ANNUAL MEETING ABSTRACTS

1503  Inflammatory Pseudotumors of the Central Nervous System
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Background: Inflammatory pseudotumors (IPT) is a disease with unsettled pathogenesis.

Aims of the study: To investigate ALK+ protein expression and IgG4-positive plasma cells (PC) in 3 intracranial IPTs.

Design: Three intracranial IPTs and the corresponding clinical information were retrieved from hospital archive.

Results: All cases displayed typical histologic features of IPT with dense lymphoplasmacytic infiltrate admixed with bland spindle cells in a collagenous stroma.

Conclusions: ITPs were included in the revised 2016 IHC and immunohistochemistry sections including ALK+ and IgG4.

1504  Repeat Molecular Testing in Gliomas: A Retrospective Study of 53 Patients
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Background: Molecular testing for deletions on chromosomes 1p and 19q and for EZH2 amplification has implications for the clinical management of certain glioma tumors. The value of repeat testing in patients with multiple resections is unclear. The purpose of this study is to add previously reported data assessing for evidence of molecular changes in gliomas which have undergone repeat testing.

Design: 53 patients (31 males; age range 45-54 years) who had repeat molecular testing on specimens from two different resections for chromosome 1p deletion, chromosome 19q deletion and/or EZH2 amplification by fluorescent in situ hybridization (FISH) were studied.

Results: Original diagnoses included 27 diffuse fibrillary astrocytoma (11 low grade, 3 anaplastic and 13 GBM), 16 oligodendrogliomas (11 low grade and 5 anaplastic), 6 mixed gliomas (4 low grade and 2 anaplastic) and 4 gliomas not otherwise specified. Nine tumors upgraded during the interval between the initial and the subsequent resection (4 astrocytomas, 2 oligodendrogliomas and 3 mixed gliomas). Paired results for 1p evaluation demonstrated a change in the profile from intact to loss in 15/50 patients (30%). Two of these tumors diagnosed as GBM on the initial and subsequent resections changed profile from 19q loss to intact. The remaining 2 tumors (1 astrocytoma and 1 mixed glioma) were initially 19q intact and changed to loss on the subsequent resection. The mixed glioma upgraded to anaplastic mixed glioma on the subsequent resection. There was no change in the EZH2 expression in any of the patients tested (N=34; 28 with no amplification, 6 with amplification). There was no change in the clinical management based on the repeated molecular tests in patients with discordant repeat results.

Conclusions: There was only rare evidence of profile change in 1p and 19q status (5/53 tumors) and no change in the EZH2 amplification status with repeated testing. None of the tumors with change in molecular status were oligodendrogliomas. This appears to be no indication for repeat 1p or 19q or EZH2 FISH testing in gliomas at the time of repeat biopsy or resection.

1505  Isolation & Characterization of Brain Tumor Stem Cells (BTSC) in Human Glioblastomas (GBs)
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Background: Recent studies are suggesting that gliomas, develop from a subset of cells with self-renewal capacity stem-like cells. GB research, is showing evidences that brain tumor stem cells (BTSC) drive tumorigenesis. GB isolated from GBs transplanted into immunodeficient animals generate GBs. However transplanted GBs cell lines devoid of BTSC do not generate tumors. BTSC are identified by their capacity to form neurospheres in culture, that express progenitor stem markers, like CD133, Nestin, Wnt, CXCR4, etc. Furthermore, BTSC expressing CD133 have been shown to be more resistant to radiation, being responsible of radiation treatment failure. Most studies have been done in vitro or in animal models. We have addressed whether a population of BTSC exists in human GBs, that can be characterized phenotypically, to study patterns of expression & get insights into the biology of GBs.

Design: GBs disaggregated to single cells, were cultured with EGF & FGF. Neurospheres were harvested at 6 weeks. After centrifugation, the pellet was fixed, paraffin embedded and sectioned. Neurosphere & original GB specimens from which they were generated, were immunostained with CD133, Nestin, Wnt, CXCR4 & VEGFR2.

