Comorbidities and Complications among Pemphigus patients: a retrospective cohort study

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Pemphigus is a chronic bullous disease with a poor prognosis, especially in case of a mucocutaneous involvement. Due to immune destruction of adnexal epithelial cells, skin and mucosal complications are frequent. We performed a retrospective cohort study based on medical records of 303 hospitalized pemphigus patients in the Dermatology department of Ibn Sina University Hospital between 1980-2020. Data collected include: age, history, mean duration of disease before consultation, bedridden duration, clinical phenotype, death. The mean age was 53 year-old, average duration of disease was 13.5 months, bedridden duration was 75 days, steroids were used in 55%, steroids + azathioprine in 45%. Among 303 patients: 42% developed complications, these were distributed as follows: 73.4% (50 cadillians, 36 herpes-simplex, 10 pseudomonas aeruginosa, 1 varicella-zoster, 7 Civid, 4 erysipelas, 20 patients died due to a severe septic shock), vascular 25.4% (9 venous thrombosis, 8 high blood pressure, 4 acute ischemic stroke), osteoradicular 18.2% (20 osteoporosis), endocrine dysfunction in 17.4% (12 diabetes, 10 Cushing syndrome), psychiatric and ocular complications in 8.7% each: mainly 10 depression, 7 cataract and 3 glaucoma. Patients with pemphigus vulgaris were more likely to develop complications (59 versus 35 pemphigus erythematosus). The risk of complications was closely related to pre-existing comorbidities: 10 patients with diabetes, 10 tuberculosis, 6 cardiovascular disease, 6 thyroid dysfunction, 2 atopic dermatitis, 1 hidradanite suppurativa, 6 neoplasms (1 ovary cancer, 1 breast cancer, 2 myelodyplasia, 1 neuroendocrine, 1 unknown cancer, 1 histiocytosis xanthogranuloma). Our findings demonstrated the role of anterior comorbidities, the late time of consultation and the long-term use of steroids in the promotion of various complications. A special care provided by a multi-disciplinary team is therefore required to prolong survival and improve the quality of life.

Human desmocollin 3-specific IgG antibodies are pathogenic in a humanized HLA-Clss II transgenic mouse model of pemphigus


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Pemphigus is a potentially lethal autoimmune bullous skin disorder, which is associated with IgG autoantibodies against desmoglein 3 (Dsg3) and Dsg1. Notably, a subset of pemphigus patients presents with a similar clinical phenotype in the absence of anti-Dsg IgG, suggesting the presence of serum IgG reactive with desmosomal components other than Dsg1 or Dsg3. We and others have previously shown that such patients have serum IgG autoantibodies against other desmosomal proteins. In addition, it was shown that loss of keratinocyte adhesion ex vivo. Moreover, Dsc3 hypomorphic mice show a severe blistering phenotype of the mucous membrane which is highly characteristic in pemphigus. These findings prompted us to study induction and regulation of anti-human Dsc3 IgG in humanized mice transgenic for HLA-DRB1*04:02, which is a highly prevalent haplotype in pemphigus. We here showed that IgG from sera of Dsc3-immunized mice leads to a significant proliferative response after local re-exposure to Dsc3. Epitope mapping yielded five putative binding sites within this domain. As 20B12 displays cross-reactivity to human skin and the murine and human BP230 protein show a high degree of homology, we hypothesized that 20B12 might induce their pathogenic phenotype through autocrine IL-9 signaling. 20B12 recognizes a Dsg3 epitope in the N-terminal domain of Dsc3. This N-terminal domain is not involved in keratinocyte adhesion and is expressed at high levels in the skin and in the localization of the autoantibody 20B12. Our findings suggest that induction of pathogenic anti-Dsc3 IgG is associated with Dsc3-specific T cells that recognize Dsc3 in association with HLA-DRB1*04:02.

Investigating the role of skin-resident T cells in pemphigus vulgaris in humans

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Pemphigus vulgaris (PV) is an autoimmune blistering disease, in which autoantibodies against desmogleins (Dsg) 1 and Dsg3 interfere with epidermal cell-cell adhesion, thereby causing blister formation and erosions of the skin and/or mucous membranes. Autoreactive Dsg-specific T cells play a central role in the PV pathogenesis. However, little is known about T cells in PV skin lesions and the detailed phenotypical and functional analysis is currently missing. Therefore, we aimed to comprehensively characterize T cells residing in lesional skin and to identify critical potential therapeutic targets.

Pathogenic murine anti-BP230 autoantibody 20B12: Elucidating the mechanism of blister formation

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In PV, pathogenic antibodies reacting against structural proteins of the skin cause severe skin diseases summarized as autoimmune bullous dermatoses (ABD). One model to study this group of diseases is the scurvy mouse model. These mice are lacking functional Tregs due to a disrupted production of the forkhead-box-protein 3 (Foxp3)-gene. Detailed analyses showed that Scurvy sera contain polyclonal antibodies against several ABD autoantigens. One of these Scurvy-derived mAb, called 20B12, induces blisters in vivo after injection into newborn mice and birds to the epidermal side of basement membrane zone (BMZ). In further analyses we identified the hemidesmosomal protein BP230 (Bullous Pemphigoid 230 or BPAG1-e), a cytoplasmic protein in basal keratinocytes, as the target antigen of 20B12. First, we used Western Blot analyses to confirm the binding site of 20B12 in the N-terminal domain of BP230. In subsequent experiments we showed that 20B12 reactivity is dependent on the expression of human skin and the murine BP230 protein show a high degree of homology. Furthermore, we investigated the expression pattern of the murine BP230. Western Blot and ELISA analyses, using fragments covering the five possible epitopes, indicate binding of 20B12 to the BP230 protein to the N-terminal domain of BP230. To further elucidate the pathomechanism of blisters we analyzed the involvement of complement system (CS) and Fc-receptors. Preliminary results of 20B12 injection into Fc−/− mice, which are resistant for induction of ABD, led us to hypothesize a unique Fc-receptor independent mechanism. Indirect immunofluorescence of 20B12 injected WT mice using anti-C3 antibodies yielded no C3 complement deposition at the BMZ suggesting a CS-independent mechanism. In summary, we mapped the binding of the pathogenic murine autoantibody 20B12 to the Scurvy receptor in 9 on the N-terminal domain of BP230 and have evidence for a CS- and Fc-receptor independent mechanism of blistering.