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22nd LJUDEVIT JURAK INTERNATIONAL SYMPOSIUM ON COMPARATIVE PATHOLOGY

MAIN TOPIC

PATHOLOGY OF THE SKIN

CONFERENCE PAPERS

June 3 - 4, 2011
ZAGREB, CROATIA

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Under the Auspices of European Society of Pathology
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LECTURES

CONCERNING APPEARANCE, BENIGN BEHAVIOUR: THE PSEUDOLYMPHOMA SPECTRUM

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The spectrum of cutaneous pseudolymphomas (reactive lymphoid hyperplasia, lymphocytoma cutis) is very wide and the histologic differential diagnosis is often difficult. In only a proportion of cases, the aetiology of the process can be elucidated and close clinicopathological correlation is essential to reach the diagnosis. Even with adequate clinical information and detailed microscopic examination, in a proportion of cases the diagnosis of lymphoma cannot be entirely ruled out. In this setting, ancillary techniques including molecular biology studies and further biopsy or biopsies may be necessary over time for the diagnosis to be made. Cutaneous pseudolymphomas can be divided into two categories, T cell and B cell pseudolymphomas. This distinction is artificial, since the infiltrate is frequently composed of both B and T cells. The separation is, therefore, mainly based on the overall pattern of the infiltrate rather than the type of cell that predominates. Infiltrates with a T cell pattern tend to be focal with a predominant perivascular and periadnexal distribution and involvement of the epidermis and/or adnexal structures. Infiltrates with a B cell pattern are more diffuse and nodular and tend to spare the epidermis and adnexal structures. As it will be seen during discussion, this is an oversimplification that mainly serves a didactic process.

PROBLEMATIC MELANOCYTIC TUMOURS IN CHILDREN

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The diagnosis of melanocytic tumours remains one of the most important challenges to the practicing pathologist. This is largely due to the wide morphological spectrum with often only subtle differentiating features resulting in potential for both over- as well as underdiagnosis of melanoma. Problems arise especially with the diagnosis of unusual variants of melanoma and tumours closely resembling benign naevi (naevoid melanoma). In addition, a subset of melanocytic naevi show features more typically associated with melanoma. In the paediatric patient population, spitzoid tumours in particular pose a diagnostic dilemma, as they are notoriously difficult to classify and their biological potential is not fully understood. Furthermore, mitotic activity and active regression (halo phenomenon) is not infrequently observed in this age group giving cause for concern. Finally, neonatal and congenital naevi may show atypical architectural and cytological features including the formation of proliferative cellular nodules. While the vast majority of melanocytic lesions in the paediatric patient population are benign, distinction from childhood melanoma is essential, as it is associated with significant morbidity and even mortality. The histological spectrum and clinical behaviour of the rare melanomas of childhood and adolescence will be discussed in the context of the relevant differential diagnosis and diagnostic pitfalls to increase awareness of this difficult topic.

HPV GENITAL INFECTIONS FROM THE PERSPECTIVE OF DIFFERENT MEDICAL SPECIALTIES

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In spite of the fact that human papillomavirus (HPV) genital infections represent a significant dermatovenereological disease, the interdisciplinary team of different medical specialists including pathologists should be involved in the comprehensive management of this complex issue. Anogenital warts (condylomata acuminata) are the most common HPV lesions presented in men, however, during the last decade other HPV associated exaggerated lesions such as condylomata plana, penile, scrotal, and anal intraepithelial neoplasias, as well as the penile, urine bladder and prostate cancer have been studied a little bit more extensively. Consistent studies are still sparse in male population. More than 35 types of HPV infect genital tract, with types 16 and 18 inducing about 70% of high-grade intraepithelial genital neoplasias, such as penile, anal, scrotal, vulvar, vaginal, etc. (thus not only cervical), whereas HPV 6 and 11 cause 90% of anogenital warts. However, the 'banality' of anogenital warts should not be underestimated providing that the high risk HPV DNA 16 and 18 can be isolated (PCR) from 'benign' HPV associated genital lesions (anogenital warts) in 10%-20% of patients, i.e. more than usually expected. On the other hand, the presence and the recalcitrant course of HPV DNA 6 and 11 associated diseases pose a significant physical and psychological problem for both men and women. A prophylactic vaccine that targets these types should thus substantially reduce the burden of HPV associated clinical diseases. Ultimately, within the spectrum of therapeutic options for condylomata, no method is superior to others; recurrences occurred in 30%-70% of cases. We definitely need the HPV vaccination program to get rid of one of the oldest and up to now unsolved problems of mankind. Since HPV is transmitted by sexual intercourse, managing both partners is necessary to eliminate the virus in the population. Approaches to this include prophylactic vaccines such as quadrivalent HPV vaccine for both men and women. This should be the only way to significantly decrease the numbers of infected persons. Besides, proper dermatologic training is required as the clinical criterion is still very important and the HPV induced lesions get quite often misdiagnosed unless managed by the skilled professional. Thus, it can be concluded that the dermatovenereologists, together with the representatives of other medical specialties, should definitely be part of the HPV vaccine program team.

THE SIGNIFICANCE OF HISTOPATHOLOGIC FACTORS OF MALIGNANT SKIN TUMORS IN DERMATOLOGIC PRACTICE

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Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common types of non-melanoma skin cancer (NMSC) with the incidence increasing globally every year. However, in the last decades, the incidence rates of cutaneous melanoma, one of the most aggressive skin tumors, have also been increasing markedly worldwide. BCC is the most common human malignancy, which presents as a slowly growing, locally aggressive epithelial tumor histologically composed of palisading basaloid tumor cells. There are numerous clinical variants of this tumor and the histologic features to some extent correlate with clinical appearance. BCC extremely rarely metastasizes, usually in cases of large, ulcerated and infiltrative tumors, or with the presence of histologic features such as blood vessel invasion or perineural infiltration. Also, sclerosing or morpheaform BCC is often clinically aggressive and may involve deeper structures, therefore requiring more aggressive therapy. The metatypical BCCs (showing features of both BCC and SCC) are alleged to behave more aggressively. Cutaneous SCC is less common than BCC, however, it represents one of the most common skin malignancies in dermatologic practice. Valuable prognostic factors of SCC included in a routine dermatopathology report are diameter and thickness of the lesion, as well as the level of invasion. Lesions less than 1 cm in diameter have an extremely high cure rate. As the diameter increases, both the risk of local recurrence and distant metastases increase. Perineural involvement and poorly differentiated cells are also unfavorable signs. There are numerous prognostic information available in a routine melanoma histopathology report. Features associated with a potentially worse prognosis of melanoma are increasing Breslow tumor thickness, increasing Clark's level, ulceration, increasing number of mitoses/mm^2 (mitotic index), vertical growth phase, regression, absence of host inflammatory response, increased tumor vascularity, vascular invasion, neurotropism, marked atypia and satellite metastases.

