Treatment Experience of Pelvic Osteosarcoma Arising in Li-Fraumeni Syndrome

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Abstract: We report the case of a woman in her 20s who developed osteosarcoma in the right iliac bone with germline variants in the *TP53* gene (*TP53*: c.220Y＞C). She was referred to a university hospital and imaging studies and biopsy led to a diagnosis of Li-Fraumeni syndrome. After she underwent proton-beam therapy combined with chemotherapy along with weekly hyperthermia, she had been referred to our institution for easier access since 20XX+6. She noticed ipsilateral gluteal pain and swelling in 20XX+8. Imaging and histopathology were consistent with recurrence of the pre-existing osteosarcoma. The palliative interventions enabled her to stay at home; however, her pain consequently exacerbated in 20XX+9. She was admitted emergently, and she died after several days.

Keywords: Li-Fraumeni syndrome, Osteosarcoma, *TP53* pathogenic variant, Social support, Palliative care.

INTRODUCTION

Li-Fraumeni syndrome (LFS) is a hereditary cancer syndrome characterized by germline variants in the *TP53* gene [1]. *TP53* is located on chromosome 17p13.1 and crucial in cell-cycle control, DNA repair, and the induction of apoptosis (programmed cell death) [2]. The protein encoded by this gene, p53, responds to DNA damage by arresting cell proliferation to allow repair; when damage is severe, it can trigger cell death to maintain organismal health. When TP53 is mutated, normal p53 is not produced, resulting in inadequate repair, and an increased likelihood of abnormal cells proliferating.

LFS is an inherited tumor syndrome caused by pathogenic variants of the tumor-suppressor gene *TP53* and follows an autosomal dominant mode of inheritance. Affected individuals have a markedly elevated lifetime cancer risk compared with the general population, with a tendency toward early-onset disease. Cancers associated with LFS include breast cancer, osteosarcoma, brain tumors, and adrenocortical carcinoma, among others [3]. Not all individuals with LFS develop cancer, and risk is heterogeneous across cases; some persons remain unaffected throughout life. As multiple primary cancers can occur in the same individual, early diagnosis and periodic surveillance are important. Families often exhibit an aggregation of diverse cancers, making family history informative. Therefore, family-wide health screening and genetic counseling are recommended. Patients and their families face substantial medical and psychosocial burdens, requiring extensive social support [4].

Osteosarcoma is a malignant tumor defined histopathologically by the production of osteoid and/or bone by tumor cells. In Japan, it is a rare cancer affecting approximately 1–1.5 per million population [5]. It typically presents with localized pain and swelling that persists for weeks to months, and serum alkaline phosphatase (ALP) levels are often elevated. Osteosarcoma is strongly associated with LFS and frequently arises in younger individuals. The cumulative risk of developing sarcomas, including soft-tissue sarcoma and osteosarcoma, reaches 50% by age 40 and 90% by age 60 in LFS [6]. We encountered a case of pelvic osteosarcoma occurring in the setting of LFS that proved difficult to manage, and we report the clinical course.

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Case Report

Female in her 20s

Chief complaint: Right gluteal pain

Past history: Unremarkable.

Family history: Mother developed breast cancer before age 45 and died at the age of 45; younger brother had a brain tumor and died at the age of ten.

Children: Three sons (ages at first presentation to our hospital: 8 years, 4 years, and 6 months) (Figure **1**)

Social history: Divorced; single-mother household.

History of present illness: In 20XX, at age 18, she presented with buttock pain and was found to have a pelvic bone tumor; she was referred to Hospital A (university hospital).

Initial physical examination: Pain and swelling over the right iliac region with a limping gait.

Pelvic radiograph: Mixed osteolytic and sclerotic changes in the right ilium.

Laboratory tests: Elevated ALP of 311 U/L.

Imaging studies (Figure **2**) and biopsy (Figure **3a**) led to a diagnosis of osteosarcoma.

Clinical course: Chemotherapy was initiated at Hospital B (general hospital). As the tumor was unresectable, she was referred to Hospital C (university hospital). She participated in a clinical study, in which a *TP53* pathogenic variant was identified (*TP53*: c.220Y＞C), and received genetic counseling. She underwent proton-beam therapy (72.6 Gy in 22 fractions) combined with chemotherapy—ifosfamide (IFO), carboplatin (CBDCA), and etoposide (VP-16)—plus once-weekly hyperthermia for four sessions. Thereafter, chemotherapy with methotrexate (MTX), cisplatin (CDDP), IFO, and doxorubicin (DXR) was continued at Hospital B. In total, MTX 80 g/m², CBDCA560mg/m², CDDP 360 mg/m², IFO 56 g/m², and DXR 300 mg/m² were administered. Residual right L5–S1 neuropathy resulted in a persistent limp and weight-bearing pain.

