Abstracts from the Conference

NEUROPATOLOGIA. NEURORADIOLOGIA. 2022

25 NOVEMBER, 2022

PLENARY MEETING

Neuroimaging of gliomas

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The main tasks of diagnostic imaging in neuro-oncology:

1. Differential diagnosis between neoplastic and non-neoplastic brain lesions;
2. Brain tumor localization based on morphologic and functional imaging;
3. Evaluation of tumor phenotype and tumor grading;
4. Evaluation of tumor genotype;
5. Presurgical cortical and white matter mapping;
6. Post-treatment brain tumor imaging.

The gold standard in neuroimaging of gliomas is multiparametric MRI (mpMRI). The 18 F FET PET/CT is useful in select cases.

The standard of MRI examination in brain tumors includes:

- morphological sequences: T1-weighted images without and gadolinium contrast, T2-weighted images, FLAIR, SWI (Susceptibility Weighted Imaging);
- DWI – Diffusion Weighted Imaging;
- PWI – Perfusion Weighted Imaging.

Options:

- MR spectroscopy (1HMRS);
- angioMR;
- DTI (Diffusion Tensor Imaging).
- Before surgery:
- fMRI BOLD (cortex mapping);
- DTI (white matter tracts mapping).
- Imaging findings of higher grade gliomas are:
- heterogenous contrast enhancement especially a thick ring of enhancement;
- necrosis;
- hemorrhage;
- mass effect and edema;
- the restricted diffusion which reflects increased cell density (cellularity) seen on DWI/ADC MRI. Apparent diffusion coefficient (ADC) maps are calculated from the DWI, Mean ADC values in high grade gliomas are lower than in LGG;
- increased perfusion. The cerebral blood volume (CBV) is the most frequently assessed. It is semi-quantitative, the relative CBV is calculated by comparing with the normal- appearing contralateral white matter. rCBV is higher in neoplastic tumor than in non-neoplastic lesions. Law *et al*. found that a relative CBV ≥ 1.75 indicates higher grades gliomas (*Law M, Yang S, Wang H, et al. Glioma grading: sensitivity, specificity and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. AJNR 2003; 24: 1989-1998*);
- increased choline, lactate and lipids levels in MRI spectroscopy.

2021 WHO Central Nervous System Tumor classification has presented neuroradiologists with new, difficult challenges. The most important is to link specific imaging features with tumor genomic signature (genotype). Such radiogenomics are for example: "T2-FLAIR mismatch" sign consider as a marker of an IDH mutant 1p/19q noncodeleted astrocytoma; elevated levels of 2-hydroxyglutarate in IDH – mutant gliomas (*Iv M, Bisdas S. Neuroimaging in the era of the evolving WHO classification of brain tumors. AJR 2021; 2017: 3-15*).

Radiological aspects of infectious encephalitis

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Infectious encephalitis is a life-threatening disease and can be caused by viruses, bacteria, and other pathogens. Diagnosis of encephalitis is difficult especially in the early stages of the disease due to its uncharacteristic clinical signs. Fever may be present at the time of hospital admission or within 4 weeks prior to this time. Altered states of consciousness, headaches, as well as seizures and focal neurological deficits may be primary symptoms. Blood tests are not specific enough in many cases. Hence, MR imaging has a critical role in the evaluation of patients with suspected encephalitis. It can aid diagnosis of its etiology and exclude other mimicking diseases. Furthermore, MRI is useful in prognosis and patient follow-ups.

A rapid diagnosis is essential to apply effective treatment and increase the chance of patient survival and recovery. MRI should be performed at the onset of patient symptoms using the multiparametric protocol, which consists of morphological sequences (T1- and T2-weighted scans), contrast-enhancement study, perfusion-weighted imaging, diffusion-weighted imaging, as well as spectroscopy. Patterns of imaging findings will be presented in this lecture using cohorts of more common encephalitis aetiologies. In addition, the differential diagnosis will also be discussed in the context of clinical symptoms.

Malformations of brain development

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Malformations of the cerebral cortex include a large, heterogeneous group of disorders of the formation of the cerebral cortex of various etiologies. They are divided into three groups related to abnormal cell proliferation or apoptosis, abnormal neuronal migration and abnormal cortical organization.

The following pathologies are discussed: microcephaly, hemimegalencephaly, agyria-pachygyria spectrum and subcortical band heterotopia, heterotopia, polymicrogyria, schizencephaly, focal cortical dysplasia. The presentation presents also selected midline brain abnormalities like septo-optic dysplasia and subtentorial malformations, such as: molar tooth malformations including Joubert syndrome, rhombencephalosynapsis, Dandy-Walker malformation.

