РЕЗЮМЕТА НА ТРУДОВЕТЕ, СЛЕД ПРЕДХОДНА ХАБИЛИТАЦИЯ

на Доц. д-р Юлиан Руменов Ананиев, дм
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"THE RHYTHM OF CANCER" – UNEXPECTED AUTOPSY FINDING IN A PATIENT WITH GASTRIC ULCERATION

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Abstract. *Malignant tumors of the heart are rare. Even rarer, however, are metastases to the heart from cancers originating from the gastrointestinal tract. This case report involves a 63-year-old patient who presented into the clinic with a gastric ulcer and subsequent haemorrhage, and who died after sudden cardiac arrest. Autopsy revealed a metastatic involvement of the heart muscle from low-grade carcinoma of the stomach, as well as many other organ metastases.*

Key words: *autopsy, cardiac metastases, gastric cancer*

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BIOFIBRE HAIR IMPLANT: WHAT IS NEW, WHAT IS TRUE?

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Ensuring the safety of hair implant fibers is essential. At the same time, good aesthetic quality and durability should also be considered in order to maintain expected result over the years. The main features required are biocompatibility, resistance to traction, absence of capillarity, resistance to physical-chemical stress, and low tissue trauma, in addition to good aesthetics. Biofibre® medical hair prosthetic fibers meet all the biocompatibility and safety requirements established by international standards for medical devices. They are available in 13 colors, with different lengths (15, 30 or 45 cm) and various shapes (straight, wavy, curly and afro). Biofibre® hair implants are indicated for diffuse hair loss or hair thinning in cases where an immediate aesthetic result is required, when patients request minor surgery without hospitalization, both for male and female patients, in combination with other hair restoration techniques to improve the final aesthetic result, to correct scars or scalp burns and in cases of poor donor areas. Biofibre® Hair Implant is in fact a minor surgery technique, performed under local anesthesia by either a manual implanter or an automatic machine which enables an immediate aesthetic result and the desired quantity of hair without pain or hospitalization. Clinical and histological studies have demonstrated that Biofibre® hair Implants are safe and well tolerated by patients and can be totally reversible if the need arises. This technique requires good after-care, periodical check-ups and yearly implant re-touches to maintain the best cosmetic result.

Key words: biofibre, hair implants, alopecia, treatment

BIOFIBRE HAIR IMPLANT – IMPACT ON THE QUALITY OF LIFE

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Body image refers to how we feel about our bodies. It does not refer to what we actually look like, but rather to our perceptions, opinions and ways of thinking about our appearance. How we feel about our appearance is part of our body image and self-image. The hair is a significant part of this image. The problem of alopecia affects both sexes and all ages with significant sequelae. Along with androgenetic alopecia, there are forms of alopecia of various origins: traumatic, surgical, pharmacological and others. Polyamide artificial hair implant (Biofibre®) is one of the current techniques used to treat this problem.

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GHRELIN EXPRESSION IN MAST CELLS OF INFANT LUNG WITH RESPIRATORY DISTRESS SYNDROME

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Abstract. *This article sheds light on some features of ghrelin (GHR)- and tryptase (Try)-positive mast cells (MCs) distribution in human lung of preterm newborns with respiratory distress syndrome (RDS). GHR possessed anti-inflammatory activity and reliable therapeutic properties in some lung diseases. So far, GHR expression has been defined predominantly in neuroendocrine cells of bronchial mucosa in fetal and infant lungs. Lung tissue from 8 dead newborns with RDS were investigated immunohistochemically with anti-GHR and anti-Try antibodies. The number of GHR+ and Try+ MCs was determined in three locations –bronchi, bronchiole and in alveolar septa. MCs were more numerous around main bronchi with diminishing numbers around bronchiole and in alveolar septa. The number of MCs in the latter was increased in newborns with pneumonia. The number of GHR+ MCs in alveolar septa was lower in newborns with RDS as compared to newborns with RDS combined with pneumonia (2.83 ± 1.13 vs 4.81 ± 2.6, $p < 0.001$). The amount of Try+ MCs along bronchial wall was significantly more than GHR+ MCs in RDS newborns (6.97 ± 4.53 vs 3.85 ± 4.30, $p = 0.001$). It could be supposed that pulmonary MCs increased in newborn lungs in inflammatory process. MCs in human lung contained GHR peptide that had immunomodulatory function and participated in hormone regulation of inflammation.*

Key words: *ghrelin, mast cells, respiratory distress syndrome*

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case report

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The "different face" of esophageal cancer: cutaneous manifestation of visceral malignancies

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Summary Squamous cell carcinoma is the most common type of neoplasm of the esophagus with global incidence. Its early symptoms are often nonspecific as the disease could be detected only when metastases in various organs are already presented. Esophageal metastases present an extremely small part from all cutaneous metastases as the real incidence of cutaneous metastases due to cancer of the esophagus account for 0.5–9 % and only a small part of them are reported and rarely involve the facial region. Despite this, cutaneous metastases may be the first sign of malignancy of the esophagus, which immediately determined the worst prognosis and fatal outcome in these patients. Average survival prognosis at the time of diagnosis of esophageal carcinoma in stage IV is 4–6 months, while the survival-associated expectations in cases of associated skin lesions manifestation is 4 months. We present a rare case of esophagus carcinoma in advanced stage, presented with severe cutaneous metastasis in the face region, accompanied by heavy blood coughing and hematemesis, which led to fatal outcome in the reported patient. The incidence of cutaneous metastases due to this visceral malignancy is discussed, as we highlight the frequency of metastases as a first clinical sign in esophageal cancer. The mortality rate is high due to the advanced stage of progression of the disease or presented metastases spread at the time of diagnosis, while treatment-related mortality accounts 10.3 %.

