Li-Fraumeni Syndrome with Unilateral Cerebellopontine Angle Lesion: A Case Report and Literature Review Postprint

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Abstract

Objective: To summarize the clinical characteristics of a patient with Li-Fraumeni syndrome accompanied by a unilateral cerebellopontine angle lesion, and to explore the treatment modalities and familial management of patients with Li-Fraumeni syndrome. Methods: A retrospective analysis was conducted on the clinical manifestations, pathological features, genetic testing, and familial analysis of a patient with Li-Fraumeni syndrome associated with vestibular schwannoma, along with a review of relevant literature. Results: The patient was a 52-year-old female who presented with facial deviation without obvious predisposing factors. Cranial MRI revealed a space-occupying lesion in the right frontal lobe. Under general anesthesia, a right frontal glioma resection was performed under magnetic resonance navigation. The integrated pathological diagnosis after surgery showed: glioblastoma, WHO grade IV, IDH wild-type with TERT promoter mutation (C250T). A TP53 germline mutation c.637(exon6)C>T, a truncating mutation, was detected in the patient's peripheral blood. The patient was ultimately diagnosed with Li—Fraumeni syndrome, and her family was diagnosed as a Li—Fraumeni syndrome family. Conclusion: Li-Fraumeni syndrome (LFS) is a hereditary tumor syndrome with autosomal dominant inheritance; TP53 gene mutation is the most common pathogenic mutation in Li-Fraumeni syndrome.

Full Text

Abstract

Objective: To summarize the clinical characteristics of a patient with Li-Fraumeni syndrome (LFS) presenting with a unilateral cerebellopontine angle lesion, and to explore therapeutic approaches and family management strategies for LFS. **Methods**: We retrospectively analyzed the clinical manifestations,

pathological features, genetic testing results, and pedigree analysis of a patient with LFS complicated by vestibular schwannoma, supplemented by a review of relevant literature. **Results**: A 52-year-old female patient presented with facial deviation without apparent precipitating factors. Brain MRI revealed a space-occupying lesion in the right frontal lobe. Under general anesthesia, the patient underwent magnetic resonance-guided resection of the right frontal glioma. Integrated postoperative pathological diagnosis demonstrated glioblastoma, WHO grade IV, IDH wild-type with TERT promoter mutation (C250T). Peripheral blood testing identified a TP53 germline mutation c.637(exon6)C>T, classified as a truncating mutation. The patient was ultimately diagnosed with Li-Fraumeni syndrome, and her family was identified as an LFS pedigree. **Conclusion**: Li-Fraumeni syndrome is an inherited tumor predisposition syndrome with autosomal dominant inheritance, and TP53 gene mutation represents the most common pathogenic alteration.

Keywords: Li-Fraumeni syndrome; Glioblastoma; Choroid plexus tumor; Pathology; Genetics

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Li-Fraumeni syndrome is an inherited tumor predisposition syndrome transmitted in an autosomal dominant pattern, characterized by high risks of sarcoma, breast cancer, leukemia, and adrenal tumors [1, 2]. The most common causative gene is TP53, with germline pathogenic mutations detectable in 70-80% of LFS families [3-5]. Brain tumors constitute a hallmark feature of LFS, occurring in approximately 40% of families [6, 7], with astrocytoma, medulloblastoma, and choroid plexus carcinoma being the most frequent types. This report presents a retrospective analysis of a patient with LFS complicated by vestibular schwannoma, examining clinical presentation, pathological characteristics, genetic testing, and pedigree analysis to enhance clinical awareness of this condition.

1 Clinical Data

The patient was a 52-year-old female admitted on July 1, 2021, with a three-month history of facial deviation. She denied fever, headache, vomiting, ocular pain, limb convulsions, altered consciousness, weakness, or vertigo. Brain MRI performed at a local hospital revealed a space-occupying lesion in the right frontal lobe, initially diagnosed as a brain abscess. During hospitalization, she developed headache with left-sided weakness. On May 20, 2021, she underwent stereotactic biopsy of the right frontal lesion at a higher-level local hospital, with pathology reporting anaplastic astrocytoma, WHO grade III. Two days postoperatively, she developed consciousness disturbance; cranial CT demonstrated a high-density lesion in the surgical field consistent with hemorrhage, prompting emergency right frontal hematoma evacuation and decompressive craniectomy. She subsequently presented to our emergency department for further diagnosis and treatment. Since symptom onset, the patient experienced poor mental status, sleep disturbance, decreased appetite, and a 6 kg weight loss, though bowel

and bladder function remained normal.

