A Novel TP53 Germline Mutation in a Family with a History of Multiple Malignancies: Case Report and Review of the Literature

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Abstract
Objective: Choroid plexus carcinoma (CPC) has been associated with TP53 germline mutations and Li-Fraumeni syndrome (LFS). We describe our finding of a novel germline mutation in the TP53 gene in a family with multiple malignancies and in association with a child presenting with CPC.

Method: An 8-month-old male presented with seizure-like activity; imaging disclosed a 1.5-cm left ventricular mass confirmed to be CPC intra- and postoperatively. Family history was significant for a half-sister who died of a primary CNS sarcoma and a paternal grandmother negative for BRCA1, BRCA2, MLH1, and MSH2 mutations with multiple (>6) LFS spectrum malignancies. Results: Familial TP53 testing revealed an A→T substitution at DNA position 13071, creating a deleterious Asn→Ile substitution at amino acid 131 in exon 5. Conclusion: Physicians treating patients with CPC should be attuned to reviewing family history for risk factors suggestive of genetic cancer syndromes such as LFS. These syndromes markedly influence both the patient and family members and may alter postoperative treatment regimens.

Introduction

Li-Fraumeni syndrome (LFS) was first described in 1969 and is an autosomal dominant hereditary cancer syndrome conferring high susceptibility to breast cancer, sarcomas, and childhood malignancies including brain tumors in affected individuals [1–5]. Li-Fraumeni-like (LFL) syndromes have also been described and have been defined in various ways [6, 7]. Germline mutations in the TP53 gene are associated with the majority of families with LFS and LFL. The TP53 tumor suppressor gene on chromosome 17p13 encodes the p53 protein which is a transcription factor important in apoptosis and cell cycle control and frequently mutated in human cancers [8–11]. Table 1 summarizes the diagnostic criteria for both LFS and LFL.

Primary choroid plexus carcinoma (CPC) in childhood has sporadically been associated with the LFSs [12–15]. We describe here a new TP53 germline mutation arising in an LFS family with a proband who was an infant when diagnosed with a primary CPC, a half-sibling who died of primary leptomeningeal sarcomatosis as an infant, and a paternal grandmother diagnosed with multiple malignancies before 45 years of age, including breast cancer [16]. This unique family and germline mutation are described and the literature linking LFS and CPC is reviewed.
History
An 8-month-old Caucasian male presented to his primary care pediatrician with 6 weeks of sporadic tremors of both upper extremities. At the pediatrician’s office, the patient’s physical and neurological exam was normal, but as the patient’s half-sister had died of disseminated meningeal sarcomatosis 2 years before, the pediatrician obtained a head computed tomography scan (CT) which revealed a 1.5-cm hyperdense lesion in the atrium of the left ventricle (fig. 1a). There was mild prominence of the ventricles and the subarachnoid space overlying both frontal lobes and no evidence of midline shift or herniation. Subsequent MRI of the brain demonstrated a 1.2 × 1.6 × 1.8 cm avidly enhancing lobulated mass within the atrium extending into the occipital horn of the left lateral ventricle, lateral to the choroid plexus (fig. 1b, c). The lesion had restricted diffusion, but MR spectroscopy was not suggestive of a high-grade tumor (not shown). The cerebellar tonsils were in normal position and spinal imaging was negative.

Past Medical History
The patient was the product of a full-term pregnancy complicated by maternal lupus and was delivered by a normal spontaneous vaginal delivery. He was healthy except for the sporadic tremors and met all developmental milestones. His immunizations were complete and he was on no medications at the time of diagnosis.

Family History
The patient’s family tree is shown in figure 2. The patient’s mother and father were both in their early twenties and were healthy with no known medical problems. However, the patient’s father had an infant daughter from a previous relationship who died of diffuse CNS cancer. This paternal half-sister (III-A) presented 2 years previously, also at 8 months of age, with vomiting, dehydration, acute otitis media, and what was thought to be gastroenteritis. The symptoms worsened and the patient became lethargic, then acutely nonresponsive while hospitalized. MRI showed diffuse cerebral edema with abnormal leptomeningeal enhancement of the brain and spine, with no definitive mass identified (fig. 3a). The patient met brain death criteria and was taken off of life support.

