LETTERS TO THE EDITOR

Delayed immunologic evidence in pemphigus vulgaris

Editor

Any proper diagnosis of pemphigus vulgaris is supported by the combination of clinical aspects, a histological examination via biopsy, an assay of serum antibody titres by indirect immunofluorescence (IIF) and an enzyme-linked immunosorbent assay (ELISA) to detect antibodies against desmoglein 1 and 3 (Dsg 1/3).[1] Controversial is the diagnostic value of the direct immunofluorescence (DIF) performed on fresh specimens. DIF might be a more reliable tool for reaching a sure diagnosis in pemphigus vulgaris cases[2] and, perhaps, any other autoimmune muco-cutaneous blistering diseases (AMBDs), where there has been a lengthy period of negative IIF and ELISA testing.

In July 2005, a 24 year-old woman was referred to our Oral Medicine Unit for desquamative gingivitis at the gingiva of the anterior lower teeth. The lesions were painful and persistent and, in September 2005, started spreading to the tongue (Fig. 1a) and upper gingival fornix (Fig. 1b), showing a positive Nikolsky's sign. She was skin lesion-free. An oral biopsy for histology,

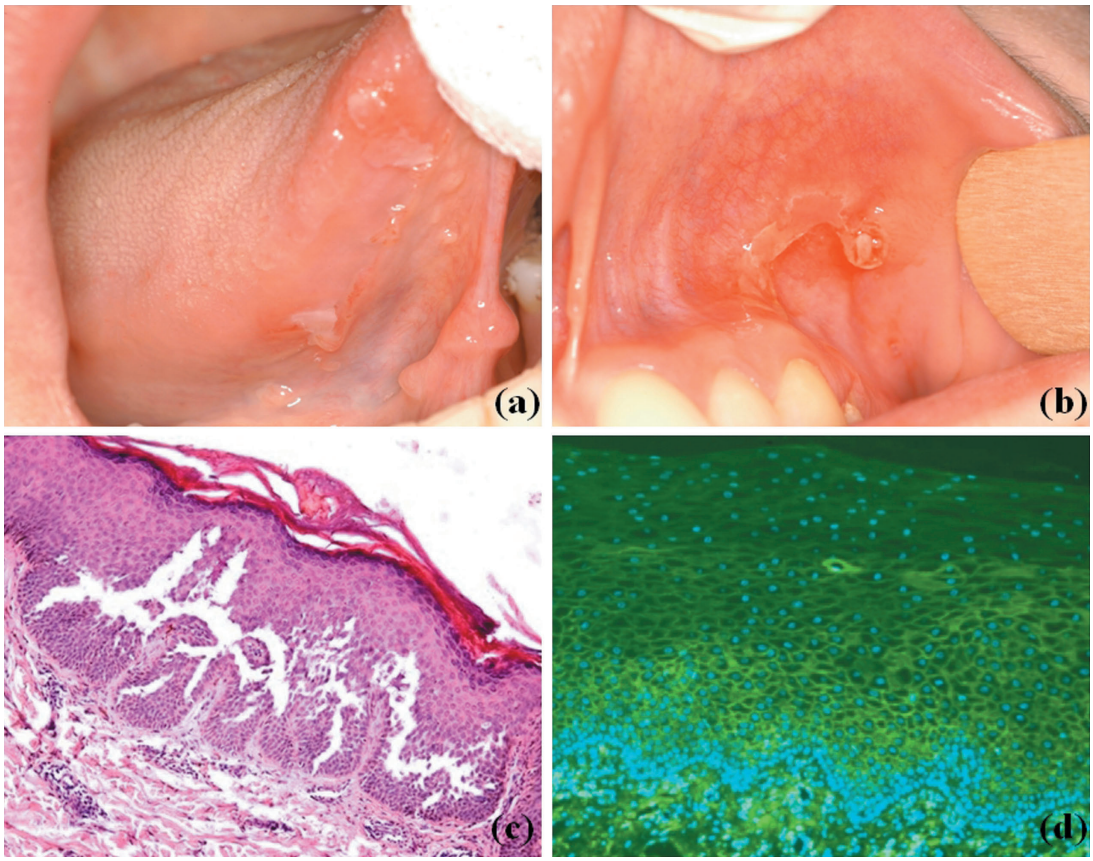

Figure 1 (a) Bullous-erosive lesions of the right ventral side of the tongue and (b) of the left upper gingival fornix. (c) Suprabasal acantholytic bullous lesion with hyperplasia of epithelial crests and focal aspects of 'en mass' acantholysis with an underlying corium rich in a mixed inflammatory infiltrate (haematoxylin–eosin, magnification ×100). (d) DIF, after 1 year, showed a clear intercellular signal.

