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Bericht der Sitzung der Arbeitsgemeinschaft Dermatopathologie

104. Jahrestagung der DGP, Berlin 04.06.2020

Die diesjährige Jahrestagung der Deutschen Gesellschaft für Pathologie stand ganz im Zeichen der Corona-Pandemie und wurde daher als virtueller Kongress organisiert. Die Beiträge wurden in Form einer „audio lecture" übermittelt. Zudem gab es Posterpräsentationen.

Frau PD Dr. Almut Böer-Auert, Dermatohistopathologie Hamburg, Universitätsklinikum Münster, Dermatologie, präsentierte eine Übersicht über: *Histopathology and molecular diagnostics of skin infections*.

Hautinfektionen sind ein häufiges Problem in der dermatologischen Praxis. Für viele dieser Erkrankungen stehen kulturelle und/oder serologische Methoden zur Diagnostik zur Verfügung. Es gibt jedoch auch Erreger, die nur schwer kultivierbar sind oder bei denen die Serologie nicht verlässlich ist. Mitunter ist das klinische Bild auch untypisch, sodass nicht gleich an eine Infektionskrankheit gedacht wird. Daher bleibt die Hautbiopsie ein wichtiger Baustein in der Diagnostik von Hautinfektionen. Wenn ein Direktnachweis des vermuteten Erregers histomorphologisch auch unter Zuhilfenahme von Spezialfärbungen oder Immunhistochemie nicht möglich ist, kommt der genauen Analyse des Infiltratmusters, der Infiltratzusammensetzung und möglicher epidermaler Veränderungen große Bedeutung zu. Es wurden zahlreiche Infiltratmuster („patterns") definiert, die auf bestimmte Erreger hinweisen können. Für den Histopathologen ist es wichtig, diese Reaktionsmuster zu kennen, da er den Kliniker auf die zur Bestätigung der Infektion notwendige Zusatzdiagnostik (Kultur, Serologie) aufmerksam machen sollte. Das paraffineingebettete Material kann außerdem durch molekularbiologische Verfahren wie In-situ-Hybridisierung oder PCR gezielt auf bestimmte Erreger untersucht werden. Diese Diagnostik ist zwar bisher nur nach GOÄ abrechenbar, jedoch in bestimmten Konstellationen (z. B. bei der frühen Borreliose oder auch bei Leishmanien-Infektionen) den serologischen und kulturellen Methoden in Präzision und Praktikabilität überlegen. Studien mit molekularbiologischer Erregerdiagnostik aus Biopsiematerial haben in den letzten Jahren wesentlich dazu beigetragen, das histomorphologische Spektrum erregerbedingter Hautinfiltrate besser zu charakterisieren. Im Vortrag wird auf neue oder noch wenig bekannte Reaktionsmuster und auf differenzialdiagnostische Schwierigkeiten bei der Diagnostik von Hautinfektionen aufmerksam gemacht. Die sinnvolle Einbindung molekularer Diagnostik als nachgeschaltete Methode in der Dermatopathologie wird unter erkrankungsspezifischen Gesichtspunkten erörtert.

Eine weitere Übersicht zum Thema ist in einem aktuellen Themenheft zu entzündlichen Hautveränderungen in *Der Pathologe* publiziert [1].

Dimitry V. Kazakov, Pilsen, zeigte einen Überblick über: *Histology and genetics of cutaneous adnexal tumors*.

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berichteten über: *The sentinel node invasion level (SNIL) – a simple, nonmetric classification for sentinel node tumor burden in melanoma*.

Question. In light of new adjuvant melanoma therapies, we aimed to improve a new pathologic staging by introducing the sentinel node invasion level (SNIL) as a simple, nonmetric classification of nodal tumor burden.

Methods. The SNIL describes which intranodal microanatomic structures are infiltrated by melanoma cells, taking into consideration the SN with the highest tumor burden. The tumor burden categories were defined as follows: SNIL 0 – SN negative; SNIL 1 – melanoma cells confined to intracapsular lymph vessels, subcapsular sinuses, or intermediate sinuses; SNIL 2 – melanoma cells infiltrate

the cortex or paracortex; and SNIL 3 – metastasis infiltrating the medulla or the fibrous SN capsule. In the present study we investigated 1250 patients with an SN biopsy (SNB), of which 344 patients were SN positive (median follow-up time 75 months) and compared the SNIL with established SN tumor burden classifications.

Results. In multivariate analyses, the SNIL allowed for separating three clearly distinct groups of SN-positive patients with regard to their prognosis. The 5-year melanoma-specific survival (MSS) rates for patients classified as SNIL 1, SNIL 2, and SNIL 3 were 91.4 %, 83.5 %, and 31.7 %, respectively. After adjustment for the Breslow index, ulceration, and age, the MSS of patients classified as SNIL 1 was virtually identical to that of SN-negative patients. The accuracies of the AJCC N-, the Rotterdam-, and the S-classification were confirmed. The maximum diameter of the largest SN metastasis and the tumor penetrative depth were not significant predictors in cases classified as SNIL 1.