An autopsy revealed extensive and diffuse involvement of the leptomeninges, posterior fossa and spinal cord by a polymorphic variant of primary leptomeningeal sarcomatosis. There was no clearly identifiable mass lesion. Microscopic examination showed diffuse involvement of the leptomeninges and Virchow-Robin

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**Fig. 1.** Axial radiographic images of proband at time of presentation showing enhancing left ventricular mass. **a CT. b T1-weighted MRI without contrast. c T1-weighted MRI with contrast.**

**Fig. 2.** Family history of patient. The numbers in parentheses refer to the age at diagnosis in years. The father of the proband is considered to be a nonpenetrant carrier who may manifest disease.
Fig. 3. a Axial contrast-enhanced MRI showing diffuse cerebral edema with abnormal leptomeningeal enhancement. b Low-power image with diffuse neoplastic involvement of the leptomeninges and Virchow-Robin spaces. Medium-power (c) and high-power (d) images of tumor with pleomorphism, necrosis, apoptosis, and high mitotic activity. e Immunohistochemical staining negative for epithelial markers (EMA). f Immunopositivity for intermediate filament marker, vimentin.

Fig. 4. a Papilloma regions of neoplasm with preserved papillary morphology and moderate atypia, with rare mitoses. b Carcinoma regions of neoplasm with marked atypia, loss of papillary architecture, and a high mitotic rate (arrow shows mitotic figure). c MIB-1 proliferation index was 25%. d Positive keratin stain. e Positive epithelial marker antigen (EMA) staining. f High levels of nuclear TP53 expression in papilloma (p) as well as carcinoma (c) regions.
Robertsonian translocation, 45,t(13;14), that was thought to be MLH1 and MSH2. She was, however, found to have a balanced previously tested and found negative for the breast cancer genes and 58 and ovarian and lung cancer at age 53. She also reported 27 and 34 years. She was diagnosed with colon cancer at ages 53 and had separate primary breast cancers diagnosed at ages of 58 years, but has a long history of multiple primary malignancies in multiple chromosomes, but no clear diagnostic pattern.

The patient’s paternal grandmother (I-A) was alive at the age of 58 years, but has a long history of multiple primary malignancies. She had separate primary breast cancers diagnosed at ages 27 and 34 years. She was diagnosed with colon cancer at ages 53 and 58 and ovarian and lung cancer at age 53. She also reported having over 40 basal cell carcinomas removed to date. She was previously tested and found negative for the breast cancer genes BRCA1 and BRCA2 and for the DNA mismatch repair genes MLH1 and MSH2. She was, however, found to have a balanced Robertsonian translocation, 45,t(13;14), that was thought to be unrelated. Testing for TP53 was requested, but insurance requests to fund it were denied and the testing was not performed at that time. Additional malignancies in the family include a paternal great-grandmother with chronic lymphocytic leukemia at the age of 48 and colorectal cancer at the age of 62.

Operation
Following the MRI diagnosis of a mass, the patient underwent a left parieto-occipital craniotomy to establish a tissue diagnosis and decompress the ventricular system. Intraoperative ultrasound enabled a minimal corticectomy; the edge of the left ventricle was opened longitudinally and the tumor presented as grayish, friable, and hemorrhagic. It was well encapsulated, did not appear to adhere to the surrounding brain, and arose from a pedicle of choroid which was gently freed. It was felt that a gross total resection was achieved as the entire tumor was removed and the ventricle was inspected for any remaining tumor, with none found.

Pathology
The neoplasm was composed of a variable mixture of regions corresponding to CPC with small regions of choroid plexus papilloma (fig. 4a, b). Papilloma regions exhibited preserved papillary morphology and moderate atypia, with rare mitoses (fig. 4a). Carcinoma regions had marked atypia, loss of papillary architecture and a high mitotic rate (fig. 4b). The MIB-1 proliferation index was 25% (fig. 4c) and the tumor exhibited characteristic staining for epithelial markers (keratin and EMA; fig. 4d, e). The tumor had high levels of nuclear TP53 expression in papilloma as well as carcinoma regions (fig. 4f).

Postoperative Course and Adjuvant Treatment
The postoperative MRI was negative for residual tumor, but for definitive therapy the patient was enrolled in a Pediatric Brain Tumor Consortium Clinical Trial consisting of systemic and intrathecal (IT) chemotherapy for infants with embryonal tumors. An Ommaya catheter was placed for IT delivery of mafosfamide and a Port-A-Cath was placed for venous access. The patient began 20 weeks of chemotherapy consisting of intravenous administration of cyclophosphamide, vincristine, cisplatin, followed by 21 days of oral etoposide. Mafosfamide was administered IT twice weekly concurrent with the systemic chemotherapy. However, the IT chemotherapy was discontinued after 4 doses due to an adverse reaction.