Post-Treatment Course

She underwent post-treatment surveillance at Hospital A (university hospital). As regular outpatient visits were difficult due to work, daily life, and childcare, she was referred to our institution for easier access. In 20XX+8, she noticed ipsilateral gluteal pain and swelling; computed tomography (CT), magnetic resonance imaging (MRI) (Figure **4**), and core-needle biopsy (Figure **3b**) confirmed recurrent osteosarcoma. Laboratory tests: ALP 1144 U/L.

Palliative Interventions

Due to bilateral ureteral obstruction, a left renal double-J ureteral stent was placed. The prescription of medical narcotics was initiated for pain control; however, analgesic efficacy was insufficient. Therefore, the opioid was switched to continuous intravenous infusion of oxycodone. In addition, transcatheter arterial embolization of the tumor-feeding arteries was

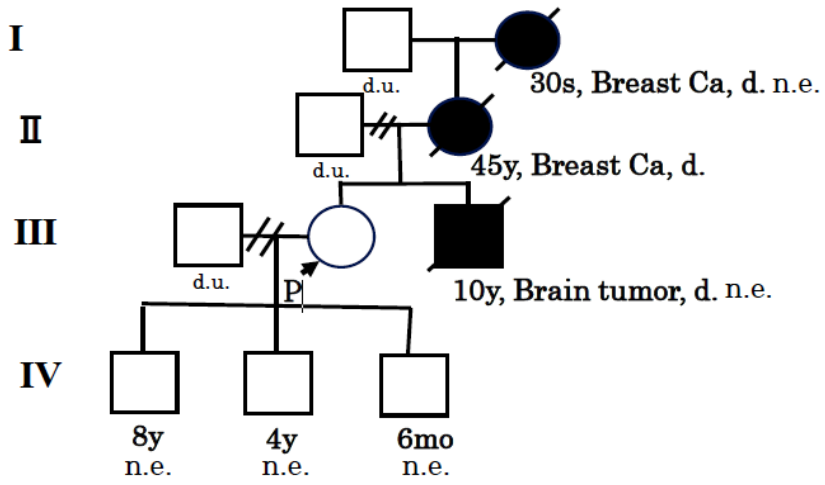


Figure 1: Detailed family pedigree.

d.: died, d.u.: details unknown, n.e.: Germline *TP53* testing is not examined.

