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Case Report

Choroid plexus carcinoma in two siblings, with a novel genetic mutation in TP53 – A case report and review of literature

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ABSTRACT

Background: Choroid plexus carcinoma (CPC) is an uncommon aggressive neuroectodermal-derived childhood brain malignancy with a dismal prognosis, especially when tumor protein p53 (TP53) mutations or malfunctions are present. The occurrence of these cancers is linked to germline and somatic anomalies at a number of genetic loci. We present a case report of CPC in two siblings which was found to be linked to a unique genetic mutation of TP53 in heterozygous state in both the father and the patient.

Case Description: A 2-year-old female child presented with a history of vomiting, headache, and seizures. A brain magnetic resonance imaging discovered a large-sized lesion in the left lateral ventricle with infiltration to surrounding brain parenchyma suggestive of aggressive choroid plexus neoplasm. Her only sibling (sister) died of CPC 1 year ago. Her parents are apparently healthy with no history of the central nervous system malignancies in the maternal and paternal sides. Since two children in a family were affected with CPC, genomic profiling of parents and patients was done. A novel frameshift variant c.72dupA,p. (Leu25Thrfs Ter4) was observed in exon 2 of TP53 in a heterozygous state in the proband. This variant was observed in her father in the heterozygous state.

Conclusion: CPC affecting siblings, associated with novel frameshift mutation in *TP*53 and inherited in an autosomal dominant pattern, is a rare entity. It has importance in genetic counseling and planning targeted molecular treatment. Genetic profiling is important for prognostication, as P53 pathway dysfunction carries a dismal prognosis, especially when it is associated with Li-Fraumeni syndrome.

Keywords: Choroid plexus carcinoma, Li-Fraumeni syndrome, Siblings, TP53 mutation

INTRODUCTION

Choroid plexus carcinomas (CPCs) are uncommon neuroectodermal tumors that makeup 10–20% of intracranial cancers in children. They are aggressive tumors with a 0.3 case per million annual incidences.[10] The most common treatment is maximum safe resection, yet 5-year survival rates range from 10% to 50%.[14] CPC is linked to a variety of genetic abnormalities, particularly tumor protein p53 (TP53) mutations and Li-Fraumeni syndrome. The underlying molecular and biologic changes in these malignancies are yet to be fully understood. Some of the most prevalent abnormalities are variation in genomic sequence, copy number alterations, and methylation.[8] However, the genetic landscape of CPC is still unknown. Either *TP*53 mutations

or alterations in the p53 pathway can result in CPC. P53 signaling dysfunction is thought to be the basic cause of CPC formation.[11] Patients with TP53 mutations have had a poorer prognosis when compared to TP53 wild-type tumors and TP53-negative immunostaining.

This case report is presented for three reasons. First, as per our knowledge is concerned, this is the first case report of CPC occurring in two siblings with the unique frameshift variation c.72dupA,p. (Leu25Thrfs Ter4) in TP53, which was inherited from the father in an autosomal dominant pattern. Second, it is important for implications in genetic counseling while planning the next pregnancy. Third, it is relevant in planning tailored individualized molecular treatment based on genetic abnormality.

CASE DESCRIPTION

A 2-year-old female child presented with a history of vomiting, headache, and seizures. A brain imaging (computed tomography and magnetic resonance imaging [MRI] scans) discovered a large-sized lesion in the left lateral ventricle with infiltration to surrounding brain parenchyma suggestive of aggressive choroid plexus neoplasm [Figures 1-3]. Her only sibling (sister) died of CPC within 1 year of diagnosis, despite gross total excision and adjuvant therapy, suggesting the very aggressive nature of the tumor. Her parents are apparently healthy with no significant illnesses; there is no history of the central nervous system (CNS) malignancies in the maternal and paternal sides. Since the lesion was very vascular, preoperative embolization of the posterior choroidal artery was done to make the tumor less vascular and this was followed by gross total excision. The child withstood the surgery well and had no fresh neurological deficits. The histopathological examination reported it as CPC (WHO Grade III) [Figure 4]. A postoperative MRI scan revealed no significant residual lesion. The child received adjuvant chemotherapy as per our institutional tumor board discussion (12 cycles of cyclophosphamide, carboplatin, and etoposide). Since two children in a family were affected with CPC and the tumor was very aggressive in one child, it was decided to do a genomic study of the patient and the parents. Singleton exome sequencing was done using the TWIST capture kit. Validation and segregation analysis of the variant were done by Sanger sequencing.

A novel frameshift variant c.72dupA,p. (Leu25Thrfs Ter4) was observed in exon 2 of *TP*53 in the heterozygous state in the proband; this variant was observed in her father in the heterozygous state. This was not observed in the mother and in the Genome Aggregation Database. It is noteworthy that the MRI or histopathological report of the elderly sibling was not available, and the parents had document about the CPC diagnosed and managed at some other hospital. Due to lack of availability of the tissue of elderly sibling, its genomic analysis could not be performed. Considering the Chompret criteria (2015), Li-Fraumeni syndrome is the likely cause for CPC in our cases.[9,12] Accordingly, the family was advocated with screening of related cancers and genetic counseling.