Results: CD133, Nestin, Wnt, CXCR4 & VEGFR2 were expressed by neurospheres with variable intensity, consistent with their heterogenous nature. GBs displayed expression of these antigens by groups of neoplastic cells identified as BTSC with the following patterns: 1) Frequent expression by perivascular cells, neoplastic vessels & perivascular pseudocysts, independent expression by infiltrating marginal cells, versus the central tumoral areas. 2) High levels at the most anaplastic areas. Conclusions: The patterns of expression of the BTSC subpopulation in GBs argue for their role as cancer driving cells. 1) The expression of stemocyte markers reflect their property as self-renewal neoplastic elements. 2) The perivascular and endothelial proliferating cells location of BTSC, argue for a role in neoplastic angiogenesis. The high levels of BTSC observed at infiltrating margins and perivascular pseudocysts, should be confirmed by larger studies.

1506  Molecular Alterations of PDGFRa and PDGFRf in Gliomas
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Background: Malignant gliomas are the most prevalent primary brain tumours, have an aggressive clinical course and lack effective treatment options. PDGFB signalling is one of the key regulators of glioma development. The efficacy of anti-PDGFRa drugs for the management of patients with glioblastomas is currently being tested in clinical trials. The aim of this study was to determine the expression of PDGFRa and PDGFRf and the underlying genetic mechanisms driving their expression in a large series of gliomas.

Design: We investigated the frequency of PDGFRa and PDGFRf expression by immunohistochemistry in 169 gliomas and screened for PDGFRa gene mutations and gene amplification in 86 and 57 gliomas using a combination of direct sequencing, quantitative copy number PCR and microarray-based comparative genomic hybridization.

Results: We found that PDGFRa was largely expressed in different glioma histological types and its absence was associated with a poor prognosis. PDGFRa was significantly expressed at high levels in malignant astrocytic tumours. Moreover, we have observed the existence of putative PDGFRa/PDGFRf autocrine/paracrine loops in glioblastomas. Finally, although PDGFRa gene activating mutations were not found, PDGFRa gene
amplification was observed in 21% of gliomas and was significantly associated with PDGFRA expression in diffuse astrocytoma.

Conclusions: The study presents a comprehensive molecular analysis of PDGFRA and PDGFRα in gliomas. Taken together, these results provide a molecular basis for anti-PDGFRA therapies in gliomas.

1507 Quantitation of Large Subarachnoidal Mitochondrial Aggregates Improves Specificity for Diagnosis of Mitochondriopathy in Children L. Morley, KE Brown, PA others Children's Hospital of Atlanta, Atlanta, GA, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background: In the diagnosis of mitochondrialopathy the presence of ragged red fibers and COX-negative fibers is helpful, but these features are uncommon in muscle biopsies from children. Until recently >2% of myofibers containing subarachnoidal mitochondrial aggregates (SSMA) was proposed as a minor criterion for diagnosis of mitochondrialopathy. The current authors suggested previously that only large SSMA (LSSMA), >40μm in thickness, are useful for the diagnosis of mitochondrialopathy. The current study compared the sensitivity and specificity of % of myofibers containing LSSMA, SSMA, type I myofiber, and for each patient, the lowest individual electron transport chain (ETC) complex activity in the diagnosis of mitochondrialopathy.

Design: Only patients with previously identified LSSMA and ETC testing in muscle were included. Patients were assigned to the LSSMA group if >2% of myofibers containing SSMA, and the type I myofiber proportion (% of control) were evaluated for the diagnosis of mitochondrialopathy using receiver operating characteristic (ROC) analysis. Results are expressed as mean±SD.

Results: In 35 patients with LSSMA, 9 [age 7.3±3.8] y had mitochondrialopathy (group 1) and 26 [age 4.3±2.9] y had no evidence of mitochondrialopathy (group 2). Group 1 patients were compared to group 2 controls by comparing SSMA >6.7±4.9% vs. 1.7±1.0%, respectively. Type I myofiber (% SSMA) and SSA were similar between groups. ETC complex activities were similar except for increased complex I and I activity in group 1 by 1.5±2.6%. ROC analysis results are summarized in the table. Logistic regression modeling indicated that the diagnostic performance was significantly improved (Area Under the ROC Curve=0.938) with the combined use of LSSMA and ETC testing.