Tuberous sclerosis complex – pediatric neurologist perspective
Stwardnienie guzowate okiem neurologa dziecięcego

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Tuberous sclerosis complex (TSC) is a genetic disorder affecting 1 in 6,000 livebirths. It is characterized by an overactivation of mTOR pathway leading to the development of tumors in various organs, including the brain, heart, kidneys, liver, skin, retina, and others. Cardiac rhabdomyomas and cortical tubers as well as subependymal nodules in the brain usually develop prenatally, whereas other manifestations, including subependymal giant cell astrocytomas (SEGA) grow later over time. About 80-90% of TSC patients suffer from epilepsy and in about 70% seizures begin in infancy. Epilepsy in TSC is frequently resistant to medications and associated with high risk neuropsychiatric comorbidities, especially intellectual disability and autism. There are several therapeutic options in TSC-related epilepsy, including classical antiseizure medications, mTOR inhibitors, epilepsy surgery, ketogenic diet, and, very recently, preventive strategies. Early treatment is associated not only with the higher chance to achieve good seizure control, but also improves neuropsychological outcome. New therapeutic modalities are currently in clinical trials.

Subependymal giant cell astrocytomas develop in about 20% of TSC patients and present an important cause of mortality and morbidity in TSC children and adolescents. Until recently, surgery was the only therapy for SEGA, but was associated with significant risk of complications. Currently, mTOR inhibitors are used for the treatment of SEGAs in TSC patients.

In conclusion, there is a great progress in our understanding of mechanisms underlying the neurological presentation of TSC and in the available treatment options.

Tuberous sclerosis (TSC) – neuropathological point of view

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Tuberous sclerosis (TSC) is a multisystem neurocutaneous genetic syndrome that affects multiple organs, including CNS, caused by mutations of *TSC1* (9q) or *TSC2* (16p) genes. Major CNS lesions include cortical tubers, white matter glioneuronal hamartomas, subependymal nodules (SENs), and subependymal giant cell astrocytomas (SEGAs). Cortical tubers consist of a disorganized cortex with disrupted cortical architecture and the presence of dysmorphic, markedly enlarged neurons, balloon cells, fibrillary gliosis, calcification of blood vessel walls and parenchyma, and myelin loss. SENs are typically located around the wall of the lateral ventricles and are considered as the precursor lesion of SEGAs, which are defined as having diameter > 1 mm. SEGAs develop from smaller, histologically similar lesions SENs, near the formanen of Monro. Histologically they are composed of large cells resembling gemistocytes, spindle and ganglion-like cells that are arranged in fascicles, sheets and nests. The tumour cells show variable expression of glial and neuronal markers, with high levels of phospho-S6K, phospho-S6, and phospho-Stat3, proteins downstream of mTORC1. Treatment options for SEGA and cortical tubers include mTORC1 inhibitors, rapamycin and everolimus, termed rapalogs, as well as surgical resection.

An atomic level of CNS tumors biology – an introduction of the isotope ratio mass spectrometry method and a preliminary report from the first interdisciplinary evaluations

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Interdisciplinary advanced approaches look beyond traditional methods of evaluation in oncology. Awarded four Nobel Prizes mass spectrometry (MS) and its the most reliable technique – isotope ratio mass spectrometry (IRMS) for the first time has crossed neuropathology and revealed an atomic level of CNS tumors biology. MS analytical methods gives the possibility of identifying substances present in very low concentrations, as well as the analysis of complex mixtures. The use of MS in medicine, especially in proteonomics opened a new area of biomarkers. IRMS technique with the documented highest precision of determinations estimates the heavier to a lighter isotope ratio of elements, which reveals the phenomenon of isotopic enrichment or depletion characterized biological samples. Furthermore – IRMS technique known from its highest versatility seems to be devoted to the studies with potential clinical impact which has started to be conducted nowadays in oncology and has already brought new cancer biomarkers. A relation between cancer disease and the assessment of natural abundance of stable isotopes with the use of IRMS belongs to distal interdisciplinarity which makes challenges for the scientist who want to carry out this type of interdisciplinary projects, however at the same time may result in innovatory concepts and clinical utility.

Epigenetic research in neurological diseases

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Testing for *MGMT* gene promoter methylation has for years been performed in planning of treatment of glioblastoma multiforme. Latest World Health Organization guidelines (WHO CNS 5th) recommend the use of genome methylation profiling in classification of tumors of central nervus system (CNS). Those examples illustrate increasing significance of methylation changes profiling in CNS tumors. At the same time research findings increasingly show that epigenetic changes including DNA methylation are key players in development of the not only CNS tumors but also other CNS diseases. Moreover, those research results indicate that epigenetic changes that occur during CNS development can not only be targeted by the therapies but also applied as biomarkers in clinical management of the CNS diseases.

In my talk I will review current applications of methylation biomarkers in clinical management of CNS tumors as well as key research indicating increasing potential of application of methylation biomarkers in management of other CNS diseases.