MOLECULAR MECHANISMS OF SKIN DISEASES

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Three main forms of skin cancer, depending on the type of epidermal cells affected, are basal cell carcinoma, squamous cell carcinoma and cutaneous melanoma. Our research is focused on two of them, i.e. basal cell carcinoma (BCC) as the most common skin neoplasm, and melanoma as the most aggressive skin cancer. Although widespread and with increasing incidence, both were not well understood at the level of molecular pathogenesis until recently. Progress over the past decade has identified an array of molecular alterations in these neoplasms that may provide opportunities for new molecular therapeutics. A number of genetic alterations have been characterized, some of them involving gain-of-function changes in oncogenes, whereas others involve loss-of-function of genes that act as suppressors of tumor formation. The spectrum of changes differs among these tumor types. Major events in BCC onset and development are various alterations in the Sonic Hedgehog/Patched/Smoothened (SHH/PTCH/SMO) pathway, in particular PTCH1 loss-of-function, as well as gain-of-function by SHH, SMO and GLI. An important role in the genesis of melanoma plays CDKN2A locus on 9p21, encoding a cyclin-dependent kinase inhibitor p16 that acts to inhibit cell cycle progression in the G1 phase by binding and inhibiting CDK4/6 kinases. Loss of p16 leads to deregulated CDK4/6 action and to promotion of cell divisions. Involvement of p16 in melanoma development has been demonstrated either through loss of heterozygosity (LOH) for DNA markers within chromosome 9p21, or by mutational screenings of p16. We have been investigating the roles of both markers, PTCH and p16, in the pathogenesis of both cancers, cutaneous melanoma and basal cell carcinoma, and suggested the involvement of SHH/PTCH/SMO pathway by different mechanisms. Our particular interest in the role of SHH/PTCH/SMO pathway in various human cancers, which started with BCC and has more recently included melanoma, is motivated by the potential therapeutic use of small molecule antagonists that block the pathway. Another promising approach in melanoma research is the mitogen-activated protein (MAP) kinase pathway, which is affected in 40% to 60% of these carcinomas. The pathway is activated by mitogenic signaling from the membrane receptors towards the nucleus, which begins with the RAS, a small G protein, to protein kinase BRAF (an enzyme that adds phosphate groups to proteins to alter the substrate's function). The BRAF mutation (the V600E mutation) constitutively activates the pathway by increased kinase activity, leaving the 'growth' signal always turned on. It has been shown that RAS with oncogenic potential to induce melanoma in transgenic mice requires the active SHH/PTCH/SMO pathway. Additionally, it was found that RAS mediated by MAP and downstream AKT signaling regulates the nuclear localization and transcriptional activity of GLI1, which is a main citoplasmatic oncogene of the SHH/PTCH/SMO pathway in melanoma cells. All these recent findings suggest that an integrated approach to the RAS/AKT and SHH/PTCH/SMO pathways has a great and possibly synergic potential for future therapies of BCC and particularly of melanoma.

DERMATOPATHOLOGY OF DOMESTIC ANIMALS

Suzana Tkalčić

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Animals present with many skin conditions and diseases that are similar to those in humans, but also come with some quite specific features for a given species or breed. We will review common pathologies of the skin in domestic/companion animals. In recent years, atopic dermatitis/atopy, a genetically predisposed allergic dermatitis with extensive inflammation and pruritus, is on a rise among dogs in urban settings fed processed dog food. Urticaria and angioedema initiated by many immune stimuli occur in dogs and horses. Juvenile pyoderma affects pups less than 4 months of age that present with multiple pustular and nodular lesions on the face, ears and mucocutaneous junctions. Among autoimmune disorders, pemphigus foliaceus and pemphigus vulgaris occur in dogs, cats, horses and goats, and present with various degrees of acantholysis. In domestic animals, parasitic diseases of the skin or adnexa are common. Mites cause severe cutaneous lesions (mange) in food animals, dogs, cats and rabbits (*Sarcoptes* sp., *Psoroptes* sp., *Demodex canis*). Dermatophytoses (the genera *Trichophyton* and *Microsporum*) commonly present a zoonotic issue between companion animals and their owners. Of viral diseases, some with zoonotic potential, calicivirus and poxvirus infections of many terrestrial and marine mammals, present with vesicular dermatitis and proliferative lesions (hyperkeratosis/parakeratosis), respectively, while herpes virus infection in cattle and horses will result in large areas of alopecia and depigmentation. Equine papilloma virus in young horses present with warts on the skin of ears, legs, lips and nares. Cutaneous manifestations of some endocrine disorders or systemic diseases include laminitis in horses, cutaneous paraneoplastic syndromes (pancreatic paniculitis, thymoma) in dogs and cats, hepatocutaneous syndrome, and Cushing's disease (hyperadrenocorticism). Hypothyroidism in dogs typically presents with obesity, symmetric alopecia, and hyperpigmentation, while pituitary adenomas of pars intermedia in older horses present with hirsutism and excessive sweating. Of neoplastic diseases, malignant mast cell tumors (most common in boxer dogs), squamous cell carcinomas, basal cell tumors, cutaneous histiocytomas, melanomas, adenocarcinomas of perianal glands are most prominent. Cutaneous lymphomas-epidermal form (T lymphocyte), also known as mycosis fungoides, occurs in dogs. Extramedullary plasmacytomas occur in dogs and cats. Acral lick granulomas (neurodermatitis) are common on the legs of dogs and are associated with boredom or separation anxiety.

A RETROSPECTIVE STUDY OF CANINE CUTANEOUS TUMORS IN CROATIA

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During a three-year period, from January 2006 to December 2009, a total of 1658 canine biopsy specimens including post mortem samples were received and histopathologically examined at Department of Veterinary Pathology, Faculty of Veterinary Medicine, in Zagreb. Out of these, 717 or 43.24% were canine cutaneous tumors, among which 340 (47.42%) were malignant, 365 (50.90%) benign and 11 were not specified. The most frequently diagnosed tumors were hepatoid gland tumors (13.94%), mast cell sarcoma (10.38%), lipoma (10.10%), canine cutaneous histiocytoma (6.69%) and squamous cell carcinoma (5.69%). The rest of 31 different types of skin tumors were diagnosed with a frequency less than 5%. The average age of dogs was 8 years and three months, with a range from two months (papilloma) to 21 years (lipoma). There was no sex difference in the rate malignancy.

POSTERS

PRIMARY CUTANEOUS MENINGIOMA OF THE SCALP: CASE REPORT

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Meningiomas arise from the meninges of the brain or spinal cord. They are the most common tumors of the central nervous system (CNS). Cutaneous meningiomas are rare tumors. Most of them occur in the head and neck. Several theories exist to explain their histogenesis. Lopez *et al*. have postulated classification of cutaneous meningiomas based on simple clinical and pathological features. Three different types are described. Type I have benign behavior and are localized in the skin of the scalp, forehead and paravertebral areas. Type II are meningiomas of the soft tissue with extension to the skin, have a less favorable prognosis and usually are situated in periorbital, perineural and periauricular soft tissue. Type III are meningiomas of the CNS with extension to the skin, with dismal prognosis. We present a case of primary cutaneous meningioma in a 39-year-old man with a history of myasthenia gravis. Physical examination revealed a subcutaneous, firm, painless lump of the left parietal scalp. Computed tomography showed a homogeneous well-delineated soft tissue mass, without bone or intracranial invasion and communication between the tumor and subdural space. The mass was excised. Grossly, the tumor measured 5 cm in greatest dimension, with a white, firm cut surface. Microscopically, it was composed of solid sheets and strands of meningothelial cells embedded in dense collagenous tissue, without atypia, mitoses or necrosis. Psammoma bodies were present. In our patient, the tumor was classified as a type II. Immunohistochemical staining showed positive expression for epithelial membrane antigen, vimentin and negative for smooth muscle actin, cytokeratins (CKAE1/AE3, CK20), chromogranin, desmin, sarcomeric actin, NSE, S100, CD68, GFAP, CD34, CD31 and HMB45. The patient did not show any sign of recurrence one year after the procedure. Cutaneous meningiomas are microscopically and immunohistochemically identical to their meningeal counterparts. Extracranial cutaneous meningiomas should be considered on differential diagnosis of unusual scalp lesions. The diagnosis is based on histologic and immunohistologic examination confirming the meningothelial origin of the neoplastic cell population.

