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Case Study

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A novel *TP53* somatic mutation involved in the pathogenesis of pediatric choroid plexus carcinoma

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Choroid plexus carcinoma (CPC) is an uncommon, aggressive, malignant, central nervous system neoplasm that typically occurs in children, presenting with the signs and symptoms of intracranial hypertension and cerebrospinal fluid obstruction.

Case Report: We report the case of a 2.5-year-old girl with CPC. The tumor was subtotally removed by microsurgery, followed by gamma knife radiosurgery for the residual lesion. H&E staining indicated that this was a rare case of CPC. Neuropathological studies, assayed by immunohistochemical staining, showed that the tumor sample was positive to antibodies against S-100, CgA, AE1/AE3 (cytokeratin), Ki-67, INI1 and TP53, and was negative to antibodies against Nestin, GFAP, CD133, EMA and AFP. Moreover, stainings for transthyretin and vimentin were focally positive. Interestingly, direct DNA sequencing of the paraffin-embedded tumor sample identified a novel R248Q mutation in the *TP53* gene. In contrast to previous reports suggesting that *TP53* germline mutations were associated with the pathogenesis of CPC, here we provide a rare case of CPC with *TP53* somatic mutation, as evidence that the peritumoral tissue possesses the non-mutant *TP53* allele.

Conclusions: Our finding suggests that *TP53* somatic mutations, in addition to its germline mutations, may also be involved in the pathogenesis of pediatric CPC.

key words: **choroid plexus carcinoma (CPC) • *TP53* • somatic mutation • immunohistochemical stain (IHC)**

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Background

Choroid plexus tumors (CPTs) are uncommon neoplasms derived from choroid plexus epithelium and characterized by papillary and intraventricular growth. Within this family of tumors there are benign and malignant variants, typically classified as choroid plexus papilloma (CPP), atypical CPP and choroid plexus carcinoma (CPC), respectively. CPTs account for approximately 0.3% to 0.6% of all brain tumors [1]. Within the pediatric population, however, these neoplasms are more common, representing approximately 1% to 4% of all childhood brain tumors, with 10% to 20% occurring during the first year of life. Although reported in adults, 80% of CPTs occur in children, and 20% of all choroid plexus tumors in children are CPCs. CPC is a highly aggressive malignant tumor (WHO grade III) which must be distinguished from CPP (WHO grade I). The prognosis of CPP and CPC is quite different for their histopathologic features and biological behaviors [2]. Most CPP cases can be cured by total removal, but CPC cannot be cured by neurosurgical procedure alone. CPC is associated with a poor outcome because the tumor cells diffuse through the cerebrospinal fluid (CSF) pathways. Radiotherapy and/or chemotherapy should be performed after subtotal removal for CPC patients [3]. Neuropathologic features of CPC include blurring of papillary architecture, layers of neoplastic choroid plexus epithelial cells with pleomorphic nuclei, increased nuclear-to-cytoplasmic ratio, increased mitotic activity, areas of necrosis, and brain invasion [4]. Recently, some reports showed that *TP53* germline mutation was associated with the pathogenesis of CPC and CPP [5,6]; few reported CPC children with *TP53* somatic mutation. Here, we document a rare case of CPC with a novel *TP53* somatic mutation.

Case Report

A 2.5-year-old girl presented to our Department of Neurosurgery with 4 weeks of progressive headache and vomiting, weakness of the left limbs and unstable walking. Physical examination on admission found a slight left hemiparesis, muscle powers of left limbs were grade III to IV, her head circumference was 4 cm larger than the average for children of the same age, the 2 pupils were normal size, light reflexes were sensitive, and chronic papilledema due to increased intracranial pressure were found in the double optic discs. Babinski sign of the left foot was found, and tendon reflexes were normal. Her IQ test score was normal, and no speech and language disorders were found. No other neurologic findings were found. The patient's family was without a history of multiple malignancies, her parents and grandparents were healthy, and the girl had no siblings. Non-enhanced brain CT revealed an ovoid lesion (8×4×6 cm-sized) in the right lateral ventricle and a marked dilation of the right ventricle (Figure 1A). T1-weighted MRI showed that a huge tumor, enhanced homogeneously by gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA), in the right lateral ventricle, and necrosis was shown in the center of lesion (Figure 1B, C). Diffusion-weighted imaging (DWI) revealed an iso-intense mass with multiple small hypo-intense "cystic-like" areas. She underwent microsurgery via rigth posterior temporoparietal craniotomy. The surface of the tumor was not easily separated from the surrounding normal brain tissue. The blood supply from the choroid plexus was rich and the tumor tended to bleed easily. Then, the tumor was subtotally resected (95% removed). Her intraoperative and postoperative courses were uneventful. She received radiosurgery (gamma knife) for the residual lesion 10 days after surgery; a median margin dose of 12.0 Gy (range, 11.5–15) was used for this. Chemotherapy was refused by her parents postoperatively. Four months after the operation, she presented vomiting, rhinorrhea, weight loss and high temperature (38.8°). Brain CT revealed that the tumor had recurred. The lesions were located at the right lateral ventricle and suprasellar cistern (Figure 1D). Obviously, the lesion of suprasellar cistern was a metastasis through CSF pathways. Repeat surgery was recommended. Unfortunately, her parents refused the next treatments and she died after 6 months due to disease progression.