Keywords Esophagus · Cancer · Metastasis · Bleeding · Death

Olgu Sunumu JCAM Case Report

Two Cases of Meningococcal Sepsis Caused By Neisseria Meningitidis Serogroup B

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Abstract

Thirteen serogroups of bacterium Neisseria meningitidis (N. meningitidis) have been identified, but 5 of them - A, B, C, W-135 and Y - are responsible for majority of the infections worldwide. Serogroup B meningococcus is uncommon in Bulgaria. In 2014 two cases of meningococcal sepsis caused by N. meningitidis serogroup B were diagnosed and treated in the Clinic of Infectious Diseases of University Hospital of Stara Zagora, Bulgaria. They were 10-months old female and 1-year old male. The diagnosis was based on the clinical, epidemiological, laboratorial, microbiological and molecular-genetic analysis. Both cases presented with a sudden oncet of fever, marked asthenia, refusing feeds and hemorrhagic-necrotic skin rash. In the first case the disease evolved to meningococcal sepsis with meningitis with a favorable outcome. The second case rapidly developed fulminant meningococcal sepsis without meningitis with a lethal outcome. In both cases N. meningitidis serogroup B as etiological agent was confirmed.

Keywords

Meningococcal Sepsis; Neisseria Meningitidis Serogroup B; Suckling

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ORIGINAL ARTICLE

Association of *IL-12Bpro* polymorphism with tumor-infiltrating dendritic cells in colorectal cancer

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Summary

Purpose: *Chronic inflammation is a key component in the development and progression of colorectal cancer (CRC). A notable hallmark of the inflammation process is the release of pro-inflammatory cytokines by infiltrating cells of the immune system. Defects in dendritic cells (DCs) recruitment, maturation and cytokine release are a hallmark of the CRC strategy to escape immune surveillance.The purpose of our study was to evaluate the possible role of IL-12B polymorphism in the promoter region of the IL-12B gene (rs17860508) as a genetic factor contributing to the risk for CRC development. Additionally, we aimed to evaluate the influence of this polymorphism on DCs infiltration in tumor microenvironment.*

Methods: *IL-12Bpro polymorphism was genotyped by Amplification Refractory Mutation System- Polymerase Chain Reaction (ARMS-PCR). Immunohistochemistry was performed for DCs infiltration.*

Results: *Statistically significant correlation between the expression of S100 and CD1a DCs and the 11- genotype of the studied polymorphism was found. No statistically significant difference in genotype distribution between cases and controls was observed (p=0.163). Analysis of the overall survival (OS) of genotyped patients revealed a tendency among the carriers of the 22-genotype to have shorter survival of 36 months versus the 11- and 12-cariers- 61 months (log rank, p=0.117).*

Conclusions: *The IL-12Bpro polymorphism does not constitute a risk factor for CRC development. However, genotype-11 might have a complex role in the recruitment and maturation of DCs in tumor microenvironment.*

Key words: *colorectal cancer, dendritic cells, gene polymorphism*

LETTER TO THE EDITOR

IMP-3 EXPRESSION IN BENIGN MELANOCYTIC NEVI, DYSPLASTIC NEVI AND MALIGNANT MELANOMA: PRELIMINARY FINDINGS IN BULGARIAN PATIENTS

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IMP-3 is generally considered as an oncofetal protein, which plays a critical role in regulation of cell proliferation via an IGF-II-dependent pathway in K562 leukemia cells. IMP-3 expression has been detected in malignancies with various origins, while its appearance in adult tissue is generally considered abnormal, with some exceptions. IMP3 is also considered a prognostic biomarker in patients with renal cell carcinoma and clear-cell type ovarian carcinoma, hepatocellular carcinoma, pancreatic ductal adenocarcinoma and in patients with poorly differentiated thyroid carcinoma and uterine cervical carcinomas, testicular cancer and malignant melanoma. To our knowledge, no more than 4 PubMed-indexed studies have investigated the expression of IMP-3 in melanocytic lesions, namely its role in the differentiation between benign and malignant neoplasms. We investigated the expression of IMP-3 in a small series of benign melanocytic lesions, dysplastic nevi and melanomas, aiming to establish its significance as a marker for their distinction, comparing the results with those from the literature. IMP-3 immunostaining was performed in 30 melanocytic lesions: 10 malignant melanomas, 10 dysplastic nevi and 10 benign melanocytic nevi. Our results revealed expression in 20% of dysplastic lesions and 40% of melanoma cases, while none of the benign nevi showed positive expression. These data contradict some of the results from other studies and raise some questions regarding the correlation between IMP-3 and the degree of dysplasia of melanocytic nevi, as well as its potential relationship with prognostic parameters in melanoma, including tumor thickness and mitotic rate. Our results suggest that IMP-3 expression could be only an auxiliary marker for differentiation between dysplastic nevi and benign nevi, since although it is not expressed in all dysplastic lesions, staining correlates with the degree of dysplasia/atypia. It seems that IMP-3 expression is not a useful discriminator between dysplastic nevi and melanoma nor a good prognostic marker in melanoma.