MOSAIC MORPHOLOGY OF LEYDIG CELLS IN INFERTILE PATIENTS WITH NON-OBSTRUCTIVE AZOOSPERMIA

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One of the most severe forms of male infertility is non-obstructive azoospermia (NOA). NOA is frequently characterized by heavy damage to seminiferous tubules that has already been described in the literature. Much less is known about changes of Leydig cells. The hypothesis of this study is based on the assumption that Leydig cells in patients with NOA are significantly different (damaged) from the same type of cells in the control group. Therefore, the aim of the current survey was to investigate Leydig cells in two groups (control and the group of infertile men with NOA) by use of qualitative and quantitative histologic methods and immunohistochemistry (the expression of testosterone *in situ*). In addition, blood levels of gonadotropins and testosterone were determined. Results of qualitative histologic analysis showed a kind of a 'mosaic' picture of regular and irregular Leydig cells in NOA cases. Quantitative histologic analysis indicated a significantly lower number of testosterone-producing cells. NOA patients also had significantly lower testis volume and status of spermatogenesis when compared to controls. The results of the study pointed out that the patients with NOA could suffer from a deficit of androgens as well as from premature andropause.

PRIMARY LOCALIZED CUTANEOUS NODULAR AMYLOIDOSIS: CASE REPORT

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Primary localized cutaneous nodular amyloidosis (PLCNA) is a rare form of primary localized cutaneous amyloidosis that presents as yellowish or reddish waxy nodules on the extremities, face, trunk or genitalia. It is characterized by amyloid deposits in the dermis that are produced by local plasma cells. Histologic findings are indistinguishable from those of primary systemic amyloidosis. A 75-year-old man presented to our ENT department with solitary tumor located on the right nostril. Complete excision was made and the material was referred for pathologic examination. The tumor was 1 cm in diameter, grey reddish on the cutting surface. Microscopic examination revealed deposits of eosinophilic amorphous material in the dermis. Mild infiltrate of plasma cells (CD138 positive) could be seen in the amorphous material and next to small blood vessels in the dermis. The amorphous material stained positively with Congo red and demonstrated green birefringence with polarizing microscopy. The immunohistochemical imaging revealed the cytoplasm of infiltrating plasma cells to stain with both anti-kappa and anti-lambda chains. Additional extensive clinical and laboratory workup revealed no systemic involvement. The patient's medical history revealed no diseases and previous or current medical treatments. The patient was treated surgically. The diagnosis of PLCNA was made in February 2011, and no further information on this case can be presented. In conclusion, immunohistochemical analysis revealed polyclonality of the infiltrating plasma cells, which is generally a less common characteristic of primary localized cutaneous amyloidosis. However, extensive clinical and laboratory workup showed no systemic involment of amyloidosis nor revealed any other acute or chronic disease that could result in secondary amyloidosis. This is an even rarer case of PLCNA with plasma cell polyclonality.

EX VIVO DEVELOPMENT OF SKIN IN THE RAT LIMB BUD

V. Mužić[1,2], F. Bulić-Jakuš[1], G. Jurić-Lekić[3], M. Himelreich[3], Ž. Majić[1], N. Sinčić[1], A. Katušić-Bojanac[1], M. Vlahović[1], Lj. Šerman[1]

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The aim of this investigation was to explore the *ex vivo* developmental potential of rat limb buds to develop skin in a serum-supplemented organ culture system. Fisher rat fore- and hind-limb buds were microsurgically removed under a dissecting microscope from 13- and 14-day-old embryos and placed on a lens paper supported by a stainless steel grid, where they spent three days or two weeks at the air-liquid interface. Eagle's Minimum Essential Medium was supplemented with 50% rat serum and changed every other day. Samples were processed by routine histology, embedded in paraffin, and uninterrupted serial sections were stained by HE, Masson trichrome or Azan stain. In isolated limb bud, immature epithelium covering its surface was present. During the 3-day culture period, stratified epithelium developed. In limb buds that spent two weeks in culture, keratinization of the stratified epithelium and fully developed stratum granulosum could be discerned in some explants. It is concluded that limb bud organ-culture provides an appropriate model to follow skin development *ex vivo*, which might be of interest for investigation of pharmacological compounds in skin development.

INFLUENCE OF THE ANTIOXIDANT PBN AND TERATOGEN 5-AZACYTIDINE ON RAT EMBRYO DEVELOPMENT *EX VIVO*

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The influence of the antioxidant PBN (N-tert-butyl-a-phenylnitrone) and the DNA demethylating agent 5-azacytidine (5-azaC) on the most critical stage of mammalian development (gastrulation) was investigated *ex vivo*. Microsurgically isolated 9.5-day-old Fisher rat embryos were cultivated for two weeks at the air-liquid surface in Eagle's MEM with 5-azacytidine (5 μM) and/or PBN (22.6 μM) and controls in MEM or in MEM with 50% rat serum. Explant diameters were measured by an ocular micrometer at the beginning of culture and then every other day. Growth areas were determined in arbitrary units and data normalized to those obtained in MEM. 5-azaC impaired growth in comparison to MEM by approximately 40%. PBN applied with 5-azaC ameliorated growth of 5-azaC treated explants by approximately 25%, and in comparison to control grown in MEM by 25%, although it was less than in the medium with serum. *Ex vivo* in a chemically defined proteinless medium, it was possible to discover an ameliorating influence of PBN alone upon the embryo development, which was not possible before in the complicated *in vivo* system during gestation. These results are of importance for new therapeutic strategies in human medicine using antioxidants and epigenetic drugs.

MESENCHYMAL CHONDROSARCOMA OF THE SUBOCCIPITAL REGION: CASE REPORT

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Mesenchymal chondrosarcoma is a rare malignancy, which differs from conventional chondrosarcoma by both specific morphology and clinical features. The rare mesenchymal variant is characterized by a biphasic histologic pattern of small undifferentiated round cells intermixed with islands of malignant cartilage differentiation. Areas resembling a vascular tumor such as hemangiopericytoma may also be present. It typically occurs in young adults, rarely after 40 years of age, with no sex predilection. Mesenchymal chondrosarcoma is a particularly aggressive neoplasm with a strong tendency toward late local and metastatic recurrences, leading to 10-year survival rates below 50%. A 45-year-old female presented with a history of right-sided hearing impairment and headache in the right suboccipital region. Apart from the hearing loss, neurologic examination revealed no other deficits. Multislice computed tomography identified the presence of a poorly vascularized tumor of the suboccipital region. The tumor was surgically resected *in toto* and referred for pathologic analysis. Histology revealed tumorous tissue consisting of small uniform mesenchymal cells with hyperchromatic nuclei and sparse cytoplasm. Some tumor regions showed hemangiopericytoma-like features. Areas of chondroid differentiation with focal ossification were noted between the sheets of small round cells. The cells showed a low mitotic count, without pathologic mitosis. Immunohistochemical staining revealed CD99, BCL2 and vimentin positivity. The diagnosis of mesenchymal chondrosarcoma was made. Because of its specific biological and clinical behavior, it is important to differentiate mesenchymal chondrosarcoma histologically from similar lesions such as hemangiopericytoma, Ewing's sarcoma, primitive neuroectodermal tumor, and other subtypes of chondrosarcoma.