Written informed consent was obtained from her parents, which included the tumor tissue and peritumoral brain tissue. H&E staining and immunohistochemistry (IHC) were carried out. A few antibodies were used for the IHC staining, which included S-100, CgA, AE1/AE3 (cytokeratin), INI1, TP53, transthyretin, Vimentin, Nestin, GFAP, Ki-67, CD133, EMA and AFP (the sources of the antibodies and dilutions are summarized in Table 1). The levels of immunostaining were evaluated as previously described [7]. In brief, nuclear expression is divided into grades 0 through 4 – grade 0 means no positive cells or very few, and grade 4 means well-defined areas of positive cells with strong expression (>50%). Cytoplasmic expression is evaluated as a percentage of positive cells – score 0 (<10%), score 1 (10–50%), and score 2 (>50%). A semiquantitative scale was defined as follows: –, negative (grade 0 or score 0); +, weak (grade 1–2 or score 1); and ++, moderate to strong (grade 3–4 or score 2). DNA was extracted from the paraffin embedded tissues (tumor and peritumoral tissue) using a previously reported protocol [8]. Exon 5–8 of *TP53* gene was further analyzed by direct DNA sequencing (ABI 3100 Prism DNA Sequencer, Applied Biosystems, CA). The primers of exon 5-8 of *TP53* and PCR conditions were designed by IARC, WHO (*http://www-p53.iarc.fr/p53sequencing.html*).

Neuropathological findings

H&E staining revealed a blurring of papillary architecture, pleomorphic nuclei, and brain invasion (Figure 2A, B). IHC stainings (Figure 2C–F) showed AE1/AE3(+), INI1(++), TP53(++). S-100(+), CgA(+), Ki-67(+), transthyretin(–/+), Vimentin(–/+), Nestin(–), GFAP(–), CD133(–), EMA(–), and AFP(–).

Cytogenetic findings

Cytogenetic analysis of the peritumoral tissue and the paraffin-embedded tumor sample revealed a novel *TP53* missense mutation by DNA direct sequencing. A CGG->CAG substitution at codon 248 (exon 7), creating an Arg->Gln substitution of amino acid, was found in tumor tissue. No mutation was found in peritumoral tissue, which indicated that the mutation was a somatic mutation (Figure 3A, B). Sequencing of an independently amplified fragment in the opposite direction confirmed the mutation.

Discussion

In the differential diagnosis of pediatric CPC it is difficult to distinguish it from atypical teratoid/rhabdoid (AT/RT),