Pitfalls in diagnosing PitNETs

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The newest WHO classification of pituitary neuroendocrine tumors – PitNETs[1], commonly named as "adenomas" systematizes them accordingly to the cell lineages defined after transcription factors (TFs) Pit1, TPIT, SF1 playing a decisive role in adoption of particular functional "mature" hormonal role, consequently naming them as "Pit1-lineage" etc. But do the cell lineages mark out "straight lines" infallibly guiding toward desirable targets in pathological diagnosis and clinical objectives? Definitely not, or not entirely. For instance, they do not exhaustively cover all PitNETs hence the separate entity "PitNET with no distinct lineage", which leaves the field for potential pitfall in diagnosis... There are however some other potential pitfalls in pathological diagnosis of PitNETs within the framework of new WHO classification. They will be tentatively reviewed,

this time systematizing and naming them after some imaginary/arbitrary "keywords" i.e.: Pitfall "C" from "Complication", pitfall "T" from "Transcription factors vs. *trophs*", pitfall "S" from "Shakespearian (dilemma: to be adenoma or not to be...)", pitfall "N" from "Null-cell", pitfall "MP" from "multi/pluri (hormonal)", pitfall "SPADE" from "Sparsely vs. densely (granulated)", pitfall "E" from "extra"(particular problems)", and ultimately pitfall "I" from "Incompleteness" (addressing problem of "no distinct lineage", which in fact started these considerations). To present in the shortest fashion the aforementioned "Pitfalls" (in PitNETs...): "C-Complication" underscores increased laboratory demands to follow the classification. Not only antibodies against "lineage-naming" transcription factors (and tropic hormones) are necessary but also other transcription factors as GATA3, EstrogenR are desirable, together with anti Cytokeratins (CAM 5.2, CK18), alpha-subunit, and (in fact most crucial to substantiate "neuroendocrinal" character of a tumor) chromogranin and synaptophysin. To this, one may/should add some not necessary but important somatostatin receptors. All this enormously elevates pathologist's and laboratory workload and the risk of misinterpretation and blunder. "Shakespearian" potential pitfall remains to be there since especially in sometimes ultraminimal material from transsphenoidal operation the dilemma "to diagnose or not to diagnose..." (PitNET) might be challenging. New WHO classification does not provide new adjunct formulas in this matter. Pitfall "T" addresses the question of mutual relations between immunoexpression of tropic hormones and lineage-defining TFs especially complicated in Pit1-lineage PitNETs which encompasses most of PitNET entities. Another question is related to "null cell PitNET" (Pitfall "N") that according to WHO "shows no evidence of adenohypophysial differentiation by immunohistochemistry for pituitary hormones and transcription factors PIT1, SF1, and TPIT". Problem is when only singular immunopositive cells/nuclei appear in apart from that totally negative tumor. Still another (potential) pitfall ("MP") lies in the distinction between Multiple synchronous PitNETs of distinct lineages and plurihormonal PitNETs. Noteworthy is that a "multiple" tumor may be consisting of null cell "compartment" (?) combined with any lineage-specific pituitary neuroendocrine tumour (this also relates to Pitfall "N") but mutual not only qualitative but quantitative relations between "compartments" (this is our term not used in WHO) were not specified. Pitfall "SPADE" lies in not always straightforward distinction between the form of immunoexpression of some hormones denoted as sparsely or densely granulated, which is (and was also in previous classifications) clinically important. The last but surely not least is to be watchful in evaluating operational material to discern and properly interpret admixtures of other structures like normal anterior, posterior, intermediate pituitary, cyst etc. In conclusion, pitfalls in PitNETs are multifarious and let them not make the work of pathologist a piteous one... The "pitfalls" will be illustrated exclusively by our own material.

Funding: This report received financial support from Jagiellonian University grant No. N41/DBS/000792.

Reference

WHO Classification of Tumours. Endocrine and Neuroendocrine tumours [Internet]. International Agency for Research on Cancer, Lyon, France, 2022. (WHO classification of tumours series, 5th ed. Available from: https://tumourclassification.iarc.who.int. Website beta version).

ORAL PRESENTATIONS

Cognitive testing and diffusion tensor imaging as joined diagnostic procedures in tuberous sclerosis complex

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Introduction: Tuberous sclerosis (TSC) is a genetic disease in which cell differentiation, proliferation and migration are disturbed in the early stages of development. As a result of the disease, brain lesions show altered regional architecture, abnormal cellular morphology, and excessive numbers of astrocytes. Neuronal abnormalities are present in 80-95% of TSC patients and include cortical and subcortical nodules, subependymal periventricular nodules, subependymal giant cell astrocytomas, and white matter migration lines. In addition, most patients develop neuropsychological disorders, the mechanisms of which are not fully understood. Aim of this study was to assess the linkage between cognitive functioning and the microstructure of the normal appearing white matter of TSC patients.

Method: Magnetic resonance imaging (MRI) including diffusion tensor imaging and cognitive assessment of memory, learning, psychomotor speed, attention and executive function were performed in the study and control groups. The study group consisted of patients with tuberous sclerosis divided into two subgroups – with epilepsy and without epileptic seizures.

