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HGG-16. PEDIATRIC-TYPE DIFFUSE HIGH-GRADE GLIOMA OF METHYLATION-BASED RTK2A AND RTK2B SUBCLASSES PRESENT DISTINCT RADIOLOGICAL AND HISTOMOLECULAR FEATURES

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BACKGROUND: Diffuse pediatric-type high-grade gliomas (pedHGG), H3-wildtype and IDH-wildtype, encompass three main methylome-based subclasses: pedHGG-MYCN, -RTK1A/B/C, and -RTK2A/B. Since their first description in 2017, tumors of pedHGG-RTK2A/B have not been further characterized and their clinical significance is unknown. METHODS: A not yet published cases series on pedHGG with a gliomatosis cerebri (GC) growth pattern showed an increased incidence of pedHGG-RTK2A/B (n=18/40). We assembled a cohort of 14 additional methylation-based pedHGG-RTK2A/B tumors and pooled them with the GC tumors providing centrally reviewed radiological, histological, and molecular characterization. RESULTS: Our cohort of 32 pedHGG-RTK2A/B tumors consisted of 25 RTK2A (78%) and seven RTK2B (22%) cases. The median age was 11.6 years (4-17) with an overall survival of 15.9 months (interquartile range 12.1-25.8). Of the additional unselected cases with available imaging (10 of 14), seven showed a GC phenotype at diagnosis or follow-up. In addition, pedHGG-RTK2B tumors exhibited bithalamic involvement (6/7, 86%). Histopathology confirmed a diffuse glial neoplasm in all cases with prominent angiocentric features in both subclasses. Most tumors (24/29, 83%) diffusely expressed EGFR, notably with a focal perivascular enhancement. Cells of pedHGG-RTK2A lacked Olig2 expression, whereas 43% (3/7) of pedHGG-RTK2B expressed Olig2. Loss of ATRX expression occurred in four pedHGG-RTK2B samples (57%). In sequencing analyses (RTK2A: n=18, RTK2B: n=5), *EGFR* alterations (n=15/23, 65%; predominantly point mutations) were commonly found in both subclasses. Mutations in *BCOR* (n=14/18, 78%), *SETD2* (n=7/18, 39%), and *TERT* promoter (n=6/18, 33%) occurred exclusively in pedHGG-RTK2A tumors, while pedHGG-RTK2B tumors were enriched for *TP53* mutations (4/5, 80%). CONCLUSIONS: In conclusion, genotype-phenotype correlations in a multicenter series of pedHGG-RTK2A/B tumors revealed a highly diffuse-infiltrating tumor frequently exhibiting a GC phenotype. The two subclasses share particular histomolecular features (*EGFR* alterations, angiocentric pattern), whereas they differ in specific characteristics (pedHGG-RTK2A: Olig2 negativity, *BCOR* and *SETD2* mutations; pedHGG-RTK2B: *ATRX* and *TP53* alterations).