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Case Report

A pediatric bithalamic high grade glioma with concomitant H3K27M and EGFR mutations

Buket Kara[1], Ayça Ersen Danyeli[2], Mehmet Öztürk[3], Kübra Ertan[4], Yavuz Köksal[1]

Departments of [1]Pediatric Hematology and Oncology, [3]Radiology and [4]Pediatrics, Selçuk University Faculty of Medicine, Konya; [2]Department of Pathology, Acıbadem University School of Medicine, İstanbul, Turkey.

ABSTRACT

Background. Despite many treatment approaches, survival rates in high grade glial tumors are still not at the desired level. One of the cause of this failure might be that although having similar histologic features, they may display different biological behaviors depending on molecular heterogeneity.

Case. A 10-year-old girl presented with sudden onset left sided hemiparesis, headache, and ataxia. Physical examination was normal except for left sided hemiparesis and ataxia. A hyperintense mass lesion involving the bilateral thalamus was detected in the axial T2-weighted and coronal FLAIR sequences on brain MRI. There was no enhancement in axial T1-weighted contrast-enhanced sequences. Due to the size and location of the tumor, the patient was considered inoperable. Intensity modulated radiotherapy was intended for curative treatment to the patient because the radiological findings suggested a low-grade glial tumor. Tumor was unresponsive to radiotherapy but biopsy could be performed. The histopathological examination revealed a diffuse glial tumor with increased cellularity, mild nuclear atypia and rare mitosis. Due to the infiltrative pattern of the tumor, it was accepted as a high grade diffuse glial tumor. A chemotherapy protocol including cisplatin and etoposide in the first cycle, vincristine and cyclophosphamide in the second cycle, and carboplatin and vincristine in the third cycle were instituted to the patient. After the third cycle of chemotherapy, the tumor progressed radiologically. H3.1 K27M c.83A>T (HIST1H3C p.Lys28Met), ATRX c.2169_2170del (p.Glu723AspfsTer9), TP53 c.338T>C (p.Phe113Ser), and EGFR c.2300_2308dup (p.Ala767_va1769dup) were detected in the genetic assessment of tumor tissue. The patient's treatment was changed to vincristine, temozolomide, and irinotecan. Unfortunately, MRI showed progression after three cycles of second-line chemotherapy. The patient's family refused any further treatment, and the patient died with progressive disease in a short time.

Conclusions. EGFR mutation along with H3.1 K27M mutation is extremely rare in children to our knowledge. It should be kept in mind that if there is a possibility of targeted therapy, there may be a treatment option in this malignant disease with a poor prognosis.

Key words: children, bithalamic high grade glioma, H3K27M mutation, EGFR mutation.

Astrocytomas constitute an important part of childhood central nervous system tumors. High grade glial (HGG) tumors (Grades III and IV) constitute approximately 44.5 % of astrocytomas and 10% of all childhood CNS cancers.[1-5] Despite many treatment approaches, survival rates in HGG are still not at the desired level. One of the possible causes of this failure is that although having similar histologic features, they may display different biological behaviors depending on molecular heterogeneity. In recent years, the biological behavior of these tumors has been better understood with the advances in molecular biology.[6,7]

In adult patients with HGG telomerase reverse transcriptase promotor (TERTp) mutation, epidermal growth factor receptor (*EGFR*) amplification, chromosome7q gain, and 10q

✉ Yavuz Köksal
yavuzkoksal@yahoo.com

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loss can be seen, while platelet-derived growth factor receptor alpha (*PDGFRA*) amplification and activation of the PI3-kinase/Akt/mTOR pathway are more common in children.[8-12] The mutations such as in the *H3F3A*/*ATRX*/*DAXX* pathway, *H3.3K27M, H3.3 G34R/V* can be detected in children. PDGFRA, MYCN or EGFR amplifications, although extremely rare, can be seen.[13-16]

Herein, we present EGFR c.787A>c mutation in a child with H3K27M-mutant diffuse midline glioma.