After 20 weeks of treatment, a surveillance MRI revealed the patient had developed a trapped left lateral horn; the patient underwent a left pterional craniotomy for fenestration of left temporal horn with microdissection and biopsy of tumor bed. There was no recurrent tumor visible during the secondary operation, and all biopsy specimens were negative for tumor.

At this point in the patient’s treatment, the patient’s paternal grandmother had been confirmed to have a new TP53 mutation and due to the increased risk of secondary malignancy in this genetic background the decision was made to forgo any additional chemotherapy or radiation therapy. Thus, all tumor-directed therapy was completed and the patient entered a period of close observation. Two months after fenestration, routine CT and MR imaging showed an increasing dilatation of the left temporal horn and re-entrapment, for which the patient had ventriculoperitoneal shunt placed. The patient is currently doing well.

Genetic Testing
During the patient’s treatment, the family was referred for genetic counseling. The patient’s paternal grandmother was tested for TP53 mutation given the concern for TP53-related hereditary cancer syndrome, and she was found to harbor a new germline TP53 mutation. The mutation is a single basepair substitution, A→T, at DNA position 13071, resulting in a deleterious Asn→Ile substitution at amino acid 131 in a conserved region of exon 5, a component of the DNA-binding domain [11]. Given the evidence of a familial cancer syndrome, the patient’s father was later tested and was found to have the identical germline TP53 mutation. The patient himself was not tested for two significant reasons: (1) The family would have endured significant cost to themselves for further genetic testing of the patient as their insurance company refused testing given the clear evidence of a hereditary TP53 mutation, and (2) there remains significant ethical discussion on genetic testing of minors when they are not capable of making an informed decision of whether they wish to be tested themselves.

Discussion
While astrocytomas (40–55%), medulloblastomas (20–30%), and ependymomas (10–15%) account for the majority of CNS tumors in children under the age of 15, choroid plexus tumors (CPTs) represent 1–5% of CNS tumors in this population according to several large series, with an even higher incidence in patients under the age of 2 [16–21]. About 20% of these are CPCs which are more malignant than choroid plexus papillomas [16, 19, 22]. Interestingly, the location of CPTs in pediatric patients primarily tends to be supratentorial – particularly the left atrium – while the adult population has infratentorial CPTs [16]. The survival in the pediatric population with CPTs is higher for papillomas than carcinomas [18, 19].
Despite the rarity of CPCs, there is growing evidence for the association of these carcinomas with familial cancer syndromes, particularly LFS. Li and Fraumeni defined their eponymous syndrome based on a specific autosomal dominantly inherited pattern, including specific cancers [2, 4, 5, 23]. The Li-Fraumeni ‘narrow spectrum’ of cancers includes soft-tissue sarcomas, osteosarcomas, CNS tumors, adrenocortical tumors, and premenopausal breast cancers [9, 24, 25]. Birch et al. [1] broadened the original definition by codifying the LFL. The diagnostic criteria for both LFS and LFL are given in table 1. Because of our patient’s dominant inheritance pattern, our patient’s family fits the LFS criteria: with the patient’s half-sister defined as the proband with a sarcoma, our patient is a first-degree relative with a CNS tumor, and the grandmother is a second-degree relative with cancer before the age of 45. It is important to note that the association of primary leptomeningeal sarcomatosis with TP53 mutation and hereditary syndromes has not been well described, although LFS patients frequently develop sarcomas at a young age. In 1990, both Malkin et al. [3] and Srivastava et al. [26] found associations between germline TP53 mutations and families with LFS. Numerous studies have found a similar association, although germline TP53 mutations are only found in approximately 70% of classic LFS cases with an even lower incidence in LFL or families with a history of primary LFS spectrum tumors [1, 7, 10, 27–31].

The TP53 tumor suppressor gene on chromosome 17p13 encodes a 53-kDa, 393-amino-acid phosphoprotein (hence p53) which is a transcription factor important in apoptosis and cell cycle control [8–11]. The p53 protein has four major functional domains: transactivation (1–50), DNA binding (102–292), tetramerization (323–356), and negative regulation (363–393) [11, 32]. Furthermore, cross-species sequence analysis has revealed five major regions of conservation within the following amino acid residues: 13–23, 117–142, 171–181, 234–250, and 270–286. Pathological consequences of p53 mutation include loss of normal p53 function, dominant-negative mutations that can alter wild-type p53 function, and even a rare form of translocation defect with cytoplasmic accumulation and nuclear exclusion, seen particularly in certain regulatory domain mutations [32]. The proband’s N311I missense mutation falls within a conserved region in the DNA-binding domain and led to a loss of function of tumor suppressor activity [11]. Based on a functional analysis with 8 different promoters, the N311I mutation was found to have less than 20% transactivational activity and is a nonfunctional mutant [33, 34]. Having consulted three major p53 databases, we report this N131I germline mutation as a novel germline TP53 mutation and add to previous reports of N131I as a somatic mutation [34–42].

