Extraventricular Neurocytoma: a Case Report and Literature Review

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Case Report

Keywords: Extraventricular neurocytoma (EVN), Glioneuronal and neuronal tumors, FGFR1-TACC1 fusion, Methylation profiling, MGMT

Posted Date: April 5th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1377401/v3>

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Abstract

Extraventricular neurocytoma (EVN) is a rare intracranial tumor. The most common locations of EVN were frontal lobe and cerebellum, followed by temporal lobe. Heterogeneous contrast enhancement, cystic changes, perilesional edema and calcification were a few distinct imaging characteristics. EVN is a primary tumor with either glial or neuronal differentiation or potential for atypical changes. The lack of characteristic manifestations in histopathology makes EVN difficult to distinguish from other low-grade neuronal and mixed neuronal-glial tumors. Herein, we describe a case of frontal extraventricular neurocytoma in a 37-year-old male presenting with dizzy and review the literature on this rare tumor. Pathological examination reveals that the tumor mainly composed of oligodendroglia-like cells, with expression of synaptophysin (SYN) and Olig2 (oligodendrocyte transcription factor 2), and microcalcifications. Methylation profile and t-SNE analysis show our sample cluster with the other two reference EVNs. Next-generation sequencing (NGS) shows FGFR1-TACC1 fusion. We report a case of EVN with expression of Olig2, FGFR1-TACC1 fusion, methylation of MGMT promoter, and discuss our experience along with a review of the published literature.

Introduction

Extraventricular Neurocytoma (EVN) refers to tumors with biological and histopathological characteristics similar to central neurocytoma but arise from extra ventricular parenchymal tissue¹. A subset of EVNs is associated with a more aggressive biological behavior than central neurocytoma (CN)². The World Health Organization (WHO) in 2007 classified them as a separate, grade II intracranial tumor [International Classification of Diseases-Ocode (9506/1)]³. EVN was a type of neuronal and mixed neuronal-glial tumour, which was contrast-enhancing, well circumscribed, and often had a cyst-mural nodule complex. Less cellular, and more likely to contain smaller ganglioid cells or ganglion cells with nuclei that are large and pale. Dense calcification and hyalinized vessels were common. In the revised fourth edition of WHO Classification of tumours of the central nervous system (CNS)⁴, EVN was described as a IDH-wildtype tumor composed of small uniform cells, was not associated with ventricular system. Ganglion cell differentiation was common, a glial astrocytic component was difficult to distinguish from reactive gliosis. Diffuse cytoplasmic immunoreactivity for synaptophysin (SYN) was characteristic of EVN. However, just synaptophysin expression was not sufficient to the diagnosis of EVN, strong and diffuse Olig2 expression was not compatible with the diagnosis. Neither IDH1/2 mutation nor MGMT methylation has been reported. According to the 2021 WHO classification, it belongs to 'glioneuronal and neuronal tumor'⁵. Extraventricular location, IDH-wildtype neurocytic tumor, synaptophysin expression and a methylation profile indicates for EVN (for unresolved lesions) are essential factors for the diagnosis of extraventricular neurocytoma. FGFR1 alteration (mostly FGFR1:TACC1 fusion) was regarded as one of the desirable diagnostic criteria of EVN^{5,6}.

The most frequently documented locations for EVN was frontal lobe, then cerebellum, and temporal lobe⁷. Generally, EVN has a favorable prognosis^{8,9}. However, in some cases, increased mitotic activity

and more aggressive behavior can be seen¹⁰. The incidence rate of EVN is 0.009 per 100,000 and the tumor showed no sex predilection⁷, which tends to affect children and young adults¹¹. The common symptoms of EVN are seizures and headaches^[8]. The characteristic histological feature of EVN is their composition of monotonous neoplastic cells with round and regular nuclei, named neurocytes¹², embedded in a matrix of fine neuronal processes (neuropil). Histologically, EVN mostly resembles oligodendroglioma. Both of them have round, regular nuclei, often with clear cytoplasm. Ganglion cell differentiation often suggests EVN^{10,13,14}. Oligodendroglioma is typically more infiltrative than EVN. Immunostaining is usually positive for synaptophysin, glial fibrillary acidic protein (GFAP), neurofilament and neuronal nuclear antigen (NeuN)^{9,15–18}. There were rare cases reported Olig2 expression in EVN^{19–22}, immunonegative for Olig2 was more convinced. EVN is a rare parenchymal tumor with conspicuous glial or ganglionic differentiation²³.