Case Report

A ten-year-old girl presented to the pediatric emergency department with sudden onset left sided hemiparesis, headache, and ataxia. The patient's medical and family histories were unremarkable. Physical examination was normal except for left sided hemiparesis and ataxia. A hyperintense mass lesion involving bilateral thalamus was detected in the axial T2-weighted and coronal FLAIR sequences on brain MRI. There was no enhancement in axial T1-weighted contrast-enhanced sequences (Fig. 1 a-c).

Due to the size and location of the tumor, the patient was considered inoperable. Intensity modulated radiotherapy was intended for curative treatment to the patient because the radiological findings suggested a low-grade glial tumor. The performed dose for radiotherapy was 50 Gy, 25 fractions, 5 fractions a week. After radiotherapy, only biopsy could be performed because of the unresponsive disease. The microscopic examination revealed a diffuse glial tumor with increased cellularity mild nuclear atypia and rare mitosis (Fig. 2). No vascular endothelial proliferation or necrosis were identified. Due to the infiltrative pattern of the tumor, it was accepted as a high grade diffuse glial tumor. A chemotherapy protocol including cisplatin (20 mg/m^2/day, days 1-5) and etoposide (50 mg/m^2/day, days 1-5) in the first cycle, vincristine (1.5 mg/m^2/day, days 1) and cyclophosphamide (900 mg/m^2/day, days 1-2) in the second cycle, and carboplatin (150 mg/m^2/day, days 1 and 15) and vincristine (1.5 mg/m^2/day, days 1 and 15) in the third cycle were given to the patient. After the third cycle chemotherapy, the mass was found to have progressed radiologically.

Thereafter, the tumor was screened for molecular alterations by targeted next generation deep DNA and RNA sequencing using Acibadem Molecular Pathology Customized Brain Tumors Panel (Archerdx Fusionplex and Variantplex via Miniseq Sequencing System, Illumina).

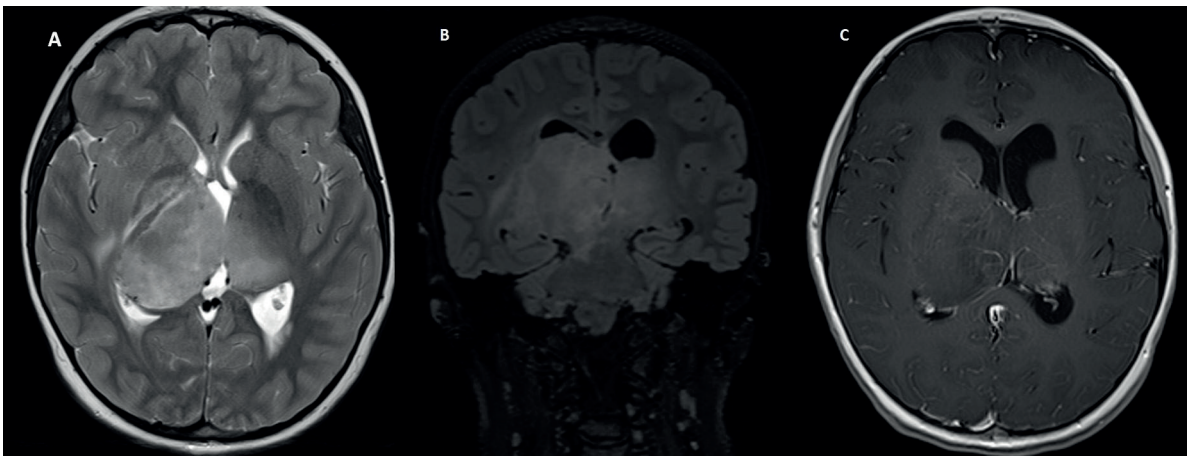

Fig. 1 a-c. Axial T2-weighted and coronal FLAIR image shows hyperintensity and diffuse enlargement of the bilateral thalamus (A, B). Axial T1-weighted gadolinium enhanced image showed low signal intensity in both thalamus and no associated contrast enhancement (C).