Key words: IMP-3 expression, immunohistochemistry, melanocytic lesions, melanoma, prognostic marker

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Basic Science

Expression of E-Cadherin/Beta-Catenin in Epithelial Carcinomas of the Thyroid Gland

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Keywords: E-cadherin, β-catenin, thyroid cancer, survival, tumorogenesis.

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Abstract

BACKGROUND: The aberrant activation of Wnt signalling pathway may be a common denominator for the development of thyroid tumorigenesis. It was announced that the loss of E-cadherin rather than β-catenin mutation represents a crucial event in determining the degree of differentiation of thyroid carcinomas.

AIM: The aim of the study was to evaluate the expression of E-cadherin and β-catenin in the thyroid cancer tissue and to correlate these data with some histological and clinical parameters of the tumours.

MATERIAL AND METHODS: We investigated 112 patients, having thyroid tumours – papillary, follicular, anaplastic and oncocytic carcinomas immunohistochemically with antibodies against E-cadherin and β-catenin. Survival analyses were done.

RESULTS: E-cadherin expression was focally retained in the tumour cell membranes and the tumour cell cytoplasm of the papillary, follicular and oncocytic thyroid cancers, weather in anaplastic cancers it was almost lost ($p = 0.0042$, and $p = 0.019$, respectively, Fisher's Exact Test). The expression of β-catenin in tumour cytoplasm and membrane in papillary cancers was higher as compared to that in the other tumours ($p = 0.111$, and $p = 0.0104$, respectively).

CONCLUSION: Not surprisingly, the presence of aberrant expression of E-cadherin and β-catenin in thyroid cancer has been associated with better patients' prognosis and better differentiated tumour histology.

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Ghrelin and gastric cancer

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Ghrelin is a recently discovered peptide, described predominantly in gastric endocrine cells. Gastric ghrelin – positive cells were studied in chronic atrophic gastritis, H. Pylori-related gastritis and gastric carcinoids mainly. Presence of ghrelin- positive cells in gastric cancer was less investigated. The aim of the present study was to describe ghrelin-positive cells in gastric cancer of diffuse and intestinal types and in surrounding mucosa from antral, fundic and corpus regions. Endocrine cells were revealed immunohistochemically with antibodies against chromogranin (Cha), gastrin (Gas), somatostatin (Som), serotonin (Ser) and ghrelin (Ghr). Ghrelin positive cells were found in all cancers (diffuse type gastric cancer), (1,93±1,76 cells/mm^2). In antral mucosa Ghr$^+$ cells were between 42,37±4,8 cells/ mm^2 followed by corpus mucosa between 27,6±1,27 cells/ mm^2 and by fundus mucosa between 25,2±6,3 cells/ mm^2. Co-localization studies showed that some of the Cha$^+$cells, Gas$^+$ cells, and Som $^+$cells were also Ghr $^+$. In conclusion we may state that in gastric cancer from the diffuse type there could be detected Ghr $^+$ECs. Ghrelin could be secreted not only by separate Ghr $^+$ ECs but also by ECs positive for gastrin and somatostatin.

Keywords: ghrelin, endocrine cells, gastric cancer

medicina

MDPI

Case Report

Paroxysmal Finger Hematoma—A Probable Vascular Disorder in Post-COVID-19 Condition: Two Clinical Case Presentations

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Abstract: *Background and Objectives*: Achenbach's syndrome is usually a benign, self-limiting clinical condition presented with finger discoloration, pain, and edema. Etiology, pathogenesis, and incidence remain unknown due to the variety of clinical features and the diversity of disease states leading to digital ischemia. COVID-19 primarily affects microcirculation, causing endothelial damage and disseminated microthrombosis. *Materials and Methods*: We reviewed two cases of Caucasian women with Achenbach's syndrome after COVID-19 infection recovery between April and May 2021. *Results*: Here are presented two extremely rare cases of paroxysmal finger hematoma in two female patients after COVID-19 infection recovery. *Conclusions*: The exact etiology and pathophysiology of Achenbach's syndrome remain unclear. It is assumed that SARS-CoV-2 infection could be the triggering factor in the pathophysiological mechanism of paroxysmal finger hematoma. We highly recommend the implication of the synthetic prostacyclin receptor agonist (Iloprost) as a first-line conservative treatment in patients with Achenbach's syndrome and COVID-19 infection recovery.

Keywords: Achenbach's syndrome; post-COVID-19; endothelial dysfunction; paroxysmal finger hematoma; vascular disorders

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CASE REPORT

Gastric Antral Vascular Ectasia and Vitamin D Deficiency: New Associated Disease and Proposed Pathogenetic Mechanisms

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Keywords Gastric antral vascular ectasia · Associated diseases · Gastrointestinal dysmotility · Vitamin D deficiency · Iron deficiency anemia · Gastroduodenal and intestinal permeability

Gastric antral vascular ectasia (GAVE) was described by Ryder in 1953 [1]. Publications in the 1980s and 1990s established GAVE as a distinct entity [2–4]. The main characteristics are the pathognomonic endoscopic appearance, the specific histology, the association with certain diseases and the treatment, including medications, surgical and endoscopic methods.