Results: The results of the study showed a strong relationship between the radial diffusivity parameter and the performance of verbal memory tests. It has been observed that in the group of patients with epilepsy, in the fibers connecting distant lobes of the brain, the indicators of myelin and axon abnormalities are higher. Moreover, the average diffusivity index correlated positively with the test of visuospatial functions. However, in the subgroup with concomitant epilepsy only the measures of attention and working memory correlated with tumor volume indices.

Conclusions: MRI of patients with TSC shows both focal lesions and extensive anatomical abnormalities in the brain structures. The obtained data show that the microstructural changes observed in patients with TSC probably indicate damage to the brain, in both myelin and axons. It is worth emphasizing that in the group of patients with epilepsy, changes are more severe. As a consequence, patients develop neuropsychological deficits caused by regional morphometric disorders of the brain co-occurring with migration changes.

Key words: tuberous sclerosis complex, cognitive functioning, diffusion tensor imaging, white matter structural connectivity.

Progressive multifocal leukoencephalopathy, neuroradiology-neuropathology

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Introduction: Progressive multifocal leukoencephalopathy (PML) is an unfavorable demyelinating disease of the CNS caused by reactivation of JC virus (JCV). JCV is a double-stranded DNA human polyomavirus predominatingly acquired in childhood. Blood samples taken from healthy persons indicate that 50-90% of adults have been exposed to this virus. JCV is an opportunistic pathogen, with PML manifesting primarily in patients with immunodeficiency or taking immunomodulatory treatments or with lymphoproliferative diseases. We report a patient who developed PML shortly after diagnosis of follicular lymphomma.

Case presentation: A 70-year-old-woman admitted to the neurological departament with hemiparesis, psychomotor slowing down, balance problems, dizziness and in depressed mood.

The patient underwent aorto-femoral transplant 12 years ago and for 10 years was under constant observation of a hematologist due to enlarged lymph nodes. Five years ago, the patient had planoepithelial cell carcinoma removed. The patient also suffered from COVID-19 infection and suffered from depression. Elevated leukocytosis and D dimers, were the only abnormal results obtained in laboratory tests. However, pulmonary embolism was excluded in CT angio.

Cytometry of blood showed follicular lymphoma.

Radiological findings: MRI and CT scans showed multiple asymmetrical pathological areas of hyperintense signal in T2-dependent images, hypointense in T1-dependent ones and CT-hypodense regions which extended continuously in control examinations. They were located in the white matter of multiple lobes of both brain hemispheres subcortically and periventricullary. The subcortical U-fibers were involed. They did not show contrast enhancement and mass effect. They showed peripheral ring and patchy diffusion restriction particularly at their leading edge.

In spite of the used steroid therapy the patient's health deteriorated rapidly. The patient died of symptoms of cardio-respiratory failure 1 month after admission to hospital.

Neuropathological features: The neuropathological examination revealed numerous foci of demyelination in the white matter of the frontal lobe, the parietal lobe in the pons and in the cerebellum. Myelin losses were accompanied by damage to oligodendrocytes and proliferation of macrophages. The nuclei of the damaged oligodendrocytes were enlarged and hyperchromatic, and some had a "ground-glass" appearance typical of viral infection. The astrocytes were bizarre with lobulated, hiperchromatic or hypochromatic nuclei and damage of cytoplasmic procesesses (clasmatodendrosis).

Conclusions: The triad of neuropathological injuries: destruction of oligodendrocytes with intranuclear viral inclusions ("ground-glass" appearance), multifocal demyelination and bizarre astrocytes allowed for the diagnosis of late form of classical progressive multifocal leukoencephalopathy (cPML), despite the short time since diagnosis of follicular lymphoma, but with many years of enlargement of the lymph nodes.

Radiological and neuropathological correlation in the child with atypical genetic variant of Leigh's syndrome

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We present the case of the girl with Leigh's syndrome. Her adaptation period after birth was complicated by general hypotonia and therefore MRI was performed on day 11 of her life. MRI revealed changes suggesting the prenatal hypoxic-ischemic pathology. In the first months of life the baby began to focus her eyesight and started to smile.

At age of 3-months the girl was urgently admitted to Department of Neurology because of polymorphic seizures. Neurological examination showed general axial and limb hypotonia, there was no eye contact. Very high concentration of lactic acid in the serum as well as CSF were detected. MRI of the head showed symmetrical changes in the brain stem nuclei and nerve pathways, starting from the substantia nigra. Because the clinical and radiological picture suggested mitochondrial disease, molecular analysis was performed, but genetic tests for the most common mutations have not confirmed the Leigh's syndrome. Despite the treatment, the child's condition gradually deteriorated. Molecular testing was re-commissioned.

At the age of 8-months, the child developed a respiratory tract infection, and after a few days died suddenly. General autopsy showed interstitial pneumonia. Neuropathological examination revealed symmetrical changes in medulla oblongata, pons, midbrain, thalamus, putamen and cerebellum. Microscopically: foci of necrosis with macrophage infiltration with preserved neurons, vascular proliferation, and hypertrophy of astrocytes were found. Neuropathological findings closely correlated with the radiological image, although they showed significant progression of changes.