Her medical history was significant for right breast cancer in 2004 treated with radical mastectomy and adjuvant chemoradiotherapy, and left breast cancer in 2010 also managed with radical mastectomy and adjuvant chemotherapy. Both specimens revealed invasive ductal carcinoma without significant lymph node metastasis. Immunohistochemistry demonstrated ER(-), PR(+), Her-2(+++). In 2010, surveillance imaging identified a left cerebellopontine angle lesion diagnosed as left vestibular schwannoma, which was treated with radiotherapy. In 2016, she underwent cholecystectomy for gallstones; intraoperative findings of bile duct dilation and a suspicious mass prompted biopsy, which revealed bile duct adenoma. The patient and family declined further surgical intervention due to operative risks.

Family history revealed a healthy father, a mother who died of breast cancer at age 42, and a younger brother who died of glioma at age 13. The patient had one son and one daughter, both in good health. No chronic diseases, infectious diseases, or drug/food allergies were reported.

Physical examination revealed a temperature of 36°C, pulse 87/min, respiratory rate 18/min, blood pressure 124/78 mmHg, height 165 cm, weight 55 kg (BMI 20.2). The patient appeared developmentally normal but cachectic with chronic facies and dull affect. She was lethargic and poorly cooperative. Bilateral breasts were absent, and a 15 cm "H"-shaped incision was visible over the right frontal region. Multiple café-au-lait macules approximately 2 cm × 2 cm were present throughout the body [FIGURE:1D, E]. No jaundice, petechiae, or nodules were observed, and superficial lymph nodes were non-palpable. Cardiopulmonary and abdominal examinations were unremarkable.

Neurological examination demonstrated lethargy with dysarthria. Pupils were unequal (right 3.5 mm, left 2.0 mm) with sluggish right pupillary light reflex and normal left reflex. The right extremities followed commands with grade V strength and normal tone, while left extremities exhibited grade I-II strength with normal tone. Left-sided pathological signs were positive. Meningeal signs were absent, and further neurological examination was limited by poor cooperation.

Laboratory studies showed essentially normal complete blood count, liver function tests, and coagulation parameters. Brain MRI demonstrated absence of the right frontal bone with a 9.7 cm × 7.3 cm × 5.7 cm round space-occupying lesion in the right frontal lobe, appearing hypointense on T1WI, hyperintense on T2WI, with heterogeneous enhancement and ill-defined margins [Figure 1A: see original paper]. A 2 cm × 2 cm × 1.5 cm lesion was visible in the left cerebellopontine angle, extending from the left lateral foramen of the fourth ventricle into the CPA region with a lobulated appearance. CT showed calcification-like density; MRI revealed low signal on T1WI, isointense signal on T2WI, heterogeneous enhancement, and no significant diffusion restriction on DWI [Figure 2: see original paper].

On July 4, 2021, the patient underwent right frontal glioma resection under general anesthesia with intraoperative magnetic resonance navigation. A 1 cm cortical fenestration exposed the tumor, which appeared grayish-red, fish-flesh-like, soft, ill-defined, and highly vascular. Piecemeal resection was performed, with intraoperative MRI confirming gross total resection. Integrated pathological diagnosis [Figure 1B: see original paper] revealed glioblastoma, WHO grade IV, IDH wild-type with TERT promoter mutation (C250T). Based on the 2009 Chompret diagnostic criteria [8] and the patient's clinical phenotype plus family history, a diagnosis of LFS was established.

[Figure 1: see original paper] shows pre- and postoperative MRI images of the right frontal round lesion (A), pathological diagnosis of the right frontal lesion (B), sagittal, coronal, and axial MRI images with three-dimensional reconstruction (C), and multiple round café-au-lait macules throughout the body (D, E), plus a survival curve for glioma patients with TP53 mutations from the CGGA database (F). [Figure 2: see original paper] demonstrates the left cerebellopontine angle lesion extending from the left lateral foramen of the fourth ventricle, with lobulated morphology, calcification-like density on CT, low T1WI signal, isointense T2WI signal, heterogeneous enhancement, and no significant diffusion restriction.

2.1 Differential Diagnosis of the Left CPA Region Lesion

Brain tumors represent a characteristic feature of LFS and are closely associated with patient prognosis. Approximately 40% of LFS families have at least one member with a brain tumor [7]. David et al. reported brain tumors in 12% of patients across 43 LFS families [4], while Kleihues et al. found central nervous system tumors in 12% of 91 LFS families [11]. In carriers of germline TP53 mutations, brain tumor onset shows a bimodal age distribution, with the first peak at 0-5 years and the second at 30-40 years; 26% of children and 4% of adults develop brain tumors [6]. Histological types correlate with age: choroid plexus tumors predominate in infants, medulloblastoma in children, and astrocytoma in adults [12].

