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P 10: Cutaneous basement membrane formation in organotypic culture
I-01
Autoimmune bullous disorders of the dermo-epidermal junction
C. Bedane
Department of Dermatology, Dupuytren, Limoges, France
During the last few years, considerable progress has been made in the understanding of the structure and function of various components of the dermo-epidermal junction. Bullous pemphigoid is a disease of the elderly characterized by the production of autoantibodies mainly directed against a 220–240 kDa polypeptide, the major BP antigen located in the hemidesmosome. Several studies have demonstrated that a 180 kDa protein was also recognized by a number of pemphigoid sera. The 180 kDa BPA is a transmembrane molecule with a predicted type II orientation. The C-terminal domain is extracellular and consists of a series of collagen triple helix domains. Recent studies have demonstrated that the major epitopes are located in the non-collagenous stretch of the extracellular domain of the 180 kDa BPA very close to the keratinocyte membrane receptors. Evidence from DNA sequencing suggest that multiple alleles are present on the 180 kDa BPA. Using rabbit antisera raised against different domains, we have demonstrated that the C-terminal domain was localized in the lower part of the lamina lucida. Double labelling performed with C-terminal antibodies and anti-kalinin antibodies have shown a common localization in the interface of the lamina lucida and lamina densa where it is believed to be associated with anchoring filaments. Our ultrastructural mapping confirm that the 180 kD BPA has a very long extracellular domain extending on the entire lamina lucida from the hemidesmosome to the lamina densa. Recent report of non-lethal junctional epidermolysis bullosa have demonstrated that absence of expression of the 180 kD BPA may have a critical pathogenic significance in adhesion between epidermis and the dermis. The 180 kDa BPA which is mainly in its extracellular portion a collagenous molecule is probably a major component of the anchoring filaments network and certainly plays an important role in the adhesion process between basal keratinocytes and the dermis. The 87 and 120 kDa antigens recognized by bullous pemphigoid antibodies in linear IgA disease correspond to the soluble extracellular domain of 180 kDa BP. The development of Elisa systems using recombinant or synthetic proteins will be a very sensitive tool for the detection of antibodies and new antigen sites allowing a better classification and understanding of the pathogenesis of sub-epidermal bullous disorders in the future.

I-02
Bullous disorders: the gray zone
C. Kowalewski
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Numerous cases of bullous disorders with atypical clinical and histological features, and immunofluorescent findings characteristic of pemphigus or pemphigoid defy conventional classification. These disorders may be characterized with classic form of pemphigus with clinical signs of pemphigus vulgaris in a 33-year-old female with clinical features of pemphigus herpetiformis, non diagnostic histological findings, and the absence of anti-cell surface antibodies of both IgG and IgA classes reactive exclusively with desmoglein 1 is presented. This atypical bullous disease with immunological pattern differing from pemphigus herpetiformis by presence of IgA antibodies, and from IgG pemphigoid that IgA antibodies, could be classified as a novel atypical subset of pemphigus tentatively named IgA/IgG pemphigus. 54-year-old female with tense blisters forming targetoid-like lesions and the presence of IgG and C3 linear deposits along the basement membrane zone (BMZ) and circulating anti-BMZ antibody directed against 200 kD protein is presented. In contrast to previously described cases with bullous eruptions and pсорiasis in which anti-BMZ antibodies were directed against 200 kD protein in the present case there is no history of psoriasis. In vivo bound antibodies are found to be localized at the lamina lucida-lamina densa border thus this case could be classified as atypical pemphigoid with antibodies against 200 kD protein. Two patients with scarring conjunctivitis and widespread mucous membrane involvement developed tense blisters and extensive well-defined pustules and vegetating erosions symmetrically distributed in the inquinal and axillary folds. Skin biopsy specimens showed acanthosis, papillomatosis, subepidermal blister and infiltrate consisting of leukocytes and eosinophils. Direct immunofluorescence of the perilesional skin showed linear distribution of IgA within BMZ, ultrastructurally localized at the lamina lucida-lamina densa border. Vegetating skin lesions have antibodies against 200 kD protein and were described in autoimmune bullous diseases, most often in pemphigus vegetans, rarely in bullous pemphigoid, whereas present cases could be classified as vegetating cicatricial pemphigoid. Despite of advances in diagnosing of autoimmune bullous diseases the classification of some cases is still a matter of controversy.

I-03
Lysosomal Storage Diseases
T. Kanazaki, T. Fukushige, T. Kanekura
Department of Dermatology, Field of Sensory Organs, Kagoshima University, Graduate School of Medical and Dental Sciences, Kagoshima, Japan
There are more than 60 enzymes in lysosomes in human cells. Each enzyme hydrolyses the substrate, i.e., unnecessary cellular substances such as intermediates of cellular metabolites, or exogenous foreign materials such as bacteria. If any one of these enzymes is deficient in its enzymatic activity, the substrate, usually an intermediate metabolite, will not be hydrolysed. It leads to the accumulation of the metabolite in lysosomes, resulting in cell death and subsequently organ failure (lysosomal storage disease, LSD). There are more than 30 diseases which are known to be caused by known enzyme deficiency at the present time. The rest of them, about 30, are still unknown. There are 7 LSD's which will clinically present as an--

I-04
Recent advances in our knowledge of the dermo-epidermal junction
H. Shimizu
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The dermo-epidermal junction or epidermal basement membrane (EBM) comprises a multilayered complex that plays a pivotal role in the attachment of basal keratinocytes to the underlying dermis. A variety of recently developed immunoelectron microscopic techniques have contributed to determining the molecular organization of these EBM components. We now, not only understand the ultrastructural localization of each molecule, but also the more precise orientation of each epitope within the entire protein molecule. In this lecture, I shall present updated information on the precise orientation of crucial EBM molecules, such as type XVIII and VII collagen, and laminin 6, and their relationship to a variety of skin disease.

I-05
Hair and hair disorders: histological aspects
D. Innocenzi
Department of Dermatology and Plastic Surgery, "La Sapienza" University, Rome, Italy
Humans are naked only at first glance. Human bodies are covered almost entirely by hardly visible hairs. The soft, fine, lightly pigmented hairs that cover most of the body of children and adults are termed "vellus". Similar vellus-like hairs in a fetus are termed "lanugo". The long, pigmented, terminal hairs on scalp, axilla, pubes, eyelashes, eyebrows, etc., are termed "terminal". Qualitative differences in hair between sexes or among races exist only pigmented hairs with large diameter (hairs on the scalp, eye-brows, eyelashes, etc.) are

I-06
Modern Dermatopathology
H. Kutner
DermPath, Friedrichshafen, Germany
More than 25 years after the advent of immunohistochemistry molecular methods have finally entered the routine laboratory. From the plethora of modern methods, PCR, PCR-ELISA, sequencing, FISH, and the detection of microsatellite instability will be shown as exception--

ABSTRACTS THE JOURNAL OF INVESTIGATIVE DERMATOLOGY
A88 INVITED LECTURES
I-07
Dermatopathology: from light to ultrastructural microscopy
D. Metze
Department of Dermatology, University of Münster, Germany
Many skin diseases are histologically characterized by distinct intra- & extracellular changes that only can be explained by electron and immuno-electron microscopy (EM, IEM). Thereby, new re-embedding procedures are helpful to study paraffin material as available for routine histology at ultrastructural level. Using various ultrastructural techniques, we examined specific and unspecific findings in disorders of epidermal differentiation (Hailey-Halley-like pattern of acantholysis, epidermodysplasia hyperkeratosis, confetti-like ichthyosis, focal epidermal dyskeratosis, dyskeratosis congenita, granular parakeratosis, chemotherapeutic reactions), disorders of pigmentation (Hypo-melanosis guttata, Dowling-Degos disease, melanosis cutis, drug-induced hyperpigmentation), and cutaneous drug deposits (aluminum and hydroxyethylstarch). In addition, EM is able to specify alterations of connective tissue fibres (Pseudo-xanthoma elasticum) and basement membranes (Kindler-syndrome, collagen-hydroxyethylstarch). In addition, EM is able to specify alterations of connective tissue fibres and to investigate skin diseases far beyond immunohistological and molecular techniques.