Conclusion. The SNIL is a simple SN tumor burden classification that can assist in individual decisions for or against adjuvant therapy.

I. Petersen, SRH Poliklinik Gera GmbH, Waldklinikum Gera, Deutschland, trug zum Thema *Pathway pathology of cutaneous drug eruptions* vor.

Question. The skin is the most frequent site of adverse drug reactions (ADRs). Classical morphological patterns of drug eruption are urticaria, erythema multiforme (EM), vesiculobullous reactions like Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) = Lyell syndrome, (generalized bullous) fixed drug eruption (FDR), acute generalized exanthematous pustulosis (AGEP), and drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS). Drugs may have a direct toxic effect on skin cells, e.g. keratinocytes. Additionally, immunological mechanisms are in place to generate the reactions that were traditionally classified as drug allergies by the Gell–Coombs pathophysiological system established in 1963. Although the basics of the system have stood the test of time, it is not well positioned to incorporate the wealth of genetic and molecular data that is now available. Furthermore, drug eruptions represent complex patterns of skin manifestations that can mimic almost every dermatological disease, many of which are not or at least not entirely immunologically driven. This study represents a first attempt to rationalize drug eruptions using the principles of pathway pathology.

Methods. Pathway pathology is a three-tier concept aiming at a) identifying the main cell(s)/the cellular context of the pathological process, b) defining the cellular mechanisms/pathways being operative, and c) characterizing the molecular pathways causing the specific eruptions.

Results. The predominant cell types of cutaneous ADRs are eosinophils (DRESS), neutrophils (AGEP), histamine producing cells/mast cells (urticaria), and keratinocytes (SJS/TEN, EM, FDR). However, these cells probably do not represent the culprits as T cells are central in mediating delayed (cell-mediated) hypersensitivity reactions. The identification of specific HLA alleles in association with drug eruptions like abacavir hypersensitivity underscores the relevance of the patient's genotype in the development of drug eruptions. Reactivation of viral or bacterial infections like HHV6/herpes zoster in DIHS/DRESS also seem to play an important role, at least in some ADRs. In general, the molecular basis of most cutaneous ADRs, are still insufficiently characterized.

Conclusion. Using a holistic approach like pathway pathology that is not restricted to immunology may help to better understand cutaneous drug eruptions and to find new therapeutic options.

Als Posterbeiträge der AG Dermatopathologie wurden gezeigt:

R. Casadonte[1], M. Kriegsmann[2], K. Kriegsmann[3], K. Schwamborn[4], C. Bollwein[4], T. Boskamp[5], A. Ly[6], S. Deininger[6], R. R. Meliß[7], J. Kriegsmann[1,8]

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Mass spectrometry imaging-based proteomic analysis to differentiate melanocytic nevi and malignant melanoma.

Question. Histological criteria for the diagnosis of melanocytic skin lesions such as benign nevus and malignant melanoma may be equivocal. We used mass spectrometry imaging (MSI) technology to determine proteomic differences between these lesions. These proteomic patterns may assist in the differential diagnosis.

Methods. Formalin-fixed paraffin-embedded tissue from cutaneous melanomas ($n = 27$) and melanocytic nevi ($n = 12$) were cut at 3 µm. One section per case was mounted onto a conductive glass slide for IMS analysis, while the adjacent serial section was used for hematoxylin and eosin (HE) staining and annotation of the tumor area. Unstained sections were processed for deparaffination, heat-induced epitope retrieval, in situ trypsin digestion and matrix application. From these sections, mass spectral data were acquired at a spatial resolution of 50 µm using a rapifleX MALDI Tissuetyper mass spectrometer. The histology-annotated image was merged to an image of the MSI section and spectra were collected from each tumor annotation from each section. The MSI

data were then imported into SCiLS Lab software and R for processing, generation of peptide profiles, and statistical analysis.

Results. Spectra were extracted from both benign and malignant lesions and compared. Principal component analysis highlighted spectra patterns correlating with melanoma and nevus tissue. Comparison of the mass spectra average profiles revealed several significant peptide peaks ($P < 0.001$, AUC > 0.7) between the two tissue types. Specifically, 137 and 89 peptides were overexpressed in melanoma and nevus, respectively. These peaks were used to generate a linear discriminant analysis classification model, which could discriminate melanoma from nevus with an accuracy of 100 %. Some significant discriminant peptides such as m/z 976.5, 1287.5, 1410.6, and 1428.7, were identified as actin, macrophage migration inhibitory factor, CK5, and vimentin.

Conclusion. A proteomic signature discerning melanoma from benign nevus was established using MSI and might be used as a supplement to standard histology.

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Lymphadenopathy due to tattoo pigment. Clinicopathological analysis of sentinel lymph nodes.

Question. There is an increasing number of case reports with patients suffering from lymphadenopathy due to migration of skin tattoo pigment. In addition, this phenomenon might influence therapy management of cancer patients. We therefore studied tattoo-associated lymphadenopathy (TAL) of axillary sentinel lymph nodes in a cohort of patients suffering from breast cancer.