Materials And Methods

Immunohistochemical staining

The specimens were fixed with 10% neutral formalin, embedded in paraffin, routine sections, HE staining, and the morphology of the tumor was observed under light microscope. Immunohistochemical staining was performed by EnVision two-step method, mouse anti-synaptophysin (SYN) monoclonal antibody (1:100; Tongling, Xiamen), acid calcium binding protein (S-100) monoclonal antibody (1:100; Tongling, Xiamen), neuron specific enolase (NSE) monoclonal antibody (1:100; Tongling, Xiamen), mouse anti-glial acidic fiber (GFAP) monoclonal antibody (1:100; Tongling, Xiamen), rabbit anti-oligodendrocyte transcription factor 2 (Olig2) monoclonal antibody (1:100; ZhongShanGoldenBridge, Beijing), tumor suppressor protein (P53) monoclonal antibody (1:100; Tongling, Xiamen) and anti-Ki-67/MIB-1 monoclonal antibody (working solution:Roche). All antibodies were repaired with high pressure.

Methylation Profiling

DNA sample of tumor tissue was been applied for methylation analysis with Illumina Infinium Human Methylation EPIC (850 K) BeadChip array (Illumina, San Diego, CA, USA), according to the manufacturer's instructions. The methylation data of the sample was processed with R/Bioconductor "minfi" package (version 1.20) and then compared with selected reference sets from the GEO database by using t-SNE and cluster analysis as described before²⁴.

Targeted DNA next-generation sequencing (DNA NGS)

Genomic DNA was extracted from tumor tissue using the QIAamp DNA Micro Kit (Qiagen). Capture-based next-generation DNA sequencing was performed using an assay that targets 136 brain tumor-related genes, enable detection of mutation and CNV analysis. 300ng DNA was fragmented with a Bioruptor Pico (Diagenode, Denville, NJ) to 200–300 bp, multiplex library preparation was performed using the Rapid Plus DNA Lib Prep Kit for Illumina (ABclonal, RK20208) according to the manufacturer's specifications.

The libraries were incubated with a pool of biotin-labeled bait oligos targeted 136 genes commonly involved in tumor for 16 h. Targeted regions were enriched by pull-down with streptavidin beads, amplified by PCR, and sequenced as paired-end 150bp reads on an Illumina NextSeq 6000 instrument. Reads were aligned to the reference genome (hg19) using BWA-MEM. Genome Analysis Toolkit (GATK) was used to mark the duplicates and perform base quality score recalibration. Coverage and sequencing statistics were determined using Bamdst and in-house script. Single nucleotide variant and small insertion/deletion mutation was called with VarDict and annotated with Annovar. Raw vcf files were filtered by general population frequency in several databases(1000 genomes, GnomAD etc.), allowing only variants with minor allele frequencies < 1% to keep. In addition, variation with an allelic fraction less than 5% were removed. Copy number variation was analyzed by in-house software.

Targeted RNA next-generation sequencing (RNA NGS)

Total RNA was extracted from tumor tissue using the RNAsimple Total RNA Kit (TIANGEN, DP419). 100ng total RNA was used for first Strand cDNA Synthesis by incubating with NEBNext First-Strand Synthesis Enzyme Mix (NEB; Ipswich, Massachusetts) for 10 minutes at 42°C. The second strand synthesis was performed by incubating with NEBNext Second Strand Synthesis Enzyme Mix (NEB) for 1 hour at 16°C. cDNAs were purified with AMPure XP beads and subjected to end-polishing, phosphorylation, and dA extension by incubating with end-repair mix, Klenow exo-, and Taq polymerase (Enzymatics, Beverly, Massachusetts) for 15 minutes at 12°C, 15 minutes at 37°C, and 15 minutes at 72°C. A custom-made sequencing adaptor was added by incubating with Ligase (Enzymatics) for 20 minutes at 22°C. PCR enrichment was performed using primers specific to a group of 56 genes commonly involved in various solid tumors, and the PCR products were sequenced as paired-end 150bp reads on an Illumina NextSeq 6000 instrument. Sequencing results were analyzed with SeqNext software (JSI, Ettenheim, Germany), STARfusion and FusionCatcher to identify fusion genes. As most of fusion genes reported by them were false positives, several filtering steps were conducted. First, fusion genes found by both software were retained. Second, we selected those fusion genes which are at least one of the fusion gene partners in our capture panel. Third, we removed some known false gene fusions in our manually curated blacklist. Finally, we check each fusion genes in Integrative Genomics Viewer (IGV) to ensure the true fusion events.

MGMT hypermethylation analysis by MSP

The DNA methylation status in the CpG islands of the MGMT gene was determined after chemical modification of unmethylated but not methylated cytosines to uracil. Subsequently, MSP with primers specific for either modified methylated or unmethylated DNA sequences was carried out. The amplified products of MSP were analyzed by CE on Seqstudio Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Data were collected by the GeneMapper Software v4.0 for fragment analysis (Applied Biosystems). The MSP products for the methylated and unmethylated allele corresponded to a 81 and 93-base pair peak, respectively.