GAVE is more often encountered nowadays. It is due to an increase in the incidence of the associated diseases because of the population aging. Another reason is the increased awareness of the endoscopists for the specific antral changes. A lot of information is accumulated, in about 500 publications. Nevertheless, the pathogenesis remains unclear and treatment is not effective enough.

According to the mechanical theory, the pathologic changes of the antrum (and subsequent blood loss) are secondary to chronic trauma, caused by vigorous peristalsis of the antral mucosa and prolapse through the pylorus. The long-lasting injury causes chronic, low-grade, intermittent obstruction of the veins and capillaries, followed by tissue ischemia and hypoxia. This induces oxidative stress, endothelial dysfunction, and activates angiogenesis [2–4].

The main treatment is endoscopic. As GAVE is superficial and affects the mucosa and submucosa, all the ablative endoscopic techniques have been applied. But the result remains insufficient—the recurrence of the blood loss and the need for repetitive procedures [5].

One of the features of GAVE is the associated diseases [4]. About a third of the cases (30%) have underlying liver cirrhosis. 60% of cases are associated with autoimmune and connective tissue diseases. In the remaining cases, GAVE is combined with chronic kidney diseases (CKD), heart diseases, endocrine diseases, bone marrow transplantation, and more. Recent publications find different ratios of the associated diseases, with a prevalence of obesity, metabolic syndrome, and diabetes mellitus rather than autoimmune diseases [6].

We represent, to our knowledge, the first case of GAVE associated with vitamin D deficiency, successfully treated with supplementation.

Case Presentation

We present a 60-year-old male. Known to the clinic since 2014 when he had dyspeptic symptoms, mild anemia, impaired liver function. Upper endoscopy was significant for grade 1 esophageal varices and antral gastritis. The procedure revealed pyloric spasm and forceful antral peristalsis which pushed the antral mucosa toward the pylorus (Fig. 1). On a stretched fold in the prepyloric region, there were signs of mucosal trauma, looking like petechial hemorrhage (Fig. 2). (We did not diagnose GAVE then.) Comorbidities included obesity, arterial hypertension and diabetes mellitus (at that time treated with gliclazide). Viral, auto-

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Strengthening CoViD-19 therapy via combinations of RAS modulators

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ABSTRACT

Evidence has accumulated that the pathology of CoViD-19 is strongly related to the renin-angiotensin system (RAS). The blockage of the angiotensin converting enzyme 2 (ACE2) by the SARS-CoV-2 virus leads to downstream consequences such as increased vascular tone, extensive fibrosis and pronounced immune reactions. Different approaches to tackle the adverse viral effects by compensating the lost ACE2 function have been suggested. Here, we use an unequal-arm lever model to describe a simplified version of the biased regulation exercised by the angiotensin II and angiotensin-(1–7) hormones, which are the substrate and the product of ACE2, respectively. We reason upon the lever dynamics and its disruptions caused by the virus, and propose that a combination of RAS modulators will most efficiently compensate the imbalance due to the excess of angiotensin II and the scarcity of angiotensin-(1–7). Specifically, we focus on the possible benefits of the simultaneous application of two agents, a MAS-receptor agonist and an angiotensin-II-type-2-receptor agonist. We conjecture that this combination has the potential to introduce a beneficial synergistic action that promotes anti-hypoxic, anti-fibrotic and anti-proliferative effects, thereby improving the clinical management of acute and chronic CoViD-19 pathologies.

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ORIGINAL ARTICLE

Fructose-induced metabolic disturbances in rats and its impact on stomach endocrine cell number and smooth muscle contractility

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ABSTRACT

Context: Gastric ghrelin-positive endocrine cells (GHR + EC) were most dense in the oxyntic mucosa.
Objective: We evaluated ECs and contractile activity in rat stomach with metabolic disorders.
Materials and methods: Male Wistar rats were divided into two groups: Control ($n = 9$) received tap water and Fructose ($n = 9$) drank 15% fructose solution for 12 weeks. Streptozotocin was applied in a dose of 20 mg/kg b.w. two weeks after the beginning of the experiment on Fructose group. Smooth-muscle strips from the stomach were influenced by Angiotensin II for analysis of parameters of contractions. Stomach samples were elaborated with immunohistochemistry for ghrelin, somatostatin, gastrin antibodies and with double immunofluorescence.
Results: In treated animals, GHR + EC were significantly increased in the corpus where somatostatin-positive cells were decreased. Contractile activity was decreased.
Conclusions: The increase number of GHR + EC was discussed in the context of Somatostatin and Gastrin-positive ECs variations and correlated with the decrease of smooth muscle contraction.