TRANSITION OF EPIGLOTTAL EPITHELIUM DURING HUMAN DEVELOPMENT

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Our previous results have shown that human epiglottal epithelium changes during development, from single-layered squamous epithelium in the 6-week-old embryo to two-layered cuboidal epithelium in the early 8-week-old embryo; in the newborn, pseudostratified epithelium with goblet cells predominates and after the air-flow is established, stratified squamous epithelium predominates. Seven-week-old and 9-week-old embryo epiglottal epithelium was now analyzed in more detail and compared. Embryos from the celloidin collection of human embryos belonging to the Archive of the Department of Histology and Embryology were stained by HE, Azan, Masson trichrome stain, Verhoeff iron hematoxylin and PAF-Halmi. Epiglottal epithelia were investigated by light microscopy. In the 6-week-old embryo, epiglottal swelling was covered by a single layer of cuboidal cells. In the 7-week-old embryo, two-layered cuboidal epithelium was discovered. In 9-week-old fetus, epiglottal epithelium was multilayered columnar without cilia and goblet cells. It has now been confirmed that single-layered epiglottal epithelium has changed to the two-layered epithelium already in the 7-week-old embryo. Developmental studies like this one might be of importance for tissue engineering purposes.

DETECTION OF CLONAL T-CELL RECEPTOR GAMMA CHAIN GENE REARRANGEMENTS IN SUSPECTED CUTANEOUS T CELL LYMPHOMAS

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Molecular analysis of rearranged T cell receptor (TCR) represents an important diagnostic tool in diagnosing cutaneous T cell lymphomas. We report here three cases suspected of cutaneous T cell lymphomas, for which dermatopathologists were unable to give final diagnosis without the use of T cell clonality analysis. Working diagnoses in study patients were mycosis fungoides, cutaneous lymphoma and pseudolymphoma. DNA was extracted by NucleoSpin Tissue XS kit (Macherey-Nagel, Germany) designed for extra small amount of material (less than 100 cells), and suspected cells were selected by laser-microdissection from microscopic slides of paraffin embedded biopsy materials. Using modified BIOMED multiplex nested PCR and primers specific for gamma chain of the T cell receptor (TCR-γ), we were able to amplify the specific gene region. The PCR products of 65 to 95 bp in length, labeled with 6-FAM flourescent dye, were separated by capillary electrophoresis on the ABI Prism 310 Genetic Analyzer; results were analyzed by use of GeneMapper software (Appl. Biosystems). In all experiments, positive and negative controls were included. Multiplex nested PCR analysis was performed in triplicates. Specific amplification products of 65 to 95 bp were obtained in all experiments, and separation and analysis of amplicons revealed polyclonal rearrangement patterns in all three cases. The results obtained showed absence of clonal rearrangement and indicated reactive proliferation. In conclusion, capillary electrophoresis sensitivity reached down to1 bp, so we were able to easily distinguish different clones. The multiplex nested PCR method and capillary electrophoresis proved to be a highly sensitive screening tool for clonal TCR-γ chain gene rearrangements.

ROE DEER (*CAPREOLUS CAPREOLUS*) WARTS – FIBROMAS, PAPILLOMAS OR FIBROPAPILLOMAS

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Roe deer fibropapillomatosis is mainly a benign neoplastic disease caused by papillomaviruses. Previously, based on the gross appearance of the lesions, such skin tumors were usually classified by practitioners as fibromas and papillomas. On the other hand, a part of the literature describes these lesions as fibropapillomas. The aim of the study was to determine histologic characteristics of the lesions in roe deer in order to improve the knowledge of the appearance of papillomavirus induced neoplastic lesions in roe deer in Croatia. As part of the surveillance of wildlife diseases, three roe deer with few clearly visible skin lesions were presented to the Faculty of Veterinary Medicine. Gross examination was taken on the field, while samples of the lesions were alcohol fixed and submitted for histopathologic analysis (routine HE staining). Grossly, lesions were ranging in size from 1.5 to 19 cm. Some of these lesions were covered with intact skin, while in others the surface was hyperkeratotic and hyperpigmented with several ulcerations. Histopathologic analysis revealed elements that are characteristic of both fibromas and papillomas. Roe deer fibropapillomatosis is present in Croatia as an endemic disease, similarly to other European countries. It is a benign, in wild animals incurable disease, which depending on the location of the lesions can, with duration of the disease, cause severe or minor effects on the overall health and survival rate of the affected individual. From the results obtained, it is concluded that the majority of analyzed lesions contain both fibromatous and papillomatous characteristics, and therefore we find the term fibropapillomatosis suitable to describe this condition. Systematic survey and detailed examination of papillomavirus induced neoplasms is necessary for better understanding of its epidemiology.

MORPHOLOGICAL FEATURES OF PLAQUE LESION OF MYCOSIS FUNGOIDES

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The aim of the study was to show the frequency of lichenoid dermal infiltrate, Pautrier's microabscesses, sentinel lymphocytes, atypia and antigen loss of T cells in mycosis fungoides (MF). The diagnosis of early patch lesion of MF is difficult because of the lack of characteristic morphological features. This study showed that even in plaque lesions, not all MF features are always present. In this retrospective study, we reviewed 54 skin biopsies from patients with plaque stage MF diagnosed and treated at Department of Pathology and Cytology and Department of Dermatology and Venereology, Zagreb University Hospital Center from January 2006 to December 2010. There were 25 females and 29 males, median age 48 (range 38-77) years. The following criteria of MF were evaluated: presence of lichenoid infiltrate, Pautrier's microabscesses and sentinel lymphocytes, atypia and surface antigen loss of T cells. Lichenoid infiltrate and atypia of T cells with intermediate size lymphocytes and irregular or cerebriform nuclei were found in all 54 study cases. Pautrier's microabscesses were found in 33 (61.1%), sentinel lymphocytes in 32 (59.3%) and antigen loss in 38 (70.4%) cases. On antigen loss analysis, the most frequent feature was loss of CD7 (36/54; 66.6%), followed in the order of frequency by CD2 (6/54; 11.1 %), CD5 (8/54; 14.8%) and CD3 (2/54; 3.7%). There were 25 cases with the loss of only one surface antigen, 10 cases with the loss of two surface antigens and two cases with the loss of three surface antigens. Two of our cases were found to be double positive for both CD4 and CD8. In conclusion, since the morphological criteria are not invariably present in all biopsies of MF cases, it is crucial to know the clinical appearance of the lesion but also the information about previous treatment.