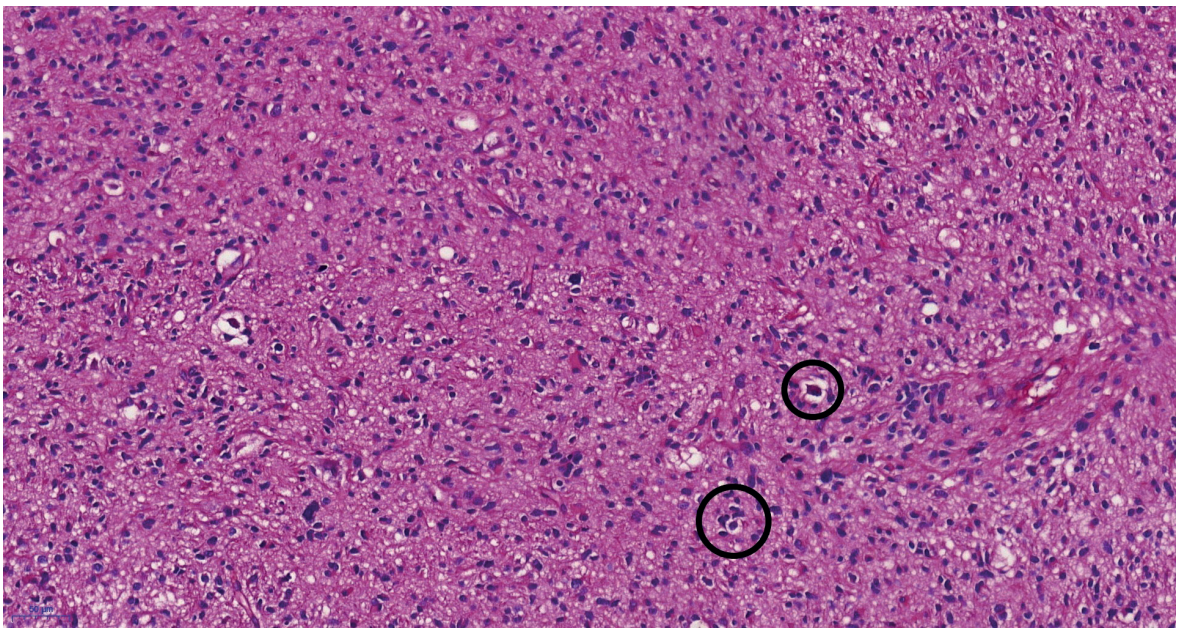

Fig 2. The tumor was composed of glial cells with mild atypia. The entrapped non-neoplastic neurons are seen (circle) which is an evidence of the diffuse infiltrative pattern. (20X, H&E)

H3.1 K27M c.83A>T (HIST1H3C p.Lys28Met), ATRX c.2169_2170del (p.Glu723AspfsTer9), TP53 c.338T>C (p.Phe113Ser), and EGFR c.2300_2308dup (p.Ala767_va1769dup) were detected in the genetic assessment of tumor tissue.

The patient's treatment was changed to vincristine (1.5 mg/m^2, on day 1), temozolomide (150 mg/m^2/day, on days 1-5), and irinotecan (50 mg/m^2/day, on days 1-5). Unfortunately, MRI showed progression after three cycles of second-line chemotherapy. Due to progressive disease the patient's family refused treatment and the patient died in a short time.

Written consent for publication of this case report and accompanying images were obtained from the parents of the patient.

Discussion

High grade glial tumors constitute approximately 10% of all childhood CNS cancers.[4] The biology of childhood HGG tumors has not been exactly explained. However, our knowledge about the biology of childhood HGG tumors is increasing, especially in line with the developments in molecular biology in recent years.[1-4,15] Another problem in childhood HGG tumors is that the desired treatment outcomes have not been achieved yet. Poor outcome and failure to achieve the desired success in treatment increases the interest in investigating the biological behavior of childhood HGG tumors.[15,17,18] Herein, our aims are to present a case of *EGFR c.787A>c* mutation in a child with *H3K27M*-mutant diffuse midline glioma and discuss in light of the literature.