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Ghrelin; fructose; stomach; angiotensin II

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ORIGINAL PAPER

CD11c- AND CD123-POSITIVE DENDRITIC CELLS IN DEVELOPMENT OF ANTITUMOUR IMMUNITY IN NON-SMALL CELL LUNG CANCER PATIENTS

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Our aim was to analyzed the significance of CD11c and CD123 positive DCs and their relations with some clinical and pathologic parameters of patients with non-small cell lung cancer (NSCLC).

The immunohistochemical expression of CD11c and CD123, was evaluated in 40 patients with NSCLC.

After analysis we found that 35.3% of the patients in the T3-4 tumour stage had a high CD11c infiltration in the tumour stroma, while 100% of the patients in the T1-2 tumour stage had low infiltration ($p = 0.03$). We also found that 71.4% of patients in the M1 stage had a high infiltration with CD123 in the tumour stroma, whereas only 15.6% of patients without metastases had high infiltration, analogous data are also found in comparing the distribution of CD123 in the tumour border ($p = 0.002$ or $p = 0.002$). Comparing the density of CD123 in the border of lymph node involvement, we found that only 7.14% of patients without metastases had low infiltration with dendritic cells, whereas in patients with metastatic lymph nodes that percentage was 41.7% ($p = 0.008$).

In conclusion results suggest that CD11c- and CD123-positive DCs play an important role in antitumour immunity and can be predictive factor for tumour development in patients with NSCLC.

Key words: NSCLC, dendritic cells, CD11c, CD123.

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Research article
Ερευνητικό άρθρο

In ovo hepatocarcinogenicity of N-nitrosodimethylamine and N-nitrosodimethylamine in White Leghorn chickens

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ABSTRACT. Avian embryos have been gaining an increasing scientific interest as a valuable model system for the experimental cancer research that could contribute to a significant reduction of the number of laboratory animals. In the present study, the liver lesions induced by N-nitrosodimethylamine and N-nitrosodiethylamine in 15I line, White Leghorn embryos were identified and studied by routine histopathological methods. Foci of altered hepatocytes with basophilic and eosinophilic phenotype, well known as preneoplastic alterations were identified in the avian embryonal livers after *in ovo* exposure to both N-nitroso compounds. These studies were further extended by histopathological, haematological and biochemical examinations on the effects of N-nitrosodimethylamine in chickens hatched from carcinogen-inoculated eggs. In addition to the preneoplastic lesions observed in the avian livers, proliferations of oval and hepatocellular carcinoma cells, with clearly expressed signs of malignancy were found. The *in ovo* application of the chemical carcinogen was found to affect both hematological and blood biochemistry parameters measured in experimental birds. The established conditions such as thrombocytopenia and increased levels of liver enzymes, as an essential part of the paraneoplastic syndrome, were associated with the process of hepatocarcinogenesis. The results of this study confirm the preneoplastic nature of the focal lesions in embryonal avian liver and their progression to liver neoplastic alterations after a single *in ovo* application of known hepatocarcinogens. Moreover, the results indicate that 15I line, White Leghorn embryos are a new, valuable *in ovo* model for studies on hepatocarcinogenicity of chemical compounds and underline the importance of research on the development of different avian models of carcinogenicity.

Keywords: *in ovo* models, avian embryos, nitrosamines, hepatocarcinogenesis

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OPEN ACCESS

Distribution of ghrelin-positive mast cells in rat stomach

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ABSTRACT

It is known that the gastrointestinal peptide hormone ghrelin is expressed in human and rodent B lymphocytes, T lymphocytes, monocytes and natural killer cells. However, there are no data about ghrelin expression by mast cells. These facts, as well as the common progenitor cells of mast cells and the above-mentioned immune cells, motivated us to undertake the current work in order to prove that like other granulocytes, rat gastric mast cells are capable of immunohistochemical expression of ghrelin. Gastric wall sections of Wistar rats were studied immunohistochemically for detection of ghrelin and tryptase and histochemically for toluidine blue in order to identify ghrelin-positive mast cells as well as to establish their localization and distribution. Results showed that mast cell granules expressed ghrelin. The ghrelin-positive mast cells were the least numerous as compared to tryptase-positive mast cells and toluidine blue-positive mast cells. Based on the observed expression of ghrelin in granules of mast cells localized in the rat gastric wall, we suggested that this type of cell can be regarded as an important source of ghrelin and suggested that ghrelin may exert different physiological functions, such as regulation of muscular, epithelial and glandular functions.

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Ghrelin; mast cells; stomach; rat

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SEBACEOUS CARCINOMA – UNEXPECTED TUMOR OF THE NASAL ALA DORSUM

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Abstract. *Today, the extraocular variant of sebaceous carcinoma is still being poorly recognized. This type of carcinoma is rarely diagnosed correctly, which, together with its aggressive behavior, contributes to its poor prognosis. We present a case of an 84-year-old man with a history of left nasal ala tumor formation, diagnosed morphologically and immunohistochemically as sebaceous carcinoma.*

Key words: *sebaceous carcinoma, nasal dorsum, immunohistochemistry*

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original article

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Wiener Medizinische Wochenschrift

Impact of HER2 codon 655 polymorphism and expression of HER2 and HER3 in non small cell lung cancer patients

Julian Ananiev · Elina Aleksandrova · Desislava Skerleva · Maya Gulubova · Anastasiya Chokoeva · Torello Lotti · Uwe Wollina · Georgi Tchernev · Milica Kontić · Jelena Stojšić

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Summary The aim of the study was to assess the expression and significance of HER2 and HER3, and Ile/Val single nucleotide polymorphism (SNP) of HER2 in lung cancer patients. Thirty seven cases of lung cancer were investigated immunohistochemically for HER2 and HER3 expression. PCR followed by restriction fragment length polymorphism (RFLP) was used to analyze the presence of HER-2 SNP at codon 655 in 20 samples. The results were compared with clinical and pathological parameters of investigated patients.