I-08
Pandora’s box of cutaneous lymphomas
G. Kunz1, P. Sator1, J. Breier-Maly3, W. Jurecka4, G. Stanek5
Departments of Dermatology: 1Lainz-Vienna, Vienna; 2Hospital St. Pölten; 3Vienna Medical University, Vienna; 4Department of Dermatology and Plastic Surgery, “La Sapienza” University, Rome, Italy
Acne is an extremely common condition, affecting almost 80% of adolescents and young adults aged 11 to 30. In recent years, research has led to a greater understanding of the pathogenesis of this widespread disease. The pilosebaceous unit is the target organ in acne, explaining the distribution of acne primarily on the face, chest, and back-areas with the greatest concentration of pilosebaceous glands. The most notable pathophysiologic factors that influence the development of acne are: sebaceous gland hyperplasia with seborrhoea, altered follicular growth & differentiation, Propioni-bacterium acne colonization of the follicle, inflammation & immune reaction. The primary lesion of acne is the microcomedo, that can evolve into either a non-inflammatory comedo or becomes inflamed and present as a papule, pustule, or nodule. The improved understanding of the pathophysiology of acne has brought about changes in acne management. The pathophysiological features of acne suggest that combination therapy should be used as early as possible preferably at the initiation of therapy to simultaneously attack two or three pathogenic factors.

I-09
Clinical-pathological aspects of acne
D. Innocenzi
Department of Dermatology and Plastic Surgery, “La Sapienza” University, Rome, Italy
Acne is an extremely common condition, affecting almost 80% of adolescents and young adults aged 11 to 30. In recent years, research has led to a greater understanding of the pathogenesis of this widespread disease. The pilosebaceous unit is the target organ in acne, explaining the distribution of acne primarily on the face, chest, and back-areas with the greatest concentration of pilosebaceous glands. The most notable pathophysiologic factors that influence the development of acne are: sebaceous gland hyperplasia with seborrhoea, altered follicular growth & differentiation, Propioni-bacterium acne colonization of the follicle, inflammation & immune reaction. The primary lesion of acne is the microcomedo, that can evolve into either a non-inflammatory comedo or becomes inflamed and present as a papule, pustule, or nodule. The improved understanding of the pathophysiology of acne has brought about changes in acne management. The pathophysiological features of acne suggest that combination therapy should be used as early as possible preferably at the initiation of therapy to simultaneously attack two or three pathogenic factors.

I-10
Advances in cutaneous lymphoproliferative disorders
N. Pandolfini
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The most recent advances in cutaneous lymphomas (CL) concern molecular diagnosis (identifying its relationship to staging), new clinical-pathologic entities, and treatment modalities. The main topics of interest in the molecular diagnosis of CL are early lesions and early involvement of lymph nodes and peripheral blood. The finding of a clonal rearrangement of TCR genes may be very important in the early diagnosis of cutaneous T-cell lymphomas (CTCL). In this regard, however, it has to be stressed that a careful and balanced combination of clinicopathologic features with molecular findings is to date the only crucial key to final diagnosis of CTCL. The biological and prognostic significance of early molecular involvement of lymph nodes and/or peripheral blood is still debated, although there is an increasing evidence for the prognostic value of the finding of an identical clone in skin and in blood and/or in lymph nodes. Among newly described CL entities, epidermotropic cytotoxic CTCL is a distinct type of aggressive CL, characterized clinically by ulcerocerebriform, rapidly spreading plaques and nodules, with extracutaneous spread to unusual sites (lung, oral mucosa, CNS) and rapidly fatal outcome. Historically, the intradermal infiltration of medium to large pleomorphic T-cells expressing TIA-1 (specific cytotoxic marker) is the clue to diagnosis. CD4+ /CD8- (NK7) CL is mostly characterized by disseminated plaques and nodules, dermal infiltration by pleomorphic or blast-like cells typically compressing CD4+, CD68, and CD8 antigens, and bad prognosis. Regarding treatment, the most interesting advances concern the treatment of CTCL: new retinoids (oral bexarotene), nucleoside analogues (ganciclovir, pegylated doxorubicin), and targeted immunotherapies (IAB-12, anti-CD20 – alemtuzumab) can be usefully combined with other modalities. Among skin-directed procedures, monochromatic excimer light (308 nm) and imiquimod deserve particular attention in early CTCL. Rituximab (anti-CD20 immunotherapeutic) can be used systemically (pluri-relapsed or aggressive CBCI), or intrataneously (local recurrences in areas previously treated with radiotherapy).

I-11
Cutaneous lymph borreliosis: which morphological alterations can be detected? F. Breier1, G. Kurz2, P. G. Sator3, J. Breier-Maly4, W. Jurecka5, G. Stanek6
Departments of Dermatology: 1Lainz-Vienna, Vienna; 2Hospital St. Pölten; 3Vienna Medical University; 4Wilhelminen Hospital, Vienna and 5Hygiene Institute, Vienna, Austria
The aim of this study was to determine the general light and electron microscopic findings which lend support to the histopathologic diagnosis of the main cutaneous manifestations of Lyme borreliosis. The diagnostic criteria are delineated and illustrated. In culminating lesions of erythema migrans and acrodermatitis chronica atrophicans, a peculiar connective tissue reaction includes an increase in the number of fibroblasts, proliferation of collagen fibres and interstitial mucinous oedema. The cellular infiltrates are patchy and perivascular in erythema migrans and either patchy and/or band-like and interstitial in acrodermatitis chronica atrophicans. They consist of lymphohistiocytic cells with a variable admixture of plasmacytoma cells. The damage to elastic (and even collagen) fibres occurs in early acrodermatitis chronica atrophicans and is reflected by the phenomenon of elastophagocytosis with a fragmentation of elastic and oxytalan fibres. Reduction of the number or lack of pilosebaceous units is a constant finding. In advanced lesions of acrodermatitis chronica atrophicans a thinning of the dermal breadth is noticed, resulting from a decrease of collagen and elastic fibres. Fibrous nodules and morpho-like conditions are characterized by excessive formation of collagen. Borelial lymphocytoma exhibits two different patterns of infiltration, accompanied by dermal fibrosis and increased numbers of fibroblasts. Recent skin biopsies show a predominantly neovascular infiltrate, with an admixture of eosinophilic granulocytes. By applying the results of this synaptic study, histopathologic diagnosis including the histological and ultrastructural findings of cutaneous borreliosis infections should be possible without the absolute necessity of clinical correlation.

ORAL PRESENTATIONS

O 1
The ultrastructural localization of desmosomal components in Desmoglein3 knockout mouse
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Desmoglein3 (Dsg3) is known as a target antigen of pemphigus vulgaris (PV), a severe autoimmune blistering skin disease. Dsg3±/± mouse has been reported to present PV-like phenotype including oral erosion with suprabasal acantholysis indicating that loss of Dsg3 itself or its function is the main pathophysiological mechanism of the acantholysis in PV. However, keratin retraction from desmosomal attachment plaque after autoantibody binding to Dsg3 may be another explanation for the acantholysis. Although the molecular composition of desmosome is clarified, the intermolecular interaction of the desmosomal components is not fully elucidated. The purpose of this study is to clarify the molecular composition of Dsg3±/± mouse desmosomes to characterize the acantholysis in this mouse. For this, we analysed the ultrastructural localization of well established members of desmosomes in Dsg3+/+ mouse epithelium using post-embedding immuno-EM and compared specificity with that in normal mouse with desmosomes obtained from oral mucosa of Dsg3+/+ mouse and normal control mouse, cryofixed with liquid propane at −190 ºC, freeze substituted with tert-butanol, and embedded in LR white. On-section immuno-EM was performed using six antibodies against Dsg1, desmocollin 1, desmocollin 3, plakoglobin, plakophilin 1, and desmoplakin (DP). The distances between the gold labelling of each mol- ecula and the plasma membrane were measured and statistically compared. As results, DP in Dsg3+/+ mouse was localized 11 nm further from the plasma membrane than that in normal mice. On the other hand, the localization of other desmosomal molecules was not significantly different between Dsg3+/+ and control mouse. Our results suggest a molecular interaction between Dsg3 and DP in desmosomes and may give insights to the mechanism of PV blister formation.
Ultrastructural assessment of the splice variant-specific function of Dsc1 in the epidermis

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Department of Molecular & Cellular Biology, Department of Dermatology, Baylor College of Medicine, Houston, TX, USA

Dsc1 and desmocollin 1 (Dsc1) are expressed in the suprabasal layers of epidermis, as Dsg3 and Dsc3, isoforms of the desmosomal cadherin are more strongly expressed basally. This differential expression pattern may have a function in epidermal development. The aim of the current study is to evaluate the different functions of the described splice variants. The Dsc1 gene encodes two proteins (Dsc1a and 1b) that differ with respect to their C-terminal cytoplasmic amino acid sequences. Previously, a study demonstrated the C-terminal domain of Dsc1, not 1b, could recruit plakoglobin (P) and desmoplakin (DP) to the plasma membrane of epithelial cells and serve as a nucleation site for the assembly of an electron-dense plaque with attached intermediate filaments. Therefore, one would expect that absence of the C-terminal domain of Dsc1a would affect desmosome (DM) assembly. We have recently generated a Dsc1 mutant mouse, which expressed novel 13 amino acid sequences instead of the Dsc1a and 1b-specific C-terminal cytoplasmic domains. The purpose of this study is to assess the function of the C-terminal domain of Dsc1 in DM assembly and epithelial barrier function. In conclusion, the C-terminal domain of Dsc1 is considered to be not essential for the DM assembly. In other words, the extracellular domain and transmembrane domain of the Dsc1 receptor is necessary to maintain the structural integrity of the skin.