Methods. Patients were retrospectively reviewed from the breast cancer center of Klinikum Lippe hospital between 2013 and 2017 ($n = 778$). Out of this cohort, 13 patients obtained TAL (all f; median age 50.69 years); we compared these patients in a matched-pairs study with a nontattooed patient group (all f; median age 51.23 years). Furthermore, histological analysis was performed applying standard procedure as well as immunohistochemistry using antibodies against CD3, 20, 68, and S100.

Results. The matched-pairs analysis showed that the size of the sentinel lymph node did not differ between the tattooed group and nontattooed cohort (1.48 cm vs. 1.58 cm); however, in patients with TAL, significantly more sentinel nodes were excised than in the nontattooed group (3.15 vs. 2.0, $p = 0.039$). With regard to morbidity, there were no differences between both groups (e.g., lymph edema was not observed). By means of microscopy, we found that tattoo pigment was most commonly localized perisinusoidal and in the sinus of the lymph node and only rarely detectable in the germinal centers and/or the capsule. Furthermore, pigment occurred mainly in the cytoplasm of CD68+ macrophages, while lymphocytes (CD3/20) or dendritic cells (S100) did not obtain significant amounts of pigment.

Conclusion. Our study confirms previous case reports on lymphadenopathy in patients with tattoos demonstrating pigment in perisinusoidal and sinusoidal compartment of the lymphatic pulpa, but rarely in the capsule or germinal centers. Moreover, the macrophages are suggested to play a central role in intracorporal processing of the pigment particles. Soran et al. investigated 15 patients with TAL suffering from breast cancer and suggested that the number of sentinel lymph nodes might be increased due to macroscopic alterations; comparable to our results, they found a median number of 3.5 lymph nodes in TAL. Thus, tattoos could lead to increased number of unnecessarily excised lymph nodes; however, it remains to be studied in long-term follow-up whether tattoo pigment might influence the outcome of the patients.

I. Petersen, SRH Poliklinik Gera GmbH, Waldklinikum, Gera, Deutschland *Regression of skin neoplasms*.

Question. Regression of skin neoplasms is clinically relevant and may occur spontaneously or after therapy. The aim of this study is to gain an overview of this phenomenon, which is particularly well known in melanoma. Questions of interest were the following: a) Which nonmelanocytic tumor types show tumor regression? b) Does (primary) tumor regression have prognostic significance? c) Which molecular mechanisms are associated with tumor regression? d) Are there established classification systems for skin cancer regression grading? e) Which molecular therapies of skin neoplasms lead to tumor regression?

Methods. The PubMed database was searched by using appropriate MESH keywords like "skin neoplasms," "neoplasm regression, spontaneous," "molecular targeted therapy," "melanoma," "carcinoma, squamous cell," "carcinoma, basal cell," "skin," and "review."

Results. Spontaneous tumor regression is quite frequently reported for Merkel cell carcinoma, but it may also occur in basal cell carcinoma, particularly in certain conditions/subtypes (Gorlin–Goltz syndrome, withdrawal of immunosuppression, giant cell BCC). Immunosuppression, in general, is a well-known risk factor for the development of various types of skin neoplasms including squamous cell carcinoma and Bowen's disease, and reinforcement of the immune system may induce tumor regression. Involution of congenital hemangioma is frequent and has also been reported for neonatal Langerhans cell histiocytosis. Spontaneous regression may also occur in B- and T-cell cutaneous lymphoma like DLBCL. Regression of primary melanoma was associated with reduced sentinel lymph node metastasis. However, regression does

not inhibit the possibility of distant recurrence in melanoma and MCC. Therapy-associated regression of melanoma is well documented for BRAF-mutated neoplasms treated with appropriate inhibitors as well as immune checkpoint therapies. Vismodegib, a hegdehog inhibitor, may lead to complete regression of BCC. Similarly, cemiplimab, a PD1 immune checkpoint inhibitor recently approved against advanced squamous cell carcinoma, does induce regression. So far, no standardized regression grading for skin neoplasms could be retrieved in PubMed.

Conclusion. Skin tumor regression is a multidimensional phenomenon. It is very likely that evaluation of skin cancer regression will gain diagnostic relevance for dermatopathologists. Further research in this area is warranted.

Geschäftssitzung. Eine Mitgliederversammlung wurde unter Berücksichtigung der speziellen Umstände nicht durchgeführt und ist wieder für die Folgetagung der DGP geplant.

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Einhaltung ethischer Richtlinien

Interessenkonflikt. E. Bierhoff und D. Metze geben an, dass kein Interessenkonflikt besteht.

Für diesen Beitrag wurden von den Autoren keine Studien an Menschen oder Tieren durchgeführt. Für die aufgeführten Studien gelten die jeweils dort angegebenen ethischen Richtlinien.

The supplement containing this article is not sponsored by industry.

Literatur

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