QUIZ SECTION

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Painful Mucocutaneous Blistering in a Young Male Patient: A Quiz

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A 22-year-old man from Kosovo presented to the dermatology clinic with a 9-month history of violaceous erosive blistering of oral mucosa and the scalp. He reported that symptoms had started spontaneously during army training. PCR testing performed by the local physician was positive for HSV-1. Thus, systemic treatment with valaciclovir for 10 days was initiated. However, symptoms persisted despite virostatic treatment, food intake and dental hygiene became more difficult, and after 2 months the patient was hospitalized with superinfection of the oral mucosa and weight loss of 13 kg. Systemic and local antibiotics, virostatics and high dose steroids led to partial regression of the lesions and the patient was transferred to the department of dermatology for further investigation. Oral examination revealed multiple tender ulcers with non-adherent white-yellowish pseudomembranes leaving an erythematous area that bled on palpation. On the scalp several crusted erosions were noted with a positive Nikolsky sign (radial extension of the blister upon applying tangential pressure) (**Fig. 1**).

What is your diagnosis?

Differential diagnosis 1: Pemphigus vulgaris
Differential diagnosis 2: Herpes simplex
Differential diagnosis 3: Paraneoplastic bullous pemphigoid
Differential diagnosis 4: Bullous Lupus erythematosus

See next page for answer.

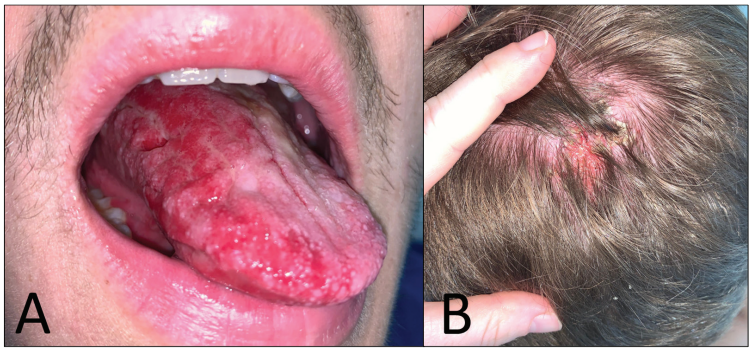

Fig. 1. (A) Haemorrhagic, erythematous erosions of the oral mucosa on the tongue and (B) multiple tender, crusted ulcers on the scalp.

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ANSWERS TO QUIZ

Painful Mucocutaneous Blistering in a Young Male Patient: A Commentary

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Diagnosis: **Pemphigus vulgaris**

Two biopsies from the scalp were performed and submitted for histopathologic analysis. Haematoxylin-eosin (HE) staining of the lesion revealed an ulceration acantholysis of the interfollicular epidermis and the epithelium of the hair follicle. Basal keratinocytes remained attached to the basement membrane, creating a characteristic "tombstone pattern" (Fig. 2). Immunohistochemical staining was negative for HSV and VZV, and Brown–Brenn staining (modified Gram staining) revealed no bacteria (Fig. 3). Direct immunofluorescence of perilesional skin showed intercellular deposits of IgG and C3 in the epidermis in a "chicken wire/fishnet pattern" (Fig. 3). Enzyme-linked immunosorbent assay (ELISA) showed elevated anti-desmoglein 3 IgG autoantibodies and anti-intercellular substance autoantibodies (anti-ICS Ab), confirming the diagnosis of pemphigus vulgaris. Systemic glucocorticoids were given followed by rituximab and azathioprine with satisfactory response.

Pemphigus vulgaris is one of the rare autoimmune disorders with intraepithelial blisters involving the skin and mucous membrane. The term "*pemphigus*" originated from the Greek word Pemphix (bubble or blister) (1). It is a very rare disease with a prevalence of 0.1–0.5 cases per 100,000 inhabitants per year (1) and both sexes are equally affected (2). Ashkenazi Jews and patients with DQB1*0503 as well as DRB1*0402 alleles have been found to have an increased incidence of PV with an average onset between the ages of 40 and 60 years (3). Furthermore, environmental factors in addition to diet, stress, medications, radiation therapy, allergens, and viral infections may all induce immune dysregulation leading to a flare of PV (4). The characteristic pathology of the disease and the immunofluorescence findings suggest that immunoglobulin G (IgG) autoantibodies against desmoglein Dsg 3 (Dgs3) (130 kD glycoprotein) and Dsg1 (160 kD antigen) initiate the destruction of cell–cell adhesions between stratified keratinocytes leading to intraepidermal acantholysis (5) causing painful vesicles, erosions, or bullae on erythematous or normal-appearing skin (3). According to the clinical presentation of PV other vesiculobullous skin disorders including erythema multiforme, bullous impetigo, linear IgA disease, epidermolysis bullosa, mucous membrane pemphigoid, bullous pemphigoid, paraneoplastic pemphigus, and acute herpetic gingivostomatitis need to be ruled out (6).