Tacrolimus reduces the expression of GLI-1 by basal cell carcinoma

R. Sestini1, A. Pacini2, P. Di Gennaro3, S. Bacci4, P. Pinzani4, V. Cesati1, P. Cardi4, D. Massi4, M. Genuardi2, P. Romagnoli2

1Department of Clinical Pathophysiology, 2Anatomy of Anatomy, Histology and Forensic Pathology, 3Department of Dermatological Sciences, 4Department of Human Pathology and Oncology, Universita` di Pavia, Pavia, Italy

The product protein of GLI-1 oncogene mediates the physiological effects of the intercellular signaling molecule Sonic hedgehog (Shh) and controls the cell proliferation and differentiation of the suprabasal cells in developing and in mature organs. Overexpression of GLI-1 is characteristic of basal cell carcinoma (BCC) and is considered pathognomonic for this disease. Tacrolimus (FK506) has extensive homology and uses the same receptor as rapamycin, which can antagonize the cellular transformation caused by GLI-1 overexpression. We have therefore addressed whether tacrolimus affects the expression of GLI-1 in a biphasic model using this mutant mouse cell line 4T1-3D. To examine GLI-1 expression (with RT-PCR) in 4T1-3D cells, the quantitative TMEM8B mRNA levels were determined by real-time PCR. The differential expression of GLI-1 was confirmed by quantitative RT-PCR and Western blotting. Tacrolimus (0.5-50 ng/mL) led to a dose-related drop in the expression of GLI-1 mRNA (significant for 50 ng/mL) and, to a lesser extent, in the number of GLI-1 immunoreactive cells. The cell proliferation rate was not affected by tacrolimus. Tacrolimus affects the expression of GLI-1 in a basal cell carcinoma cell line; this result opens the pathway to investigate whether such effects can be correlated with altered expression of other genes related to neoplastic behavior.

Merkel cell carcinoma with atypical clinical presentation associated with chronic lymphoctic leukemia

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A 71-year-old white woman presented with an 8 month history of a slowly growing painless nodular subcutaneous mass of the left arm. Her past medical history was unremarkable except for a recent onset thrombocytosis. At the beginning she tried to manually extrude the “content” of the growing “cyst”. On examination telegenic skin showing a subcutaneous tumour was present. Numerous roundish mass measuring 4 cm in diameter, poorly mobile and of elastic and lipomatous consistency was observed. The skin lesion was surgically removed and the histopathologic examination showed a diffuse infiltrating subcutaneous nodule characterized by a trabecular pattern composed of round to oval mononuclear cells with scant cytoplasm and oval to round nuclei that focally expressed GLI-1. GLI-1 overexpression has been observed in basal cell carcinoma (BCC) and has been considered a key event in its pathogenesis, leading to increased cell proliferation and expression of the anti-apoptotic molecule Bcl-2 as well as to a reduced expression of the adhesion proteins CD117 and CD44. We report here a new case of a BCC expressing different transcriptional molecules in a series of BCCs and in a BCC cell line, TE 354.T. Immunohistochemical expression of GLI-1, Bcl-2, and laminin was evaluated in 15 sporadic BCCs of various subtypes and different clinical behavior (3 nodular, 3 superficial, 3 infiltrating, 3 metastatic, 2 recurrent and 1 metastatic), and, for comparison, in 20 benign hair follicle-related tumors and in 5 cases of basaloid hyperplasia overlying dermatofibromas. Suspended and adherent TE 354.T basal cell carcinoma cells were fixed with paraformaldehyde and immunostained for anti-GLI-1 and anti-Bcl-2 antibodies. BCCs consistently showed GLI-1 immunoreactivity, the staining being quite heterogeneous in the neoplastic aggregates, with a stronger intensity at the periphery. BCCs also expressed Bcl-2, with a staining similar to that of TE 354.T. An immunohistochemical analysis was also performed on an expression panel of keratin markers and + vimentin. The expression of GLI-1 and Bcl-2, however, was not related to the diagnosis of the neoplasms, to the expression of keratin and vimentin, or to the presence of other markers. The clinical presentation of a Merkel cell carcinoma (MCC) and in the simultaneous association with a second neoplasia. Patients with chronic lymphocytic leukemia (CLL) have a threefold risk of developing a second tumor, and this risk increases to eightfold when considering skin tumors only. In addition a high incidence of second neoplasms in MCC is also reported. Just a small number of cases of MCC arising in patients with CLL could be reviewed and the fact that this is more than coincidental remains to be established.

Control Of Basement Membrane Formation In Skin-Organotypic 3d-Coculture

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Basement membrane (BM) formation was functionally dissected in 3d-cocultures of human keratinocytes (HK), human fibroblasts (HF) and HK-HF 3d-cocultures. BM-formation, demonstrated by combining either perlecan (C0) or BM-40 with BM-44 and BM-10. Total absence of nidogen (G1) also deleted collagen-IV & laminin-5, integrins (β1, β2, β3). Especially nidogen (G1) and collagen-IV were expressed with variable intensity among cells. The expression of GLI-1 was only mildly affected, EM and IEM revealed that this is more than coincidental remains to be established.

Control Of Basement Membrane Formation In Skin-Organotypic 3d-Coculture

A90 ABSTRACTS
Two cases of CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) diagnosed by skin biopsy electron microscopy

O 8

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary disorder of small artery walls resulting in microangiopathic cerebral ischemic strokes starting in the third or forth decade as a result of mutations in the NOTCH3 gene. Granular osmiophilic material (GOM) deposition around the vascular smooth muscle cell is a specific feature and electron microscopic observations of skin biopsies are useful for the diagnosis of CADASIL.

We previously reported two cases of CADASIL who presented with vegetating papillomatous lesions of the oral mucosa. Both patients were diagnosed with CADASIL years before the appearance of the lesions. In one case, the lesions were present from birth. The biopsy material showed hyperplastic epithelium, angiomatoid papillomatosis and a granulation-like tissue with mixed cell infiltrate, mostly composed by inflammatory cells. We are reporting the histopathological features of the other case, a 43-year-old male patient, referred to our dermatology department for persistent ulceration of the oral mucosa.

In conclusion, we are not reporting two cases of CADASIL who presented with ulceration of the oral mucosa. In both cases, the lesions showed histopathologically features of papillomatous lesions, but the presence of granular osmiophilic material (GOM) deposition around the vascular smooth muscle cell is consistent with CADASIL. Further molecular studies are warranted to confirm the diagnosis of CADASIL in these cases.

O 9

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Von Willebrand factor (vWF) is a major player of primary haemostasis. Weble had previously reported that vWF is also released at the luminal surface of EC mediating platelet adhesion. By using atomic force microscopy (AFM) we visualized the luminal surface topography of EC. Submembrane Weibel-Palade bodies (WPB; storage vesicles of vWF) can be imaged as bumps characterized by decreased cell membrane stiffness. After cell stimulation (hyperosmotic solutions or histamine) these denuded WPB fuse with the plasma membrane forming large exocytotic pores (d ~ 300 nm). Release of vWF from these pores was visualized by using immunofluorescence staining after staining the same cell surface with vWF-specific antibodies. Surprisingly, high molecular weight vWF fibres on EC at the intact human vessel wall. In contrast to the exogenous vWF fibres, these vWF fibres were at least 200 nm. The study shows that AFM enables to visualize and cell surface topography with a nanometer resolution. The data indicate a new concept for a physiological function of vWF to effectively recruit platelets and leukocytes to the intact but stimulated vessel wall surface.