Extended analysis of DNA showed rare pathogenic variant m.13042G>A p.Ala236Thr in *MT-ND5* gene.

Osteoblastoma odcinka szyjnego kręgosłupa

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Osteoblastomas represent 1% of all bone tumors, and close to 40% are localized to the spine. Osteoblastomas of the spine typically affect the pediatric population, predominately children 10-15 years of age. They encompass 10% of all osseous spinal neoplasms and typically involve the posterior elements. Extension from the posterior elements into the vertebral body is quite common, however, and has been reported in approximately one-third of cases. The cervical and lumbar spine to be the predominant spinal segments involved, followed by the thoracic region and sacrum Two types of osteoblastomas have been described in the literature; conventional osteoblastomas and aggressive osteoblastomas. Aggressive osteoblastomas more often display paravertebral and epidural extension, and they also are on average approximately 1.5 cm larger than conventional osteoblastomas. The mainstay of treatment involves surgical intervention. Marginal excision or wide *en bloc* resection are preferred options.

A 14-year old male patient was admitted with a one year history of cervical scoliosis, difficulty of swallowing, increasing upper extremity weakness and pain. X-ray and MRI indicated massive involvement of the anterior and posterior elements of the C3-C4-C5 vertebrae with a large soft tissue mass. After embolizadion of tumour, anterior and dorsal resection with anterior and posteriori fixation and stabilisation were performed. MRI investigation one year later showed no signs of recurrence.

Neuroimaging in selected experimental animal models

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Animal models allow for a better understanding of the processes involved in the growth and development of cancer. Similar to human medicine, imaging is the main way of cancer visualization. Preclinical imaging in the animal model is divided into anatomical (radiography, computed axial tomography scan, ultrasonography, magnetic resonance imaging [MRI]) and functional (positron emission tomography, bioluminescence, fluorescence). Among described techniques, the MRI is widely used in preclinical tumor imaging, as it is a non-invasive method that does not require the use of radiation and allows for taking a wide-range of pictures. In this study, we used MRI to investigate the phenomenon of perineural invasion and its role in local and distant Ewing sarcoma (ES) and prostate cancer (PC) spread. MRI allowed us to monitor primary and secondary tumors in ES and PC mouse models. Following injections of cancer cells and the development of primary tumors, the mice were assessed by MRI every two weeks. In ES, we found frequent perineural dissemination manifested by the presence of ES cells along the nerves adjacent to the primary tumors. This phenomenon was associated with the formation of secondary tumors along the sciatic and femoral nerves, the connections between the primary tumor site, and the spine. In PCa MRI, however, we observed the metastases into the paraspinal area without spine infiltration in histopathological examination. Results of our study show that MRI constitutes an additional source of information which improved our knowledge about mechanisms involved in cancer progression.

*The publication was written as a result of the author's internship in Georgetown University, co-financed by the European Union under the European Social Fund (Operational Program Knowledge Education Development), carried out in the project Development Program at the University of Warmia and Mazury in Olsztyn (POWR.03.05. 00-00-Z310/17).

POSTER PRESENTATIONS

Glioblastoma with osteosarcomatous transformation – case report

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Introduction: Sarcomatous differentiation in glioblastoma accounts for less than 2% of all diffuse gliomas, and may occur *de novo* or secondarily after conventional treatment of high-grade glioma. Biphasic histological pattern consist of glial and sarcomatous components; fibroblastic is the most common mesenchymal differentiation. Here, we present a very rare case of a patient with glioblastoma with osteosarcomatous transformation.

Case report: 51-year-old woman presented with headache, vomiting, memory impairment and deterioration of visual acuity for 2 weeks. Brain magnetic resonance imaging (MRI) showed a large cystic heterogeneous mass lesion with peri-tumoral oedema in the left parietal and occipital lobe. The histopathologic examination from the tumour resection revealed Glioblastoma, IDH-wildtype, CNS WHO G4. Conventional chemoradiation and additional three resections were perfomed because of tumor recurrence in the following 15 months. The latter showed sarcomatous tumour composed of areas of ill-defined spindle cells and lace-like osteoid depositions intermingled with neoplastic cells corresponding with the diagnosis of glioblastoma with osteosarcoma component.

Conclusions: Glioblastoma with osteosarcomatous differentiation is a very rare mesenchymal variant of glioblastoma. The histogenesis is still not fully understood, and could be a result of a metaplastic change or divergent differentiation from a common progenitor cell.

Primary intracerebral synovial sarcoma with unusual glial differentiation markers

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A teenage girl patient was admitted due to a tumor of the left occipital lobe. She had a history of behavioral changes, depression and periodic headaches for few months, with no neurological abnormalities. On neuroimaging, a solid-cystic lesion of size 52 × 36 × 40 mm with scattered calcifications, connecting to the left lateral ventricle, and the adjacent occipital bone scalloping was detected. The tumor was completely removed in the Department of Neurosurgery at Copernicus Hospital in Gdansk. Histopathologically it was composed of atypical spindle cells forming gland-like structures focally. Foci of calcifications and necrosis were visible. Immunophenotype showed: EMA(+), bcl2(+), CD99(+), vimentin(+), Olig2(+), focal GFAP(+), focal pan-cytokeratine(+), focal CK7(+), focal synaptophysin(+), TLE1(+), Ki67 10%, and several more mesenchymal and neuronal markers – negative.

