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Li-Fraumeni Syndrome–Related Malignancies Involving the Genitourinary Tract: Review of a Single-Institution Experience

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Abstract

Objectives—To report a case of pelvic angiosarcoma in a 27-year-old man with Li-Fraumeni Syndrome (LFS) and evaluate the presentation and timeline of genitourinary (GU) tract involvement in LFS patients.

Methods—We retrospectively identified 39 LFS patients treated at our institution between 2000 and 2014; 7 (18%) had experienced a GU malignancy or an LFS-related malignancy involving the GU tract. Clinical characteristics, including dates of onset of first GU tract malignancies; pathologic findings; multimodal management; and familial history of LFS were reviewed.

Results—Median age at first malignancy was 14.0 years (interquartile range [IQR] 5.5–24.0). There was a slight male predominance (4 of 7). Median time between first malignancy and the malignancy involving the GU tract was 10.1 years (IQR 8.0–19.5). Six of the 7 patients (86%) had

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a form of sarcoma involving the GU tract; 1 developed adrenocortical carcinoma. The cancer pedigree of all patients showed LFS-associated malignancies in family members. Multimodal management included surgical resection in 6 patients with adjuvant chemotherapy or radiotherapy in 1 patient each. One patient received chemotherapy only. Following diagnosis of malignancy involving the GU tract, 5 of the 7 patients developed additional primary malignancies. At a median follow-up of 4.7 years (IQR 3.0–12.1), 2 patients are alive, 3 died of disease, and 1 died of unknown cause. One patient was lost at follow-up.

Conclusions—Continued follow-up of LFS cancer patients aimed at the determination of optimal screening, management, and surveillance protocols is recommended and may result in longer survival expectations.

Keywords

Li-Fraumeni Syndrome; malignancy; management; outcome assessment; urologic cancer

INTRODUCTION

The Li-Fraumeni Syndrome (LFS), first defined in 1969, is a highly-penetrant autosomal dominant predisposition for the development of sarcoma, adrenocortical carcinoma, breast cancer, leukemia, and brain tumors at young age.¹ LFS is associated with germline mutations of the tumor suppressor gene p53 (TP53), which is implicated in cell proliferation, apoptosis, and genomic stability.^{2–4} In the classical definition of LFS, the proband needs to be diagnosed with sarcoma before age 45, have a first-degree relative with any cancer under age 45, and an additional first- or second-degree relative with any cancer before age 45 or sarcoma at any age.^{2,5–8} Li-Fraumeni-like Syndrome (LFS-L) has also been used to define families with extensive cancer history resembling but not conforming (yet, in some cases) to the classical definition of LFS.^{2,3,6}

As many as 1:5000 individuals have TP53 germline mutations, which are familial; these are currently being identified more commonly due to increasing use of genetic screens.⁹ Carriers of TP53 gene mutation have the following probabilities of developing cancer: approximately 40% by age 20, more than 90% by age 70, and an 83-fold increased risk of developing multiple malignancies.¹⁰ Early detection and surveillance of individuals with LFS may lead to earlier detection of LFS-related malignancies and higher cure rates. However, the optimal management of LFS cancer patients is still not defined.

The objective of this study is to report a case of pelvic angiosarcoma in a 27-year-old man with LFS and to evaluate the presentation and timeline of genitourinary (GU) tract involvement in patients with LFS treated at Memorial Sloan Kettering Cancer Center (MSK).

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, our prospectively maintained institutional database was queried for all patients with a diagnosis of LFS between 2000 and 2014. We then further limited the cohort to patients who had been diagnosed with either a

GU malignancy or an LFS-related malignancy involving the GU tract. Of a total of 39 LFS patients identified, 7 patients (18%) developed a malignancy involving the GU tract. Demographic, clinical, and pathologic characteristics of each of the 7 study patients were reviewed.

The date of first malignancy was defined as the date of initial abnormality or suspected malignancy noted on imaging. The date of malignant involvement of the GU tract was defined as the date of first detection of GU abnormality or suspected GU or GU-tract-involving malignancy on imaging. Each patient's multimodal treatment approach was determined. Familial history of LFS, including presence of GU and other malignancies, was collected.