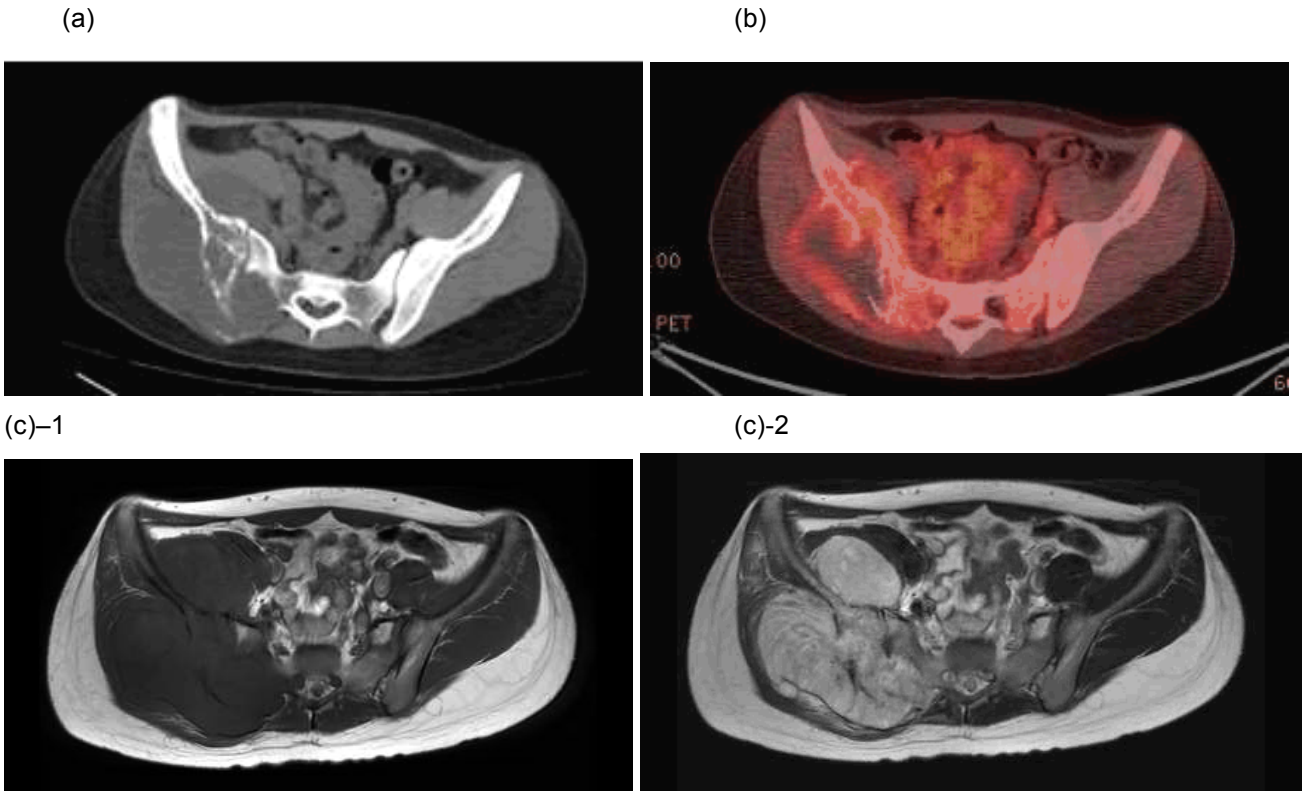


Figure 2: At initial presentation.

(a) Non-contrast CT: Osteolytic lesion centered in the right ilium extending to the right sacrum with an associated soft-tissue mass of approximately 10 cm.

(b) PET–CT: Mild uptake predominantly around the mass; no findings suspicious of metastases.

(c) Non-contrast MRI

(c)-1 T1-weighted imaging (T1WI) shows a low signal,

(c)-2 T2-weighted imaging (T2WI) shows a heterogeneously high signal.

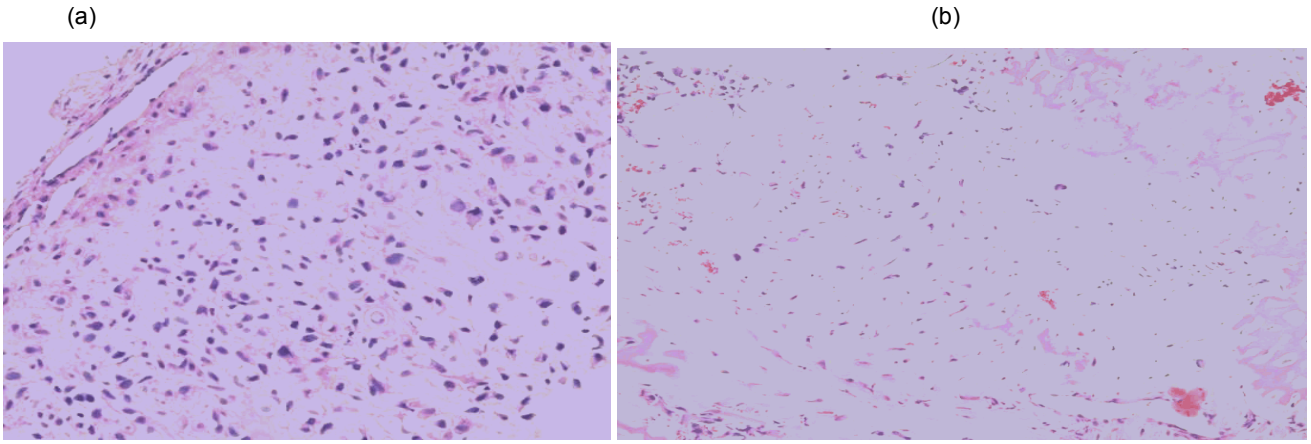
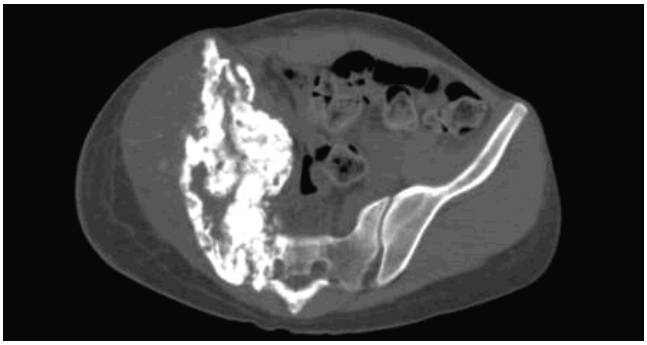


Figure 3: Pathological findings of biopsy specimens（hematoxylin and eosin staining）.