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DIF, IIF using monkey oesophagus as the preferred substrate and ELISA testing for Dsg 1/3 were performed. Histology with haematoxylin/eosin revealed acantholysis and a prominent eosino-neutrophilic infiltrate, suggesting possible pemphigus vulgaris. Unfortunately, DIF did not show any immunoglobulins, and complement staining, IIF and ELISA testing were also negative.

Throughout 2006, we performed IIF and ELISA tests three times and DIF twice, but the results were still negative. Since no inducing or triggering risk factors were found, and since the histological aspect appeared similar to a dilapidated brick wall (clumped acantholytic cells with a few intact intercellular bridges holding the keratinocytes together; Fig. 1c), our differential diagnosis included a Hailey–Hailey Syndrome. We performed a genetic analysis for the *ATP2C1* gene, but no mutation was detected. We therefore decided to give her topical steroids, obtaining a partial clinical remission.

In January 2007, we performed a new biopsy for histology and DIF. Even though the IIF and ELISA tests were still negative, conversely DIF showed a positive fluorescence for intercellular cement substance, with the classic 'net-like' aspect (Fig. 1d). IgG was positive, while IgA, IgM and C_{3C} were negative. Thus, we made a diagnosis of pemphigus vulgaris and treated the patient with conventional immunosuppressive therapy (75 mg/day of prednisone and 100 mg/day of azathioprine) for 3 months, thereby gaining complete clinical remission.

The diagnostic protocol of AMBDs envisages the use of histopathology, DIF, IIF and Dsg 3 – ELISA testing, which was found to be a highly specific and useful diagnostic tool for pemphigus vulgaris.[3] Different studies have emphasized that IIF and ELISA tests are indispensable for a correct sero-diagnosis of pemphigus vulgaris, underlining that ELISA tests proved to be slightly more sensitive than IIF,[4] which is in turn more sensitive than immunoblotting.[5]

Our case highlights the likelihood that pemphigus vulgaris may flare up in a 'silent' immunological pattern, confirming previous observations[6] and be sero-negative over an indeterminate period of time, thus making a correct diagnosis very difficult. We therefore recommend performing DIF and serologic analysis several times, since an immunological response might be unmasked later on. Indeed, in our case, DIF became positive after 1 year, whereas the IIF and ELISA test still remained negative, so that the combination of clinical, histological and DIF findings were sufficient to support the diagnosis of pemphigus vulgaris.

It's likely that a prolonged negative immunological response was due to a titre so low as to be undetectable by our tests, but capable of inducing clinical manifestations of pemphigus vulgaris, or that an unknown non-immunological acantholytic mechanism might have revealed pathogenic epitopes of Dsg 3, triggering an autoimmune humoral response later on. Nonetheless, since no evidence is present in the literature to support this hypothesis, further investigations need to be performed.

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DOI: 10.1111/j.1468-3083.2008.03084.x

Clarithromycin-induced Hoigne syndrome in a patient treated for rosacea

Editor

Hoigne syndrome (also called antibiomania) is an uncommon condition usually presents as an acute psychiatric disorder following the administration of antimicrobials.[1,2] Although commonly used, antibiotics induced psychiatric reactions are infrequent, rarely seen in dermatologic setting. We present a case of clarithromycin-associated Hoigne syndrome.

A 37-year-old female with rosacea, unresponsive to a 2-month course of minocycline and topical metronidazole, was referred to our department. At the time of the examination, she had multiple telengiectasias, diffuse erythema and several inflammatory papules on the nose and cheeks. She did not receive any medication and she had no known neurologic or psychiatric disorder. According to family history, her mother had also rosacea.

She was prescribed clarithromycin 500 mg twice daily, and after the third dose, she presented confusion, sleep disturbance and disorganized thinking with auditory hallucinations. She was also hyperactive and tearful. Clinical examination, laboratory tests including thyroid levels and toxicology and computer tomography of brain were unremarkable. She underwent psychiatric evaluation, and clarithromycin was discontinued. A significant improvement in patient's mood was seen 2 days after the cessation of clarithro-