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Case Report

Diffuse Pediatric-Type High-Grade Glioma H3-/IDH-wildtype with *MYCN* Deletion and Constitutional Mismatch Repair Deficiency: Case Presentation

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Summary

Diffuse pediatric-type high-grade glioma H3-wildtype and IDH-wildtype (pHGG H3/IDH WT) is a heterogeneous entity that is currently defined by a combination of highly malignant morphology, glial or primitive neuroectodermal differentiation, and a number of molecular features. Depending on the DNA methylation profile in pHGG H3/IDH WT, three molecular subgroups are distinguished, one of which (pHGG *MYCN*) is characterized by amplification of the indicated gene. We report a unique case of pHGG H3/IDH WT in a 19-year-old girl with a deletion of the *MYCN* gene and constitutional mismatch repair deficiency syndrome.

More Information

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Introduction

Diffuse pediatric-type high-grade glioma H3-wildtype and IDH-wildtype (pHGG H3/IDH WT) is a heterogeneous entity that is currently defined by a combination of highly malignant morphology, glial or primitive neuroectodermal differentiation, and has a number of molecular features. Initial testing should exclude changes in histone *H3* and the *IDH1* or *IDH2* genes (isocitrate dehydrogenase 1/2) [1]. Alterations commonly found in these tumors include *PDGFRA* (platelet-derived growth factor receptor, alpha) amplification or mutation, *TP53* (tumor protein p53) mutation, *NF1* (neurofibromin 1) alterations, *EGFR* (epidermal growth factor receptor) amplification or mutation, or *MYCN* amplification (myelocytomatosis, neuroblastoma-derived). Depending on the DNA methylation profile in pHGG H3/IDH WT, three molecular subgroups are distinguished: pHGG RTK1 (receptor tyrosine kinase), pHGG RTK2 and pHGG *MYCN*. pHGG RTK1 is enriched for *PDGFRA* amplifications (~33% of cases), pHGG RTK2 is enriched for *EGFR* amplifications (~50% of cases), and *TERT* (telomerase reverse transcriptase) promoter mutations (~64% of cases) [2] and pHGG *MYCN* is enriched for *MYCN* amplifications (~50% of cases).

pHGG H3/IDH WT represents a large proportion (~ 40%) of pediatric high-grade gliomas, with pHGG *MYCN* and pHGG RTK2 representing the largest and smallest subgroups, respectively. Regarding etiology, it is noteworthy that the pHGG RTK1 subgroup includes most radiation-induced gliomas developing in patients previously treated for medulloblastoma or acute lymphoblastic leukemia, as well as most gliomas arising in syndromic contexts (eg, Li Fraumeni, constitutional deficiency mismatch repair and Lynch syndrome) [3-5].

Except for a higher degree of genomic instability associated with radiation-induced DNA damage, no significant biological differences have been identified between sporadic and

radiation-induced pHGG RTK1 [4,5]. In terms of localization, the vast majority of pHGG H3/IDH WT occurs in the supratentorial anatomical compartment. A minority of pHGG *MYCN* (about 15%) originate in the brainstem [6-8]. Regarding outcome, the overall prognosis of pHGG H3/IDH WT is poor (WHO grade 4). pHGG *MYCN* is associated with the lowest survival rates [2], and in this subgroup pontine tumors behave more aggressively than supratentorial counterparts, likely due to tumor location, with median overall survival of 16.5 and 1.5 months for supratentorial and HGG*MYCN* bridges, respectively [9]. The occurrence of *TP53*, *ATRX* (alpha-thalassemia receptor, X-linked), and mismatch repair gene mutations in the context of pHGG H3/IDH WT have been associated with adverse outcomes [10].

However, cases of *MYCN* deletion in pHGG H3/IDH WT have not previously been reported.