The differential diagnosis included several possibilities, but finally Synovial sarcoma was recognized, and typical gene fusion (SYT-SSX) was molecularly proved. The patient was treated according to CWS Guidance chemotherapy protocol, with full remission 9 months since the operation. This is the extremely rare case of a intracerebral synovial sarcoma, showing expression of glial markers.

Classification of gliomas based on the assessment of genome-wide DNA methylation profiles – a pilot study

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Introduction: The results of recent studies have shown that tumors of the central nervous system (CNS) display specific DNA methylation changes within the tumor

genome. Methylation profile analysis is therefore included as one of the diagnostic methods in the new 2021 World Health Organization classification of CNS tumors.

Material and methods: In our pilot study we performed methylation profiling of 16 gliomas with an established histopathological diagnosis, using commercial Infinium Methylation EPIC (Illumina, CA, USA) microarrays. In seven cases, DNA was extracted from freshly frozen (FF), and in nine cases from formalin-fixed paraffin-embedded (FFPE) tissues. For samples derived from FFPE, the Infinium HD FFPE Restore Kit (Illumina, USA) was additionally used. The tumor type was classified using a bioinformatics platform ("Brain classifier" version 12.5, Heidelberg). Additionally, we assessed *MGMT* gene promoter methylation status with methylation sensitive-high resolution melting (MS-HRM) technology, using EpiMelt MGMT methylation detection kit (MethylDetect ApS, Denmark) and mic-qPCR instrument (Bio molecular systems, Australia).

Results: All cases were informative, with no differences in quality between FF and FFPE material. The histopathological diagnoses were fully consistent with the methylation profiles. In one tumor, due to the borderline quality of the genetic material, the algorithm generated two diagnoses. The results of *MGMT* methylation status were consistent between microarray and MS-HRM technologies.

Conclusions: Classification of CNS tumors based on genome-wide methylation profiles may lead to an increase in the precision of histopathological diagnosis. However, this method requires further validation on large series of tumors based on pathoclinical correlations. EpiMelt MGMT methylation detection kit allows cost and labor efficient method for *MGMT* methylation testing.

Funding: This study was funded by Polish National Agency for Academic Exchange grant number: PPN/PPO/2018/1/00088/U.

Effect of hyperbaric oxygen conditions on cytotoxic action of modified isothiourea derivatives (ZKK1, TRIM, BEN) against glioblastoma cell line *in vitro*

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Glial tumors constitute a large group of primary neoplasms of the central nervous system. Most of them are astroglial neoplasms, the cells of which proliferate rapidly and diffusely infiltrate structures of the brain, making it impossible to complete a radical neurosurgical procedure. An example of such-neoplasm is glioblastoma, which is one of the most malignant neoplasms with the fourth degree of histological malignancy according to the WHO classification. It may occurr at any age, but is most often diagnosed between 35-75 years of age. Treatment of human gliomas by means of various therapeutic strategies still yields very poor results and unfortunately remains a challenge. In search for new therapeutic solutions, in our studies we used a combination of selected modified isothiourea derivatives ZKK1, TRIM, BEN with hyperbaric oxygen (HBO) on the cells of malignant glioblastoma of the T98G line in vitro, and our ultimate goal was to investigate whether HBO can increase the antitumor efficacy of these modified isothiourea derivatives. Our research showed that the best cytotoxic effect in reducing the viability of T98G cells was obtained for the compounds ZKK1 and TRIM, while the exposure to hyperbaric oxygen additionally increased this effect. In summary, antineoplastic effects of isothiourea derivatives and hyperbaric oxygen may provide for a therapeutically beneficial combination, however, further detailed studies are needed in order to determine which compounds are suitable for such combination treatments.

Funding: This work was supported by the Foundation for the Development of Diagnostics and Therapy, Warsaw.

Congenital subcutaneous neuroglial heterotopia in the coccygeal region

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Glial heterotopia is the presence of mature nervous tissue outside its anatomical location. They are rare congenital changes, most often located within the nasal tissues. Extranasal tumors are mainly observed in the orbit, oral cavity, middle ear, neck or scalp. There are single reports of subcutaneous lesions in the lumbosacral region.

We show a case of a 2-year-old girl with an exophytic nodule in the coccygeal region presenting from birth. In magnetic resonance imaging, the tumor was well-circumscribed, superficial, irregular, localized subcutane-

ously, not enhancing after contrast. Ultrasound shows a lesion without connection with the spinal canal. Macroscopically, a yellowish, poorly demarcated nodule of up to 6 mm in diameter was found in the subcutaneous tissue. Histological examination revealed lesion composed of small elements of glial tissue embedded in a fibrous stroma with the immunophenotype: S100+, CD68, GFAP+, olig2–.