Conclusion: LSSMA >3.3% should be considered as a potential major criterion for diagnosis of mitochondrialopathy in children.

1508 Caveolin-1 Expression Predicts Outcome in Oligodendrogliomas Tumors Regardless of 1p/19q Status I. Molinero, R. Serrato, E. Maldonado, R. Zicari, B. Serrato, S. Ferrari, P. Caccioni. University of Turin, Turin, Italy.

Background: Caveolin-1 (Cav-1) is the basic component of caveole, omega-shaped membrane microdomains involved in various cell functions. In tumours, Cav-1 can be either overexpressed, suggest neo-angiogenesis role, or downregulated, therefore, its role in oncogenesis is still debated. Regarding brain tumours, our group demonstrated that Cav-1 is significantly more expressed in astrocytic-derived tumours than in oligodendrogliomas, suggesting how this marker could be used as a valuable tool in the differential diagnosis between these two categories. Moreover, in tumours of astrocytic origin, we reported that Cav-1 expression increases accordingly to tumour grade, thus suggesting that tumour aggressiveness relies on Cav-1 expression and envisaging a possible role for Cav-1 in predicting patients’ prognosis.

Design: We have studied Cav-1 expression in oligodendrogliomas, tumours such as astrocytomas (ISO), oligoastrocytomas (OA) and glioblastomas with oligodendrocyte component (GBM) to evaluate its potential role as a prognostic factor and to determine if its expression is related to 1p/19q deletions, to date the hallmark prognostic factor for these gliomas, and to elucidate a possible role for Cav-1 in predicting patients’ prognosis.

Results: In 1p/19q deletion was expressed in a minority of cases (21.8%), mostly grade III OAs and GBMO. 1p/19q deletion was expressed in 45.7% cases, mostly grade II and III OAs. The correlation between 1p/19q deletion and loss of Cav-1 staining was proven to be statistically significant (p<0.002), as well as organisation of Cav-1 (p<0.05), suggesting the involvement of Cav-1 in the prognosis of astrocytic tumours.

Conclusion: We here provide the first evidence that Cav-1 is a new trustworthy, easy to manage, independent prognostic marker in oligodendroglial-derived tumours regardless of the 1p/19q status. Since Cav-1 has been also associated with glioma underlying multi-drug resistance, we feel thus entitled to preliminarily suggest that the worse outcome in Cav-1-positive patients in our series could be at least partially related to an acquired chemoresistance resistance.


Background: From 1992, parenchymal counterpart of central neurocytoma (CN), extraventricular neurocytoma (EVN) started to be recognized, which share the histopathological features of the CN but are known to show a wide morphological spectrum.

Design: Five recent cases of EVNs along with the clinicopathological and radiological features are reviewed.

Results: The mean age of the patients was 36.2 years old (6 yrs–66 yrs) and a female predominance (M:F=1:6) was found. The most common symptom was seizure (n=4) and the tumors were located in the temporal lobe (n=3), frontal lobe (n=1), and hippocampus (n=1). MRI showed nonenhancing cystic lesion (n=2), infiltrating solid mass (n=2), and well circumscribed mass with high signal intensity lesion on T2 and FLARE (n=1). Near total resection of the tumors was performed in every case. The tumor cells in all cases, regardless of the tumor grade, were composed of small round cells with round nuclei and clear or eosinophilic cytoplasm. These cells were arranged in sheet, in association with broad based fronds of fibrillar neuropil. The nuclei of these undifferentiated cells were not focally ovoid. The cellularity was variable area by area. Often smaller ganglioid cells with nuclei that are larger and paler than neurons were detected. Three high grade cases showed high mitotic activity (7 to 9/10 HPF) and high level of MIB-1 labeling indices (6–29%). Two of them had vascular endothelial hyperplasia and necrosis. Almost tumor cells were immuno-labeled for synaptophysin and Neurofil, and, additionally, expressed the nestin. GFAP expressing cells were focally observed, but pseudopapillary configuration was not shown. Ultrastructurally, neurite tubules and synapses with synaptic junctions and synaptic vesicles were well observed. 1p/19q FISH study performed in 2 cases revealed no deletions. Radiotherapy was offered to three patients with high grade cases. There were no case of recurrence in the course of follow-up period (2–10 months) even though the follow up duration was not sufficiently long enough to confirm the biologic behavior.

