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Invited Speakers – Plenary Sessions

PL1

Subepithelial bullous diseases – topic overview

M Mravak-Stipetić[1], B Marinović[2]
[1]*Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia,* [2]*University Department of Dermatology and Venereology, Zagreb University Hospital Center, Zagreb, Croatia*

Subepithelial bullous diseases comprise the group of mucocutaneous autoimmune blistering diseases characterized by subepithelial separation and the deposition of immunoglobulin and complement against several antigens along the basement membrane zone (BMZ). This result in spectrum of diseases that affect skin, oral mucosa, and other mucosal membranes and include bullous pemphigoid (BP), mucous membrane (cicatricial) pemphigoid (MMP), linear IgA disease (LAD), and chronic bullous dermatosis of childhood (CBDC). The most common clinical features are oral erosions, desquamative gingivitis and conjunctival fibrosis, as well as skin lesions, predominantly in older female population. The heterogeneity of clinical presentation and diversity of target autoantigens have contributed to difficulties in characterizing this condition immunologically. In addition to the clinical presentation and a subepithelial vesicle or bullae on routine histologic analysis, the diagnosis is based on direct and indirect immunofluorescence studies. The nature of the disease is determined by the target antigens in the epithelium and BMZ such as antigen 180 (BP180), antigen 230 (BP230), laminin 5, and beta 4 integrin. Circulating IgG and IgA antibodies bind to different epitopes of BP180. The use of salt-split skin substrate enables differentiation between epidermal and dermal 'binders'. Since the antigen and the antibody titer appear to have direct relationships with the disease severity, and a combination of clinical finding and antibody titer provides valuable prognostic data, these investigations should be carried out routinely. Clinicians should recognize clinical spectrum of SBD, the histopathologic and immunopathologic characteristics, the differential diagnosis, the treatment, and the natural history of the disease. Involvement of oral medicine specialists, dermatologists, ophthalmologists, otolaryngologists and gastroenterologists contribute to early diagnosis and will aid in providing SBD patients with the highest quality of care.

PL2

Subepithelial bullous diseases – dermatoimmunological and molecular basis

PM Marinkovich
Bullous Disease Clinic, Stanford University, Stanford, CA, USA

Significant advances have recently taken place in our understanding of inherited and acquired subepithelia bullous diseases. Inherited disorders are collectively termed epidermolysis bullosa and include simplex, junctional and dystrophic categories. Elucidation of the structure and function of the basement membrane underlying stratified squamous epithelial tissues has provided a foundation of knowledge, which has permitted application to clinical diseases. Advances in our understanding of the physiological basis for mucosal cohesion and molecular diagnosis of inherited diseases have resulted in the elucidation of DNA mutations, which correlate with the molecular pathology. Current preclinical efforts in this field are largely directed at development of a specific and effective molecular therapy and several approaches will be discussed. The molecular etiology of the development of squamous cell carcinoma in a subset of dystrophic EB patients has also been recently elucidated and will be discussed. Acquired subepithelial bullous disorders are becoming better understood as well, through the development of several preclinical animal models, including models for bullous pemphigoid and epidermolysis bullosa acquisita. Autoantibodies in each of these diseases appear to require complement and other local immune components, in contrast to pemphigus antibodies, which appear to be pathogenic themselves. In particular, bullous pemphigoid blister formation shows reliance on metaloproteinase expressed by immune cells, suggesting new targets for molecular therapy.

PL3

Stevens Johnson syndrome and mucous membrane pemphigoid: ocular manifestations and their management

JKG Dart[1,2]
[1]*Corneal and External Disease Service, Moorfields Eye Hospital, London, UK,* [2]*Department of Clinical Pathology, The Institute of Ophthalmology, University College London, UK*