DISCUSSION

Although CPC is a rare pediatric brain neoplasm accounting for <1% of total cases of CNS tumors, CPC forms the classic brain tumor in patients with Li-Fraumeni syndrome.[3] There lacks a standardized therapeutic approach for CPC, due to a lack of epidemiological data and a relatively fewer number of cases. The conventional treatment is a maximum safe resection followed by adjuvant therapy. Despite aggressive treatment with surgical excision, radiation, and chemotherapy, the 5-year

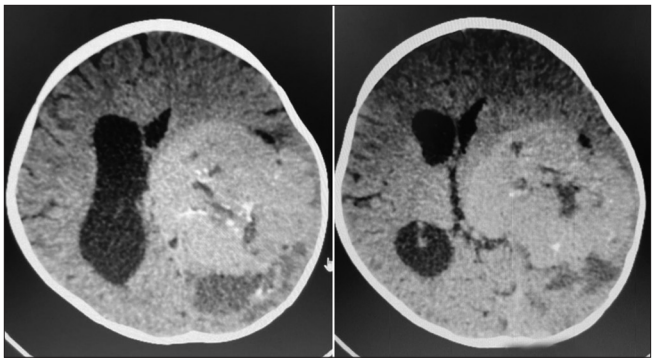

Figure 1: CT brain showing a mass lesion in the left lateral ventricle with surrounding infiltration.

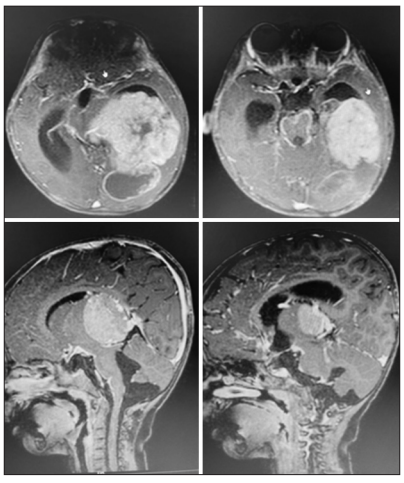

Figure 2: MRI brain showing a large-sized lesion in the left lateral ventricle with infiltration to surrounding brain parenchyma, suggestive of aggressive choroid plexus neoplasm.

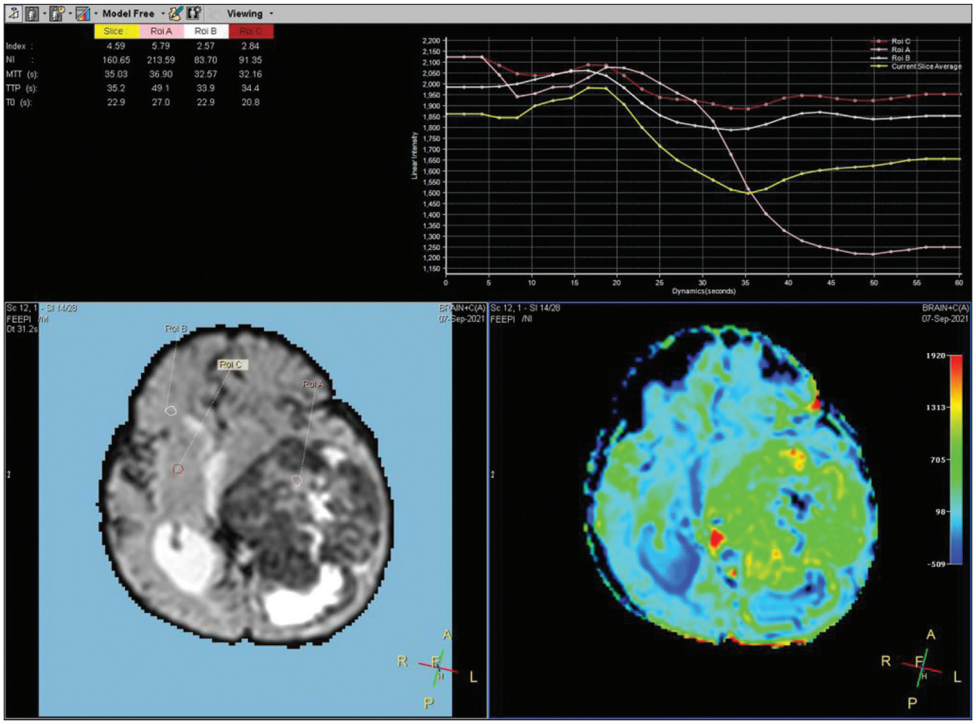

Figure 3: MRI brain perfusion image showing excessive vascularity of the tumor.