Pseudomembranous angiomatoid papillomatosis of mucous membrane (PAPM) in bone marrow transplanted patients

O 12

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Pseudomembranous angiomatoid papillomatosis of mucous membrane (PAPM) is a rare and unusual condition that may arise in bone marrow transplanted patients. The lesions can affect any mucosal area, including the oral cavity, nose, pharynx, and genital tract. The condition is characterized by the presence of a pseudomembrane, which is composed of necrotic epithelial cells and a mixed inflammatory infiltrate. The etiology of PAPM is unknown, but it is thought to be related to the immunosuppressive therapy used in bone marrow transplantation.

We report a case of PAPM in a 35-year-old woman who underwent allogenic bone marrow transplantation for acute myeloid leukemia. The patient developed a pseudomembranous lesion on the tongue and hard palate, which was characterized by a thick, white, friable membrane covering the affected mucosa. The patient was treated with systemic antibiotics, and the lesion resolved completely within a few weeks.

In conclusion, PAPM is a rare and unusual condition that may arise in bone marrow transplanted patients. The condition is characterized by the presence of a pseudomembrane, which is composed of necrotic epithelial cells and a mixed inflammatory infiltrate. The etiology of PAPM is unknown, but it is thought to be related to the immunosuppressive therapy used in bone marrow transplantation.

Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory and autonomic nervous system in human skin

O 11

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Cannabinoids are known to modulate psychopharmacological, analgetic and immune functions of exogenous and endogenous cannabinoids. They are known to be localised in the central and peripheral nervous system as well as in immune tissue. Up to now, cannabinoid receptors (CB) were cloned. Recent studies gave evidence for the presence of CB in the skin. To determine the precise localization of CB1 and CB2 in nerve fibres, epithelial cells of the autonomic nervous system, and mast cells, we performed an immunohistochemical study in a series of normal human skin and mastocytosis. CB1 and CB2 receptors were present in the sensory nerves. In mast cells, epidermal keratinocytes, epithelial cells of hair follicles, sebocytes, and eccrine sweat glands. Interestingly, in epidermal keratinocytes, hair follicle and sebaceous glands, CB1 and CB2 were distributed in a complementary fashion. Our study confirmed previous reports describing that cutaneous application of the selective CB1 and CB2 agonist HU210 significantly reduced capsaicin-induced burning pain as well as histamine-evoked itch. Together, these findings suggest that CB agonists could be effective in pain and itch.

Detection of high-risk human papillomavirus infection in penile lichen sclerosis

O 13

G. Miccioni1, M. R. Nasca1, D. Innocenzi2
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Lichen sclerosis (LS) is a chronic inflammatory disease of the skin that affects the genital and perianal areas. It is associated with an increased risk of penile cancer. The risk of penile squamous cell carcinoma is estimated at 3% for men with LS.

We aimed to investigate the prevalence of human papillomavirus (HPV) infections in patients with genital lichen sclerosis (LS), in order to highlight the possible role of HPV in enhancing the risk of penile cancer arising on LS. We enrolled 46 adult patients (mean age 59.5 years; range 27–79 years) with histologically confirmed penile LS, randomly selected from our hospital pathology files, and an equal number of randomly selected control males, matched for age and with no history of LS, phimosis, chronic balanitis, or other HPV-related disorders, attending our referral center for genitourinary complaints, were enrolled. HPV infection was assessed in paraffin-embedded penile biopsies of genital LS patients and in brush cytology smears of penile healthy mucosa by a highly sensitive two-step nested polymerase chain reaction (PCR) technique based on general Gp5+/Gp6+ PCR primers and consensus primers MY11/MY09 followed by cycle sequencing. HPV PCR disclosed the presence of HPV DNA in 17.4% of LS patients (HPV 16: 6 cases; HPV 18: 1 case; HPV 45: 1 case). There seemed to be no relationship between histopathologic features and presence of HPV infection. Among controls, incident HPV infection occurred in 8.7% of patients (HPV 16: 2 cases; HPV 53: 1 case; HPV 70: 1 case). Our results support the hypothesis of a causative link between genital HPV infection and a high risk of penile cancer development in men with genital LS. Further investigations to assess the significance of our findings are warranted.

To determine the precise localization of CB1 and CB2 in nerve fibres, epithelial cells of the autonomic nervous system, and mast cells, we performed an immunohistochemical study in a series of normal human skin and mastocytosis. CB1 and CB2 receptors were present in the sensory nerves. In mast cells, epidermal keratinocytes, epithelial cells of hair follicles, sebocytes, and eccrine sweat glands. Interestingly, in epidermal keratinocytes, hair follicle and sebaceous glands, CB1 and CB2 were distributed in a complementary fashion. Our study confirmed previous reports describing that cutaneous application of the selective CB1 and CB2 agonist HU210 significantly reduced capsaicin-induced burning pain as well as histamine-evoked itch. Together, these findings suggest that CB agonists could be effective in pain and itch.

Detection of high-risk human papillomavirus infection in penile lichen sclerosis

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Lichen sclerosis (LS) is a chronic inflammatory disease of the skin that affects the genital and perianal areas. It is associated with an increased risk of penile cancer. The risk of penile squamous cell carcinoma is estimated at 3% for men with LS.

We aimed to investigate the prevalence of human papillomavirus (HPV) infections in patients with genital lichen sclerosis (LS), in order to highlight the possible role of HPV in enhancing the risk of penile cancer arising on LS. We enrolled 46 adult patients (mean age 59.5 years; range 27–79 years) with histologically confirmed penile LS, randomly selected from our hospital pathology files, and an equal number of randomly selected control males, matched for age and with no history of LS, phimosis, chronic balanitis, or other HPV-related disorders, attending our referral center for genitourinary complaints, were enrolled. HPV infection was assessed in paraffin-embedded penile biopsies of genital LS patients and in brush cytology smears of penile healthy mucosa by a highly sensitive two-step nested polymerase chain reaction (PCR) technique based on general Gp5+/Gp6+ PCR primers and consensus primers MY11/MY09 followed by cycle sequencing. HPV PCR disclosed the presence of HPV DNA in 17.4% of LS patients (HPV 16: 6 cases; HPV 18: 1 case; HPV 45: 1 case). There seemed to be no relationship between histopathologic features and presence of HPV infection. Among controls, incident HPV infection occurred in 8.7% of patients (HPV 16: 2 cases; HPV 53: 1 case; HPV 70: 1 case). Our results support the hypothesis of a causative link between genital HPV infection and a high risk of penile cancer development in men with genital LS. Further investigations to assess the significance of our findings are warranted.
O 14

Cellular reactions of malignant, semimalignant and premalignant conditions of the skin under immunostimulating therapy with imiquimod

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O 15

Lymphocytes subtypes expression and prognosis of squamous cell carcinoma of the lower lip

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Squamous cell carcinoma (SCC) of the lip is a relatively common malignancy of the head and neck region. Tumor thickness, grading and perineural invasion are significant prognostic indicators. However, there is still the need of new reliable biological markers able to predict the prognosis of the single cases with an unfavourable biological behaviour unpredictable by classical pathological parameters. 32 cases of SCC of the lower lip were analysed for their clinicopathologic features, and immunohistochemical expression of Fas/FasL in neoplastic and perineural infiltrating lymphocytes (TIL) was analysed. The results were related with follow-up of the patients ranging from 2 to 5 years. The cases with overexpression of FasL in neoplastic cells and Fas +ve T cells preferentially showed a more aggressive clinical behaviour (p < 0.01). Moreover we found an alteration of the normal expression of CD4 and CD8 lymphocyte types in these cases. These data suggest a role of apoptosis in the development of these tumours.

O 16

The role of immunohistochemistry in the grading of actinic keratosis

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It has been shown that actinic keratosis is a cutaneous lesion induced by UV sunlight exposure. It is considered a malignant lesion in the intraepidermal location, before its transformation into invasive carcinoma of the skin. Four intraepidermal stages are described and a tumoral progression from a non-malignant to the most malignant to the most premalignant to the malignant counterparts. A different histological varieties are described, like hypertrophic, acantholytic, b Bowenoid and atrophic. The immunohistochemistry plays a relevant role in the treatment with inactivation of the paraffin block, of different oncocogenes and related products and of different extracellular matrix proteins, and also permits a count of some proliferation indexes. The substances more frequently studied are p53, p63, PCNA, MMP-2, MMP-3, and p16. Tresults show a great inter-individual variety for all the above parameters, showing an interesting correlation in the different stages and malignancy grade. The thickening of the dermo-epidermal junction and its thickness is related to the amount of dysplasia. MMP-2 is always present with a higher degree of expression in the neoplastic cells in comparison to the dysplastic cells, whereas p16, negative or weak, is always related to dysplasia, p53 is overexpressed in 80% of the cases, and a staining with bcl-2 is related to the reported thickness of the dermo-epidermal junction. Regarding the extracellular matrix proteins, tenascin is present as a band under the dermo-epidermal junction and its thickness is related to the amount of dysplasia. MMP-2 is always present with a higher degree of expression in the neoplastic cells in comparison to the dysplastic cells, whereas p16, negative or weak, is always related to dysplasia, p53 is overexpressed in 80% of the cases, and a staining with bcl-2 is related to the reported thickness of the dermo-epidermal junction. The immunohistochemistry plays a relevant role in the evaluation of the grading of the lesion, in the identification of the infiltrating lymphocytes, and in inflammatory infiltrate. Moreover the density and phenotype of tumor-infiltrating lymphocytes (TIL) was analysed. The results were related with follow-up of the patients ranging from 2 to 5 years. The cases with overexpression of FasL in neoplastic cells and Fas +ve T cells preferentially showed a more aggressive clinical behaviour (p < 0.01). Moreover we found an alteration of the normal expression of CD4 and CD8 lymphocyte types in these cases. These data suggest a role of apoptosis in the development of these tumours.

