Am J Surg Pathol. 2023 Sep 22. doi: 10.1097/PAS.0000000000002118. Online ahead of print.

A Novel Type of IDH Wild-type Glioma Characterized by Gliomatosis Cerebri-like Growth Pattern, TERT Promoter Mutation, and Distinct Epigenetic Profile

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PMID: 37737691 DOI: 10.1097/PAS.0000000000002118

Abstract

Diffuse gliomas in adults encompass a heterogenous group of central nervous system neoplasms. In recent years, extensive (epi-)genomic profiling has identified several glioma subgroups characterized by distinct molecular characteristics, most importantly IDH1/2 and histone H3 mutations. A group of 16 diffuse gliomas classified as "adult-type diffuse high-grade glioma, IDH-wildtype, subtype F (HGG-F)" was identified by the DKFZ v12.5 Brain Tumor Classifier. Histopathologic characterization, exome sequencing, and review of clinical data was performed in all cases. Based on unsupervised t-distributed stochastic neighbor embedding and clustering analysis of genome-wide DNA methylation data, HGG-F shows distinct epigenetic profiles separate from established central nervous system tumors. Exome sequencing demonstrated frequent TERT promoter (12/15 cases), PIK3R1 (11/16), and TP53 mutations (5/16). Radiologic characteristics were reminiscent of gliomatosis cerebri in 9/14 cases (64%). Histopathologically, most cases were classified as diffuse gliomas (7/16, 44%) or were suspicious for the infiltration zone of a diffuse glioma (5/16, 31%). None of the cases demonstrated microvascular proliferation or necrosis. Outcome of 14 patients with follow-up data was better compared to IDH-wildtype glioblastomas with a median progression-free survival of 58 months and overall survival of 74 months (both P<0.0001). Our series represents a novel type of adult-type diffuse glioma with distinct molecular and clinical features. Importantly, we provide evidence that TERT promoter mutations in diffuse gliomas without further morphologic or molecular signs of high-grade glioma should be interpreted in the context of the clinicoradiologic presentation as well as epigenetic profile and may not be suitable as a standalone marker for glioblastoma, IDH-wildtype.