RESULTS

Case Report

A 27-year-old man was referred to the MSK Urology Service in September 2014 after multiparametric magnetic resonance imaging (MRI) identified a heterogeneously enhancing, diffusion-restricting mass in the recto prostatic space (Fig. 1).

The patient was initially diagnosed with diffuse large B-cell lymphoma in mid-2004, at age 17. After experiencing progression and vincristine-related neuropathy during R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisolone), R-ICE chemotherapy (rituximab, ifosfamide, carboplatin, and etoposide) was started in September 2004. Three episodes of deep vein thrombosis during R-ICE led to the diagnosis of factor V Leiden deficiency. Conditioning chemotherapy and autologous stem cell transplant in November 2004 was followed by consolidative radiation therapy to the abdomen with pelvic boost (4,140 cGy) in January 2005. However, follow-up computed tomography (CT) showed progression with worsening para-aortic lymphadenopathy. Between July 2005 and June 2006 the patient underwent additional maintenance rituximab (2 doses); 3 cycles of modified EPOCH-R (etoposide, prednisone, cyclophosphamide, doxorubicin, and rituximab but no vincristine due to prior secondary neuropathy), and HLA-matched unrelated-donor allogeneic stem cell transplant.

Approximately 5 years later, the patient developed a right lower extremity subcutaneous angioleiomyosarcoma, which was surgically excised in December 2011. Concurrently, a fluorodeoxyglucose positron emission tomography-CT scan showed hypermetabolic foci in the right thyroid lobe. Total thyroidectomy was performed followed by 30 mCi of radioactive iodine. Pathologic examination revealed poorly differentiated carcinoma with papillary nuclear features, focal vascular invasion, two foci of papillary carcinoma, and increased (>60%) p53 staining. The patient's cancer family pedigree subsequently compiled by our Clinical Genetics Service showed maternal family members affected by malignancy, including lung cancer (grandfather); breast, ovarian, and colon cancer (grandmother); and thyroid cancer (mother) (Fig. 2). Further genetic testing showed heterozygous change from thymine to adenine at nucleotide 712 and missense mutation from cysteine to serine at codon 238 in the p53 gene.

Upon referral to urology service in 2014, clinical exam noted the pelvic mass was palpable, firm, tender to palpation, and involved the anterior rectal wall, prostate, and seminal vesicles. Finger-guided mass biopsy under anesthesia revealed high-grade epithelioid angiosarcoma, which was managed with 6 cycles of gemcitabine and docetaxel. After initial complete response and maintenance, doses of gemcitabine and bevacizumab, pelvic recurrence occurred in June 2015. Despite additional gemcitabine and docetaxel, the pelvic mass continued to progress and remained not amenable to surgical resection. Bowel perforation with related acute abdomen and deterioration of clinical condition led to death of disease in December 2015.

MSK Experience of LFS Patients with GU Malignancies

Table 1 lists demographic, clinical, and pathologic characteristics of the 7 LFS patients who developed a GU malignancy or a malignancy involving the GU tract. Median age at first malignancy was 14 years (interquartile range [IQR] 5.5–24.0). There was a slight male predominance (4 of 7). A GU malignancy was the first malignancy in none of the 7 patients; the second diagnosed malignancy in 5 patients; and the fourth and fifth malignancy in the remaining 2 patients, respectively. Median time between first malignancy and the malignancy involving the GU tract was 10.1 years (IQR 8.0–19.5). A variety of primary tumors and malignancies involving the GU tract were found in these patients. Six of the 7 patients (86%) had a form of sarcoma involving the GU tract, 1 developed a sarcomatoid carcinoma of the bladder, and 1 developed an adrenocortical carcinoma (ACC).