In children with HGG tumors, the failure of treatment success is thought to be related with the heterogeneity in biological behavior of the tumor. The well-known genetic alterations seen in these children are *PDGFRA* amplification, +1q, and the mutations in the *H3F3A*/*ATRX*/*DAXX* pathway.[6-12] It is known that *H3.3K27M* or *H3.1K27M* mutations in patients with midline and pons HGG tumors, and *H3.3 G34R/V*, *IDH* genes or *BRAF^{V600E}* mutations in patients with hemispheric HGG tumors are more common.[13-18] Also, *PDGFRA*, *MYCN* or *EGFR* amplifications can be detected extremely rarely in patients with hemispheric HGG.[13-18] *H3K27M*,

ATRX, *IDH1*, *BRAF*^{V600E}, and *p53* genes were investigated in children diagnosed with HGG tumors with *H3K27M* in Turkey.[16] Overlapping mutations *ATRX* loss and *p53* were detected. Rarely *BRAF*^{V600E} mutation, but no *IDH1* mutation has been detected. In this study, no statistical difference was found between HGG tumor patients, *H3K27M*-mutated patients and wild-type *H3K27M* tumor patients in terms of overall survival rates.[16]

Until the study of Mondal et al.[14], no mutations in EGFR exon 20 were reported in children.[19] In this study, 13 children with bithalamic HGG tumors were re-investigated. Among these patients, *EGFR* mutation was detected in 11 cases. Nine of the patients with *EGFR* mutations were on exon 20, which is the area associated with intracellular tyrosine kinase. In the other two patients, mutation was detected on exon 7. Two cases in their series (15%) harbored H3 K27M mutations along with EGFR alteration. Sievers et al.[13] also investigated pediatric thalamic gliomas for EGFR mutations. Twenty of the genetically evaluated 30 patients demonstrated EGFR alterations, with 15 showing missense mutations and 5 showing in frame insertions. Eight of the 30 tumors (27%) harbored an H3.1 or H3.3 K27M mutation (6 of them with a concomitant EGFR alteration).

Our case has similar features with the cases published in two above mentioned studies. Our patient is a pediatric case, with a bithalamic glioma, harboring EGFR mutation which is an in frame insertion in exon 20. Yet the rare feature seen in both studies; a concomitant H3 K27M mutation was also present in our case.

In the cell-line portion of the study by Mondal et al.[14], it was found that tyrosine kinase inhibition decreased the viability of the astrocytes expressing mutant *EGFR* isoforms. In the light of this data, the authors administered different tyrosine kinase inhibitors to four of their patients and found a slowdown in tumor growth in their patients. However, the important finding is that the median survival time (21.5 months) of the patients in whom tyrosine kinase inhibitor was added to their treatment was higher than the patients whose treatment did not contain tyrosine kinase inhibitors (13 months).

In our patient, both platinum-based chemotherapy scheme and vincristine + irinotecan + temozolomide treatment did not prevent progression. The addition of a tyrosine kinase inhibitor was considered as reported in the study of Mondal et al.[14], but could not be given because the family refused the treatment.

In conclusion, the recent studies by Mondal et al.[14] and Sievers et al.[13] demonstrated that pediatric tumors located in thalamus, mainly bilaterally, frequently harbor EGFR mutations and reveal a distinct methylation profile which makes them a distinct subtype of pediatric thalamic HGG. We believe our case also belong to these rare pediatric thalamic HGGs with EGFR mutation and also has a concomitant H3.1 K27M mutation, which was rarely shown in this distinct tumor group. It is important to note that molecular biological studies should be performed in children with HGG tumors, especially with bithalamic locations. In the light of these findings, it should be kept in mind that if there is a possibility of targeted therapy, there may be a treatment option in this malignant disease with a poor prognosis.