An important learning point of our case is that a positive PCR test result for HSV does not exclude pemphigus vulgaris but may delay the correct diagnosis and treatment. There is published literature discussing an association of herpes simplex virus (HSV) with severe, persistent, recalcitrant pemphigus lesions and also with exacerbations and relapse of pemphigus (7). Since Krain et al. (8) first noted the possible role of viruses, especially herpes simplex virus (HSV) in the pathogenesis of pemphigus in 1974, numerous case reports have described an association between pemphigus and viral infections (mainly from the herpetoviridae family) (9). There are several possible explanations for an association of pemphigus with HSV. It may be an opportunistic infection in a setting of the immunosuppressive therapy

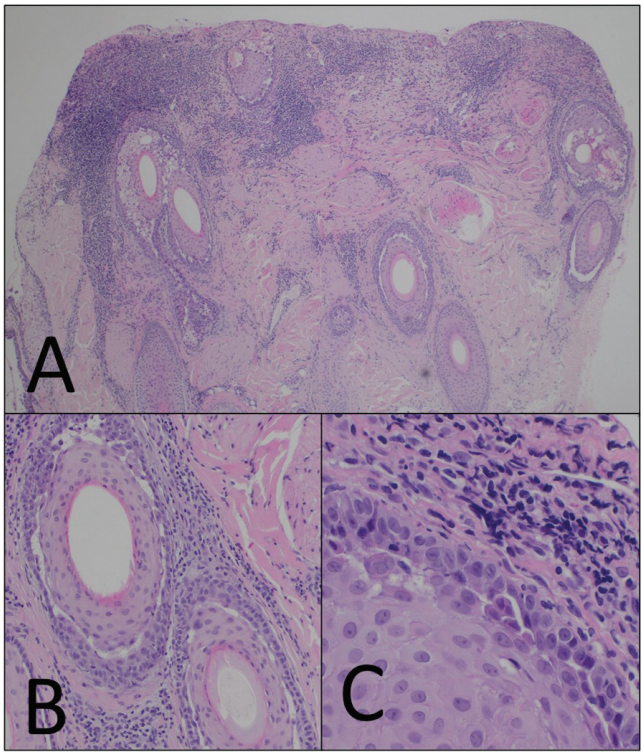

Fig. 2. Ulceration of the scalp with dense inflammatory infiltrate and intraepidermal acantholysis down the hair follicle epithelium: (A) haematoxylin and eosin [HE] 50x magnification, (B) inset 200x magnification, (C) inset 400x magnification.

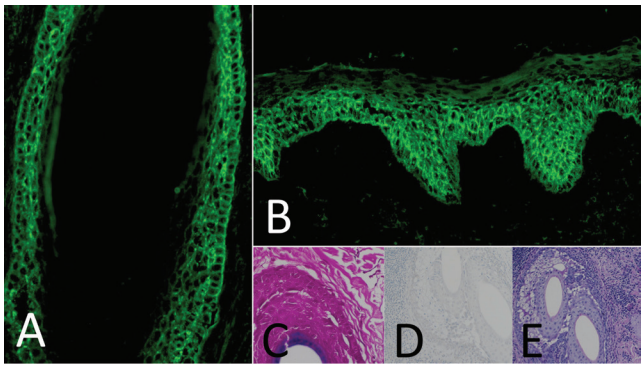

Fig. 3. Direct immunofluorescence of perifollicular skin. (A) Immunoglobulin G autoantibodies in the intercellular spaces in a "chicken wire/fishnet" appearance (100x magnification); (B) perilesional skin showing intercellular deposition of complement 3 (C3) (100x magnification); (C) Brown–Brenn staining showed no skin resident bacteria (200x magnification); (D) no herpes simplex virus was detected by immunostaining (200x magnification); (E) periodic acid–Schiff (PAS) staining revealed no fungal elements (100x magnification).

of pemphigus. However, a positive HSV-PCR test of the oral mucosa may also be a coincidence of asymptomatic viral shedding (without signs of infection) in the same anatomic area as pemphigus vulgaris. Asymptomatic HSV shedding in clinically unaffected skin of the perioral region is a common phenomenon (9). Some cases, similar to our patient, were reported in which the viral infection was diagnosed before the pemphigus eruption; in those cases, it has been speculated that the virus might trigger pemphigus by upregulating and increasing the production of humoral and cellular factors that contribute to the development of the disease (10).

In summary, our case seeks to emphasize that a positive HSV test result of the mouth or perioral region does not exclude pemphigus vulgaris and should not impede and delay the correct diagnosis. Pemphigus vulgaris is still a life-threatening autoimmune disease requiring systemic immunosuppressive therapy.

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