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Treatment of pemphigus vulgaris with rituximab effective, but not harmless

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Background: Pemphigus vulgaris (PV) is a rare, potentially life-threatening autoimmune disease with a chronic relapsing course. The typical manifestation is characterized by fragile blisters and erosions of skin and mucosa, mediated by IgG autoantibodies targeting the transmembranous adhesion molecules desmoglein 1 and 3. The mainstay of therapy has been oral corticosteroids and second-line immunosuppressive or -modulating therapies. Rituximab, a chimeric monoclonal anti-CD20 antibody, has been reported to be effective in PV. Its use results in clinical remission and has a steroid sparing effect. However, as shown in one of our two cases, severe side effects, particularly infections, must be considered.

Observations: Case 1: A 50 year-old man presented with a 10y-history of PV with skin and painful mucosal lesions. The disease had a recalcitrant, relapsing course despite adequate treatment with systemic corticosteroids and azathioprine. As a result of femur head necrosis and hepatotoxicity this therapy regime was abandoned. The patient was then successfully treated with rituximab 375mg/m² weekly for 1 month. A complete remission was observed and could be maintained so far.

Case 2: A 34 year-old man presented with blisters on the skin as well as mucosal ulcerations, persisting for 2 years. The initial therapy with systemic corticosteroids and azathioprine lead to complete remission. After 12 months it came to a relapse of skin lesions. Finally, rituximab 375 mg/m² weekly, over 4 consecutive weeks, showed a successful clinical response. After the third infusion the patient developed an enterovirus meningitis. Due to this severe side effect rituximab was discontinued.

Conclusions: PV continues to be a challenging bullous dermatosis, although its mortality rate could be decreased by immunosuppressive treatment. There is increasing evidence of the efficacy of rituximab as a second- or third-line therapy in cases resistant to previous therapies. However potential severe side-effects can occur and must be considered.

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Periungual erythemas in HIV-seropositive patient

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Background: In HIV-infected patients mucocutaneous findings are frequent, so are viral, bacterial, fun-

gal and noninfectious etiologies. Some skin disorders are nearly exclusively found in HIV-seropositive individuals, such as Kaposi's sarcoma, oral hairy leukoplakia and bacillary angiomatosis, whereas others are also observed in general population.

Periungual erythemas in HIV-infected people have been described before, often associated with antibodies against HCV.

Observations: A 50-year-old, homosexual man presented with periungual erythemas, with redness of fingers and toes restricted to the distal parts. The lesions were painless and persistent for many years. The patient's personal history revealed, except for a fourthfold myocardial infarction at the age of 48 years, no other disorders. Further blood investigations showed a seropositive HIV-test, negative HCV antibodies and negative antinuclear antibodies.

Conclusions: Dermatologic manifestations are very common in HIV-infected patients and may be the first clue of infection. The exact cause of periungual erythemas is not known yet. It was speculated that the vascular reactions resulting in red fingers might be due to association of HIV infection and hepatitis viruses. In other studies erythemas of the proximal nailfold in HIV-positive patients have been described without underlying chronic disease other than HIV, like mentioned above.

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The interaction of plectin with intermediate filaments is modulated by phosphorylation of its carboxyl extremity by MNK2 and PKA

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Plectin is a versatile cytolinker, tethering the intermediate filament (IF) network to specific plasma membrane sites and organelles, thereby contributing to the maintenance of the cytoarchitecture and cell resilience in tissues such as the skin and skeletal muscle. Nevertheless, plectin-IF connections must be transiently regulated during processes involving a remodeling of the cell shape. Here, we have identified serine 4642 in the carboxyl extremity of plectin as an *in vivo* phosphosite. In various cell lines plectin phosphorylated at S4642 was less localized to IFs than the total pool of plectin. In cell wound healing assays, migrating cells had an increased level of plectin phosphorylated at S4642, whereas in the hemidesmosomes of the epidermis and cultured keratinocytes plectin was mainly unphosphorylated at S4642. Various binding assays revealed that phosphorylation of S4642 inhibits the binding of recombinant plectin proteins to various types of IFs. The phosphorylation level of plectin S4642 in HeLa cells was increased by various stimuli. By using specific protein kinase (PK) inhibitors we identified two different kinases responsible for phosphorylating plectin S4642, the MAPK-interacting kinase 2 (MNK2), downstream ERK1/2, and cyclic AMP-dependent PK

(PKA). Our data provide novel insights into the function of the carboxyl tail of plectin, whose genetic truncation causes severe epidermolysis bullosa, myopathy and central nervous system manifestations in affected patients, by revealing its key role in the regulation of plectin linkage to IFs.