We found that 100 % of the cases were negative for HER2, 29.7 % were with moderate or strong HER3 expression and 70.3 % of the tumors—without or with low expression for HER3. Lymph node metastasis were found in 40 % of HER3 positive cases ($\chi^2 = 4.752$; $p = 0.029$). Moderately-differentiated tumors do not express neither of investigated markers ($\chi^2 = 6.719$; $p = 0.035$). HER2 RFLP—PCR analysis showed genotype AG in five patients (25 %) and the rest of 15 cases (75 %) had AA (Ile/Ile) genotype. Patients with metastasis had genotype AA (Ile/Ile) in 80 % and genotype AG (Ile/Val) in 20 % ($\chi^2 = 2.857$; $p = 0.091$).

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ORIGINAL PAPER

IMPACT OF TGF-β1 EXPRESSION AND -509C>T POLYMORPHISM IN THE TGF-β1 GENE ON THE PROGRESSION AND SURVIVAL OF GASTRIC CANCER

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The aim of this study was to examine the expression of TGF-β1 and TGF-β receptor type II (RII) and the impact of the -509C>T single nucleotide polymorphism (SNP) in the gene in relation to clinicopathological factors in gastric cancer (GC).
Using immunohistochemistry we investigated 43 patients with GC for expression of TGF-β1 and TGF-β-RII. Consequently, RFLP-PCR was performed to analyze the presence of -509C>T polymorphism in the TGF-β1 gene.
We found that 72.1% of GCs had cytoplasmic TGF-β1 expression and 27.9% were negative. The TGF-β1 receptor type II was expressed on tumor cell membranes in 58.1%. TGF-β1 positivity in tumor cytoplasm correlated positively with TGF-β1-RII expression in tumor cytoplasm in 67.4% of cases ($\chi^2 = 8.02$; $p = 0.005$). Also, the results showed that patients with low and moderate tumor differentiation had TGF-β1-RII positivity in 53.3% and 81.8% resp. ($\chi^2 = 6.58$; $p = 0,037$). The analysis of genotype distribution of the -509C>T SNP in the promoter region of TGF-β1 gene and clinical stage distribution revealed that among the 32 patients in III-IV clinical stage 53.1% were heterozygous (TC), 34.4% were homozygous for the C-allele and 12.5% were homozygous for the variant T-allele ($\chi^2 = 3.31$; $p = 0.069$).
In conclusion the expression of TGF-β1 was related to shorter survival time and rapid progression for the GC patients. Additionally, the variant T-allele of the studied polymorphism was associated with worse prognosis for GC patients.

Key words: gastric cancer, TGF-β1, -509C>T SNP.

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Clinical Science

The Position of Neutrophils-To-Lymphocytes and Lymphocytes-To-Platelets Ratio as Predictive Markers of Progression and Prognosis in Patients with Non-Small Cell Lung Cancer

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Keywords: Lung cancer; NLR; PLR; Prognosis

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Abstract

BACKGROUND: Non-small cell lung cancer (NSCLC) is an insidious metastasis condition of the lungs often presenting no symptoms at the onset. Defining markers for quick determination of prognosis is essential for building up a treatment strategy.

AIM: The aim of this study is to define the role of the Neutrophils-to-Lymphocytes ratio (NLR) and Platelets-to-Lymphocytes ratio (PLR) as biomarkers in patients with NSCLC, according to the stage and prognosis of the disease.

METHODS: We investigated 20 patients with NSCLC. NLR and PLR are calculated and are evaluated according to the presence or absence of metastasis, stage of the disease, histological type and survival rate.

RESULTS: We found that thirteen of the patients had low NLR, while the rest 7 had high NLR (mean 3.15). By analysing PLR we found that 11 patients have low and 9 have high level of PLR (mean 1.42). After the correlations have been made we discovered that in 90.1% of the patients with low PLR no lymph metastasises were detected, while in 50% of the patients with high PLR lymph metastasises were observed ($\chi 2 = 3.99$; $P = 0.046$). We also discovered that in 84.6% of the patients with low NLR lymph metastases were absent, while in 42.9% with high NLR lymph metastasises were present ($\chi 2 = 1.83$; $P = 0.176$).

CONCLUSION: In conclusion, NLR and PLR were discovered as prominent biomarkers which provide relatively fast determination for prognosis in patients with NSCLC.