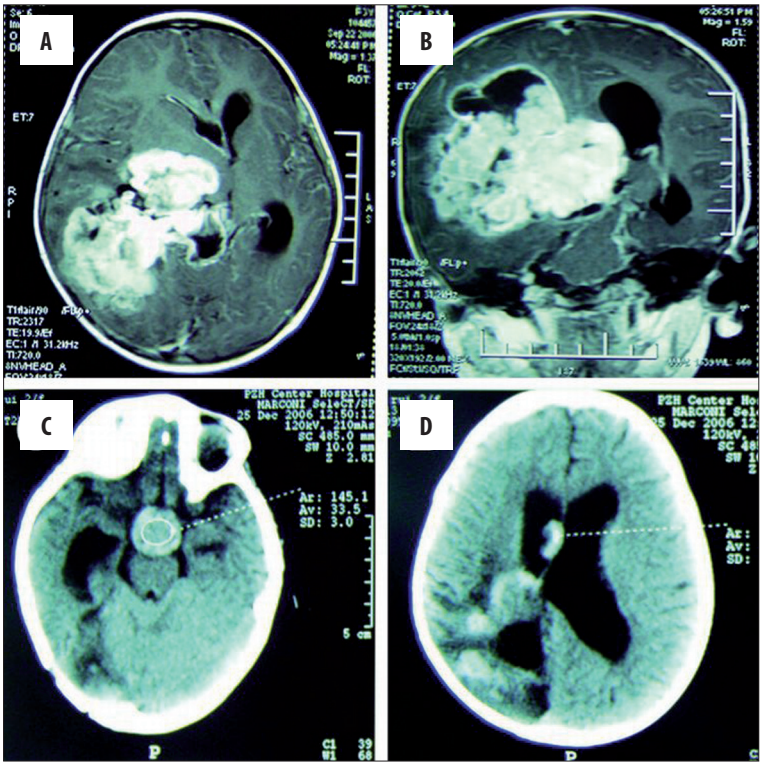

Figure 1. Radiologic images. (**A**) Enhanced MRI: a huge tumor with homogeneous enhancement by Gd-DTPA in the right lateral ventricle, necrosis in the center of lesion (Axial); (**B**) Enhanced MRI (Coronal); (**C**) Enhanced CT (4 months postoperation): a metastasis in suprasellar cistern (via CSF pathways); (**D**) Enhanced CT (4 months postoperation): a recurred tumor located at right lateral ventricle.

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Table 1. The sources and dilutions of antibodies for immunohistochemical staining.

Antibodies	Manufacturer	Dilutions
TP53	Cell Genesys, USA	1:1000
INI1	BD Transduction Labs, USA	1:500
AE1/AE3	Invitrogen, USA	1:100
S-100	Abcam, USA	1:200
Ki-67	Abcam, USA	1:200
CgA	Abcam, USA	1:200
Nestin	Abcam, USA	1:100
GFAP	Sigma, USA	1:500
CD133	Abcam, USA	1:200
EMA	Abcam, USA	1:200
AFP	Abcam, USA	1:150
transthyetin	Abbiotec, USA	1:500
vimentin	Abcam, USA	1:200

primitive neuroectodermal tumor (PNET), and medulloepithelioma on CT/MRI scans or histological features. The typical image of CPC always includes a large, irregular enhancing mass surrounding the lateral ventricle or 4th ventricle on MRI, heterogeneous signal on long TR/long TE images and short-TR images, edema in adjacent brain, hydrocephalus and presence of disseminated tumor [9]. IHC staining should be done in some difficult cases. Our results of IHC staining showed positive TP53 nuclear expression; INI1 and AE1/AE3 were also strongly immunopositive. A previous study suggested that positive staining for INI1 protein is retained in the majority of CPC and lost in AT/RT [10]. CPCs express cytokerations and positivity for S-100 and AE1/AE3 proteins, transthyretin is less frequent than in CPP, about 20% of CPC are GFAP-positive, and EMA is usually not expressed [11]. In adults, metastatic carcinomas to the choroid plexus are possible. Expression of carcinoembryonic antigen (CEA) or AFP suggests metastatic neoplasms, which can be distinguished from primary CPC [12]. Some biomarkers for stem cells and neurons, such as CD133 and Nestin, are negative in most CPCs. One CPP and almost all CPCs showed immunohistochemical positive for TP53 protein in 12 pediatric patients with CPTs [13].

CPCs usually grow rapidly and have a 5-year survival rate of approximately 40%, and two-thirds of CPCs disseminate throughout the CSF pathway [4]. Surgery should be performed when the diagnosis is established; gross total resection allows for the best chance of survival and improves the overall prognosis [3,14]. The use of adjuvant chemotherapy after subtotal resection remains controversial in children [15]. But a meta-analysis showed that chemotherapy improves the survival of patients with choroid plexus carcinoma [16]. Radiation is considered in the treatment of adult CPCs but not for children, due to severe long-term sequelae [17]. Radiosurgery (gamma knife) is recommended for treatment of the residual CPP by Kim [18]. The girl was also treated with gamma knife instead of whole brain radiotherapy after microsurgery.

The p53 tumor suppressor protein is one of the most important molecules in the biology of human neoplasia, with *TP53* somatic mutations present in ~50% of analyzed cancer