O 17

Superficial acral fibromyxoma: 5 case reports

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Deep seated fibromyxoma (DFM) is a very rare fibrous tumor, which appears in adulthood. DFM is usually a solitary and slow-growing neoplasm, which is designated by a rather firm and less painful mass underneath the skin, without infiltration of the bone and with normal texture of subcutaneous fat. The biotin-peroxidase technique for CD3 (pan T-lymphocytes), CD20 (B-lymphocytes), CD5 and CD45 (granulocytes), PCNA, MB-2 and p16 immunostaining was used. Ten cases were observed. The neoplasm is seen in adulthood as solitary slow-growing me-demodermatological tumor. The subcutaneous fibromyxoma shows a great cellularity, with an increase of fibroblasts, which is related to the histological grade of the tumor. The immunohistochemistry plays a relevant role allowing the identification on paraffin blocks of the tumor cells, and in inflammatory infiltrate. Moreover the density and phenotype of tumor-infiltrating lymphocytes (TIL) was analysed. The results were related with follow-up of the patients ranging from 2 to 5 years. The cases with overexpression of FasL in neoplastic cells and Fas +ve T cells preferentially showed a more aggressive clinical behaviour (p < 0.01). Moreover we found an alteration of the normal expression of CD4 and CD8 lymphocyte types in these cases. These data suggest a role of apoptosis in the development of these tumours.
Fucosidosis with angiokeratoma. Light and electron microscopic study of a new case

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Granulysin, a recently identified antimicrobial protein expressed by cytotoxic T cells, NK cells and NKT cells. It is shown that granulysin contributes to defense mechanism against mycobacterial infection. Superficial microbial folliculitis is a common skin disease. In a previous report we could show, that as a first line of defense, alpha-defensin (human neutrophil peptides) and beta-defensin (human beta-defensin-2) were expressed in infiltrating neutrophils and lesional epidermal keratinocytes respectively in superficial folliculitis. As we also observed many infiltrating lymphocytes in lesional dermatis, we hypothesized that infiltrating lymphocytes may possess antimicrobial substances such as granulysin and play a role in defense mechanism as a second line of defense. Seven specimens of superficial microbial folliculitis diagnosed clinically and histologically were examined by means of immunohistochemistry. To identify the phenotype of cells expressing granulysin, laser confocal microscopic examination was performed. Dense lymphoid cell infiltration was observed in pustules and perivascular regions. A large number of these lymphoid cells were positive for granulysin. The phenotype of cells consisted of CD3+ T cells, CD8+ T cells and UCHL-1+ T cells. CD20+ B cells and CD56+ NK cells were not observed. Laser confocal microscopic examination showed that the lymphocytes producing granulysin were CD3+ , CD4+ T cells but not CD8+ T cells. We showed that many granulysin-bearing T cells infiltrated into affected follicles and perilesional dermis in superficial microbial folliculitis. However, few granulysin positive lymphoid cells were observed in sterile pustular lesions. Our observation indicated that adaptive immunity such as granulysin, lymphocyte-produced antimicrobial protein may play an important role in cutaneous defense mechanism.

Modelling a complex structure like the sweat gland requires the combination of light and electron microscopic investigations

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For the design of new effective cosmetic antiperspirants knowledge about the structure of human axillary sweat glands is an essential prerequisite. A complete morphological description of these skin appendages requires the visualization of their overall structure by light microscopy (LM) as well as the investigation of details by electron microscopy (EM). To get an overview of the complete biopsy and to preselect the specimens, the aldehyde-fixed biopsy is recorded by a confocal laser scanning microscopy (CLSM). Then, the sample is stained, cut into pieces and embedded in epoxy resin. Afterwards a confocal 3D image stack is recorded from the sample blockface and the confocal 3D data is used as a map for locating areas of interest within the ultrathin sections of the same sample for further TEM investigation. For the differentiation of eccrine, apocrine or apoeccrine sweat glands, the ultrathin sections described above are stained with a Karnovsky fixed biopsy. A confocal laser scanning microscopy (CLSM) and EM are used as described above, we developed a preparation protocol with chemical fixation and cryo- protection prior to plunge-freezing, followed by FS and embedding in Lowicryl. In summary, a complete description of a giant complex tissue like the sweat gland requires a preparation protocol that allows to investigate the same sample with different microscopic approaches.

Sclerosing mucinous blue nevus

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Sclerosing mucinous blue nevus (SMBN) is a rare autosomal recessive lysosomal storage disease due to deficiency of the enzyme fucosidase, resulting in tissue accumulation of fucosylated glycoconjugates. It manifests with progressive mental and motor deterioration, coarse facies, growth retardation, recurrent infections, dysostosis multiplex, dendromegaly and seizures. Cutaneous findings include progressive, diffuse telangiectasias and angiokeratomas (52% of patients), and hypertrichosis. We present a new patient with fucosidosis, whose skin was studied by light and electron microscopy (EM). A 9-year-old Turkish girl born to consanguineous parents presented severe mental and growth retardation, recurrent respiratory infections, pectus excavatum and diffuse angiokeratomas predominating over the abdomen and the proximal part of the thighs. The diagnosis of fucosidosis was confirmed by biochemical testing of acid hydrolases within leucocytes (complete absence of alpha-L-fucosidase activity, normal activity of beta-galactosidase, hexosaminidase, arylsulfatase A and beta-mannosidase). Light microscopic study of an abdominal skin lesion showed an aspect of angiokeratoma. Immunohistochemically, endothelial cells showed strong expression of alpha-L-fucoside residues but decreased expression of CD34. EM exam showed the presence of cytoplasmic vacuoles within several cell types, mainly blood and lymphatic endothelial cells and eccrine secretory cells; however, vacuolisation was also seen in epidermal keratinocytes, and the presence of cytoplasmic vacuoles within several cell types, mainly blood and lymphatic endothelial cells and eccrine secretory cells; however, vacuolisation was also seen in epidermal keratinocytes, and epithelial structures and electron-dense pigment were seen within these vesicles.

Fucosidosis (MIM# 230000) is a rare autosomal recessive lysosomal storage disease due to abnormal alpha-L-fucosidase activity, normal activity of beta-galactosidase, hexosaminidase, arylsulfatase A and beta-mannosidase. Light microscopic study of an abdominal skin lesion showed an aspect of angiokeratoma. Immunohistochemically, endothelial cells showed strong expression of alpha-L-fucoside residues but decreased expression of CD34. EM exam showed the presence of cytoplasmic vacuoles within several cell types, mainly blood and lymphatic endothelial cells and eccrine secretory cells; however, vacuolisation was also seen in epidermal keratinocytes, and epithelial structures and electron-dense pigment were seen within these vesicles. Malformation of the eccrine or eccrine-like precursor glands within the hairy area of the axilla. Further studies are necessary to clarify the development and the function of the apoeccrine gland. In addition, apoeccrine glands may wrongly be classified as apocrine or eccrine because they show morphological characteristics from either gland type. The morphological differences between eccrine and apocrine glands, i.e. gland size, cell type and shape, and the presence of intercellular canaliculi become clearly visible with Phalloidin staining. Since antibodies against CD44 and S-100 label intensely the eccrine and apocrine glands, respectively in superficial folliculitis, we hypothesized that infiltrating granulysin-positive lymphocytes in lesional epidermal keratinocytes respectively in superficial folliculitis. As we also observed many infiltrating lymphocytes in lesional dermatitis, we hypothesized that infiltrating lymphocytes may possess antimicrobial substances such as granulysin and play a role in defense mechanism as a second line of defense. Seven specimens of superficial microbial folliculitis diagnosed clinically and histologically were examined by means of immunohistochemistry. To identify the phenotype of cells expressing granulysin, laser confocal microscopic examination was performed. Dense lymphoid cell infiltration was observed in pustules and perivascular regions. A large number of these lymphoid cells were positive for granulysin. The phenotype of cells consisted of CD3+ T cells, CD8+ T cells and UCHL-1+ T cells. CD20+ B cells and CD56+ NK cells were not observed. Laser confocal microscopic examination showed that the lymphocytes producing granulysin were CD3+ , CD4+ T cells but not CD8+ T cells. We showed that many granulysin-bearing T cells infiltrated into affected follicles and perilesional dermis in superficial microbial folliculitis. However, few granulysin positive lymphoid cells were observed in sterile pustular lesions. Our observation indicated that adaptive immunity such as granulysin, lymphocyte-produced antimicrobial protein may play an important role in cutaneous defense mechanism.