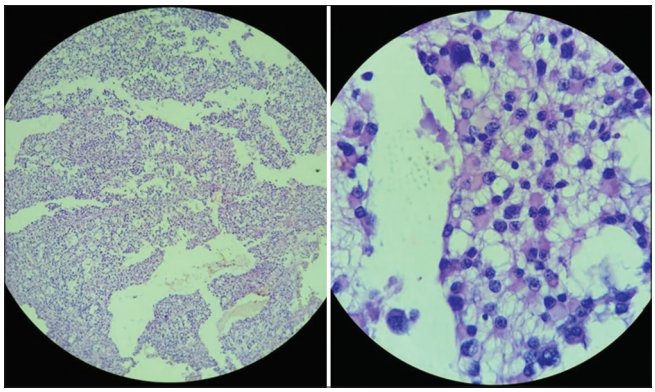

Figure 4: Histological images of the specimen showing choroid plexus carcinoma (WHO Grade III).

overall survival rate is <60%.[13] However, radiotherapy is better avoided because of the concerns about increased risk for radiation-induced second primary tumors in LFS.[9] Bettegowda *et al*. observed that after gross complete excision of the tumor, 80% of patients were disease free for a long time.[1] In our case, despite a gross complete resection and adjuvant therapy, this patient's sibling died within 1 year. This suggests that genetic factors are also important in disease outcome and prognostication of individual cases. A study by Cornelius *et al*. has shown the importance of the genetic study of CPC in formulating tailored individualized therapy as exemplified in their case report.[2]

Genetic anomalies related to CPC

CPC s is among those CNS malignancies observed in Li-Fraumeni syndrome with TP53 germline mutations.[4,6,7] About half of the CPC cases have mutations in the TP53 tumor suppression genes and are associated with poor prognosis.[13] TP53 mutations associated with the loss of heterozygosity tend to have higher rates of metastasis and resistance to chemotherapy.[5] Other genetic abnormalities include mutations in the hSNF5/INI1 gene; chromosomal imbalances such as chromosomal deletions of 5p, 9p, 15q, and 18q, and chromosomal gain of 1q, 4q, 10q, 14q, 20q, and 21q; and polyomavirus-induced changes in the tumor suppressor proteins p53 and pRb.[8] INI1 immunoexpression was formerly thought to be the most effective diagnostic marker for distinguishing CPC from atypical teratoid/rhabdoid tumors (AT/RT). Recent genetic research, however, has revealed striking parallels between CPCs and AT/RT, both of which have inactivating mutations in the hSNF5/INI-1 gene on chromosome 22q11.2. This suggests that these two conditions have a close association and that more research is needed.[8] CPC has reported changes in the number of copies, increases on chromosomes 4 and 8, and a localized deletion on chromosome 22q.[8] Recent animal studies have identified the role of Myc oncogene in coordination with TP53 in the development of CPC.[13] Li-Fraumeni syndrome is a genetic condition associated with TP53 mutations,

which predisposes the patients to a wide spectrum of high-risk childhood and adult-onset malignancies.[9] The majority of tumors related to this syndrome includes five cancer types – breast cancer, adrenocortical carcinomas, osteosarcomas, soft-tissue sarcomas, and CNS tumors.[9]

Understanding the genetic mechanism of cancer by genomic sequencing and analysis could encourage the development of new medicines (therapies) or the repurposing of older medications.[2] This case report encourages clinicians to remain vigilant by promptly performing TP53 gene testing in children with CPC regardless of the family history and thereby exclude the possibility of underlying Li-Fraumeni syndrome. However, one needs to be sensitive in identifying patients who require genetic testing so that the patients and their families can be screened for cancer earlier. According to the classic criteria of Li-Fraumeni syndrome, it is considered when the proband is diagnosed with sarcoma before 45 years of age, and a first-/second-degree relative was diagnosed to have any type of cancer or sarcoma before 45 years of age.[3] The Chompret criteria have extended the inclusion of other tumors (CNS tumor, breast cancer, and adrenocortical carcinoma) in the proband along with sarcomas.[3] Chompret criteria have been defined for the screening of germline TP53 mutation; one of them includes patients with choroid plexus tumors irrespective of their family history.[3,9,12] It has been reported that Li-Fraumeni syndrome patients with TP53 mutations have significantly higher rates of secondary neoplasms compared to those with normal TP53.[3] The germline mutation of the TP53 gene is the only known pathogenic gene in Li-Fraumeni syndrome.[3] Hence, timely detection of this mutation can aid the clinicians for effective management and achieve the best therapeutic effects, especially in children.[3] Although many other cases with TP53 mutations have been described in Li-Fraumeni syndrome, our case is interesting as it is the first case of CPC with this specific mutation as frameshift variant c.72dupA,p. (Leu25Thrfs Ter4) in exon 2 of TP53. Our case report is important because of the fact that the literature has seldom reported cases where the off-springs carried the same TP53 mutant gene as the father. Furthermore, both the siblings in an LFS family having same CNS tumors is another rare occurrence.[3]

CONCLUSION

CPC is an aggressive and rare malignancy with a genetic predisposition. TP53 pathway deficiency/dysfunction is linked to a more aggressive nature and plays a crucial role in the formation of this illness. Here, we report a novel P53 frameshift mutation with an autosomal dominant pattern of inheritance from the father that resulted in CPC occurring in two daughters. Genetic workup of CPC is important in genetic and prenatal counseling and in prognostication. In such cases, it is important to be vigilant about the presence of Li-Fraumeni syndrome through the genetic workup so that individualized tailored molecular treatment regimens can be formulated.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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