Result

Case presentation

A 37-year-old male complained of dizziness for one month. His vital signs were normal, no focal neurological deficits were observed. Computed Tomography (CT) revealed a mass in the left frontal lobe measuring 47mm×29mm×45mm, containing solid and cystic components. Calcification can be seen mainly at the left edge of the mass (Fig. 1a). The morphology of ventricles is normal and on midline shift. Magnetic Resonance Imaging (MRI) revealed that the mass was low intense on T1-weighted images and hyperintense on T2-weighted images, with a wide cystic portion (Fig. 1b, c). In contrast-enhanced sequences, the tumor displayed enhancement surrounding the unenhanced cystic area (Fig. 1d). Brain abscess can be excluded based on the above-mentioned imaging characteristics, but ganglioglioma, extraventricular ependymoma (cystic form), oligodendroglioma, and other neuronal and mixed neuronal-glial tumors could not be excluded.

During surgical removal of the mass, the cyst contained clear yellowish fluid. Histopathological examination showed that oligo-like tumor cells arranged in sheets or clusters with a sharp tumor-brain border, which differs from oligodendroglioma (more diffusely infiltrative growth pattern) — frequent calcifications and granular bodies were observed (Fig. 2a-c). Anaplasia features such as frequent mitosis, microvascular proliferation (MVP), or necrosis were absent. Tumor cells were embedded in a GFAP-positive fibrillary matrix (Fig. 2d). It was noted that the Olig2 expression was clearly positive in the neoplastic cells in our case (Fig. 2e), which is opposite from most EVNs in the literature^{23,25-30}. Strong expression of synaptophysin in the cytoplasm were observed (Fig. 2f). Ki-67 proliferation index was at a level less than 3%.

Methylation profiling

DNA sample of tumor tissue was applied for methylation analysis, the methylation raw data (.idat) of the sample was compared with selected reference sets from the GEO database by using t-SNE and cluster analysis as previously described²⁴. The sample clustered with the other two reference EVNs and showed a high methylation similarity as well (Fig. 3a, b). The results further supported our diagnosis of EVN and excluded the other potential differential diagnosis of supratentorial IDH-wt LGGs.

Genetic profiles

MAP NGS (multiplex amplification panel next generation sequencing) technology was used to detect genetic fusion. Total RNA was extracted from formalin-fixed and paraffin-embedded (FFPE) tissue samples. The FGFR1-TACC1 fusion was detected and located on chromosome 8p11 (Figure 4). FGFR1::TACC1 contained the first 17 exons of FGFR1 and the last 7 exons of TACC1. It was consistent with the report that FGFR1-TACC1 fusion was a unique and recurrent feature in the EVN methylation profile³¹.

The genomic DNA of fresh tissue samples was extracted, and the CpG island in MGMT promoter region was amplified by methylation-specific PCR with FAM fluorescent labeled primers. The PCR products labeled by FAM were analyzed in capillary electrophoresis. The control group included genomic DNA products known to be unmethylated by MGMT promoter. The result showed that MGMT promoter was methylated in fresh tissue samples (Figure 5).

Discussion

Central neurocytomas (CN) was firstly described by Hassoun et al.¹⁶ as a rare benign central nervous system (CNS) neoplasm which occurred most commonly within the ventricles near the foramen of Monro. In 1989, Ferreol et al.³² first reported the occurrence of such tumors outside the cerebral ventricles, which had been termed as extraventricular neurocytoma (EVN), and recurrence occurred statistically significantly more often in EVN than in CN. In the 2007 WHO guidelines, EVN had been listed as a distinct entity corresponding to grade III. The histopathological manifestations were similar between EVN and CN³, and immunohistochemistry revealed these tumor tissues were positive for neuronal markers such as synaptophysin and neuronal nuclear antigen (NeuN). Shahed et al. counted that the overall annual incidence of EVN was 0.009 per 100,000 population⁷. The incidence rate for EVN was the same in males and females. The peak incidence rate was noted in the 20–34 age group for EVN. Outside the ventricular system, EVN was most frequently located in the frontal lobe and cerebellum.

The diagnosis of EVN was based on immunohistochemical features, given the overlap of clinical, radiological, and histological features with other CNS tumors. SYN- and NSE(neuron-specific enolase)-positive staining suggests a diagnosis of neurocytoma; but not all reported cases were 100% SYN-positive³³. In nearly half of EVN cases, immunopositivity for GFAP (glial fibrillary acidic protein) has been reported. In the patient of the present study, NSE and SYN stained positive, while GFAP, S-100, nestin and EMA (epithelial membrane antigen) were negative, suggesting the diagnosis of a neurocytoma. Gross total resection remains the standard of care³⁴. Postoperative radiotherapy improved the local control and survival rates of patients with incomplete resection³⁵.