10-jähriger Junge mit bräunlich-schwarzen Hautveränderungen

Mediquiz

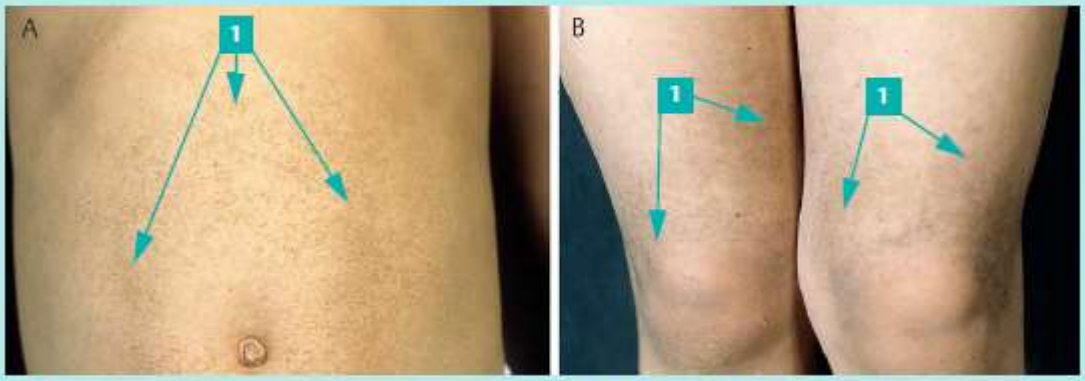

Abb. 2 Bräunlich-schwarze Pigmentierung an der Rumpfvorderseite (A) und den Knien/Oberschenkeln (B).

Befunde

1. bräunlich-schwarze Pigmentierung an Rumpf, Armen und Beinen

Diagnose

– Terra-firma-forme Dermatose

Differenzialdiagnosen

– Acanthosis nigricans
– Pityriasis versicolor

Erläuterung

Die Terra-firma-forme Dermatose oder Dermatitis neglecta ist eine benigne Hauterkrankung. Das klinische Bild ist charakteristisch mit Hyperpigmentierung, Hyperkeratose und einer schmutzig anmutenden Haut.

Die Erstbeschreibung erfolgte 1987 durch Duncan, Tschen und Knox [2, 3]. Die Erkrankung ist durch eine umschriebene bis ausgedehnte, manchmal symmetrische und scharf begrenzte bräunlich-schwärzliche Verfärbung gekennzeichnet. Häufig sind Hals und Rumpf betroffen, es können jedoch auch Kopfhaut, Arme und Beine, Achselhöhlen, Leisten und Nabel betroffen sein. Der Verlauf ist gewöhnlich asymptomatisch [2, 3].

Im Gegensatz zur Seltenheit medizinischer Publikationen scheint die Erkrankung in der Praxis eher häufiger zu sein. Es können Patienten einer großen Altersspanne betroffen sein. In der Literatur finden sich Altersangaben zwischen 4 und 70 Jahren. Am häufigsten sind Kinder und Jugendliche betroffen. Es gibt keine Geschlechterbevorzugung. Eine familiäre Häufung ist nicht bekannt [1, 2, 3, 4].

Die Ursache der Hyperpigmentierung ist nicht abschließend geklärt. Eine inkomplette Reifung der Hornschuppen, Melaninretention, Hyperkeratose und Schmutzeinsprengung infolge inadäquater Reinigung können beteiligt sein.

Diagnostische Maßnahmen wie Schuppenabnahme für Mikroskopie oder Kultur sind nicht hilfreich und ergeben häufig nur eine saprophytäre Flora. In der Histologie findet man eine uncharakteristische lamelläre Hyperkeratose mit fokaler Orthokeratose, jedoch keine Parakeratose. Die Histologie ist aus diesem Grunde verzichtbar [1, 2].

In diagnostischer und therapeutischer Hinsicht ist die Reinigung mit Isopropylalkohol-getränkten Tupfern zielführend. Es wurde auch die Verwendung von 70%igem Ethylalkohol und 2%iger Salicylsäure-Lösung beschrieben. Diese Behandlung ist einfach, schmerzlos, effektiv und preiswert. Sie findet bei den Patienten eine große Akzeptanz im Gegensatz zu den frustranen Versuchen, die Pigmentierungen durch Seife oder andere Reiniger abzureiben.

Bei diesem Patienten ist der Verlauf allerdings chronisch rezidivierend, sodass erneut lokale therapeutische Maßnahmen in regelmäßigen Abständen vorgenommen werden sollten.

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МОЛЕКУЛНО БАЗИРАНИ ТАРГЕТИ И ЕНДОМЕТРИАЛЕН КАРЦИНОМ

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Резюме:

През последните години все по-голямо внимание се обръща на честотата на разпространение на ендометриален карцином, особено в постменопаузалния период. Наред с рутинните диагностични методи, даващи информация за разположението и прогресията на заболяването, съществуват и такива морфологични методи, определящи много точно корелациите в развитието на този тип рак и прогнозата му. Нещо повече – през последните години, натрупаната информация за молекулния профил на този тип карцином, даде възможност да бъдат приложени редица нови медикаменти от молекулната терапия срещу т.нар. ‚таргети' в неоплазмения процес. Значителна част от случаите демонстрират повлияване, като това е допълнителна надежда в разработването на все по-успешни формули и базирана таргетна терапия.

В настоящия обзор ние представяме и обсъждаме ролята на някои молекулни маркери, като потенциални индикатори за прогнозата и развитието, както и при определяне таргетното лечението на ендометриалния карцином.