Description of the case

Patient K., 19 years old, was admitted to the Polenov Neurosurgical Institute – Branch of Almazov National Medical Research Center in St. Petersburg, Russia. It is known that a year before hospitalization, she began to experience diffuse headaches, dizziness, and episodes of "darkening" in her eyes. She was treated with drug therapy, which did not bring any effect. After 7 months, the headaches intensified and became localized in the left temporal and parietal region, and nausea appeared. At the height of pain, mainly in the morning, vomiting occurred. The neurologist recommended performing magnetic resonance imaging (MRI) of the brain. According to the results of the MRI, an intracerebral multinodular solid formation of a heterogeneous structure with inclusions of multiple small cysts was visualized in the structure of the left frontal, temporal, and occipital lobes. The tumor dimensions were up to 84×45×70 mm (Figure 1). Signs of mild perifocal edema and mass effect were noted. The median structures were shifted to the right by up to 7 mm. The patient underwent surgical treatment including subtotal tumor removal with Awake under neurolinguistic control and ultrasound navigation.

Histological examination of the surgical material revealed a malignant glial tumor of a diffuse structure (Figure 2A). The tumor had high cellularity, consisting of cells with rounded hyperchromatic polymorphic nuclei, which were located on a loose fibrillar background. Cellular nuclear polymorphism was moderately expressed, with a few bi- and multinucleated cells, and foci consisting of small monomorphic "homonuclear" cells with rounded hyperchromic nuclei being detected. In the stroma of the tumor, vascular cavities of different sizes were found, some with the proliferation of the endothelium and the formation of glomeruli; thin-walled vessels of small caliber were also found, partially branching like a "chain-link mesh"; signs of hyalinosis of the walls and plethora, and focal hemorrhages were present. Cysts filled with weakly basophilic contents, and foci of calcification deposits were also observed. Few mitoses and apoptotic bodies were present, but no necrosis was detected. Invasion into the cortex and spread through the molecular layer were observed. When immunohistochemical (IHC) examination was performed, the cytoplasm of tumor cells diffusely expressed GFAP+ (Figure 2B). There was a high proliferative activity of Ki67/MIB1 (10-12%, with foci up to 15%; Figure 2C), expression of IDH-1 (Figure 2D), and no detection of H3K27M. Additionally, microsatellite instability was detected with a complete loss of expression of the mismatch repair marker MSH6 by tumor cells (Figure 2E). Antibodies from Dako (Denmark) and an EnVision imaging system were used. Histological analysis and microphotography were performed using a Leica DM2500 M microscope equipped with a DFC320 digital camera and an IM50 image manager (Leica Microsystems, Wetzlar, Germany).

The diagnosis of molecular pathology revealed that the polymerase chain reaction (PCR) method did not detect mutations in the *IDH1* and *IDH2* genes, the *L858R* mutation