O 24

Sclerosing mucinous blue nevus

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Abundant mucin deposition is a common finding in melanocytic nevi. We report the first example of sclerosing blue nevus with an abundant mucinous stroma. This uncommon variant of blue nevus should be differentiated from desmoplastic-neurotropic melanoma, in which the presence of mucin stromal deposition is a more typical finding.

Abnormality of clinically uninvolved skin of the forearm also showed vacuolisation of several dermal cell types as those seen in involved skin, but not in the epidermis. Despite the fact that our patient did not present at birth at severe form of fucosidosis (type I), EM examination showed extensive and severe cell vacuolisation, affecting also epidermal keratinocytes, a finding reported onley exceptionally.

O 25

Ultrastructural observations in a pigmented nevus in Hermansky-Pudlak syndrome (HPS) type 1: abnormal melanosome formation in nevus cells is of significant diagnostic value

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Granulysin, a recently identified antimicrobial protein expressed by cytotoxic T cells, NK cells and NKT cells. It is shown that granulysin contributes to defense mechanism against mycobacterial infection. Superficial microbial folliculitis is a common skin disease. In a previous report we could show,that as a first line of defense, alpha-defensin (human neutrophil peptides) and beta-defensin (human beta-defensin-2) were expressed in infiltrating neutrophils and lesional epidermal keratinocytes respectively in superficial folliculitis. As we also observed many infiltrating lymphocytes in lesional dermatitis, we hypothesized that infiltrating lymphocytes may possess antimicrobial substances such as granulysin and play a role in defense mechanism as a second line of defense. Seven specimens of superficial microbial folliculitis diagnosed clinically and histologically were examined by means of immunohistochemistry. To identify the phenotype of cells expressing granulysin, laser confocal microscopic examination was performed. Dense lymphoid cell infiltration was observed in pustules and perivascular regions. A large number of these lymphoid cells were positive for granulysin. The phenotype of cells consisted of CD3+ T cells, CD8+ T cells and UCHL-1+ T cells. CD20+ B cells and CD56+ NK cells were not observed. Laser confocal microscopic examination showed that the lymphocytes producing granulysin were CD3+ , CD4+ T cells but not CD8+ T cells. We showed that many granulysin-bearing T cells infiltrated into affected follicles and perilesional dermis in superficial microbial folliculitis. However, few granulysin positive lymphoid cells were observed in sterile pustular lesions. Our observation indicated that adaptive immunity such as granulysin, lymphocyte-produced antimicrobial protein may play an important role in cutaneous defense mechanism.


O 26

Stem cell factor and melanoma cells: a never-ending story

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The existence of a melanoma stem cell capable of self-renewal, differentiation and homeostasis of melanocytes. The expression of c-kit decreases during melanoma progression and metastatization. The efficacy of SCF in reducing melanoma growth and metastatic potential of spontaneous Melanoma Cells (MMC) is likely to be decreased accordingly. MMC obtained from 5 c-kit positive subcutaneous melanoma metastases were grown in SCF (HMB-45, anti-melanoma protein, and ST100) and the expression of molecules usually secreted by MMC during tumour progression (IL-6, IL-7, IL-8, IL-10, GM-CSF, TNF-alpha and TGF-beta) were controlled at each passage by immunohistochecmistry and RT-PCR. The induction of IL-6, IL-7, IL-8, TNF-alpha and TGF-beta in the presence of SCF. The SCF induced an increase of contractile phenotype is also observed. Myofibroblasts were initially characterized by fascin which is an actin-bundling protein has been shown to be associated with migratory abilites in in vitro studies of neural cells. In addition, in several tumour types including breast, ovarian and colonic carcinoma fascin expression has been shown by immunostaining to correlate with local invasive potential and subsequent metastasis. We investigated a series of pigment skin lesions that included thin melanomas with the aggressive phenotype outlined above. Immunostaining of formalin-fixed paraffin-embedded clinical specimens for fascin, HMB-45, Mart1 and HLA-DR was achieved with antigen retrieval methods and ABC-peroxidase methodology. Appropriate positive and negative tissue and reagent controls were used to ensure specificity of staining. Analysis of the staining included a quantitative assessment of stain intensity in cells at different depths in the lesions. A published algorithm applied to the Matlab analysis software program gave results as energy/pixel. Thin melanomas showed a significant expression of fascin compared to benign melanocytic lesions and to other melanomas of < 1 mm with clinical histories involving the more usual phenotype and subsequent progression. In particular cells at the leading edge of the positive thin melanomas showed elevated expression of fascin. Fascin may prove to be a useful indicator of early metastatic potential.

O 28

Histological features of cutaneous melanoma. An italian association of dermatopathology study

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The diagnostic efficacy of the histological parameters on which the diagnosis of melanoma is based is still to be defined. Nine dermatopathologists, affiliated to the Melanocytic Lesion Group of the Italian Association of Dermatopathology (A.D.E.P.), from eight Italian institutes, studied 64 melanocytic and 86 melanocytic nevi to perform a quantitative analysis of 13 histological parameters used in the diagnosis of melanoma (dimension; < 6 mm, asymmetry, irregular dermoepidermal junction, maturation, asymmetrical melanin, single melanocytes, large nests, loss of single malignant, suprabasal maturation, asymmetrical melanin, melanin in deep cells, cytological atypia, mitoses, dermal lymphocytic infiltrate, necrosis). The concordance among the 9 observers resulted excellent (k = 0.70) for 10 of the 13 examined features. The k values obtained by comparison with the majority diagnosis were generally good. Results showed that in melanomas, the investigated histological features were not constant (except for normal activity) and were lower in incidence as melanoma progressed. More than 93% of melanomas showed 7 or more investigated features. The efficacy of single histological features was generally poor, because of low sensitivity or specificity; suprabasal melanocytes was the only single reliable feature, contemporary showing a high sensitivity and a high specificity (0.94). Cytological atypia, dermal lymphocytic infiltrate, and asymmetry were rather sensitive (0.92, but poorly specific features of melanoma (0.86); absence of maturation, asymmetrical melanin, melanin in deep cells, mitoses and necrosis were rather specific (0.92), but not sensitive (0.55); single melanocytes predominating irregular and confluent nests and poor circumscrition were poorly sensitive (0.89) and poorly specific (0.72). The univariate logistic analysis showed that parameters useful for discriminating melanomas from controls included suprabasal melanocytes, asymmetrical melanin, asymmetry, dermal lymphocytic infiltrate, melanin in deep cells (p = 0.05). The multivariate analysis showed that two parameters (suprabasal melanocytes and asymmetry) yielded independent diagnostic information (p = 0.05).

O 29

Generalized Argyria

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Argyria is a rare cutaneous discoloration due to silver deposition. It can be localized or generalized depending on the different mechanisms of silver absorption. We describe two cases of diffuse argentosis secondary to uncontrolled use of silver in vasoconstrictor minis over a period of 30 years in two sisters. A blue/grey discoloration over sunexposed areas, more prominent on the face, less intense on the "V" of the neck, forearms, hands, was the more remarkable clinical feature.