Stevens Johnson Syndrome (SJS), its severe form Toxic Epidermal Necrolysis (TEN), and mucous membrane pemphigoid (MMP) are the major autoimmune causes of conjunctival scarring. Between them these diseases present some of the most difficult management problems in ophthalmology. SJS/TEN develop conjunctival disease as part of the acute generalised mucosal involvement. The conjunctivitis varies from a papillary reaction with watery discharge to a membranous conjunctivitis with sloughing of the conjunctival epithelium. Corneal epithelial defects are common and may progress to corneal ulceration with or without bacterial superinfection. Although the morbidity may be due to the acute corneal complications it more usually results from the progressive effects of the conjunctival scarring, the secondary ocular surface disease, infections & treatment toxicity that occur later. Some cases of SJS/TEN develop the following late inflammatory diseases: recurrent conjunctival inflammation without scarring (recurrent SJS), inflammation with cicatrisation like ocular MMP (SJS-MMP) and scleritis. On the other hand ocular MMP (MMPO) presents with acute conjunctivitis and limbitis in only 10% of cases; the remainder present with subacute or low grade chronic inflammation and progressive scarring. Progression in MMPO is due to the same factors that cause the morbidity in SJS/TEN (conjunctival scarring, the secondary ocular surface disease, infections & treatment toxicity) coupled with the effects of the progressive conjunctival inflammation and scarring that is a feature of all cases of MMPO, but occurs in a few cases of SJS/TEN with ocular involvement. Successful management of both SJS/TEN and CP demands identification of the components of the disorder due to (i) surface disease, (ii) treatment toxicity (iii) immune mediated inflammation and (iv) infection. These problems lead to a dry eye, surface failure and corneal blindness. All these components of the problem require prompt treatment to prevent progression to surface failure because of the poor prognosis for rehabilitation, by corneal graft surgery and/or surface reconstruction, in this group of patients.

PL4

Periodontologist's viewpoint inclusive of soft tissues around implants

D van Steenberghe[1,2], K Michiels[1]
[1]*Department of Periodontology, Catholic University Leuven, Belgium,* [2]*Holder of the P-I Brånemark Chair in Osseointegration*

Integuments play a key role for the integrity of the bodily tissues. Both teeth and oral implants pierce the gingiva or alveolar mucosa with an interface acting as a relative seal. The epithelia adhering by means a basal membrane to either the implant or a tooth are not keratinized. They both contain laminin-5 with a similar structural relationship. The cytokeratins are strikingly similar in both instances. Il-1 beta and TGF-beta 1, when overexpressed jeopardize the soft tissue healing and lead to fibrosis. Subepithelial bullous diseases may thus be a relative contra-indication. Although soft tissue innervation has been described, Merkel cells seem to be absent around artificial abutments. The subepithelial vascular supply with its characteristic loops is also found in both instances. Furthermore the stroma and the outflow crevicular fluid are strikingly similar from a quantitative and compositional viewpoint. When a biofilm accumulates on a tooth or an implant, the surrounding soft tissues demonstrate an inflammatory reaction, which cannot be distinguished from eachother. This will interact with the healing of blistering diseases as observed with the natural dentition. The non-plaque related pathologies of peri-implant gingival and alveolar mucosa are hardly documented but some case reports reveal a similar reaction. For example gingival cyclosporin also induces hyperplasia around implants. Few reports provide histological insights on the mucosal pathologies such as lichen planus or pemphigoid. This part of oral pathology merits more attention. At the clinical level periodontologists can meanwhile extrapolate their expertise to the peri-implant soft tissues.

PL5

The diagnosis of sub-epithelial bullous diseases

M Carrozzo
Department of Biomedical Sciences and Human Oncology, Oral Medicine Section, University of Turin, Italy

There are a number of sub-epithelial vesiculobullous disorders that may produce similar clinical pictures in the oral cavity, with antibodies directed against various hemidesmosomal components or components of the epithelial basement membrane. The term *immune-mediated sub-epithelial blistering diseases* (IMSEBD) have therefore been used. The diagnosis of IMSEBD on clinical grounds alone is impossible and a full history, general, and oral examination, biopsy with immunostaining are now invariably required, sometimes supplemented with other special investigations. The main subepithelial blistering disease is mucous membrane pemphigoid (MMP) that includes a range of variants frequently having oral and especially gingival lesions. Exclusive oral MMP (OP) has been reported to have frequently a low frequency of positive indirect immunofluorescence (IIF) findings without serologic reactivity to recognised MMP antigens. However, the low frequency of detection of autoantibodies in the sera of OP patients may be due to insufficiently sensitive detection techniques. Indeed, most of the patients with OP have circulating auto-antibodies (autoAb) against the epidermal side of the basement membrane zone (BMZ) with IIF using normal human salt-split skin (SSS) as substrate. Combining very sensitive techniques as IIF-SSS, immunoblotting (IB) on extracts of human keratinocyte cultures and ELISA systems up to 90% of the patients have circulating autoantibodies against the BMZ.