(a) At diagnosis: Osteosarcoma (chondroblastic type); tumor with degenerative cartilage to myxoid cartilaginous matrix. MIB-1 index ~10%; p53 was diffusely positive.

(b) At recurrence: Proliferation of pleomorphic to monomorphic spindle tumor cells against a background of lace-like osteoid formation with residual chondroid/endochondral ossification-like areas.

(a)



(b)-1 (b)-2

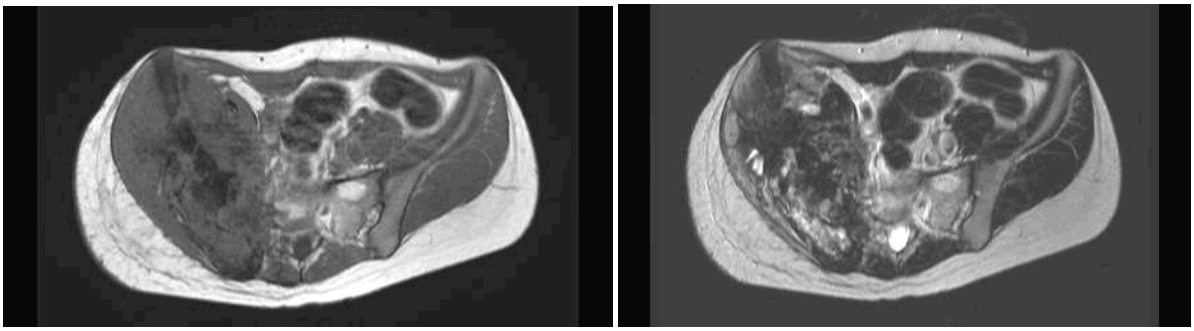


Figure 4: At recurrence.

(a) Non-contrast CT: Enlargement of soft tissue and sclerotic components.

(b) Non-contrast MRI showing irregular mass enlargement.

(b)-1 T1-weighted imaging (T1WI).

(b)-2 T2-weighted imaging (T2WI).

(a) (b)

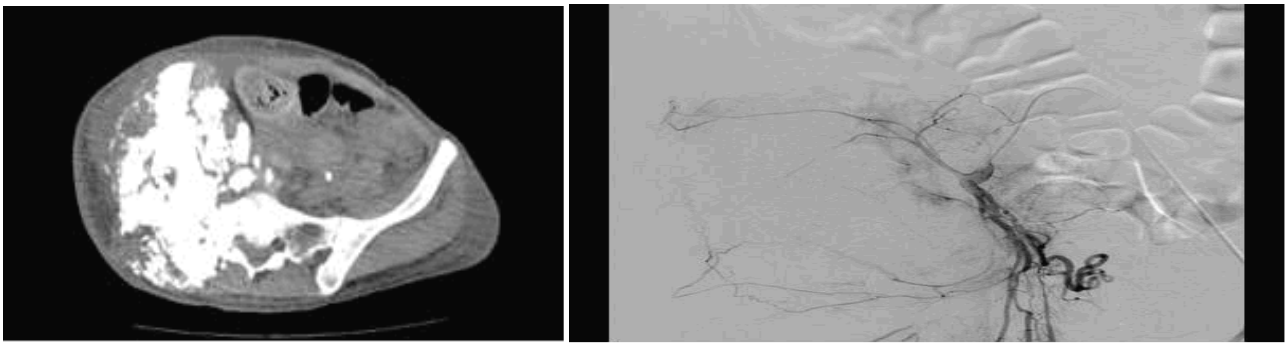


Figure 5: Interventions and course.

(a) Non-contrast CT: Further increase in sclerotic lesions.