Ключови думи: *ендометриален карцином, PTEN, EGFR, p53, VEGF, таргети*

MOLECULAR BASED TARGETS AND ENDOMETRIAL CANCER

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Abstract

In recent years, increasing attention has been paid to the rate of spread of endometrial carcinoma, especially in the postmenopausal period. Along with routine diagnostic methods, giving information on the location and progression of the disease, there are some morphological methods determining very accurately the correlations in the development of this type of cancer and his prognosis. Moreover - in recent years, the accumulated information about the molecular profile of this type of cancer, made it possible to implement a number of new drugs against the so-called molecular therapy - ‚targets' in the neoplastic process. Significant proportion of cases show response rates, it is more hope in the development of more successful formulas and target -based therapy.

In this review, we present and discuss the role of certain molecular markers as potential indicators of prognosis and development, as well as determining the target treatment of endometrial carcinoma.

Keywords: *endometrial cancer , PTEN, EGFR, p53, VEGF, targets*

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ROLE OF THE HISTOLOGICAL VARIANT FOR THE PROGNOSIS AND COURSE OF THE FOCAL SEGMENTAL GLOMERULOSCLEROSIS

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Abstract. *The focal segmental glomerulosclerosis is characterized by a morphological heterogeneity, most likely reflecting different pathogenetic mechanisms. The Colombian classification distinguishes five morphological types – non-specific (not otherwise specified or classical), perihilar, cellular, a tubular pole (tip) one and a collapsing one. Eighty-one (81) patients were studied. Their distribution according to the histological variant showed the highest frequency of the non-specific (classical) variant – 70.4%, followed by the perihilar variant – 27.20%, the cellular variant – 1.2% and the collapsing variant – 1.2%. No patients with tip lesions were identified. There were significant differences in the creatinine levels and the glomerular filtration rate (GFR) at the beginning and at the end of the follow-up between patients with the perihilar and the non-specific variants. Patients with the perihilar variant had a better treatment response with a high percentage of patients achieving complete remission – 59.1%. Patients with the non-specific variant had a high chance of treatment failure – 26.3% had no effect from treatment. The results of the study give grounds to assume that the histological variant affects the clinical picture, course and therapeutic response in patients with focal segmental glomerulosclerosis. It could be used as a prognostic marker of disease behavior and guide the clinician in treatment decisions.*

Key words: *focal and segmental glomerular sclerosis, histological variants, treatment outcome*

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antioxidants

MDPI

Article

The *Azadirachta indica* (Neem) Seed Oil Reduced Chronic Redox-Homeostasis Imbalance in a Mice Experimental Model on Ochratoxine A-Induced Hepatotoxicity

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Abstract: Liver damage severity depends on both the dose and the exposure duration. Oxidative stress may increase the Ochratoxine-A (OTA) hepatotoxicity and many antioxidants may counteract toxic liver function. The present study aims to investigate the hepatoprotective potential of *Azadirachta indica A* (*A. indica*; neem oil) seed oil to reduce acute oxidative disorders and residual OTA toxicity in a 28-day experimental model. The activity of antioxidant and hepatic enzymes, cytokines and the levels of oxidative stress biomarkers –MDA, GSPx, Hydroxiproline, GST, PCC, AGEs, PGC-1, and STIR-1 were analyzed by ELISA. The free radicals ROS and RNS levels were measured by EPR. The protective effects were studied in BALB/C mice treated with *A. indica* seed oil (170 mg/kg), alone and in combination with OTA (1.25 mg/kg), by gavage daily for 28 days. At the end of the experiment, mice treated with OTA showed changes in liver and antioxidant enzymes, and oxidative stress parameters in the liver and blood. *A. indica* oil significantly reduced oxidative stress and lipid peroxidation compared to the OTA group. In addition, the hepatic histological evaluation showed significant adipose tissue accumulation in OTA-treated tissues, while treatment with 170 mg/kg *A. indica* oil showed moderate adipose tissue accumulation.

Keywords: *A. indica* oil; OTA; GSPx; Hyd; GST; PGC-1; STIR-1; cytokines

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PHARMACIA

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Research Article

Therapeutic approach of glutathione/ glutathione peroxidase-4 axis modulation in the light of ferroptosis

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Abstract

In the 21st century beginning, the evidence of a new type of programmed cell death, different from apoptosis, began to accumulate. In 2012, the ferroptosis concept was officially introduced. It refers to a kind of cell death that is associated with iron accumulation in the cell, impaired redox potential, and ROS increment with concomitant lipid peroxidation. Ferroptosis plays an important role in the pathophysiology of several organ damages such as tumors, neurodegenerative, ischemia-reperfusion, inflammatory diseases, and others. In ferroptosis, the leading mechanism is the glutathione (GSH) depletion and inactivation of Glutathione peroxidase-4 (GPX4), which strongly shifts the oxidative balance in the cell, leading to the activation of certain signalling pathways to induce oxidative death. The article aims to focus attention on the modulation of the GSH/GPX axis as a key factor in the treatment of these diseases.

Keywords

Ferroptosis, GSH, GPX4, ROS, Lipid peroxidation