METASTATIC GRANULOSA CELL TUMOR OF THE SPLEEN: CASE REPORT

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Granulosa cell tumor is a rare and uncommon stromal cell tumor of the ovary, considered to be of low grade malignancy with an indolent clinical course. The 10-year survival is higher than 90%. These tumors are known to manifest metastatic disease years after treatment of the primary tumor. A 64-year-old female with left upper quadrant abdominal pain underwent magnetic resonance, which revealed a tumorous process of the spleen. Splenectomy was performed and the material was referred for histopathologic analysis. Pathologic examination revealed a tumor measuring up to 8 cm, with relatively sharp demarcation. The tumor was grey to brown in color, with necrotic areas and hemorrhage. Microscopically, it was composed of solid sheets, nests and papillary formations lined with atypical cells. Anastomotic vascular-like spaces were also found, lined with relatively uniform atypical cells. Mitotic rate was high (20 mitosis/10HPF). The tumor occupied almost the entire spleen. Extensive histochemical (PAS, Giemsa, Gomori) and immunohistochemical analyses (vimentin, CD31, CD34, FVIII, CD68, CK7, CK20, CD3, CD20, CD30, bcl-6, Ki-67, HMB-45) were done. Tumor cells showed positive reaction to vimentin and proliferative activity defined with Ki-67 was up to 40%. Metastatic tumor was suspected. Retrospective history data revealed a granulosa cell tumor of the ovary 15 years before. Immunohistochemical analysis with inhibin and calretinin was positive. It was diagnosed as a granulosa cell tumor metastatic to the spleen. Metastases of granulosa cell tumor are extremely rare; they are usually local recurrences or foci of peritoneal spread and occur in 25%-30% of cases. To our knowledge, this is the fourth case of a metastatic granulosa cell tumor in the spleen described in the English literature.

BILATERAL SYNCHRONOUS BENIGN AND MALIGNANT KIDNEY TUMORS: CASE REPORT

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Angiomyolipomas are renal mesenchymal neoplasms with a variable mixture of fat, muscle and blood vessels, accounting for less than 1% of all kidney tumors. They are very common in tuberous sclerosis, while renal cell carcinomas are most common accounting for 85% of all kidney tumors with several different macroscopic and microscopic appearances. We present a case of bilateral renal cell carcinomas associated with angiomyolipoma and renomedullary interstitial cell tumor. A 63-year-old woman presented with bilateral kidney tumors detected incidentally on routine CT scan with no prior symptoms. Bilateral partial nephrectomy was done and biopsy specimens were referred for histopathology. Histopathologic analysis revealed a chromophobe renal cell carcinoma in the specimen marked as left kidney tumor. In the specimen marked as right kidney tumor, clear-cell renal cell carcinoma and a small angiomyolipoma were detected, while a small renomedullary interstitial cell tumor was found in the third specimen marked as right-sided resection surface. Synchronous occurrence of benign and malignant kidney tumors is very rare. There are only few studies of the association of angiomyolipoma and adult renal-cell neoplasia. In patients with or without tuberous sclerosis, conventional clear-cell carcinoma accounted for approximately two-thirds, while oncocytoma accounted for 8%-25% of the tumors described. Papillary neoplasia, chromophobe, and collecting-duct renal-cell carcinoma were only found in sporadic cases, which also holds for angiomyolipoma, which was almost always an incidental finding.

ADENOID CYSTIC CARCINOMA METASTATIC TO THE KIDNEY

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Adenoid cystic carcinoma (ACC) is an uncommon form of malignant neoplasm that arises within secretory glands, most commonly major and minor salivary glands of the head and neck. It is a slow-growing but aggressive tumor. Kidney metastases are very rare and here we report such a case. A 76-year-old female patient presented with hematuria and flank pain. CT scan revealed a tumor mass on the right kidney. The patient was treated with right radical nephrectomy. Macroscopically, a well-circumscribed, firm, gray mass measuring up to 7.8 cm was found on one pole of the kidney. The tumor was composed of cribriform, tubular and solid formations of atypical epithelial cells with dark compact angular nuclei and frequent mitotic figures. Tumor cells showed positive immunohistochemical reaction to CKHMW and EMA, and negative to synaptophysin, CD10, CD15, CK8 and RCC. Retrospective history data showed ACC of the lacrimal gland with metastasis to the lung, which had been surgically treated 14 years before. Based on clinical data, histologic appearance and immunohistochemical analysis, the suggested diagnosis was metastatic ACC to the kidney. In conclusion, adenoid cystic carcinoma, formerly known as cylindroma, is a relatively uncommon but highly malignant neoplasm with a remarkable capacity for recurrence. Besides salivary glands, the tumor can arise in the trachea, lacrimal gland, breast, skin and vulva. The tumor is slow-growing but aggressive; 50% metastasize, often silently to the lung or bone; recurrences are frequent and often late. To our knowledge, in the English speaking area (Pub Med), 7 cases of ACC metastatic to the kidney have been described to date.

SAMPUS OR MELANOMA *IN SITU* IN THE SCROTAL AREA

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Superficial atypical melanocytic proliferations of uncertain significance (SAMPUS) is a descriptive term for a heterogeneous group of melanocytic tumors that exhibit some features indicative of possible malignancy, but in number or degree insufficient to justify a malignant diagnosis. Tumors involving the scrotum are rare and primary malignant melanoma is the rarest of these lesions. To our knowledge, only 17 cases have been described since 1949 in the English speaking area. We present a case of a 59-year-old male patient diagnosed with SAMPUS in 2009, after excision of a scrotal skin lesion. Two years later, he presented with a brown pigmented area near the postoperative scar, measuring 0.6 cm in diameter. Histology showed partially thinned epidermis on the surface. In the basal layers of the epidermis, continuous lentiginous proliferation of single atypical melanocytes with nest formation and pagetoid spread to the upper layers of the epidermis was found. The basal membrane was preserved and continuous. Among the epidermal melanocytic nests, two mitoses were found. In the dermis, there were band-like dense lymphocytic infiltrates and pigmentophages, but no melanocytes. The lesion was diagnosed as melanoma *in situ*. Although most histologic diagnoses are made with relative ease, there is a subset of cases in which diagnosis is difficult or even impossible. The SAMPUS category includes certain atypical junctional melanocytic proliferations and proliferations in both the epidermis and papillary dermis that are not accompanied by intradermal tumorigenic architecture or mitotic activity. The prognosis for cure of these lesions as for melanoma *in situ* is excellent, if they are completely excised.

PRIMARY RENAL ANGIOSARCOMA

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Angiosarcomas are localized or multicentric tumors with various grades of differentiation that originate in the endothelium of the blood and lymphatic vessels. Angiosarcoma is an extremely aggressive malignant neoplasm with a 6-month median survival. Primary occurrence in the kidney is rare, with 24 cases described to date. We present a case of primary renal angiosarcoma in a 65-year-old male patient. It was an incidental CT scan finding that showed 3 tumors in the left kidney. Nephrectomy with ureterectomy was performed. Macroscopic examination revealed 3 nodular hemorrhagic yellowish tumors located subcapsularly in the central area of the left kidney, measuring 0.5 to 4.5 cm in diameter. Microscopically, it was a malignant neoplasm composed of large sheets, cords and small anastomosing vascular spaces, covered by pleomorphic epithelioid and spindle-shaped cells with voluminous and hyperchromatic irregular nuclei. Mitotic figures were frequent. Immunohistochemically, neoplastic cells showed strong positivity for C31, C34 and factor VIII. In conclusion, primary renal angiosarcomas are extremely rare aggressive tumors of endothelial cells. About 24 cases of this tumor have been documented. The mean patient age is 58 years. The etiology is unknown. They usually occur near renal capsule. Clinical symptoms are flank pain and hematuria. Differential diagnosis includes retroperitoneal hematoma and hemorrhagic renal tumors. The prognosis of renal angiosarcoma is poor, with rapid development of hematogenous metastasis.