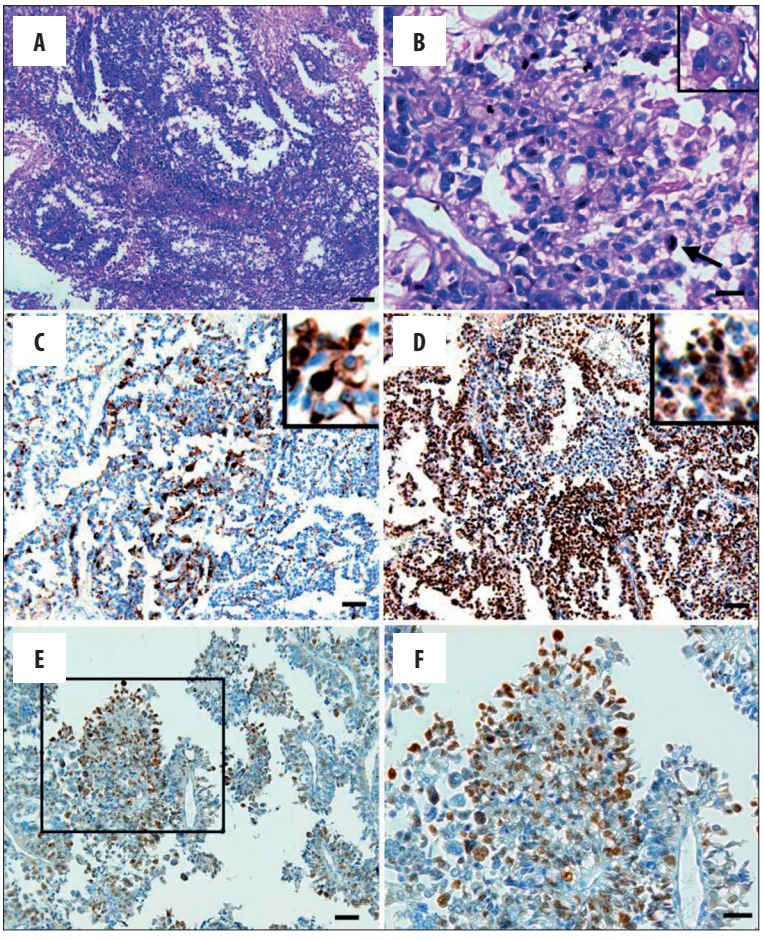

Figure 2. H&E and IHC stainings. (**A, B**) H&E staining showing a blurring of papillary architecture, increased cellular density, increased nuclear-to-cytoplasmic ratio, nuclear polymorphism (insert in **B**) and mitotic activity (arrow in **B**). (**C, D**) IHC staining showing AE1/AE3 (**C**) and strong INI1 (**D**) expression in CPC in a diffuse pattern. (**E, F**) IHC staining showing an accumulation and diffuse nuclear immunoreactivity for TP53 in tumor cells. (*Bar in **A**=100 µm; in **B** and F=30 µm; in **C–E**=50 µm*).

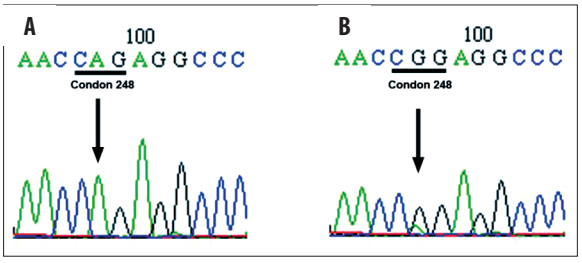

Figure 3. DNA direct sequencing. (**A**) Tumor tissue: a CGG->CAG substitution at codon 248 (exon 7) of *TP53* gene creating an Arg->Gln substitution of amino acid indicating a missense mutation; (**B**) peritumoral tissue: no mutation.

cases of all types; germline mutations are present in ~70% of families with the Li-Fraumeni syndrome (LFS) of inherited cancer predisposition [19]. Accumulating evidence shows that CPP and CPC are strongly associated with LFS in families that carry *TP53* germline mutations [1,4–6,20,21]. In 2008, a novel *TP53* germline mutation E285V substitution was identified in a rare case of pediatric adrenocortical carcinoma and choroid plexus carcinoma [22]. More recently, Tabori et al. reported that *TP53* germline mutations were found in 50% of CPCs, and patients with CPC absence of TP53 dysfunction have a favorable prognosis and can be successfully treated without radiation therapy [23]. Until now, only scattered cases with somatic *TP53* mutations at codon 179 or 242 were identified in pediatric CPCs [24].

Conclusions

In the present article, we report another novel *TP53* somatic mutation of an Arg->Gln substitution at hotspot codon 248 in a sporadic CPC girl (Figure 3A, B). Our finding suggests that *TP53* somatic mutations, in addition to its germline mutations, may also be involved in the pathogenesis of pediatric CPC.

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Competing of interest

None to declare.