(b) Transcatheter arterial embolization of the tumor-feeding arteries.

performed (Figure **4b**). Although pain relief was obtained due to the above treatment, right femoral nerve palsy persisted, resulting in severe gait impairment. Because comprehensive genomic profiling (cancer gene panel) revealed noactionable targets, she transitioned to home-based palliative care to ensure a seamless switch from the syringe pump used during hospitalization to a CADD-Legacy® electronic ambulatory infusion pump for patient-controlled analgesia (PCA) at home. This method using electronic portable pump allows the patient to perform the infusion treatment with self-control and the risky chemicals such as opioids can be safely administered at home. In 20XX+9, pain worsened despite the continuous administration of opioids through PCA pump, she was re-admitted emergently and she died several days later.

DISCUSSION

The lifetime risk of cancer in individuals with LFS exceeds 70% in males and 90% in females [7,8]. The tumor spectrum is dominated by five entities—breast cancer, central nervous system tumors, osteosarcoma, soft-tissue sarcoma, and adrenocortical carcinoma. LFS also confers increased risk for a wide range of other malignancies, including leukemia, lymphoma, gastrointestinal cancers, and cancers of the head and neck, kidney, pharynx, lung, skin (e.g., melanoma), ovary, pancreas, prostate, testis, and thyroid [8]. Patients with LFS have a high risk of cancer in childhood and young adulthood, and even among survivors, the risk of subsequent primary tumors arising at diverse sites remains elevated. As for mitigating the risk of secondary cancers in LFS, radiotherapy and certain cytotoxic chemotherapies may confer harm [9,10]. Treatment planning should incorporate strategies to reduce therapy-induced second malignancies.

When the classical LFS diagnostic criteria [11] (Table **1**) are met, LFS can be diagnosed with a high likelihood of a pathogenic *TP53* variant. Because genetic testing has relatively low sensitivity (25–40%) and is unsuitable for screening, the Chompret criteria [4] (Table **2**) should guide indications for *TP53* testing. LFS is inherited in an autosomal dominant manner. Most individuals with LFS inherit a pathogenic *TP53* variant from a parent; de novo germline variants are estimated to occur in 7–20% of cases. Germline *TP53*

Table 1: Classic LFS Diagnostic Criteria (1988) [11]

All of the following must be met:

1	Proband with sarcoma before age 45
2	1st degree relative with cancer before age 45
3	On the same family side, 1st or 2nd degree relative with diagnosed with cancer before age 45,or sarcoma at any age
	1st degree relatives: parents, children, siblings
	2nd degree relatives: uncles/aunts, nephews/nieces, grandparents, and grandchildren

Table 2: Chompret Criteria for TP53 screening (2015) [4]

Meet any one of the following:

1	Proband with before age 46 LFS-related malignancy (soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumor, adrenocortical carcinoma) and 1st or 2nd degree relative with before age 56, LFSrelated malignancy. Exclude breast cancer relatives if proband has breast cancer.
2	Proband with multiple cancers (excluding bilateral breast cancer), at least 2 of which are LFS-related malignancies,46 years old with the first before LFS-related malignancy occurring before age 46.
3	Adrenocortical carcinoma, choroid plexus tumor, or embryonal anaplastic rhabdomyosarcoma
4	Breast cancer patient under 31 years old

Table 3: Toronto Protocol [13,14]

Adrenocortical Carcinoma	Abdominal ultrasound 3–4months (from birth to 40 years old)
Breast Cancer	Breast examination: 2 times/year (from 20 years old)
	BreastMRI: Annually (20 to 70 years old)
	Consider risk-reducing mastectomy (from 20 years old, females only)
Brain Tumor	Brain MRI: Annually (initially with contrasted MRI)
Sarcoma	Whole body MRI: Annually (from birth),
	plus abdominal ultrasound (from 18 years old)
Colorectal Cancer	Colonoscopy: every 2 years (from 25 years old)
Gastric Cancer	*H. pylori* eradication, ［Colonoscopy: every 2 years (from 25 years old)］
Skin Cancer	Dermatology visit: Annually, Use sunscreen
Others	Promote the importance of maintaining a positive lifestyle.

testing is essential for definitive diagnosis (except for those who already meet classical clinical criteria). Pathogenic *TP53* variants are detected in 92% of LFS patients, with 91% identified by sequence analysis and 1% by exon/whole-gene deletion or duplication [8].