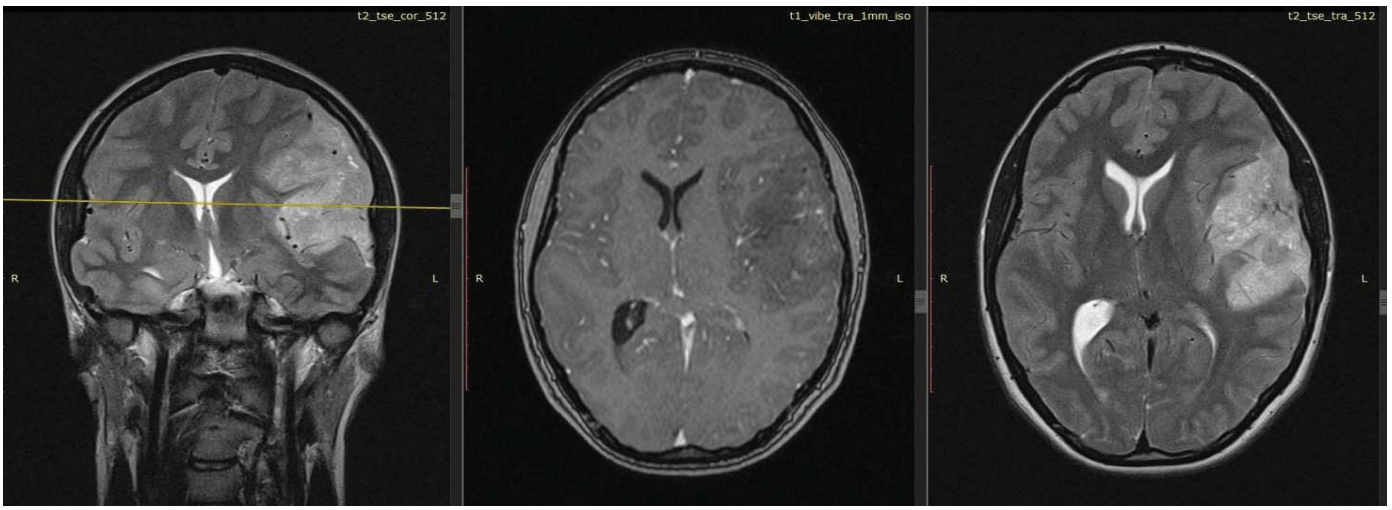

Figure 1: MRI results. Multinodular tumor of the left frontal, temporal, occipital lobes measuring 84×45×70 mm.

EGFR gene, or deletions. Direct Sanger sequencing also did not detect mutations in the *H3F3A* (*H3* histone, family 3a) gene. As an oligodendroglia-like component was identified in the tumor structure, fluorescent *in situ* hybridization (FISH) was performed using fluorescent probes, which revealed no rearrangements affecting *CHD5* (chromodomain helicase DNA-binding protein 5, 1p36) (Cytotest) и *GLTSCR1* (glioma tumor suppressor candidate region gene 1, 19q13.33). To determine the copy number of the *MYCN* gene, fluorescent *in situ* hybridization was performed using commercial fluorescent probes (*MYCN* (2p24) / *AFF3* (alf transcription elongation factor 3, 2q11), Kreatech FISH probes, Leica Biosystems, USA, KI-10706). The red signals of the probes were specific for the *MYCN* gene, and the green signals were specific for *AFF3*, which acted as a cell ploidy control. This DNA probe system was used to determine *MYCN* gene amplification in aggressive tumors. In the tissue sample under study, there were 5 fragments, in 4 of which most of the cells had fewer red signals than green ones (Figure 3), indicating a deletion of the region of the short arm of chromosome 2 containing the *MYCN* gene (region

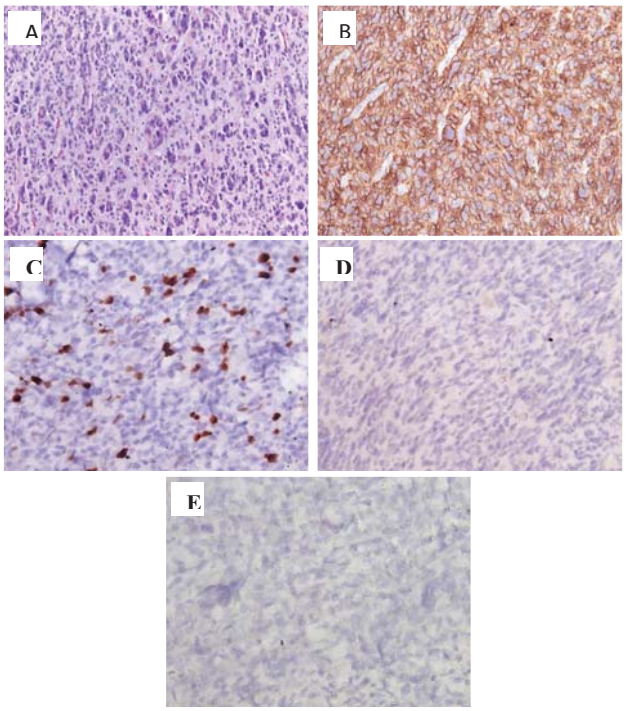

Figure 2: Results of histological and immunohistochemical examination. **A:** Highly malignant glial tumor infiltrating the cortex. H&E stain, ×200. **B:** IHC with antibodies to GFAP, ×200; **C:** Proliferative activity according to Ki67 10% - 15%, ×400; **D:** IHC with antibodies to IDH 1r132h, ×200 **E:** IHC with antibodies to MSH6, ×400.