References:

1. Louis DN, Ohgaki H, Wiestler OD, Cavenne WK (eds.): WHO Classification of Tumours of the Central Nervous System. Lyon, IARC Press, 2007
2. Cohen ME, PK D (eds.): Brain tumors in children: principles of diagnosis and treatment. 2nd ed.. New York, Raven, 1994
3. Packer RJ, Perilongo G, Johnson D et al: Choroid plexus carcinoma of childhood. Cancer, 1992; 69: 580–85

4. Gopal P, Parker JR, Debski R, Parker JC Jr: Choroid plexus carcinoma. Arch Pathol Lab Med, 2008; 132: 1350–54
5. Becherini F, Castagna M, Iannelli A et al: Choroid plexus carcinoma: a new case associated with a novel TP53 germ line mutation. Neuropathol Appl Neurobiol, 2008; 34: 564–68
6. Vital A, Bringuier PP, Huang H et al: Astrocytomas and choroid plexus tumors in two families with identical p53 germline mutations. J Neuropath Exp Neurol, 1998; 57: 1061–69
7. Hayat MA (ed.): Handbook of immunohistochemistry and *in situ* hybridization of human carcinomas, Vol. 4. San Diego, Elsevier Academic Press, 2006
8. Ohgaki H, Dessen P, Jourde B et al: Genetic pathways to glioblastoma: a population-based study. Cancer Res, 2004; 64: 6892–99
9. Baehring JM, Duncan C, Ogle E, Kim J: Images in neuro-oncology: choroid plexus carcinoma. J Neuro-oncol, 2006; 79: 31–32
10. Judkins AR, Burger PC, Hamilton RL et al: INI1 protein expression distinguishes atypical teratoid/rhabdoid tumor from choroid plexus carcinoma. J Neuropath Exp Neurol, 2005; 64: 391–97
11. Jeibmann A, Hasselblatt M, Gerss J et al: Prognostic implications of atypical histologic features in choroid plexus papilloma. J Neuropath Exp Neurol, 2006; 65: 1069–73
12. Paulus W, Janisch W: Clinicopathologic correlations in epithelial choroid plexus neoplasms: a study of 52 cases. Acta Neuropathol, 1990; 80: 635–41
13. Carlotti CG Jr, Salhia B, Weitzman S et al: Evaluation of proliferative index and cell cycle protein expression in choroid plexus tumors in children. Acta Neuropathol, 2002; 103: 1–10
14. Kumabe T, Fujimura M, Jokura H, Tominaga T: Surgical treatment for choroid plexus tumors in the fourth ventricle: brain stem infiltration hinders total extirpation. Neurosurg Rev, 2008; 31: 165–72; discussion 172
15. Berger C, Thiesse P, Lellouch-Tubiana A et al: Choroid plexus carcinomas in childhood: clinical features and prognostic factors. Neurosurgery, 1998; 42: 470–75
16. Wrede B, Liu P, Wolff JE: Chemotherapy improves the survival of patients with choroid plexus carcinoma: a meta-analysis of individual cases with choroid plexus tumors. J Neuro-oncol, 2007; 85: 345–51
17. Mazloom A, Wolff JE, Paulino AC: The impact of radiotherapy fields in the treatment of patients with choroid plexus carcinoma. Int J Radiation Oncology Biol Phys, 2010; 78: 79–84
18. Kim IY, Niranjan A, Kondziolka D et al: Gamma knife radiosurgery for treatment resistant choroid plexus papillomas. J Neuro-oncol, 2008; 90: 105–10
19. Olivier M, Hollstein M, Hainaut P: TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol, 2010; 2: a001008
20. Krutilkova V, Trkova M, Fleitz J et al: Identification of five new families strengthens the link between childhood choroid plexus carcinoma and germline TP53 mutations. Eur J Cancer, 2005; 41: 1597–603
21. Schniederjan MJ, Shehata B, Brat DJ et al: *De novo* germline TP53 mutation presenting with synchronous malignancies of the central nervous system. Pediatr Blood Cancer, 2009; 53: 1352–54
22. Russell-Swetek A, West AN, Mintern JE et al: Identification of a novel TP53 germline mutation E285V in a rare case of paediatric adrenocortical carcinoma and choroid plexus carcinoma. J Med Gene, 2008; 45: 603–6
23. Tabori U, Shlien A, Baskin B et al: TP53 alterations determine clinical subgroups and survival of patients with choroid plexus tumors. J Clin Onco, 2010; 28: 1995–2001
24. Zakrzewska M, Wojcik I, Zakrzewski K et al: Mutational analysis of hSNF5/INI1 and TP53 genes in choroid plexus carcinomas. Cancer Genet Cytogen, 2005; 156: 179–82