The patient's left CPA lesion was discovered incidentally in 2010. Due to a history of traumatic left tympanic membrane perforation, audiological evaluation was not performed. The lesion was diagnosed as left vestibular schwannoma and treated with CyberKnife radiotherapy, reportedly decreasing in size and remaining stable on follow-up imaging. Based on this history, the lesion was likely benign. Common benign tumors in the cerebellopontine angle include vestibular schwannoma, meningioma, and choroid plexus papilloma. The absence of an intra-canalicular mass, clear cerebrospinal fluid signal at the fundus of the internal auditory canal, and lack of typical vestibular schwannoma-associated symptoms argued against this diagnosis. Although CT demonstrated a calcified solid mass, MRI showed no dural base or dural tail sign, inconsistent with meningioma. Choroid plexus papilloma represents a classic LFS-associated lesion that histologically resembles normal choroid plexus. In children, these tumors typi-

cally occur in the third ventricle, while in adults they favor the fourth ventricle or its lateral foramen. They exhibit lobulated architecture on gross examination, show enhancement and calcification on CT, and demonstrate low-to-isointense T1 signal and hyperintense T2 signal for non-calcified components [13]. Considering the patient's LFS history and imaging characteristics, choroid plexus papilloma was deemed most likely.

2.2 Recommendations for Radiotherapy and Chemotherapy in LFS Patients

Reviewing the treatment course, both the left cerebellopontine angle lesion and right breast cancer received radiotherapy. Multiple studies indicate that radiation-induced tumors are common in LFS patients, mandating cautious use of radiotherapy [14, 15]. Hisada et al. reported that approximately 50% of secondary sarcomas developed within radiation fields [16], and basic research demonstrated that fibroblasts from LFS patients with germline TP53 mutations exhibit impaired repair of radiation-induced chromosomal damage, substantially increasing tumor susceptibility [17]. A study of 28 choroid plexus carcinoma patients showed no significant survival difference between radiotherapy and non-radiotherapy groups, but higher frequency of subsequent malignancies in the radiotherapy cohort [18]. Conversely, Hendrickson et al. observed that 4 of 14 LFS patients who received radiotherapy developed malignancies within the radiation field, with histology matching the primary tumor, suggesting local recurrence rather than radiation-induced malignancy [19]. Based on these findings, we recommend that radiotherapy may still be considered for LFS patients after careful multidisciplinary discussion [19]. Additionally, conventional chemotherapy also exhibits carcinogenic effects in LFS patients [20, 21]. Therefore, surgical resection should be prioritized for LFS-associated tumors, with avoidance of radiotherapy and genotoxic chemotherapies whenever possible [22].

Given these limitations of adjuvant therapies, maximal surgical resection is particularly crucial for this patient's glioblastoma [23]. However, extent of resection alone is insufficient; preservation of neurological function is equally important, as studies demonstrate that new postoperative neurological deficits correlate negatively with prognosis [24, 25]. Utilizing intraoperative MRI combined with neuronavigation, this patient achieved gross total resection without new neurological deficits.

2.3 Genetic Analysis and Family Screening

TP53 is currently the only confirmed pathogenic gene associated with LFS. TP53 mutations exhibit high penetrance, with carriers facing lifelong tumor risks. Studies show that female carriers have a near 100% lifetime tumor risk, reaching approximately 90% by age 60 [26, 27], while male carriers have approximately 73% lifetime risk [28]. Early identification of at-risk family members is therefore critical. Beyond careful phenotypic assessment and pedigree construc-

tion, genetic testing provides an accurate diagnostic modality. Knowledge of TP53 mutation status can alter the natural history of LFS-associated tumors; asymptomatic adults with first-degree relatives harboring pathogenic TP53 mutations should undergo predisposition testing, while asymptomatic children can be tested as early as infancy. Whole-body MRI combined with the detailed Toronto protocol enables early detection of asymptomatic tumors in childhood [22, 29, 30].

Peripheral blood testing in our patient identified a TP53 germline mutation c.637(exon6)C>T. Analysis confirmed this as a truncating mutation with high probability of producing a truncated protein that impairs p53 tumor suppressor function. According to American College of Medical Genetics and Genomics (ACMG) criteria, this mutation is classified as "likely pathogenic," and the ClinVar database also catalogs it as pathogenic [Figure 3: see original paper].