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Baseline serum tryptase show increasing levels with age

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Background: An elevated basal serum tryptase concentration are regarded as risk factors for more severe anaphylactic reactions especially to Hymenoptera venom. The aim of this retrospective study was to determine to what degree serum tryptase concentrations depends on age or gender.

Methods: Basal serum levels of 3648 non-mastocytotic patients investigated at our unit were retrospectively analysed. Patients had their blood examination done due to a systemic anaphylactic reaction but with at least a one month interval due to the allergic event. Serum values were determined by a commercially available ELISA kit (FluoroEnzymelimmunoAssay ImmunoCAP®, Phadia AB, Uppsala, Sweden). Patients with elevated serum tryptase levels of ≥ 11.4 ug/l were analysed separately.

Results: Over all patients (mean age 42.3 years, range 5-79 year; 1980 females/58.51%), a mean value for serum tryptase of 6.38 ug/l was found. 3384 out of 3648 patients (92.76%) showed normal tryptase values < 11.4 ug/l (mean 4.24 ug/l). For this subgroup a significant increase of mean serum tryptase according to age was found ($p < 0.001$). Looking at sex-dependent differences values, a significant difference was measured as men reached higher mean tryptase values (4.48 ug/l) than women 4.07 ug/l ($p < 0.001$).

Conclusions: Age and gender should be considered when analysing serum tryptase levels; older and tend to have higher mean levels within normal ranges of basal serum tryptase. In our collective also males tend to have higher basal levels than female patients.

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Low baseline immunoglobulin titers to pneumococcal antigens are associated with higher frequency of infections

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Objectives: To assess the utility of pneumococcal polysaccharidic vaccine (PPV) in patients with inflammatory skin disorders treated with immunosuppressive drugs.

Methods: Observational study in outpatient setting. Inclusion criteria were: age ≥ 18 years, daily Prednisone equivalent of ≥ 20 mg and/or immunosuppressive treatment. Exclusion criteria were: previous vaccination with PPV, intravenous immunoglobulins and ongoing pregnancy. Serum immunoglobulin G (IgG) levels to six *S.pneumoniae* serotypes (14, 19, 23F, 9N, 11A, 17F) and total immunoglobulin levels by nephelometry. Seropositivity was defined as IgG $\geq 0,5$ mg/l for $\geq 4/6$ pneumococcal serotypes. Patients below this threshold at baseline received PPV. Vaccine response and tolerance was assessed after one month using the physician's global assessment (PGA) score and the 36-item short form health survey (SF-36) and in psoriatics by the Psoriasis Area and Severity Index (PASI). Serology was repeated after one year and patients questioned for intercurrent infection events needing medical attention. End points were the proportion of seropositive patients, response and tolerance to PPV and the rate of infections during follow-up.

Results: Sixty-one patients were included, with a mean age of 56 ± 15 years. Forty-five (74%) had psoriasis and 16 (26%) other autoimmune skin diseases. All had immunosuppressants and 12 (20%) additional systemic corticosteroids. Immunosuppressants were TNF-alpha blocking agents in 35 (57%), human interleukin-12/23 monoclonal antibody in 6 (10%), methotrexate in 17 (23%), azathioprine in 11 (18%) and chlorambucil in one. At baseline, 11 (18%) were seronegative. This was significantly associated with low total IgG levels ($p=0.008$) and infections in the preceding 3 months ($p=0.045$). Ten patients received PPV, with excellent tolerance. Eight (80%) reached seropositive thresholds after PPV, although with modest antibody titers. Infections of any kind occurred during follow-up in 12/47 (26%) patients seropositive at baseline and in 5/7 (71%) initially seronegative patients despite immunization ($p=0.026$). The rate of airway infections was not different between study arms.

Conclusions: Low total IgG and a higher frequency of infections in immunosuppressed dermatological patients should prompt the evaluation/reactivation of pneumococcal immunity, now that more immunogenic conjugate vaccines are available.

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Captopril-induced leucocytoclastic vasculitis

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Captopril is an angiotensin-converting enzyme (ACE) inhibitor widely prescribed for hypertension and heart failure. Common cutaneous side effects of captopril include angio-edema, anaphylactoid reactions, maculopapular eruptions and exfoliative