CANINE ATOPIC DERMATITIS: THE COMPARATIVE APPROACH

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It is well known that dogs are affected with a natural homolog of human atopic dermatitis. The aim is to describe canine atopic dermatitis (CAD) and its points of clinical interests for veterinary and human dermatologists. Relevant articles were identified from three databases: MEDLINE (since 1966), ISI (Thomson) Science Citation Index Expanded (since 1945) and CAB Abstracts (since 1975). CAD is a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens. It is the most common allergic skin disease of the dog. Pruritus is the essential clinical feature, along with normal appearing skin or skin with erythema, small erythematous papular dermatitis, or erythematous macules. In dogs, pruritus is considered a hallmark of atopic dermatitis and is emphasized by feet licking and nose or head rubbing. Recently, new diagnostic criteria for CAD have been proposed by Favrot *et al*., including a set of 8 clinical features. Methods such as intradermal testing (ASIT) and allergen-specific IgE serology serve as orientation for clinicians in the diagnostic and therapeutic approach. Treatment of acute flares of CAD includes identification and removal of the allergenic causes of flares, antimicrobial therapy, improvement of skin and coat hygiene, and care and reduction of pruritus and skin lesions with pharmacological agents. Human atopic dermatitis is a common, multifactorial, chronic and often relapsing inflammatory skin disease. In the etiopathogenesis of human atopic dermatitis, there are well known interactions among genetic, environmental, skin barrier, immune factors, and stress. Current treatment of severe atopic dermatitis consists almost exclusively of topical and systemic corticosteroids. Disease management involves skin hydration through daily baths and intensive emollient therapy, avoidance of allergens, and in some cases use of anti-histamines to alleviate pruritus.

CUTANEOUS OSTEOMAS IN A SEVEN-MONTH-OLD CHILD

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Cutaneous osteoma (CO) is a rare entity with only scattered cases reported in the literature. Cutaneous ossifications are divided into primary and secondary CO. Secondary CO accounts for 85% of cutaneous ossifications and develops within preexisting neoplastic or inflammatory skin lesions. Primary CO accounts for about 15% of cutaneous ossifications and develops on its own. A 7-month-old child, born as second trigeminus by cesarean section after IVF pregnancy, presented with incidental finding of multiple firm, nontender, subcutaneous pale-brownish papules scattered on the skin of the lower abdomen, arms and legs, measuring up to 7 mm. Changes were unremarkable in neonatal period. Changes became visible by the end of the fourth month of life. History specified no trauma, inflammatory changes, nevi, dermatologic or other significant medical conditions. Family history for CO or other associated diseases was negative. First punch biopsy (3 mm) obtained from the lower abdomen showed unremarkable epidermis but the dermis underneath showed well circumscribed spicules of mature lamellar bone entrapped mature adipose tissue without hematopoietic elements. Pathologist indicated CO. One month later, second 2-mm punch biopsy obtained from the left lower extremity confirmed CO indicated in first biopsy. Laboratory revealed elevated thyrotropin (TSH) up to 8.79 mIU/L (reference range: 0.4-4.0 mIU/L) and parathyroid hormone (PTH) up to 88 pg/mL (reference range: 15-65 pg/mL). Other tests regarding thyroid hormone, calcium and phosphorous levels were unremarkable. Final pathology report of CO found in biopsies suggested three possibilities: Albright's hereditary osteodystrophy (AHO), Gardner syndrome and progressive osseous heteroplasia. CO as primary form can occur *de novo* in the form of multiple miliary osteomas, widespread osteoma or plaque-like presenting as a single lesion, both found in neonatal period. All previously mentioned osteoma changes have a good prognosis. Unlike previously mentioned states with CO, AHO-psuedohypoparathyroidism type 1a has poor long term prognosis, where besides CO it manifests with obesity, developmental disability, short stature, round face and ganglia calcification. In our case, laboratory findings supported by histology suggested the AHO syndrome, although the phenotype-associated symptoms of disease were not present yet in infancy. Further follow up is needed. The initially mild cutaneous manifestations may herald a more progressive ossification disorder, as it could be associated with multiple endocrine hormone resistance enhanced with neurobehavioral and developmental problems. Treatment of the present underlying disease is the first step. If the patient is symptomatic, surgical excision including punch excisions is currently the treatment of choice for CO.

COMBINED CARCINOID AND LOW-GRADE MUCINOUS NEOPLASM OF APPENDIX: CASE REPORT

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Mucinous tumors and carcinoids are the most common appendiceal neoplasms, but overall, they account for approximately 1% of all pathologic conditions in appendicectomy specimens. They usually appear as an incidental finding in appendices removed due to suspected acute inflammation. Synchronous occurrence of these neoplasms is extremely rare and only a few cases have been reported in the literature to date. We present a case of combined low-grade appendiceal mucinous neoplasm and carcinoid in a 25-year-old female patient. The patient was admitted to the hospital due to abdominal pain. Ultrasonography showed a tumor mass near the right ovary. Diagnostic laparoscopy was performed and enlarged appendix, but no adnexal abnormalities, was found. The appendix was removed and referred for pathology. Grossly, the appendix was enlarged and filled with mucinous material. Histologically, it contained two distinct tumor areas. The mucinous component, confined to mucosa and submucosa, was composed of mucinous-type tall

columnar epithelium, which showed positive immunohistochemical reaction to CK. The carcinoid component, composed of nests of uniform, chromogranin positive tumor cells, which showed up to 4 mitoses on 10 high power fields, infiltrated the whole thickness of appendiceal wall and extended to periappendiceal fat tissue. In conclusion, the incidence of neoplasms in appendicectomy specimens varies from 1% to 10% according to different studies. Hence, it is important to thoroughly examine the potentially inflamed appendices, particularly when there is no sign of acute pathologic condition.

ATYPICAL SYMPLASTIC GLOMUS TUMOR OF THE LEFT HALLUX

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Glomus tumors are benign perivascular tumors, which result from hyperplasia of normal glomus body, a specialized form of arteriovenous anastomosis that regulates heat. Occasionally, glomus tumors may exhibit some atypical histologic features and rarely can even metastasize. Here, we report a case of a symplastic glomus tumor, a variant of histologically atypical, but still benign glomus tumor. An 81-year-old male patient was surgically treated due to a tumor of his left great toe. Macroscopically, the tumor was well-circumscribed, measured 4x3x2.5 cm and was located in the subcutis. Histologically, it was encapsulated, composed of solid sheets of cells separated by vessels of a varying size. The neoplastic cells showed pronounced nuclear pleomorphism, hyperchromasia and occasional intranuclear inclusions. Mitotic rate was sparse, up to 2 mitoses on 50 high power fields, but proliferative rate measured immunohistochemically was extraordinarily high, about 25%. Tumor cells were immunohistochemically diffusely positive for SMA and desmin. According to classification of glomus tumors proposed by Folpe and coworkers, we declared this tumor as symplastic, considering marked cellular atypia, but the lack of other criteria that could point to its possible malignant behavior. In conclusion, glomus tumors may rarely present with atypical features, but in the absence of other criteria such as large size, deep location, high mitotic index or atypical mitotic activity, they should be considered merely as a consequence of degenerative change and not a sign of malignancy.