In summary, integrated pedigree analysis, disease phenotype assessment, and mutation analysis confirm this TP53 variant as the pathogenic mutation in this family. First-generation sequencing of the patient's children revealed the daughter to be TP53 wild-type, while the son carries the identical TP53 germline mutation c.637(exon6)C>T [Figure 4: see original paper]. The son is therefore an LFS carrier requiring tumor surveillance, potentially enabling detection of colorectal, breast, gastric, or lung cancers before clinical symptoms emerge.

[Figure 3: see original paper] illustrates the ACMG classification and TP53 germline mutation site. [Figure 4: see original paper] presents the pedigree of the Li-Fraumeni syndrome family.

2.4 Long-Term Surveillance Strategy for LFS

LFS patients frequently develop multiple primary tumors. Hisada et al. reported that 15% of 200 LFS patients developed two tumors, 4% developed three, and 2% developed four [16]. Izawa et al. described a patient who developed nine primary malignancies at different sites [31]. Consequently, long-term surveillance is essential. The LFS guidelines developed by Frebourg et al. recommend [22]: for pediatric carriers of pathogenic TP53 mutations, physical examination and abdominal ultrasound every 6 months, plus annual whole-body MRI (WBMRI) and brain MRI from birth; for adult carriers, annual physical examination and WBMRI, with brain MRI annually until age 55; for female carriers, annual breast MRI from age 20 to 65; for patients over 25, colorectal cancer screening every 2-5 years with blood pressure monitoring; and for patients previously receiving radiotherapy, monitoring for basal cell carcinoma within radiation fields. Pediatric physical examinations should identify virilization and early puberty. The first brain MRI should use gadolinium enhancement. For children, brain MRI and WBMRI should alternate to allow head imaging every 6 months [22]. Additionally, CT scans and other ionizing radiation exposures should be avoided [32]. With such surveillance, 5-year survival in TP53 mutation carriers improved from 59.6% to 88.8% [33]. LFS carriers with reproductive desires

should consult specialized genetic counseling teams to reduce offspring risk. Finally, optimizing management of hereditary central nervous system tumors requires adherence to "four early principles": early recognition, early diagnosis, early screening, and early management. Clinicians should recognize classic tumor syndrome manifestations, obtain detailed family histories when patients present with multi-system or multi-organ tumors, pursue genetic testing early to identify pathogenic mutations, and screen at-risk family members to interrupt disease transmission. For index patients, individualized and precise treatment and follow-up plans should be established, with pathogenic mutation screening and long-term disease monitoring implemented for all family members.

Health surveillance of LFS family members is particularly important. In this case, the patient's son carries the TP53 germline mutation and represents a presymptomatic LFS carrier currently without abnormal manifestations, necessitating regular follow-up to monitor his status.

References

LI F P, FRAUMENI J F, JR., MULVIHILL J J, et al. A cancer family syndrome in twenty-four kindreds [J]. Cancer Res, 1988, 48(18): 5358-62.

POWELL B C, JIANG L, MUZNY D M, et al. Identification of TP53 as an acute lymphocytic leukemia susceptibility gene through exome sequencing [J]. Pediatr Blood Cancer, 2013, 60(6): E1-3.

VARLEY J M. Germline TP53 mutations and Li-Fraumeni syndrome [J]. Hum Mutat, 2003, 21(3): 313-20.

MALKIN D, LI F P, STRONG L C, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms [J]. Science, 1990, 250(4985): 1233-8.

GONZALEZ K D, NOLTNER K A, BUZIN C H, et al. Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations [J]. J Clin Oncol, 2009, 27(8): 1250-6.

OLIVIER M, GOLDGAR D E, SODHA N, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype [J]. Cancer Res, 2003, 63(20): 6643-50.

VITAL A, BRINGUIER P P, HUANG H, et al. Astrocytomas and choroid plexus tumors in two families with identical p53 germline mutations [J]. J Neuropathol Exp Neurol, 1998, 57(11): 1061-9.

TINAT J, BOUGEARD G, BAERT-DESURMONT S, et al. 2009 version of the Chompret criteria for Li Fraumeni syndrome [J]. J Clin Oncol, 2009, 27(26): e108-9; author reply e10.

LI F P, FRAUMENI J F, JR. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? [J]. Ann Intern Med, 1969, 71(4): 747-52.

LEE S B, KIM S H, BELL D W, et al. Destabilization of CHK2 by a missense mutation associated with Li-Fraumeni Syndrome [J]. Cancer Res, 2001, 61(22): 8062-7.