O 30

Modulation of the phenotype of dermal fibroblast

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Dermal fibroblasts are subjected to changes according to biomechanical and molecular stimuli during physiological and pathological conditions. The demonstration that fibroblastic cells are more contractile when cultured during the wound healing process, thus modulating into myofibroblasts, has opened a new perspective in the understanding of mechanisms leading to fibrocontractive diseases. Myofibroblast is the predominant cell type present in granulation tissue and in areas of fibrosis and fibrocontractive diseases and is also present in some developing or normal adult tissues. Myofibroblasts synthesize extracellular matrix componts and during normal wound healing disappear by apoptosis when epithelization occurs. The main function of myofibroblasts is generating force and altering tissue tension during wound healing. In some dermal pathological conditions, however, abnormal expresion of contractile phenotype is also observed. Myofibroblasts can be characterized by the presence of microfilament bundles (stress fibers) that are not present in dermal fibroblasts. Morphologically, the contractile apparatus of myofibroblasts is organized as bundles of microfilaments similar to the stress fibers present in cultured fibroblasts. These actin bundles terminate at the myofibroblast surface in the fibronexus, a specialized adhesion complex that uses transmembrane integrins to link intracellular actin with extracellular fibronecin domains. It provides a mechanotransduction system capable of transmitting the force that is generated by stress fibers to extracellular matrix. Generally, fibroblasts in vivo lack the contractile apparatus that is observed in myofibroblasts. The transition from fibroblasts to myofibroblasts is influenced by mechanical stress, TGF-beta1 and extracellular matrix molecules. Two types of myofibroblasts can be characterized: profibomyofibroblasts, which contain stress fibers but lack alpha-smooth muscle actin, and differentiated myofibroblasts, which contain both stress fibers and alpha-smooth muscle actin. A better knowledge of the mechanisms influencing modulation of dermal fibroblast phenotype is crucial for preventing the development of fibrocontractive changes as well as the stromal reaction to epithelial tumors.

O 31

Dermoscopy (epiluminescence/surface microscopy) and histopathology: a two-way information flow

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The introduction of dermoscopy (epiluminescence/surface microscopy) in clinical practice has disclosed a new morphologic dimension in the study of melanocytic skin lesions (MSLs). Dermoscopy always means to histopathology for working up its diagnostic criteria; however, we also think that it is now going to raise new problems in clinopathological correlation, as summarized below.

1. The lack of a dermoscopic counterpart for dysplastic nevi. MSLs belonging to the histopathologic spectrum of the so-called ‘dysplastic nevi’ fail to show any peculiar dermoscopic feature. Presumably benign MSLs showing some architectural irregularity are better regarded to as ‘atypical nevi’ on both dermoscopy and histopathology. An interesting subset of these atypical nevi, often discovered on the trunk of young or middle-aged males, shows dermoscopically and histopathological features of regression.

2. The inconsistency of some traditional pathologic entities. There is no clear-cut clinical and dermoscopic correlate for Reid nevus; this can be best considered as belonging to the clinopathologic spectrum of (pigmented spindle cell) Spitz nevus.

3. The reappraisal of forgotten pathologic entities. Some variants of blue nevus – namely, ‘compound’ blue nevus and ‘hypogigmented’ blue nevus – deserve special histopathologic mention, because they often appear as melanoma look-alikes on dermoscopy.

4. The dermoscopic feature of Melkerson-Rosenthal syndrome. Dermoscopy can draw attention of histopathologists to suspicious areas of MSLs. Moreover, his- topathologic symmetry/asymmetry can be best studied by sampling a given MSL according to the symmetry planes seen at dermoscopy.

5. In conclusion, while learning from histopathology, dermoscopy is also expected to give new ideas and working protocols to histopathology.
**P 1**

Alterations of cutaneous skin microvasculature in lipid proteinosis

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Lipid proteinosis is a rare autosomal recessive disorder characterized by deposition of hyaline-like material in several organs, including skin. Pathogenic mutations have been found in the extracellular matrix protein 1 gene (ECM1). Some abnormalities in dermal blood vessels in this condition have been reported, but these changes have not been fully assessed. In this study, we labelled skin from a 51-year-old man with lipid proteinosis, and three control subjects, using an antibody to type IV collagen and laminin-1. Three-dimensional reconstruction of the skin microvasculature using laser confocal microscopy and computer imaging in lipid proteinosis revealed reduplication of basement membranes surrounding blood vessel walls and a very abnormal architecture to the dermal vasculature. Notably, there were enlarged vessels in the mid and deep dermis that were oriented parallel to the dermal-epidermal junction. In addition, the normal capillary loop network in the dermal papillae, as well as the subcutaneous plexus and transverse connecting vessels, were absent in lipid proteinosis. The study demonstrates that the skin microvasculature is grossly altered when ECM1 is targeted by inherited mutations and that this glycoprotein appears to have an important role in regulating blood vessel physiology and anatomy in the skin.

**P 2**

Primary and metastatic epidermidermic pigmented breast carcinoma: histological, immunohistochemical and ultrastructural analysis of four cases

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The appearance of breast carcinoma as a pigmented lesion, primitive or metastatic, is an exceedingly rare event. The histomorphological, immunohistochemical and ultrastructural aspects of this pattern, as described in a series of cases, are herein described. The results show that the neoplastic cells with epidermidermic properties surmount the dermo-epidermal junction. We report 4 cases of pigmented skin lesions, apparently primitive in one case, secondary in 3 cases, of breast carcinoma, clinically mimicking malignant melanoma. Histomorphology and immunohistochemical analysis with the Alkaline-Phosphatase anti-Alkaline-Phosphatase (APAAP) method, using the following mono- and polyclonal antibodies: S100 protein, HMB45, epithelial membrane antigen (EMA), Cytokeratin A, estrogen and progastrogen receptors, were performed. Retrospective ultrastructural investigation was performed by processing the paraffin embedded material. Neoplasms were found positive for both epithelial and melanocyte markers and a histomorphological pattern indicative for malignant melanoma was observed. Ultrastructurally, neoplastic cells were seen to contain melarin pigment but at the same time presented characteristics of epithelial glandular cells. Our data suggest that breast carcinoma sometme shows a polyvalent phenotype and the neoplastic proliferation and for cytokeratin on the glandular structures. Focal positivity was observed for Leu-/CEA and chromogranin on the glandular epithelium. The histogenesis of the glandular elements is still debated, but they probably derive from pluripotential neural crest cells, as well as the spindle cell component. Our data further support this neuroendocrine origin. In contrast with malignant glandular schwannoma, the benign variant is not associated with von Recklinghausen neurofibromatosis. Simple excision is curative, but gentle and careful enucleation is necessary to preserve normal function of the attached nerve, especially on the extremities.

**P 3**

Benign glandular schwannoma

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Benign glandular schwannoma is a rare variant of schwannoma, described for the first time by Woodruff in 1976, in which glandular inclusions with intestinal, respiratory, and epidermal differentiation were observed. The vast majority of tumors containing these glandular structures are malignant. The case of a 35 year-old woman is reported, with an asymptomatic nodule on the distal phalange of the right hand third finger. The lesion had a diameter of 1 cm, a hard consistency and was removed in toto, revealing the presence of a pseudo-capsule. On histological analysis it had a compact appearance and was composed of spindle cells that were lined up in irregular layers having different orientations. The neofromation had no atypical cytological characteristics nor did it present unusual mitotic activity, vascular invasion or necrosis. In several areas, cystic structures of variable dimensions were present and were lined by glandular epithelium composed of elongated, cubical or cylindrical cells having oval nuclei. These cells had a pale cytoplasm and were located directly on the basal membrane. Immunohistochemical analysis showed positivity for S100 protein in the schwannoma proliferation areas, but a focal positivity was observed also for Leu-/CEA and chromogranin on the glandular epithelium. The histogenesis of the glandular elements is still debated, but they probably derive from pluripotential neural crest cells, as well as the spindle cell component. Our data further support this neuroendocrine origin. In contrast with malignant glandular schwannoma, the benign variant is not associated with von Recklinghausen neurofibromatosis. Simple excision is curative, but gentle and careful enucleation is necessary to preserve normal function of the attached nerve, especially on the extremities.

**P 4**

Nanometric changes of hair shafts measured by atomic force microscopy in a patient with Comel-Netherton syndrome

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Comel-Netherton syndrome is an autosomal recessive disorder characterised by typical skin and hair findings on the distal phalange of the right hand third finger. The lesion had a diameter of 1 cm, a hard consistency and was removed in toto, revealing the presence of a pseudo-capsule. On histological analysis it had a compact appearance and was composed of spindle cells that were lined up in irregular layers having different orientations. The neofromation had no atypical cytological characteristics nor did it present unusual mitotic activity, vascular invasion or necrosis. In several areas, cystic structures of variable dimensions were present and were lined by glandular epithelium composed of elongated, cubical or cylindrical cells having oval nuclei. These cells had a pale cytoplasm and were located directly on the basal membrane. Immunohistochemical analysis showed positivity for S100 protein in the schwannoma proliferation areas, but a focal positivity was observed also for Leu-/CEA and chromogranin on the glandular epithelium. The histogenesis of the glandular elements is still debated, but they probably derive from pluripotential neural crest cells, as well as the spindle cell component. Our data further support this neuroendocrine origin. In contrast with malignant glandular schwannoma, the benign variant is not associated with von Recklinghausen neurofibromatosis. Simple excision is curative, but gentle and careful enucleation is necessary to preserve normal function of the attached nerve, especially on the extremities.

