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 dysregulation, pathogenic T cells, in the skin, 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 included: age, history, mean duration of disease before consultation, bedridden duration, clinical phenotype, death. The mean age was 53 years, 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: 42.5% developed complications, 40% were distributed as follows: 75.4% (50 candidiasis, 36 herpes-simplex, 10 pseudomonas aeruginosa, 1 varicella-zoster, 7 C.vid, 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 14.3% (6 psychoses, 4 acute ischemic stroke), vascular 18.2% (9 venous thrombosis, 8 high blood pressure, 4 acute ischemic stroke), skin 17.4% (9 venous thrombosis, 8 high blood pressure, 4 acute ischemic stroke), vascular 25.4% (9 venous thrombosis, 8 high blood pressure, 4 acute ischemic stroke), psychiatric and ocular complications 14.3% (6 psychoses, 4 acute ischemic stroke), vascular 18.2% (9 venous thrombosis, 8 high blood pressure, 4 acute ischemic stroke), skin 17.4% (9 venous thrombosis, 8 high blood pressure, 4 acute ischemic stroke), psychiatric and ocular complications 14.3% (6 psychoses, 4 acute ischemic stroke).

Human desmocollin 3-specific IgG antibodies are pathogenic in a humanized HLA-CLass 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, we found that Dsg3 expression is induced in keratinocytes upon T cell stimulation, suggesting 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 multidisciplinary team is therefore required to prolong survival and improve the quality of life.

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 desmoglein 3 (Dsg3) and Dsg1 interfere with epithelial 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 a detailed phenotypical and functional analysis is currently missing. Therefore, we aimed to comprehensively characterize T cells residing in lesional and perilesional skin of PV patients as well as matched peripheral blood compared to healthy controls. Skin and peripheral blood samples were obtained from PV patients, healthy controls and from healthy volunteers. Immune cells were isolated from skin and blood by apheresis and flow cytometry. CD4+ and CD8+ T cells were stained with multiple antibodies against T cell markers. Then, T cell response was assessed by intracellular cytokine staining and proliferation assays.

Involvement of innate and adaptive immunity in the development of atopic dermatitis-like skin inflammation

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3Department of Dermatology (AD) is an inflammatory dermatosis associated with Staphylococcus aureus (S. aureus) diphtheris. The immunological mechanisms by which S. aureus contributes to AD remain poorly characterized. We developed a mouse model of AD-like skin inflammation induced by repeated applications of different clinical strains of S. aureus, to explore the role of innate and adaptive immunity in AD. The surface of the S. aureus-induced AD-like skin inflammation was characterized by the presence of activated mononuclear cells and neutrophils. The inflammatory response was also detected at local re-exposure to S. aureus, but only in mice with an altered skin barrier. This study demonstrates the complementary role of innate and adaptive immunity in the development of AD-like dermatitis after exposure to S. aureus.

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

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Pathogenic autoantibodies 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 vivo is the scurvy mouse model. These mice are lacking functional Tregs due to a mutation in the forkhead-box-gene 1 (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 found that the hemidesmosomal protein BP230 (Bullous Pemphigoid 230 or BP230-e1) is a cytoplasmic protein in basal keratinocytes, as the target antigen of 20B12. We also showed that 20B12 injection into mice with skin and the murine and human BP230 protein show a high degree of homology. We further investigated binding of 20B12 to human BP230 protein and its fragments. Western Blot and ELISA analyses, using fragments covering the five possible epitopes, indicate binding of 20B12 to the Spectrin repeat 9 in the N-terminal domain of BP230. To further elucidate the pathomechanism of blistering we analyzed the involvement of complement system (C5) and Fct-Receptors. Preliminary results of 20B12 injection into Fcy- Deficient mice revealed that 20B12-induced blister formation requires an Fcy-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 Spectrin repeat 9 in the N-terminal domain of BP230 and have evidence for a CS- and Fct-receptor independent mechanism of blistering.