Subcutaneous glial choristomas are very rare and difficult to diagnose on the basis of imaging studies. They should be taken into consideration in the differential diagnosis of congenital lesions, especially after excluding teratomas and myelomeningocele.

Post-COVID anosmia and the expression of pathological proteins in nasal mucosa nerves endings

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Introduction: Anosmia and ageusia were observed as frequent neurological complications of SARS-CoV-2 infections. The aim of the study was to elaborate methods for detection of pathological proteins in nerve endings and to evaluate the frequency and intensity of pathological proteins expression in patients with persistent anosmia.

Material and methods: The study included 249 patients (181 females and 68 males) aged 47 ±14 years from NeuroCOVID Polyclinic in Poznań observed from April 2021 untill now. The mucosal biopsy was performed using endoscopy from anterior ethmoid cells. The expression of alpha-synuclein was evaluated using immunofluorescence, and amyloid, tau and TDP43 proteins – using immunohistochemistry.

Results: Anosmia was observed in 42% of patients and cacosmia – in 6%. Ageusia/dysgeusia was observed in 31% cases. In patients with mild clinical course of COVID19 – not hospitalized anosmia (45%) and dysgeusia were more frequent (33%), and cacosmia was observed only in this group. In hospitalized patients anosmia was found in 22% of cases, dysgeusia in 13%, and cacosmia was not observed at all. The expression of alpha-synuclein, amyloid, tau and TDP43 proteins was found in nerve bundles, epithelial cells and in surrounding (nerve endings) of gland cells.

Conclusion: SARS-CoV-2 infection may induce the expression of pathological proteins in olfactory mucosa of post-COVID patients with anosmia.

The expression of sphingosine-1-phosphate receptor 3 in primary and metastatic brain tumors in relation to blood-brain barrier disruption

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Introduction: Sphingosine-1-phosphate receptor 3 (S1PR3) is a G protein-coupled receptor that binds sphingosine-1-phosphate (S1P) and regulates inflammation, migration, angiogenesis, differentiation, and proliferation. S1P is involved in impaired blood-brain barrier function and tumor microenvironment processes. The aim of the study was to evaluate S1PR3 expression in primary and metastatic brain tumors in relation to neuroimaging.

Material and methods: The study included 46 brain tumors: 13 high-grade glial tumors (12 IDH-wildtype), 12 meningiomas, 21 metastatic tumors (lung cancer, clear cell carcinoma of kidneys, colon and ovarian cancer, melanoma). S1PR3 was detected immunohistochemically and then its expression was qualified as cellular/present in processes/extracellular/perivascular; its extent was quantified as 0/< 25%/50%/75%/100% and intensity as 0 – no expression/1 – week/2 – moderate/3 – intensive/4 – very intensive.

Results: The intensity of S1PR3 expression correlated with tumor size in FLAIR MRI (R^2 = 0.3895, p = 0.0171), global index correlated with midline shift ($r_{Spearman}$ = 0.475, p = 0.0462) in all tumors. The intensity of S1PR3 expression correlated with midline shift in metastatic tumors ($r_{Spearman}$ = 0.520, p = 0.0322).

Conclusions: The patterns of S1PR3 expression differ in glial tumors, meningiomas and metastatic tumors. The intensity and extend of S1PR3 expression is higher in glial tumors than in meningiomas and metastatic tumors. S1PR3 expression correlates with peritumoral edema.

Ewing's sarcoma in the skull bone in an 18-year-old woman – a rare case from medicolegal practice

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Full histopathological and molecular diagnostics of neoplasms is rare in medicolegal practice, because it is not the goal of prosecution proceedings. The aim of the study is to present a case which concerned the post-mortem diagnosis of the nature of the proliferative process in the head (subtemporal fossa) in an 18-year-old woman. The tumor soon led to massive brain oedema and fatal cardiac arrest. The clinical diagnostics has not been completed. There was also a suspicion of medical malpractice, so the forensic autopsy was performed. Post mortem histopathological examination ordered by the prosecutor's office allowed for suspicion of Ewing's sarcoma (EWS), for which specific gene rearrangements are characteristic. Histopathology revealed the presence of small cell malignant tumor with the following immunohistochemical profile: CD99 (+), LCA (–), NSE (–), synaptophysin (–), CK (–), MyoD1 (–), Myogenin (–), CD117 (–), CD57 (–), CD68 (–), TDT (–), CD34 (–), S-100 (–), PLAP (–), Melan A (–). The Ki67 proliferation index was heterogeneous, averaging 60%. The test for FLI-1, often used in EWS diagnostics, was not performed because the appropriate antibody was not available. Overall, the phenotype of neoplastic cells was consistent with Ewing's sarcoma. No rearrangement of the 22q12 region containing the EWSR1 gene was found. There was also no rearrangement of the 16p11.2 region containing the FUS gene. Only a monoallelic deletion of the 16p11.2 region containing the FUS gene was observed. From the epidemiological point of view, the presence of Ewing's sarcoma in the skull bone in an 18-year-old woman is an unusual clinical situation. Similar cases are rarely published in specialist literature.

