P03.20 Comparison of histopathology profiles in surgically resected cerebral radiation necrosis with recurrent irradiated brain tumor

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INTRODUCTION: A conundrum exists in establishing the diagnosis of cases with post-irradiation necrosis following brain radiation therapy (RT), by tissue examination because specific histologic characteristics have not been defined and distinguished from those of recurrent brain tumor (RBT) after RT. The distinction of these two entities is critical for accurate management. We retrospectively characterized the histologic characteristics identified in surgically-derived tissue specimens obtained at imaging recurrence in brain tumor patients treated with RT and in whom the specimen contained predominantly or totally RTN versus purely RBT. MATERIALS AND METHODS: Subjects in this retrospective IRB-approved study had diagnosis of RTN or RBT identified by a review of brain pathology reports at UHCMC from 2004–2013. RTN was defined by > 80% features of RTN; RBT was defined by >80% active tumor. All other cases (“mixed RTN and RBT”) were excluded. Clinical, imaging and treatment data were reviewed. Histologic profiling included vascular changes (telangiectasia, hyalinization, wall thickening and necrosis, thrombosis, endothelial hypertrophy, circumferential endothelial hyperplasia [CEN]), necrosis (coagulative [CN], pseudopalisading, zonal geographic [ZGN]), tumor features (perinuclear halos, mitoses, tumor sponginess, epithelial differentiation), tissue reaction (granulation tissue, collagen scar, senile demyelination, “RT astrocytes” [RTA]), microcysts, dystrophic calcification [DC], blood products, and inflammatory infiltrates. Each characteristic was graded: 0, 25%, 50%, 75%, 100% by a board-certified neuropathologist (MC). Profiles were compared with pretreatment tumor when available. RESULTS: 66 patients treated with EBRT and/or SRS were identified, 40 with RT (glioma 2.5, metastasis 15) and 26 with RTN (metastasis 14, glioma 12). Using Fisher’s exact and Chi-square tests we identified significant [p<0.05] differences in the frequency and severity of ZGN, RTA and DC in glioma and metastasis RTN as compared with RBT. Vascular hyalinization, hemosiderin, collagen scar and granulation tissue were increased in glioma RTN compared to RBT and correlated with RBT. Gliosis was associated with more CN, mitoses, and CEH than RTN. Metastatic RTB was associated with more epithelial differentiation than RTN. CONCLUSIONS: The quantitative histologic profiles we identified in RTN as compared with RBT may assist neuropathologists in the interpretation of resected tissue specimens following RT for a brain tumor. Grant support CTSC ULTR000439.

P03.23 CASP9 GERMINE MUTATION IN A FAMILY WITH MULTIPLE BRAIN TUMORS
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We report a novel CASP9 germline mutation that may increase susceptibility to the development of brain tumors. We identified this mutation in a family in which four brain tumors had developed within three generations, including two anaplastic astrocytomas occurring in cousins. The cousins were identified by comparison to other affected family members with similar histological features. Genetic analysis revealed somatic IDH1 and TP53 mutations in both tumors. However, no germline TP53 mutations were detected, despite the fact that this family fulfills the criteria of Li-Fraumeni-like syndrome. Whole exome sequencing revealed a germline stop-gain mutation (p.R65X) in the CASP9 gene, which encodes caspase-9, a key molecule for the p53-dependent mitochondrial death pathway. This mutation was also detected in DNA extracted from blood samples from the two siblings who were each a parent of one of the affected cousins. Caspase-9 immunohistochemistry demonstrated the absence of caspase-9 immunoreactivity in the anaplastic astrocytomas and normal brain tissues of the cousins. Both tumors and their matched normal brain tissues may have played a role at least in part to the susceptibility of development of gliomas in this Li-Fraumeni-like family lacking a TP53 germline mutation.

P03.22 BRAF, FGFR1 AND PDGFR ALTERATIONS IN OLIGODENDROGLIOMAS - CORRELATION WITH MAPK/MTOR PATHWAY ACTIVATION
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Oligodendrogliaoma (ODGs) is relatively rare, comprising approximately 2.7% of all brain tumors. They have attracted great interest in both basic and clinical neurooncology because of having a better overall prognosis as compared to other diffuse gliomas. BRAF alterations in ODG are recognized along with activation of mTOR and MAPK pathways have been identified in various glial tumors. However, these alterations and clinical outcome remain unexplored in ODGs. Hence, the aim of this study was to analyze BRAF, FGFR1, PDGFRα related genetic alterations and MAPK-mTOR signaling pathway in oligodendroglioma (ODG). Based on 1p19q co-deletion, IDH1 mutation, and ATRX immunostaining, 45 ODG cases were studied. BRAF-gain, BRAF-KIAA1549 fusion, FGFR1-TKD duplication and PDGFRα amplification were determined by quantitative real-time PCR. BRAF-V600E mutation was analysed by sanger sequencing and MAPK-mTOR pathway activation by Immunohistochemistry. BRAF-gain and BRAF-KIAA1549 fusion were detected in 40% and 23% of ODGs respectively. V600E mutation, FGR1-TKD duplication and PDGFR amplification had a low occurrence rate of 4%, 12% and 11%, respectively. Association of BRAF-gain with poor outcome and BRAF-KIAA1549 fusion with better outcome was noted. MAPK/ERK pathway activation was detected in 71% of cases and was associated with BRAF-gain. Interestingly, all the cases of detected FGFR1-TKD duplication from MAPK/ERK pathway activation. mTOR pathway was however activated in a small subset of ODGs (12/45;27%). BRAF, FGFR1-TKD and PDGFRα alterations did not show significant association with grade and age. However, V600E mutation, FGFR1-TKD duplication and PDGFR amplification had a low occurrence rate of 4%, 12% and 11%, respectively. Activation of MAPK-gain in brain metastasis maintain the same proportion. Besides, confocal images showed a polarization of AQP4 expression mostly affected areas. In conclusion, our results confirmed a cross talk between AQP4 and the microenvironment during the metastatic process involved in brain metastasis.