Children of individuals with confirmed LFS (meeting classical criteria and/or harboring a germline heterozygous pathogenic *TP53* variant) each have a 50% chance of inheriting the causative variant and associated cancer risks. Offer genetic counseling and targeted testing for the familial TP53 variant to all at-risk biological relatives. Genetic testing informs surveillance and preventive actions for patients and families, however, in Japan, germline *TP53* testing is not covered by national insurance and requires out-of-pocket payment [4,8]. Financial barriers may delay pre-treatment testing even when counseling is offered. In this case, counseling for the patient's children was sought at Hospital E, but *TP53* testing remains pending due to self-pay costs.

Structured surveillance for early detection of malignancy has shown benefit in LFS. Programs such as the NCCN Guidelines [12] and the Toronto protocol [13] enable detection at an earlier stage, allowing for curative treatment, improved quality of life, and longer survival [14]. For sarcomas, annual whole-body MRI from infancy is recommended. A meta-analysis [15] of 13 cohorts (n=578 *TP53* pathogenic-variant carriers) identified 42 new cancers in 39 individuals (6.7%) at baseline imaging; 35 were localized and treated with curative intent. False positives on whole-body MRI occurred in 173 individuals (29.9%), prompting further workup. The yield of baseline whole-body MRI must be balanced against this false-positive rate; longitudinal studies are needed to define the long-term outcome effects and optimal rescreening intervals [17].

As for preventive measures, maintaining a healthy lifestyle—characterized by a balanced diet, regular exercise, and effective stress management—may support immune function. Smoking and excessive alcohol consumption must be avoided. Genetic counseling is also recommended for those with suggestive family history. Self-exams and periodic health checkups are important for early detection [4].

This patient lacked reliable family support, because close relatives had died from LFS-associated cancers, and was a single mother caring for three young children. In particular, as she suffered from the recurrence of pelvic osteosarcoma, physical disability became dominant during the phase of palliative interventions. This situation required extensive social support, including daily living support at home and child care were mandatory along with financial support covered by physical disability welfare and public assistance.Setup of home-based medical care aimed at the management of intractable pain and arrangements for the children's care after the patient's death were also necessary for this case. Table **4** summarizes the social support actually used in this case. Enhancing LFS care systems, multidisciplinary coordination, and social support to sustain treatment and regular visits are essential, especially when family

Table 4: Social Support Services Utilized in this case

1	**Physical disability certificate** <Physical Disability Welfare Act>
	[limb disability (complete loss of right lower limb function)] 3rd grade
2	**Financial Support**
	initial 2years after the onset - living on welfare <Public Assistance Act>
	Benefits received: ① Public assistance ② Child allowance ③ Child support allowance
3	**Home Healthcare**: Costs covered by public assistance (medical aid)
	Home care support clinic (Home Clinic), Home nursing station, Insurance pharmacy
4	**Daily Living Support at home**
	Home helper dispatch: Single-parent family, daily life support program
5	**Child Care**
	Mother (during hospitalization) Under jurisdiction of child consultation center
	Foster care placement <Child Welfare Act>
	Temporary protection by child consultation center <Child Welfare Act>
	Mother (after passing) Residential facility for children with disabilities (Children #1, #2)
	Infant home (Child #3)

caregivers are limited. Timely support is also needed to maintain medical care and daily life for young children affected by or at risk for LFS [4,17].

CONCLUSION

We encountered a case of Li-Fraumeni syndrome in which pelvic sarcoma developed at the age of 18, recurred in the patient's 20s, and ultimately led to death. She faced substantial medical and psychosocial burdens including physical disability, financial support, and child care, specific for early onset. We suggest that extensive social support should be required for such young adults with LFS and their families.

AUTHOR CONTRIBUTIONS

HK, KI, and AM were involved in the drafting and revision of the manuscript. Social support was provided by KI, YK, and MK. HK, KS, TF, NO, and MT were involved in medical care and management. All authors have reviewed the manuscript and approved the final version.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethical Review Board of Nagoya Memorial Hospital (approval number: 2025-06) and conducted in compliance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects". Written informed consent for the publication of these data was obtained from the person herself.

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CONFLICTS OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ABBREVIATIONS

LFS = Li-Fraumeni syndrome

ALP = serum alkaline phosphatase

CT = computed tomography

MRI = magnetic resonance imaging

IFO = ifosfamide

CBDCA = carboplatin

VP-16 = etoposide

CDDP = cisplatin

MTX = methotrexate

DXR = doxorubicin

T1WI = T1-weighted imaging

T2WI = T2-weighted imaging

PET-CT = positron emission tomography/ computed tomography

NCCN = National Comprehensive Cancer Network

PCA = patient-controlled analgesia

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