Key words: Ewing's sarcoma, forensic histopathology, cause of death, medical malpractice.

The first evaluation of tumor and its environment in the atomic level a pilot stable isotope ratio study

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Introduction: The assessment of the tumor environment and tumor adjacent tissues is one of the most modern and the most rapidly developing areas of research which serves for better understanding of the interaction between the tumor and the host and allows to determine the differences between pathologic and normal tissues. Isotope ratio mass spectrometry gives the possibility to reveal the most versatile characteristic of biological samples. A turning point in IRMS history was its introduction to oncology. No studies of the isotopic composition of CNS tumors and their environment have been found in the literature. The aim of the study was to establish the isotopic characteristic of nitrogen and carbon in ganglioglioma and its close and distal environment to search for biological differences.

Material and methods: Tissue samples were collected from the tumor and its close and distal environment (tumor margin and morphologically normal tumor surrounding) and the assessment of isotopic composition of carbon and nitrogen was performed with the use of Sercon 20-22 continuous flow isotope mass spectrometer coupled with an elemental analyzer.

Results: Isotopic composition of carbon and nitrogen in the tumor center, tumor margin and morphologically normal tumor surrounding tissue are characterized by different $\delta^{15}N$ and $\delta^{13}C$.

Conclusions: Interdisciplinary evaluation of isotopic composition of carbon and nitrogen in ganglioglioma its margin and morphologically normal tumor surrounding has disclosed for the first time previously unknown biological differences between neoplasm and its close and distal environment in the atomic level with prospective clinical implications.

The first interdisciplinary evaluation of isotope ratio of gliosarcoma and its environment *in vivo* a preliminary study

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Introduction: Gliosarcoma is highly invasive morphological variant of glioblastoma associated with extremely poor prognosis. The most recent application of mass spectrometry for the purposes of oncology – carried out with the use of isotope technique of this method evaluates stable isotopes of elements naturally occurring in normal and pathologically altered tissues. No studies have been found to determine the isotopic composition of CNS tumors in comparison with morphologically normal tissue from cancer surrounding. The aim of the study was to establish the values of isotope ratio of nitrogen and carbon in gliosarcoma and morphologically normal tissue from cancer surrounding.

Material and methods: Tissue samples were collected from the gliosarcoma and morphologically normal cancer surrounding. The samples of 2-3 mg dry material were prepared and placed in tin capsules with 1 mg of vanadium pentoxide as an oxidant and combustion catalyst. As a local standard, thiobarbituric acid was used. The isotopic composition of carbon and nitrogen was determined with the use of Sercon 20-22 continuous flow isotope mass spectrometer coupled with an elemental analyzer.

Results: The values of carbon and nitrogen isotope ratio of gliosarcoma and morphologically normal tissue from cancer surrounding were characterized by different δ values.

Conclusions: Determining the isotope composition of carbon and nitrogen in gliosarcoma presents at the current stage of advancement of isotope studies in oncology a cognitive nature as well as for the first time reveals different atomic level structure of tumor and its morphologically normal surrounding.

Neuromorphology of cognitive changes in type 2 diabetes mellitus: a histopathological update

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Introduction: According to the WHO today about 422 million people worldwide have diabetes and chronic course of diabetes leads over time to decrease the cognitive functions and the development of dementia. The aim of this study was to decipher neuromorphological changes in type 2 diabetes that potentially affect cognitive impairment.

Methods: We have performed a clinical-morphological comparison of outpatient card data, disease histories and autopsy reports of 15 cases of type 2 diabetes.

Results: The main cyto-angio-architectonic manifestations of diabetic brain damage are diffuse alteration of the basement membranes and vascular endothelium, capillary fibrosis and hyalinosis, pericyte proliferation, congophilic angiopathy accompanied by a sharp disruption on transcapillary transport. There is a combination of acute and chronic processes, reversible and irreversible changes in nerve cells: neuronal swelling, subtotal chromatolysis, karyopyknosis and cytoplasmic homogenization, satellite disease, perikaryon enlightenment, tigrolysis, lysis of neurons with the formation of "shadow cells". In areas of chronic ischemia there are neurons or groups of neurons with morphological signs of Alzheimer's neurodegeneration (pathological neurofibrils in the form of tangles), many hematoxylin spheres and single Lafora bodies. Moreover, single terminal plaques are found in the impregnation of silver by the Bielschowsky staining method.

Conclusions: Thus, the brain morphological changes in type 2 diabetes mellitus are formation neurofibrillary tangles are thought to contribute to the degradation of the neurons in the brain, congophilic angiopathy of small vessels and vessels of medium caliber. The combination of vascular and neurodegenerative components can mutually potentiate each other, causing clinical symptoms of cognitive deficits.