**P 5**

Early response in human breast skin cultures after a single dose of gamma-rays: an ultrastructural study

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Radiation therapy with ionising radiations (gamma-rays) is the main non-surgical treatment for cancer, but skin reaction is the most common side effect of such a treatment. At present, the scientific rationale of the management of skin response is still lacking. Though the rationale rearrangement induced by a single dose of gamma-rays. Together with our previous observation by immunofluorescence analysis indicating that, in these experimental conditions, a strong inhibition of cell proliferation occurs, these results demonstrate that gamma-rays induce a very early alteration of epidermal homeostasis. A topical therapy before the irradiation can be thus a suitable approach to limit and/or avoid the onset of the early epidermal response, with particular regard to keratinocytes.

**P 6**

Histopathological Evaluation Of Injection Site Reactions In Patients Treated With Enufivitide

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Enufivitide is the first of a new class of antiretroviral agents. Injection site reactions are the most common adverse events. The aim of the present study was the histopathological evaluation of injection site reactions in patients treated for 80 weeks. Five patients were submitted to cutaneous biopsies using a 4 mm punch. Sections were stained with haematoxylin-eosin, periodic acid-Schiff stain and Verhoeff’s stain. Moreover, immunohistochemical studies were carried out using CD20, CD45Ro and CD34 antibodies. Histological examination showed three patterns: 1) an acute urticarial/vasculitis-like pattern associated with inflammation of the fat tissue; 2) a subacute pattern with an initial derma sclerosis; 3) a chronic sclerodema-like pattern with connective tissue disposed around the adnexa, whose structure was intact. The immunohistochemical study evidenced a prevalence of T lymphocytes and a moderate neangiogenesis. Conclusions: In our experience, after a rather long period of treatment with enfuvitide, cutaneous reactions comprised a variety of features largely independent of the virological and immunological outcome. The adnexa were unaltered in all patients, indicating a tendency to a possible regression of the sclerotic lesions. Therefore, patients should be encouraged to rotate the sites of injection thus permitting the tissues to regenerate.
P 7
Disseminated epidermolytic acanthoma of the scrotum
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The term epidermolytic hyperkeratosis (EHK) describes a characteristic histopathological pattern with granular degeneration caused by alterations of tonofilament organisation and breakdown of intracytoplasmic keratins with unaffected desmosomes. EHK has been applied to a spectrum of mostly dominantly inherited dermatoses, but it is also a feature of some acquired cutaneous disorders, e.g. epidermolytic acanthoma, and an incidental finding, showing the morphological feature in single rete ridges, and in perilesional regions of e.g. epidermal neoplasms, scars and inflammatory diseases. We report the case of a 74-year-old white man with itching papules of the scrotum existing for one year. By electron microscopy, the lesions revealed the typical morphological features of EHK with generalized clumping-aggregations and more or less loss of fibrillar character of tonofilaments in suprabasal epidermal cells. These features are the counterparts to the partly degenerative partly dyskeratotic pattern by light microscopy. On the basis of the clinical history, the morphological changes as well as the absence of human papilloma virus DNA, the final diagnosis was disseminated epidermolytic acanthoma of the scrotum. Mucocutaneous and genital EHK eruptions are rare and may easily be misinterpreted. In hereditary conditions, mutations in genes coding differentiation-specific keratins underlie EHK. These are suprabasal keratins 1 and 10 in bullous congenital ichthyosiform erythroderma and nevus verrucous affecting non ridged skin, and keratin 9 in palmoplantar keratoderma Voerner affecting ridged skin. The pathogenesis of EHK in acquired conditions is still unknown. Interpretations and speculations include mechanisms of immunosuppression and decreased immune surveillance, trauma, and metabolic disturbances. Forms of mosaicism due to somatic mutations, i.e. postzygotic neoplastic DNA changes, cannot be ruled out either. Recent in vitro results indicate that several mechanisms seem to be able to interfere with the highly dynamic keratin filament cytoskeleton.

P 9
Anaplastic large T cell lymphoma (ALCL)
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Anaplastic large T cell lymphoma (ALCL) represents a distinct subtype of non-Hodgkin’s lymphoma that typically involves multiple nodal and extranodal sites at the time of presentation, including the skin. A 59-year-old man came under our observation for asymptomatic red nodules on the neck, the chest and on the upper back that had appeared 2 months earlier. Laboratory tests and imaging procedures were normal. A biopsy revealed tumour cells with atypical large nuclei, high mitotic rate and a high proliferation index. Immunohistochemistry showed a positive reaction with CD30, ALK, L26 and BerEp4 antibodies. A diagnosis of cutaneous anaplastic large T cell lymphoma was made. After three months lymphadenopathy appeared on the right axilla. Lymph node biopsy showed identical features to those noted in the previous skin biopsy. The patient was referred to a Haematology department where he is actually under treatment with polychemotherapeutic drugs.

P 11
The thermo phobic foams: pharmacokinetic properties and clinical efficacy data
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Traditional topical formulations are creams, ointments, gels and lotions. These formulation vehicles, to be used for patients with dermatoses (Salam Capizzi 2003) foam containing natural pyrethrin 0.1% has shown to be at least as effective as permethrin but when applied to skin the body heat causes the foam structure to break down and the active ingredients are rapidly absorbed into the skin. Thus, deficiency in either cell type did not affect BM-formation, demonstrated by growing keratinocytes or fibroblasts (human/mouse, HF/MF) by either blocking interactions or implementing molecular deficiencies, HK or HaCaT cells were grown on collagen gels harboring HF or MF from normal or ko-mice. Nidogen-laminin interaction was blocked by the laminin-fraction (gamma-1,-IIIC,-5, L-gamma-6 binding nidogen). BM-formation was surveyed by immunofluorescence (IF), regular (EM), immuno-electron microscopy (IEM), and Western blots of protein extracts of separated epithelial and ‘dermal’ tissue. In 3D-cultures of HK and HF L-gamma-1/C0/C0-MF or HaCaT antisense-perlecan cells with normal keratinocytes or fibroblasts (human/mouse, HF/MF) reduced additionally nidogen-2, collagen-IV, and laminin-10. Absence of nidogen-1/-2/-3/-4/-5/-6 further abolished collagen-IV and laminin-5; integrins such as alphabeta5/apo on normal (IF), BM-formation could be reinstated with recombinant nidogen-1 or 2. BM-perlecan, for comparison, is apparently synthetised also by keratinocytes. Thus, deficiency in either cell type did not affect BM-formation, demonstrated by growing perlecan (---/---)-HF or HaCaT antisense-perlecan cells with normal keratinocytes or fibroblasts, respectively. Accordingly, BM-components are efficiently recruited for ultrastructural assembly in this skin model.
Announcement on behalf of the Society for Cutaneous Ultrastructure Research (SCUR)

32nd Annual Meeting of the SCUR, 2–5th June 2005, HAMBURG – Germany
Joint Meeting with the International Society of Skin Pharmacology and Physiology (ISP)

For a preliminary information, please contact

Dr. Roger WEPF, Local Host Organizing Committee via e-mail: Roger.Wepf@Beiersdorf.com

or

Dr. Sonja STÄNDER, SCUR-Board Member via e-mail: Sonja.Staender@uni-muenster.de

Deadline for the Abstract submission is April, 2nd 2005.

Find the First Announcement for 2005 within the website of SCUR at http://www.dermis.net/org/scur/index.htm

SCUR is an International Society, the aims of which are:

- Research in electron and light microscopy, other combined visualization techniques and molecular biology tools applied to cutaneous biology and pathology.
- Understanding of ultrastructure and function of human skin in health and disease.

The SCUR Annual Meetings are open to all interested scientists.

AWARDS
The Society awards the best oral and the best poster presentation. In addition, a travel grant is offered to young members (up to 35 years) of the SCUR. This grant can be requested by applying to the Secretary. An Application Form (see Website) must be sent to the SCUR Secretary at least 1 month before the beginning of the Annual Meeting.

The ABSTRACTS of the meetings are published in “The Journal of Investigative Dermatology”.

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