Conclusion: EVNs were occurred in the patients with broad age ranges and epilepsy was most common symptom. Without immunohistochemistry, EVNs had a diagnostic pitfall due to spectrum of tumor cell morphology and similar histopathological features. More reports about its clinicopathological, biological and genetic studies are needed to understand and to have confidence upon this tumor.

1510 Assessment of the 1p/19q Deletions at Different Areas in Biphasic Oligoastrocytomas by Using Chromogenic In Situ Hybridization VC Oliveira, RCV Carrara, DS Coelho, EV Cervino, SFP Carvalho, CR Cid, MS Machado, I. Neder. Faculty of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil.

Background: Oligoastrocytomas (OA) are mixed gliomas composed of tumor cells morphologically resembling oligodendroglioma and diffuse astrocytoma. Although the status of 1p/19q deletions in oligodendrogliomas is well-known, isolated or combined losses of 1p/19q in OA remains to be elucidated. The goal of this study was to evaluate the 1p/19q deletions by using CISH at different tumor areas in a series of bona fide “biphasic” OAs of different grades of malignancy.

Design: CISH was performed on formalin-fixed paraffin-embedded cores from different tumor areas of 12 OA, intermingled (“diffuse”) variant (4 grade II, and 8 grade III) by using a TMA block. The patient’s mean age was 40 years (11-54 years) with 2:1 male:female ratio. The presence or absence of chromosomal locus 1p and 19q) was analyzed in different tumor areas (oligo vs astrocytic area). The cut-off value was established by counting 500 nuclei in normal brain tissue from patients with intractable epilepsy. It was analyzed a minimum of 200 tumor nuclei for each set of probes without the knowledge of the diagnosis.

Results: Were found have combined/isolated losses of 1p/19q in 50% of the tumor samples.

Conclusion: Status of 1p/19q deletion in Oligoastrocytomas according different grades of malignancy.

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<th>Grade</th>
<th>1p</th>
<th>19q</th>
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<tr>
<td>Grade II</td>
<td>4/4</td>
<td>3/4</td>
<td>7/8</td>
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<tr>
<td>Grade III</td>
<td>6/6</td>
<td>5/6</td>
<td>11/12</td>
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The combined 1p/19q losses were detected in 2/12 cases and were present in both astrocytic and oligodendroglial components. The isolated loss of 1p was detected in 3/12 cases (25%). Interestingly, the 1p loss was present in both components in one grade III OA. The remaining exhibited isolated 1p loss in astrocytic but not in the oligodendroglial end (grade II) and vice-versa (grade III). The isolated loss of 1q was found in both components and it was present in one case.

Conclusions: 1p/19q deletions are not an uncommon event in OAs. Interestingly, in these cases, if they have combined or isolated losses, the chromosome deletions were found in both oligo and astrocytic components in 4/6 cases, which could reflect the clonal origin for both components. Furthermore, CISH is a low-cost technique, easy to perform and has a beneficial tool in the diagnosis assessment of 1p/19q status in gliomas.

1511 Adhesion Molecule Expression in Primary, Recurrent, and Metastic Medulloblastomas D Partridge, S. Crual, University Health Network, Toronto, ON, Canada.

Background: Medulloblastomas spread by leptomeningeal dissemination rather than the infiltration that characterizes other CNS tumors. Adhesion molecules in the syndecan family are important in cell adhesion and movement. Syndecan-1 is a transmembrane adhesion molecule that binds to growth factors, cytokines, and additional extracellular matrix molecules. Collagen I and IV, Tenascin, Fibromodulin, Vitronectin, osteonectin, thrombospondin and Laminin.

Results: Evaluation of the stained sections showed increased beta 1 integrin reactivity in recurrent and leptomeningeal tumors compared to their matched primary tumors.

Conclusion: The expression of syndecan-1 in medulloblastoma may have an important role in medulloblastoma progression by mediating cell adhesion and movement.