Multimodal management and outcomes of LFS patients with a GU malignancy or a malignancy involving the GU tract are shown in Table 2. Two patients underwent radiation therapy for prior management of recurrent large B-cell lymphoma (patient #2) or rectal adenocarcinoma (patient #6). Since the diagnosis of their malignancy involving the GU tract, 5 of the 7 patients developed additional primary malignancies. Four of those 5 patients developed 2 or more malignancies. Two patients developed a GU malignancy different from their prior malignancy involving the GU tract, including urothelial carcinoma of the bladder (patient #6) and clear cell renal cell carcinoma (patient #7). At a median follow-up of 4.7 years (IQR 3.0–12.1), 2 patients are alive (1 with disease and 1 free of disease), 3 died of disease, and 1 died of unknown cause. One patient was lost at follow-up.

The cancer pedigree of all 7 patients showed a family history significant for malignancies associated with LFS, although the exact number of affected family members of patient #3 could not be determined (Table 3). Each of the other patients had between 2 and 5 family members affected by malignancy; however, no family members of the 7 patients with a malignancy involving the GU tract had a GU malignancy themselves.

DISCUSSION

Our small, retrospective study summarizes the largest (to our knowledge) single-institution experience with LFS-related malignancies involving the GU tract of adult patients. With the exception of ACC, a paucity of malignancy cases involving the GU tract has been reported to date. Spees et al. performed a robot-assisted laparoscopic prostatectomy in a 50-year-old male with up to Gleason 3+4 adenocarcinoma of the prostate and a solitary skin lesion

consistent with T-cell lymphoma (mycosis fungoides).¹¹ The patient's genotype and his family history were significant for LFS. Landolsi et al. report the case of a superficial papillary carcinoma of the bladder in a 31-year-old male patient with 3 first-degree family members affected by cancer at young ages.¹² Five years later, he developed a high-grade pleomorphic sarcoma of the left thigh and died at the age of 38, of pulmonary embolism after having been diagnosed with pancreatic cancer metastatic to the bone and lymph nodes. Sequencing revealed the presence of a germline mutation (codon 1009C>T, protein Arg337Cys, exon 10 of TP53 gene) in both this patient and his nephew who died at the age of 20 from bone sarcoma. A case of mixed (malignant teratoma and seminoma) testicular germ cell tumor in a patient belonging to a Li-Fraumeni cancer family was reported by Heimdal et al.¹³ Gonzalez et al. confirmed the presence of a TP53 germline mutation in 14 of 21 patients (67%) with ACC.¹⁴ TP53 mutation was found in 80% of patients with ACC younger than 18-years-old. In the Gonzalez series, additional GU malignancies included 2 adrenal cancers and 1 prostate cancer. Within 20 LFS families and eight LFS-L families, Birch et al. identified 7 ACCs, 3 renal carcinomas, 1 bladder carcinoma, 1 carcinoma of the prostate, and 1 gonadal germ cell tumor.¹⁵ Although common GU malignancies were not associated with the TP53 syndrome (with the exception of ACC), the authors could not exclude the possibility of increased risk of these cancers in TP53 mutation carriers exposed to environmental carcinogens such as tobacco or other genetic factors.

In our small series, a pelvic sarcoma was the most common LFS-related malignancy involving the GU tract. The management of our patients was primarily surgical, with the addition of radiation therapy in 1 patient and chemotherapy in 2 patients. The rationale for surgical management of cancers in LFS patients with good performance status and adequate life expectancy resided in the relative radio- and chemo-resistance conferred to cancers by TP53 mutations, which render p53 dysfunctional.^{16,17} Resistance to docetaxel, doxorubicin, cisplatin, anthracyclines, and mitoxantrone has been reported in dysfunctional p53 malignancies,^{17,18} and efficacy of taxanes in LFS cancers is still under investigation.¹⁸ Additionally, defective DNA repair due to mutant p53 increases the risk of radiation- and chemotherapy-induced malignancies in these patients.^{9,19} Although 2 of our patients with LFS-related cancer had undergone radiation therapy prior to developing a malignancy involving the GU tract, the number of events in our small cohort was not sufficient to conclude any strong association between radiation therapy and new primary cancer development.

