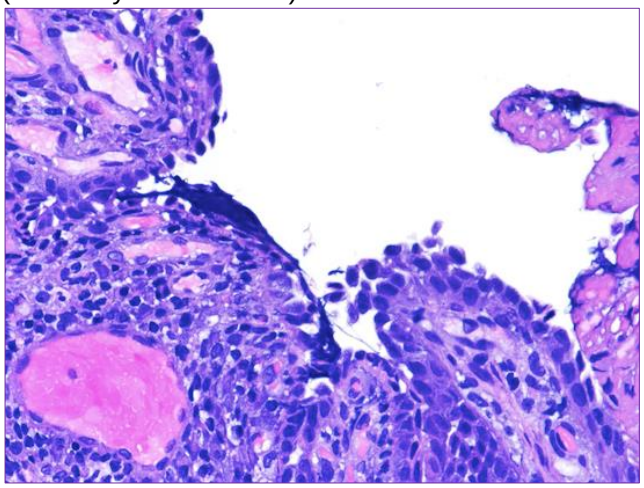

Table 1. Laboratory values from patient workup

Laboratory Test	Result	Reference Range
ESR	6 mm/hr	0-20 mm/hr
CRP	<0.5 mg/dl	0.0-0.99 mg/dl
ANA	Negative	--
M. pneumoniae Ab IgG	0.90 U/L	≤ 0.09 U/L
M. pneumoniae Ab IgM	0.03 U/L	≤ 0.76 U/L
DFA for HSV	Negative for HSV	--
HSV PCR (oral swab)	Not detected	--
HSV PCR (left eye swab)	Not detected	--
Hepatitis C Antibody	Non-reactive	--
Hepatitis B Surface Antibody	Non-reactive	--
Hepatitis B Surface Antigen	Non-reactive	--
Hepatitis B Core Antibody	Non-reactive	--
Respiratory panel*	Negative	--
Urine culture	No growth 2 days	--
Blood culture	No growth 5 days	--
Desmoglein 1 IgG	5 U	Positive: >20 U Borderline: 14-20 U Negative: <14 U
Desmoglein 3 IgG	210 U	Positive: >20 U Borderline: 9-20 U Negative: <9 U
Bullous Pemphigoid Antigen 180 kDa IgG	1 U	Positive: ≥ 9 U Negative: < 9 U
Bullous Pemphigoid Antigen 230 kDa IgG	2 U	Positive: ≥ 9 U Negative: < 9 U

*Tested by PCR for adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus NL63, coronavirus OC43, human metapneumovirus, human rhinovirus/enterovirus, influenza A, influenza A H1, influenza A H1-2009, influenza A H3, influenza B, parainfluenza 1,2,3,4, RSV, *Bordetella pertussis*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*

DISCUSSION

The immunopathogenesis of pemphigus has not been well-described, but it is thought to develop from interactions between genetic and environmental factors. Environmental factors described in the literature include stress, drugs, hormones, tumors, trauma, vaccinations, and of particular interest in this case, viral infections. It has been hypothesized that a virus can induce pemphigus in a number of different ways including through epitope spreading and molecular mimicry.

In epitope spreading, an inflammatory process may cause tissue damage such that proteins that were once hidden become exposed to the immune system, leading to a secondary autoimmune response. During a

viral infection, epitope spreading may occur when interferons lead to macrophage-mediated tissue damage with subsequent exposure to keratinocyte proteins. This exposure then induces an autoimmune response that results in pemphigus.[4,5] Supporting this theory, interferon treatment has been shown to induce both pemphigus and other autoimmune bullous diseases.[6,7,8] Epitope spreading may also explain how patients with mucosal-predominant pemphigus go on to develop skin lesions. The desmoglein 3 autoantibodies may lead to tissue damage and an exposed secondary epitope, desmoglein 1. Autoantibodies then develop to desmoglein 1 resulting in the blistering skin lesions seen in pemphigus.[4]

Molecular mimicry is another possible mechanism through which viruses and pemphigus may be related. It occurs when viral fragments, processed by antigen presenting cells, closely resemble host proteins. This leads to the viral immune response cross-reacting with host tissues.[3,5]

Given the high specificity of rapid influenza diagnostic tests (90%-95%)[9] and thus low false-positive rate, we believe this was a true case of influenza preceding the onset of pemphigus vulgaris. There have been reports in the literature of pemphigus being induced by the influenza vaccine[10,11] and a report of mucocutaneous pemphigus occurring after life-threatening H1N1 infection.[12] Taken together with the present case, we propose that influenza virus may be another potential viral trigger for pemphigus vulgaris.

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