Ethical approval

Written consent for publication of this case report and accompanying images were obtained from the parents of the patient.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: YK, BK, AED, MÖ; data collection: BK, AED, KE; analysis and interpretation of results: YK, BK, AED; draft manuscript preparation: YK, BK, AED, MÖ, KE. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Fangusaro J. Pediatric high-grade gliomas and diffuse intrinsic pontine gliomas. J Child Neurol 2009; 24: 1409-1417. https://doi.org/10.1177/0883073809338960
2. Varan A, Akyüz C, Akalan N, et al. Astrocytic tumors in children: treatment results from a single institution. Childs Nerv Syst 2007; 23: 315-319. https://doi.org/10.1007/s00381-006-0243-z
3. Pinarli FG, Oguz A, Karadeniz C, et al. Institutional experience of paediatric high-grade central nervous system tumours: an analysis of 74 patients and review of the literature. Contemp Oncol (Pozn) 2012; 16: 26-33. https://doi.org/10.5114/wo.2012.27333
4. Yazici G, Zorlu F, Cengiz M, et al. High-grade glioma in children and adolescents: a single-center experience. Childs Nerv Syst 2016; 32: 291-297. https://doi.org/10.1007/s00381-015-2980-3
5. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013-2017. Neuro Oncol 2020; 22: iv1-iv96. https://doi.org/10.1093/neuonc/noaa200
6. Kemerdere R, Kafadar AM. Molecular biology of pediatric glial tumors. Türk Nöroşir Derg 2017; 27: 143-149.
7. Sturm D, Pfister SM, Jones DTW. Pediatric gliomas: current concepts on diagnosis, biology, and clinical management. J Clin Oncol 2017; 35: 2370-2377. https://doi.org/10.1200/JCO.2017.73.0242
8. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV." Acta Neuropathol 2018; 136: 805-810. https://doi.org/10.1007/s00401-018-1913-0
9. Braunstein S, Raleigh D, Bindra R, Mueller S, Haas-Kogan D. Pediatric high-grade glioma: current molecular landscape and therapeutic approaches. J Neurooncol 2017; 134: 541-549. https://doi.org/10.1007/s11060-017-2393-0
10. Gielen GH, Gessi M, Buttarelli FR, et al. Genetic analysis of diffuse high-grade astrocytomas in infancy defines a novel molecular entity. Brain Pathol 2015; 25: 409-417. https://doi.org/10.1111/bpa.12210
11. Gielen GH, Gessi M, Hammes J, Kramm CM, Waha A, Pietsch T. H3F3A K27M mutation in pediatric CNS tumors: a marker for diffuse high-grade astrocytomas. Am J Clin Pathol 2013; 139: 345-349. https://doi.org/10.1309/AJCPABOHBC33FVMO
12. Schwartzentruber J, Korshunov A, Liu X-Y, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature 2012; 482: 226-231. https://doi.org/10.1038/nature10833
13. Sievers P, Sill M, Schrimpf D, et al. A subset of pediatric-type thalamic gliomas share a distinct DNA methylation profile, H3K27me3 loss and frequent alteration of EGFR. Neuro Oncol 2021; 23: 34-43. https://doi.org/10.1093/neuonc/noaa251
14. Mondal G, Lee JC, Ravindranathan A, et al. Pediatric bithalamic gliomas have a distinct epigenetic signature and frequent EGFR exon 20 insertions resulting in potential sensitivity to targeted kinase inhibition. Acta Neuropathol 2020; 139: 1071-1088. https://doi.org/10.1007/s00401-020-02155-5
15. Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. J Neurosurg Pediatr 2019; 23: 261-273. https://doi.org/10.3171/2018.10.PEDS18377
16. Bozkurt SU, Dagcinar A, Tanrikulu B, et al. Significance of H3K27M mutation with specific histomorphological features and associated molecular alterations in pediatric high-grade glial tumors. Childs Nerv Syst 2018; 34: 107-116. https://doi.org/10.1007/s00381-017-3633-5
17. Kasper LH, Baker SJ. Invited Review: Emerging functions of histone H3 mutations in paediatric diffuse high-grade gliomas. Neuropathol Appl Neurobiol 2020; 46: 73-85. https://doi.org/10.1111/nan.12591
18. El-Ayadi M, Ansari M, Sturm D, et al. High-grade glioma in very young children: a rare and particular patient population. Oncotarget 2017; 8: 64564-64578. https://doi.org/10.18632/oncotarget.18478
19. Mackay A, Burford A, Carvalho D, et al. Integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma. Cancer Cell 2017; 32: 520-537.e5. https://doi.org/10.1016/j.ccell.2017.08.017