According to the 2021 WHO classification of tumors of the CNS and other case reports of EVN, a distinctive feature within the DNA methylation class EVN is evidence of an FGFR-TACC fusion, and FGFR1-TACC1 fusion was found in 60% of EVN cases³¹. The positive expression of SYN was mentioned in the vast majority of cases, our case is no exception. Case reports seldom referred to the positive expression of Olig2²⁰, we found positive expression of Olig2 in this case, though Olig2 was widely expressed in oligodendroglioma, astrocytoma, and glioblastoma. The appearance of the tumor cells under the microscope is consistent with the definition of EVN, t-SNE analysis and methylation-based unsupervised hierarchical clustering analysis showed the sample referred to methylation class EVN. It was worth mentioning that methylated MGMT promoter and FGFR1-TACC1 fusion, no methylation of MGMT promoter had been reported except us.

Conclusions

EVN is a relatively rare tumor. Combined with clinical, radiological, histological and molecular features, the diagnosis of EVN is not very difficult. We first report a case of EVN not only expresses of Olig2, but also methylates MGMT promoter and has FGFR1-TACC1 fusion. To some extent, it is proved that the negative of Olig2 is not a necessary condition for the diagnosis of EVN, MGMT promoter methylation can occur in EVN. Total excision should be the goal of treatment and adjuvant radiotherapy should be considered in the case of subtotal resection.

Declarations

Funding

This work was supported with special project on diagnosis and treatment technology of Jiangsu Province Key Research and Development Program: Social Development Project (BE2021653), and Key Program of Health Commission of Jiangsu Province (ZBD2020016).

Competing Interests

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Authors' contributions

Liping Wang and Xiaoxiao Dai prepared and edited the manuscript; Yanghao Hou and Jun Dong corrected and revised the manuscript; Jun Dong treated and observed the patient; Xiaoxiao Dai, Liping Wang and Yifang Ping performed the histopathological, immunohistochemical examinations; Yanghao Hou performed the methylation profiling, tSNE, and clustering analysis; Ping Chen performed the FGFR1-TACC1 fusion; Yanming Chen, Shan Cheng, Ping Chen, Yongdong Li, Suwen Li, Haoran Li, Jiaqi Yuan prepared the literature search; All authors read and approved the final manuscript.

Data Availability

"The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request."

Ethics approval

"This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee.

Cosent to participate

"Informed consent was obtained from the patient included in the study."

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Figures

Figure 1

Imaging features of the tumor. a is CT scan, there is an oval cerebrospinal fluid density focus, typical cystic manifestations, clear boundary, and calcification at the edge. b, c and d are MRI images. T1-weighted image shows a cystic component of the left frontal region (b). T2-weighted image shows the signal in the tumor capsule is the same as that in cerebrospinal fluid (c). The contrast-enhanced sequence shows the unenhanced cystic area and slightly enhanced nodules (d).

Figure 2

Histological features of EVN (a,c-f 100 fold, b 400-fold magnification). Sharp tumor-brain border(a), granular bodies(b) and frequent calcifications(c) were observed. Oligodendro-like tumor cells (c, b) arranged in sheets(c) or clusters(a) were embedded in a GFAP-positive(d) fibrillary matrix. Nuclear positivity of Olig2 in the neoplastic cells (e) and strong expression of synaptophysin (f) in the cytoplasm.

Figure 3

a, t-SNE analysis of tumor sample and reference tumours from the GEO database. 20000 most variable CpG sites were selected. LGG_RGNT: MC rosette-forming glioneuronal tumor, GG: MC ganglioglioma, CN: MC central neurocytoma, LGG MYB: MC low-grade glioma, MYB/MYBL1, LGG_ST_PA: MC supratentorial pilocytic astrocytoma, EPN REL: MC ependymoma REL-fused, EPN_MPE: MC myxoid papillary ependymoma, EPN_YAP: MC ependymoma YAP1-fused. EVN: MC extraventricular neurocytoma. b,

Methylation-based unsupervised hierarchical clustering analysis. The sample (S, colored in red) was clustered with two reference EVNs (E, colored in black).

Figure 4

The *FGFR1-TACC1* gene is fusion. *FGFR1::TACC1* contained the first 17 exons of *FGFR1* and the last 7 exons of *TACC1*. UTR, untranslated regions; CDS, coding sequences.

Figure 5

MGMT promoter methylation status is successfully determined by MSP(Methylation-Specific PCR Assay).