CLINICAL PRESENTATION OF A PATIENT WITH PALMOPLANTAR PUSTULAR PSORIASIS: CASE REPORT

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Palmoplantar pustular psoriasis is a rare, chronic dermatosis characterized by sterile pustules that develop within areas of erythema and scaling on the palms, soles or both. The minority of patients have chronic plaque psoriasis elsewhere. Focal infections and stress have been reported as triggering factors. Smoking aggravates the disease and negatively reflects on treatment success. The disorder occurs more commonly during the fourth decade of life. There is a slight female predilection. In most patients, lesions are asymptomatic; however, intermittent pruritus, and burning have been described. The histologic hallmark of palmoplantar pustular psoriasis is large accumulation of neutrophils within the stratum spinosum, known as spongiform pustule of Kogoj. Palmoplantar pustular psoriasis must be differentiated from other dermatoses, which are characterized by intraepidermal neutrophilic pustules including impetigo, superficial candidiasis, dermatophyte infection, superficial folliculitis, dyshidrotic eczema, and pustular drug eruption. Therefore, biopsy and histologic analysis is recommended in order to confirm the diagnosis. The aim of this case report is to present our patient suffering from palmoplantar pustular psoriasis, and to evaluate clinical presentation, diagnostic and therapeutic difficulties in this rare condition. A 38-year-old female patient was admitted to our hospital due to numerous sterile pustules on well-defined erythematous plaques with desquamation on the palms and soles three months before. The pustules were large (about five mm in diameter), and several stages of evolution of

pustules were present concurrently. The patient complained of occasional pruritus and burning. Chronic plaque psoriasis on elbows was confirmed seven years before, for which she received topical corticosteroids. Focal infections were not found on clinical examination. It is important to note that the patient's smoking habit aggravated the condition. Palmoplantar pustular psoriasis was diagnosed based on clinical picture and histopathologic appearance. Histopathologic analysis of skin lesion of the sole showed epidermal acanthosis with parakeratosis and large accumulation of neutrophils within the stratum spinosum, known as spongiform pustule of Kogoj. In the dermis, the capillaries were elongated and tortuous. PUVA cream phototherapy was administered five times weekly for four weeks of her hospital stay. Topical corticosteroids were applied under hydrocolloid occlusion, which significantly enhanced regression of the skin lesions. Most patients with palmoplantar pustular psoriasis have an underlying disease that can be identified, but in our case the onset, fluctuations and duration of the disease were not associated with focal infections. It is important to note that smoking aggravates the disease and has unfavorable impact on treatment success. PUVA cream phototherapy and topical corticosteroids result in dramatic improvement of the disease with significant psychosocial benefit.

DETERMINATION OF EGFR, BCL-2 AND KI 67 IN PATIENTS WITH ORAL LICHEN PLANUS

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Oral lichen planus (OLP) affects 1% to 2% of the population. Typically, it affects middle-aged and elderly women, although it can affect men, and rarely children. The cause of OLP is not known, but it is known to be mediated through T-lymphocytes to as yet unknown antigen. There is about a 1% risk of cancerous change over a 10-year period. The main problem is to identify lesions that will transform into cancer. Normally, tumor markers are used to identify cancer, but in some instances they can suggest potentially malignant lesions. Therefore, we evaluated OLP lesions using immunohistochemistry markers (epidermal growth factor receptor (EGFR), bcl-2, Ki67) in comparison to the density of subepithelial band inflammatory infiltrate. OLP patients were divided into smokers and non-smokers. There were 15 OLP patients in smoker group (age range 28-70 years) and 49 OLP patients in non-smoker group (age range 21-72 years). The mean age at OLP diagnosis was lower in OLP smokers (48.7±10.6) than in OLP non-smokers (55.8±11.5). Conventional hematoxylin and eosin staining showed no difference in the diagnosis of OLP between smoking and non-smoking group. Spearman's correlation test for EGFR expression showed no between-group difference (P=0.4). Comparing EGFR, Ki67 and bcl-2 expression in squamous epithelium according to density of subepithelial band inflammatory infiltrate (using semi-quantitative method; low-1, medium-2, high-3), we found significant difference (P<0.01) between smokers and non-smokers with OLP. Immunohistochemical expression of EGFR, bcl-2 and Ki67 in squamous epithelium in relation to the density of subepithelial inflammatory infiltrate showed significant difference between OLP smokers and OLP non-smokers (P=0.0005). Study results suggested that smokers were younger than non-smokers at the time of OLP diagnosis, which may imply the possibility of cancer development at younger age than statistically reported for oral carcinoma. Additional immunohistochemical analysis revealed smokers with OLP to show a statistically significant expression of EFGR, Ki67 and bcl-2 markers in squamous epithelium in relation to the density of subepithelial band inflammatory infiltrate as compared to OLP non-smokers. These findings could contribute to understanding the carcinogenesis and pathogenesis of OLP. Additional researches in a larger sample are needed to confirm our presumption.

PEDIATRIC LYMPHOMATOID PAPULOSIS WITH CYTOTOXIC IMMUNOPHENOTYPE: CASE REPORT

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According to the WHO/EORTC classification, lymphomatoid papulosis (LyP) is a recurrent, self-healing papular eruption belonging to the spectrum of cutaneous CD30+ lymphoproliferative disorders. The neoplastic cell is typically a CD4+ T-lymphocyte, also manifesting CD30 expression. Three main histologic subtypes are recognized: type A (histiocytic), type B (mycosis fungoides-like), and type C (anaplastic large cell lymphoma-like). Although it is well documented in adults, LyP is very uncommon in children. Clinical presentation and histopathologic features of LyP in children are comparable to those in adults. A 6-year-old boy presented with multiple erythematous papules, measuring up to 1 cm in diameter, located predominantly on his legs. Over time, some papules would necrotize, as new ones appeared. His past medical history was unremarkable. According to this clinical presentation, referring differential diagnosis included Langerhans cell histiocytosis or lymphoproliferative disease. Punch biopsy of skin lesions was performed. Microscopically, skin sections showed a dense, nodular, perivascular infiltrate that extended throughout the full thickness of the dermis. The infiltrate consisted predominantly of large, blast-like lymphoid cells with moderate amounts of cytoplasm and irregular vesicular nuclei with prominent nucleoli. Relatively frequent mitotic figures and apoptotic bodies were seen. The blasts were admixed with occasional small lymphocytes, neutrophils and eosinophils. The overlying epidermis was ulcerated, focally infiltrated with lymphoid cells. Immunostaining revealed blast cells of T-cell lineage, with expression of pan-T-cell antigens CD2, CD3, CD5, and lack of CD7. They were positive for CD8 and the cytotoxic molecules perforin, TIA-1 and granzyme B, but negative for CD4. They also showed strong expression of CD30 and weak, focal expression of CD56, but absence of CD57. Staining for beta-F1 was positive, and there was no evidence of Epstein-Barr virus, either by immunohistochemistry (LMP1) or in situ hybridisation (EBERs). These features were consistent with a CD30-positive lymphoproliferative disorder with a cytotoxic phenotype. Definitive diagnosis required clinical correlation. The patient underwent thorough hematologic work-up, and no evidence of underlying systemic lymphoma was detected. Also, transformation of pre-existing mycosis fungoides was excluded. Final diagnosis was consistent with CD8+ lymphomatoid papulosis type C. The patient received only topical corticosteroid therapy, followed by complete regression of skin lesions. After 7-month follow-up, the patient was healthy, with no evidence of disease. The rarity of childhood LyP, the multifocal skin lesions and the atypical histologic features can produce erroneous diagnosis of malignancy, leading to unnecessary aggressive treatment. Nevertheless, compared with the general population, patients with childhood-onset LyP have a significantly increased risk of developing non-Hodgkin lymphoma. That is why they should be carefully monitored throughout their lives.

