Management of pemphigus
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2002

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter VII

Transition of pemphigus vulgaris into pemphigus foliaceus confirmed by antidesmoglein ELISA profile

Summary

We describe a case of transition from pemphigus vulgaris into pemphigus foliaceus accompanied by distinct shift in anti-desmoglein antibody profile as detected by ELISA. The patient presented with painful oral erosions, later followed by flaccid blisters and erosions on the skin. A diagnosis of pemphigus vulgaris was made based on the typical clinical presentation and histopathology, immunofluorescence, and ELISA studies. Successful therapy consisted of daily prednisolone up to 60 mg, adjuvant dexamethasone pulse therapy and azathioprine. After a period of eight months in complete remission the patient presented again with a new solitary erythematous lesion on the scalp with crusted scales. Histology showed clefting of the granular layer with acantholysis. Apparently the pemphigus vulgaris had transformed into pemphigus foliaceus. This shift from PV to PF was accompanied by the disappearance of anti-desmoglein 3 (dsg3) antibodies and the re-occurrence of anti-desmoglein 1 (dsg1) antibodies as detected by ELISA.
Chapter VII

Introduction

The main subtypes of pemphigus, vulgaris (PV) and foliaceus (PF), are characterized by distinct clinical, histological, and autoantibody features. Pemphigus autoantibodies are directed against the extracellular domains of the desmosomal adhesion molecules desmoglein 1 and 3 (1;2).

Transformation between the subtypes PV and PF is rarely reported in the literature. Nevertheless, if such transformation does occur, then a shift from PV to PF is more common (3-9) than, vice versa, a shift from PF to PV (6;9;10). Until recently only western blot was available for determining serum antibody specificity but unfortunately immunoblotting is not very reliable in pemphigus. Due to the conformational character of part of the desmoglein epitopes many sera may give false-negative results for either desmoglein 1 or 3 or both. Recently, a transformation from PF to PV was confirmed by the desmoglein autoantibody profile as detected by ELISA (10). We present a case in which the shift from PV into PF was accompanied by disappearance of anti-desmoglein 3 and autonomous reappearance of anti-desmoglein 1, demonstrated by longitudinal follow-up.

Case report

In 1997, a 28-year-old Turkish man was referred to us with since 7 months painful lesions in the mouth, later followed by flaccid blisters and erosions on scalp, slowly spreading over the face and shoulders to the groins. Dermatological examination revealed positive Nikolsky sign’s I and II. Histopathological examination of a skin lesion showed suprabasal clefting and acantholysis (Fig IA). Direct IF revealed epidermal intercellular depositions of IgG antibodies in a fishnet pattern typical for pemphigus. Indirect IF on monkey esophagus demonstrated circulating IgG antibodies against the epithelial intercellular substance (ICS) at a titre of 1:320. The ELISA assay revealed high titres of anti-desmoglein 3 (dsg3) and anti-desmoglein 1 (dsg1) IgG antibodies. A diagnosis was made of pemphigus vulgaris based on the typical clinical presentation, histopathology, IF, and ELISA studies. Figure II shows disease activity, IF titre, anti-dsg1, and anti-dsg3 titres during the course of the disease.
Initial therapy was started with prednisolone 60 mg per day. After one week no new blisters developed, however Nikolsky sign I (on apparently normal skin) remained positive. Therefore intravenous dexamethasone pulse therapy (DP) with 200 mg dexamethasone on three consecutive days every month, was introduced. After one DP the patient reached initial control characterized by Nikolsky sign I becoming negative. A total of 5 DP’s was administered. Prenisolone was tapered until zero in 5 months. Four months after complete remission he developed new blisters on the scalp, and in the mouth. DP was restarted as monotherapy, and azathioprine 200 mg per day was added to remain disease control. In this phase a total of eight DP cycles were administered. Eight months after complete remission (7/1999) the patient presented with a new solitary lesion on the scalp consisting of erythema with crusted scales. Histology showed clefting of the
granular layer, with acantholysis (Fig IB). ELISA for circulating anti-desmoglein 1 IgG gave a positive index-value of 77, whereas anti-dsg 3 was negative (Fig II). Indirect IF remained low at titre 1:20 for anti-ICS IgG. The pemphigus vulgaris had transformed into pemphigus foliaceus. Topical clobetasol dipropionate cream was applied in addition to low-dose prednisolone without success. The patient did not suffer from the lesion on the scalp, and there was no disease progression. Treatment was not necessary.

**Figure II.** Disease activity, medication history, antidesmoglein 1 and antidesmoglein 3 IgG ELISA index-values, and indirect IF pemphigus titre in our patient with pemphigus during the course of disease. Disease activity is assessed on an ordinal scale with 0: no disease activity, 1: partial remission, and 2: exacerbation. ELISA index values are considered positive if exceeding 7 (desmoglein 3 ELISA) or 14 (desmoglein 1 ELISA) according the manufacturers protocol.
Discussion

Onset, progress, and transition of pemphigus depends on genetic, and exogenous factors. The development of antidesmoglein 1 antibodies in addition to antidesmoglein 3 antibodies in pemphigus vulgaris is not uncommon and correlates with disease progression from mucous membranes to skin (11). However, switching off antidesmoglein 3 antibodies in the presence of antidesmoglein 1 antibodies is uncommon and results in transition of PV into PF (2). The reason for the persistence of antidesmoglein 3 antibodies during the course of PV is unclear.

The disease period before transition may vary between 1-20 years (3). The shift from PV to PF has been reported before, in studies using immunoblot in which a shift from 130-kDa PV antigen (dsg3) to 160 kDa PF antigen (dsg1) was shown (3-5;7). Immunoblotting however, is not quantitative and often false-negative, and therefore the relation between disease activity and anti-dsg IgG titre cannot be assessed. ELISA using the ectodomains of respectively dsg1 and dsg 3 as substrates specifically measures in a quantitative way circulating autoantibodies against desmoglein 1 and 3.

A positive correlation between ELISA titers and indirect IF titers was found in 11 PV patients by Lenz et al (12). Aoyama et al. suggested to use the ELISA titre of anti-dsg 1 IgG for determining the initial therapy for PF (13). PF patients with low ELISA titre may be treated with topical steroids, whereas those with high titres with glucocorticoid pulse therapy.

Our patient developed PF with crusted scales on the scalp two years after the initial diagnosis of PV. The positive anti-dsg 1 and negative anti-dsg 3 ELISA titres, supported by the acantholysis in the upper epidermis confirmed the clinical shift into PF. Indirect IF titre remained at 1:20. In this case the ELISA values signaled us the shift in autoantibody response, and lead to a quick diagnosis, and also our choice for a milder treatment modality, since the course of PF (although sometimes chronic and refractory) is milder than in PV. Besides, this case demonstrated desmoglein 1 and 3 to change autonomously, demonstrated by the ELISA titres during a follow-up of 55 months.
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References