It has been shown that certain mutant forms of p53 can have significantly increased half-lives and/or increased concentration when compared to wild-type p53 [43, 44]. Furthermore, an immunohistochemical analysis of the N131I mutation in a sample of urinary bladder carcinoma revealed increased staining of p53 [39]. Taken together, it is not surprising to find increased staining of p53 in our pathological specimen.

Garber et al. [14] first made the association of CPCs with LFS in 3 cases, 1 index case and 2 updated cases previously described in 1988 [2]. Since their 3 cases, there have been 17 additional cases, including this report, of primary CPC, occurring in patients with LFS/LFL, germline TP53 mutations, or both [12, 13, 15, 29, 45–50]. The number of such cases may be underestimated since many reports do not distinguish between types of CNS tumors or divide CPTs into papillomas and carcinomas [1–5, 23, 25, 26, 51, 52]. In addition, a case of a primary CPC occurring in a patient without any family history of cancer who most likely had a de novo germline TP53 mutation has been reported [53]. CPCs have also been reported in association with other cancer syndromes. Sévenet et al. [54, 55] suggest an association of CPCs with rhabdoid predisposition syndrome, characterized by mutations in hSNF5/INI and by carcinomas that have a strong phenotypic correlation to those with TP53 mutations.

While Ohgaki et al. [56] describe four CPCs without any TP53 mutation, it is nevertheless important to recognize that primary CPC in the pediatric patient, especial-

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**Table 1. Diagnostic criteria for LFS and LFL**

**LFS criteria [2]**
1. Proband with a sarcoma before age 45
2. Plus a 1st-degree relative with cancer in this age interval
3. Plus a close (1st- or 2nd-degree) relative in the lineage with either a sarcoma at any age or any cancer before age 45

**LFL criteria [1]**
1. A proband with any childhood cancer or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed under 45 years
2. Plus a 1st- or 2nd-degree relative with a typical LFS cancer diagnosed at any age (sarcoma, breast cancer, brain tumor, leukemia, or adrenocortical carcinoma)
3. Plus a 1st- or 2nd-degree relative in the same lineage with any cancer diagnosed before age 60

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ly at an early age, has been associated with an underlying hereditary disposition to cancer. Therefore, because of the association of such tumors with familial cancer syndromes, it is imperative for the treating physician who sees a CPC to record a complete family history and consider the presence of a familial cancer syndrome.

Optimal postoperative treatment for infants and children with CPC remains controversial. At the time our patient presented, most recent evidence suggested that survival was improved by radical surgical resection followed by adjuvant treatment [19]. Nevertheless, since there was no known optimal treatment, standard of care was to enroll the patient in an open clinical trial as appropriate. Instead of not pursuing further adjuvant treatment, the family chose to enroll in our clinical trial to evaluate the postoperative use of IT chemotherapy followed by radiation for intracranial embryonal CNS tumors. Since then, there has been growing evidence that there is a survival benefit to chemotherapy, particularly in cases of subtotal resection [12, 57–60].

Therefore, management goals in treating such a tumor, especially in the case of LFS/LFL, should include total resection with appropriate postoperative chemotherapy [18, 19, 61]. Patients should be started immediately on corticosteroid therapy after the diagnosis and en bloc resection should be attempted after gaining control of vascular supply intraoperatively [16]. In the case of any patient with a hereditary disposition for cancer, but especially with germline TP53 mutations, it is imperative to avoid radiotherapy due to the substantial risk of radiation-induced secondary malignancies [62] in light of the central role of p53 in the DNA damage response after radiation. Furthermore, the benefits of adjuvant or postoperative chemotherapy must be weighed against the risks, given reports of increased rates of secondary malignancies such as myelodysplastic syndrome and leukemias [45, 63]. With total surgical resection and chemotherapy, survival rates for CPCs are most likely slightly higher than the 50% recorded by Ellenbogen et al. [18].

**Conclusion**

We describe the case of a young child with CPC whose family meet the criteria for LFS. We add to both the genetic and the neurosurgical literature by reporting a novel TP53 germline mutation in this family, and in reviewing the literature emphasize that CPC in children should prompt the acquisition of a careful family history.

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**References**


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