KLEIHUES P, SCHäUBLE B, ZUR HAUSEN A, et al. Tumors associated with p53 germline mutations: a synopsis of 91 families [J]. Am J Pathol, 1997, 150(1): 1-13.

BOUAOUN L, SONKIN D, ARDIN M, et al. TP53 Variations in Human Cancers: New Lessons from the IARC TP53 Database and Genomics Data [J]. Hum Mutat, 2016, 37(9): 865-76.

LIN H, LENG X, QIN C H, et al. Choroid plexus tumours on MRI: similarities and distinctions in different grades [J]. Cancer Imaging, 2019, 19(1): 17.

LIMACHER J M, FREBOURG T, NATARAJAN-AME S, et al. Two metachronous tumors in the radiotherapy fields of a patient with Li-Fraumeni syndrome [J]. Int J Cancer, 2001, 96(4): 238-42.

HEYMANN S, DELALOGE S, RAHAL A, et al. Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome [J]. Radiat Oncol, 2010, 5: 104.

HISADA M, GARBER J E, FUNG C Y, et al. Multiple primary cancers in families with Li-Fraumeni syndrome [J]. J Natl Cancer Inst, 1998, 90(8): 606-11.

BOYLE J M, SPREADBOROUGH A, GREAVES M J, et al. The relationship between radiation-induced G(1)arrest and chromosome aberrations in Li-Fraumeni fibroblasts with or without germline TP53 mutations [J]. Br J Cancer, 2001, 85(2): 293-6.

BAHAR M, KORDES U, TEKAUTZ T, et al. Radiation therapy for choroid plexus carcinoma patients with Li-Fraumeni syndrome: advantageous or detrimental? [J]. Anticancer Res, 2015, 35(5): 3013-7.

HENDRICKSON P G, LUO Y, KOHLMANN W, et al. Radiation therapy and secondary malignancy in Li-Fraumeni syndrome: A hereditary cancer registry study [J]. Cancer Med, 2020, 9(21): 7954-63.

BOUGEARD G, RENAUD-PETEL M, FLAMAN J M, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers [J]. J Clin Oncol, 2015, 33(21): 2345-52.

KASPER E, ANGOT E, COLASSE E, et al. Contribution of genotoxic anticancer treatments to the development of multiple primary tumours in the context of germline TP53 mutations [J]. Eur J Cancer, 2018, 101: 254-62.

FREBOURG T, BAJALICA LAGERCRANTZ S, OLIVEIRA C, et al. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes [J]. Eur J Hum Genet, 2020, 28(10): 1379-86.

WEN P Y, WELLER M, LEE E Q, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions [J]. Neuro Oncol, 2020, 22(8): 1073-113.

STUMMER W, TONN J C, MEHDORN H M, et al. Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. Clinical article [J]. J Neurosurg, 2011, 114(3): 613-23.

MAI P L, BEST A F, PETERS J A, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort [J]. Cancer, 2016, 122(23): 3673-81.

CHOMPRET A, BRUGIèRES L, RONSIN M, et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals [J]. Br J Cancer, 2000, 82(12): 1932-7.

WU C C, SHETE S, AMOS C I, et al. Joint effects of germ-line p53 mutation and sex on cancer risk in Li-Fraumeni syndrome [J]. Cancer Res, 2006, 66(16): 8287-92.

BALLINGER M L, BEST A, MAI P L, et al. Baseline Surveillance in Li-Fraumeni Syndrome Using Whole-Body Magnetic Resonance Imaging: A Meta-analysis [J]. JAMA Oncol, 2017, 3(12): 1634-9.

KRATZ C P, ACHATZ M I, BRUGIèRES L, et al. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome [J]. Clin Cancer Res, 2017, 23(11): e38-e45.

IZAWA N, MATSUMOTO S, MANABE J, et al. A Japanese patient with Li-Fraumeni syndrome who had nine primary malignancies associated with a germline mutation of the p53 tumor-suppressor gene [J]. Int J Clin Oncol, 2008, 13(1): 78-82.

CRUZ O, CALORETTI V, SALVADOR H, et al. Synchronous choroid plexus papilloma and Wilms tumor in a girl, disclosing a Li-Fraumeni syndrome [J]. Hered Cancer Clin Pract, 2021, 19(1): 1.

VILLANI A, SHORE A, WASSERMAN J D, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study [J]. Lancet Oncol, 2016, 17(9): 1295-305.

Note: Figure translations are in progress. See original paper for figures.