OTENTIAL MARKERS OF MELANOMA PROGRESSION: PRELIMINARY STUDY ON NODULAR MELANOMA

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Melanoma is one of the most aggressive cancers with a constantly increasing incidence, the migration, invasion and growth of which depend on adhesive and proteolytic mechanisms of neoplastic cells. Matrix metalloproteinases (MMPs) involved in degradation and remodeling of surrounding tissue play a critical role in tumor progression. Laminin and galectin-3, involved in cell adhesion, migration and growth are also substrates for MMP-2 and MMP-9. Therefore, we presumed that they might be used as potential markers of melanoma progression. Protein expression patterns of MMP2, MMP9, laminin, and galectin-3 were determined by immunohistochemical analysis of tumor tissue obtained from 27 nodular melanoma cases (15 female and 12 male). The values obtained were correlated using Spearman correlation rank.

The median patient age was 60 years, median of tumor thickness 2.3 mm and median of Clark's level of penetration 3. Positive lymph nodes were shown in 48% of cases. All markers were expressed at higher values in melanoma cells than in surrounding tissue. MMP2 was more prominent in the zone with strong lymphocyte infiltration (P=0.018) and deeper layers of tumor penetration. MMP2 exhibited stronger correlation with laminin (P=0.035), while MMP9 correlated with galectin-3 expression (P<0.001). Laminin and galectin-3 were coexpressed in melanoma cells (P=0.044). Although not significant, decreased expression of both markers was found in cases with positive lymph nodes. The study pinpointed the possible markers of melanoma progression. A higher MMP2 expression was found in deeper layers of tumor penetration. However, additional studies in a larger cohort and other histologic melanoma types are necessary to reach more precise conclusions.

TUBULOCYSTIC CARCINOMA OF THE KIDNEY

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Tubulocystic carcinoma, in the past also known by the terms Bellini epithelioma and low grade collecting duct carcinoma, is a subtype of renal cell carcinoma, not classified in the 2004 WHO classification. It has a distinctive histology, composed of variably sized tubules and cysts surrounded by fibrotic stroma. Recent studies of tubulocystic carcinoma showed it to have a strong male predominance and low but definitive metastatic potential. A 71-year-old man with unspecific abdominal pain underwent ultrasonography and computed tomography studies, which revealed a tumorous mass of the kidney. Nephrectomy with ureteretomy was performed and materials were referred for histopathologic analysis. The tumor measured up to 4.5 cm and was partly cystic with areas of hemorrhage and necrosis. Microscopically, it was composed of irregular cysts and tubules lined with single layer of cuboidal to flat epithelial cells with abundant eosinophilic cytoplasm and large nuclei with prominent nucleoli. Immunohistochemically, tumor cells were diffusely positive for CK7. Histopathologic report corresponded to unclassified renal cell carcinoma , nuclear grade 3 according to WHO classification, and to tubulocystic carcinoma according to recent literature. Tubulocystic carcinoma is an uncommon tumor with 55 cases reported in the literature. In the Ljudevit Jurak University Department of Pathology archive, two cases of this tumor were diagnosed in the last five years. It is important to recognize this rare subtype of renal carcinoma, although appearing relatively bland, tubulocystic carcinoma can behave aggressively.

ESTROGEN RECEPTOR POSITIVE CELLS IN GASTRIC AND DUODENAL ULCER: A PILOT STUDY

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It is known that gastric and duodenal peptic ulcer is more common in males. Estrogen has an anti-inflammatory effect, acts on prostaglandin E2 induced mastocyte degranulation and release of vascular endothelial growth factor (VEGF), and also has a role in experimental model of wound healing by converting fibroblasts into myofibroblasts. It also has a sex-specific protective effect in gastroduodenal ulcer. The aim of the present study was to investigate the expression of estrogen receptors alpha (ERα) in gastric and duodenal ulcer tissue in order to elucidate the observed sex difference in the incidence and impairment process of this disease. Twelve surgical specimens of gastric and duodenal ulcer biopsies were found in the database of the Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital Center, during the 2000-2010 period. There were six male (aged 30-74 years) and six female (aged 50-81 years) patients. Paraffin embedded gastric and duodenal ulcer tissue was cut on microtome and analyzed on routine stained sections and immunohistochemically with ERα monoclonal antibody. Estrogen receptor positive cells were found in nine of twelve biopsies. ERα positive cells were neutrophils and fibroblasts in the zone of detritus, while ERα positive mastocytes were found in the zone of granulation tissue and fi-

brosis. This is the first study describing the expression of ERα in fibroblasts, neutrophils and mastocytes located in the area of gastric and duodenal ulcer. Our findings suggest that the process of ulcer healing may be modulated by estrogen. Future research should include determination of ER type (α or β) in ulcer tissue; investigation of the possible correlation of estrogen receptor distribution in ulcer versus gastric cancer (as ERβ positive); elucidation of the role of mastocytes in gastric cancer etiology as estrogen receptor positive cells that promote angiogenesis; and research of the possible application of hormone therapy in gastric and duodenal ulcer disease.

SKIN AND RENAL MANIFESTATIONS OF PAUCI-IMMUNE SMALL-VESSEL VASCULITIS

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Pauci-immune small-vessel vasculitis is characterized by leukocytoclastic necrotizing vasculitis with little or absent immune deposits. This type of vasculitis may represent localized disease (cutaneous vasculitis) or may involve, concomitantly or sequentially, other organs such as the kidneys, lungs, nervous and musculoskeletal system, eye and intestines. Up to 50% of patients with pauci-immune glomerulonephritis (GN) have skin changes related to vasculitis. We reviewed renal pathology archives over a 7-year period and identified 52 patients with pauci-immune GN, 18 of which had pre-existing/concurrent skin manifestations of small-vessel vasculitis. Clinical and laboratory data were reviewed as well as the results of skin biopsies where available. In addition, due to assessing the extent of the disease, Birmingham Vasculitis Activity Score (BVAS) was calculated. Of 52 patients (29 male and 23 female, age range 17-83; median 60.01) treated for pauci-immune GN at Dubrava University Hospital, 10 had pre-existing skin changes related to small-vessel vasculitis. Skin biopsy was performed in 8 patients and the most common finding was leukocytoclastic vasculitis (7/8) with focal fibrinoid necrosis (5/8). Circulating anti-neutrophil cytoplasmic antibodies (ANCA) were detected in 24/52 (46%), anti-proteinase 3 (cANCA) in 4/52 (7.69%), anti-myeloperoxidase (pANCA) in 18/52 (34.6%), and both pANCA and cANCA in 2/52 (3.8%) patients. All but one patient (BVAS index 3) with skin involvement had high BVAS index ranging from 12 to 33. Although most skin small-vessel vasculitides represent mild, self-limiting conditions, they could be the first sign of a more serious, potentially life-threatening systemic disease. The two organs most typically involved and often defining prognosis of systemic vasculitis are the kidneys and the lungs. Untreated patients with severe pauci-immune vasculitis and multi-organ involvement (presenting rapidly progressive crescentic GN and/or alveolar hemorrhage) have a poor prognosis, which may be improved by prompt therapy with immunosuppressive agents and plasmapheresis. Early diagnosis of small-vessel vasculitis and recognition of visceral involvement, followed by aggressive therapy is required in order to preserve or restore the function of vital organs.