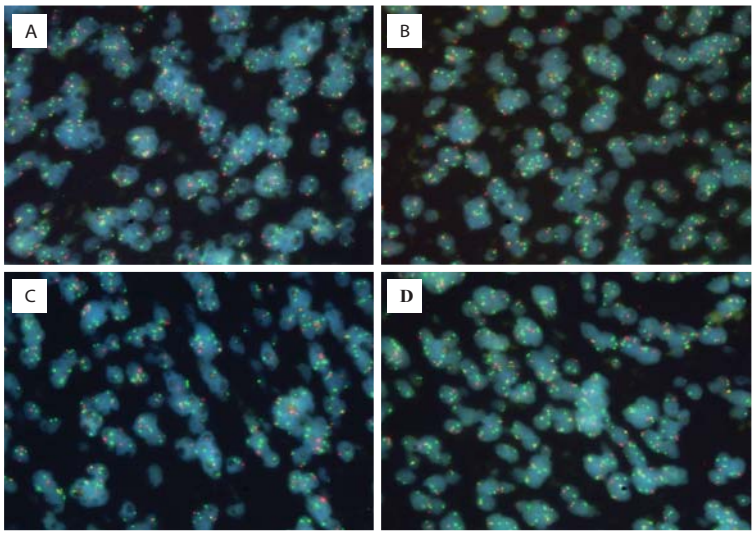

Figure 3: FISH results (A-D): Most of the cells have fewer red signals than green ones (ploidy control), which indicates a deletion of the region of the short arm of chromosome 2 containing the MYCN gene (region 2p24), ×630.

2p24). Research result: nuc ish(MYCNx2,AFF3x1)[3/188]/(MYCNx2~3,AFF3x3~4)[21/188]/(MYCN,AFF3)x2[75/188]/(MYCNx1,AFF3x2)[89/188].

Currently, the patient is still alive, having undergone 28 courses of chemotherapy with temozolomide and radiation therapy with a total dose of 60 Gray. There were no signs of disease progression or tumors in other locations.

Discussion

MYCN (OMIM 164840), the human gene encoding N-Myc, was first identified as an oncogene amplified in human neuroblastoma [11], a tumor characterized by the presence of undifferentiated neuroblasts [12]. The level of *MYCN* expression correlates with the prognosis of neuroblastoma [13] and overexpression of the human *MYCN* gene causes neuroblastoma in mice [14]. *MYCN* overexpression is also observed in other nervous system tumors such as medulloblastoma, glioblastoma, retinoblastoma, and spinal ependymoma, as well as in tumors outside the nervous system, such as neuroendocrine prostate cancer, nephroblastoma (Wilms tumor), and many others [15-17]. The nucleotide sequence of *MYCN* is very similar to that of the oncogene *MYC* [18]. Additionally, in addition to tumorigenesis in the nervous system, the *MYCN* oncogene has been shown to play a critical role in neurogenesis and oligodendrogenesis in the healthy adult brain [19]. However, the prognosis of tumors with *MYCN* gene deletion still needs to be studied.

Constitutional mismatch repair deficiency (CMMRD) is an autosomal recessive disorder caused by biallelic variants in one of four mismatch repair genes: *MLH1* (DNA mismatch repair protein 1), *MSH2* (MutS homolog 2), *MSH6* (MutS homolog 6), and *PMS2* (postmeiotic segregation increased, s. cerevisiae, 2). This condition can cause a wide range of tumors in childhood, adolescence, and young adulthood, with high-grade gliomas being the most common type. In approximately 60% of cases, CMMRD is caused by biallelic pathogenic variants of *PMS2*, in 20-30% by biallelic pathogenic variants of *MSH6*, and in 10-20% by biallelic pathogenic variants of *MLH1* or *MSH2* [20,21].

The literature describes isolated cases of deletion of the short arm of chromosome 2 at the organismal level, associated with multiple congenital malformations [22,23]. Therefore, further research is required to analyze genetic variants in malignant brain tumors.

Conclusion

Thus, a 19-year-old patient with constitutional mismatch repair deficiency syndrome developed a highly malignant diffuse pediatric-type glioma H3-wildtype and IDH-wildtype, in which a unique defect was discovered: deletion of the *MYCN* gene (region 2p24). The effect on the course of the disease and prognosis requires further study.

Institutional review board statement

The work was carried out according to the principles of voluntariness and confidentiality in accordance with Federal Law "On the Basics of Health Protection of Citizens in Russian Federation" 21.11.2011 N 323-FZ, and the Helsinki Declaration on Human Rights. The patient signed informed voluntary consent for the study.

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