It is currently not clear whether increased screening for TP53 mutation carriers would have an overall beneficial effect.⁴ Early identification of LFS by genetic profiling of patients with personal and family history of multiple malignancies at young age, and screening of their family members, may allow early identification and aggressive treatment of lower-stage cancers. This might reduce morbidity and ultimately achieve higher cure rates and survival advantages for LFS-related malignancies. However, the variety of phenotypic variation, tumor multiplicity, and degree of disease penetrance in LFS impairs the ability to design and implement adequate and effective screening and surveillance protocols for LFS patients and their family members.¹⁰ A major drawback to screening is that the identification of a mutation in an asymptomatic individual, in particular in a child or even prenatally, may prove to have low clinical relevance but devastating psychological ramifications.¹² One

might argue that until treatments targeting the molecular defects responsible for the onset and progression of LFS-related cancers become available, LFS screening programs should be reserved for specialized academic institutions actively involved in LFS research. At these institutions, consenting adult patients undergoing TP53 mutation screening should be provided with high-quality information and counseling, and made aware of their right to decide whether or not to have the genetic data disclosed to them. Such a policy would follow the precedent which acknowledges that routine testing of children is currently not recommended unless the disease is associated with childhood onset and effective screening and/or intervention options are available.²⁰ However, in recent studies, genetic counseling and mutation testing, including TP53 mutation testing, have shown benefits in young patients with osteosarcoma and history of cancer in close relatives,²¹ and also in children and adolescents with cancer and a negative family history of malignancy.²²

Clinical surveillance protocols including clinical examination, blood testing, breast cancer screening using MRI, colon cancer screening using fecal occult blood testing and colonoscopy, abdominal/pelvic ultrasound, and whole-body MRI for early detection and surveillance of LFS-related malignancies may be effective.²³ Although reliable screening tests for other LFS-related malignancies have yet to be established⁴, the utilization of one such protocol resulted in a durable 3-year survival advantage of 100% vs. 21% (95% confidence interval 4–48%, $p = .0155$), for 7 TP53 mutation carriers with asymptomatic tumors who underwent surveillance compared to 10 individuals in the non-surveillance group who developed high-stage cancers.²³ Our institution is currently participating in a multicenter trial to screen for second malignancies in patients with LFS using several imaging modalities, including whole-body MRI. Unfortunately, no patients in this series were included in this newly opened screening trial for LFS patients.

LFS-related malignancies are usually managed similarly to those in non-LFS patients. Nonetheless, the variety, location, and multiplicity of the malignancies developing in individuals who may have already undergone extensive multi-modality treatments render the management of LFS cancer patients particularly challenging. Moreover, it is currently unclear whether chemoprevention or targeted therapies might be developed based on the growing knowledge and understanding of the molecular basis of LFS.¹⁰ After showing anticancer activity in preclinical studies,²⁴ the non-integrating DNA vector contusugene ladenovec (Advexin[®]) demonstrated stabilization of tumor growth and tumor regression by inducing cell-cycle inhibition and apoptosis in treated tumors.²⁵ Clinical trials of intratumoral injection of contusugene ladenovec as monotherapy or in combination with chemotherapy or radiation therapy showed safe and well-tolerated antitumor activity.²⁶ Remission was achieved in a single-patient compassionate protocol after intratumoral injection of contusugene ladenovec, followed by chemotherapy and radiation therapy, in a young woman with LFS and progressive embryonal carcinoma refractory to prior surgical management.²⁷ Although bevacizumab showed activity on solid tumors in TP53 carriers, its role in LFS is yet to be defined.²⁸ Other strategies aiming at the degradation or inhibition of aggregation of mutant TP53, or the reactivation of wild-type functions in mutant TP53, are pending clinical investigation in LFS patients with solid tumors.²⁹

To our knowledge, we report the largest single-institution experience in LFS patients with malignancies involving the GU tract; however, the small sample size and the heterogeneity of cancers presented by our patients are significant limitations that prevent the formulation of any generalizable management recommendations. Nonetheless, findings in our small cohort could be used for hypothesis-generating purposes. We believe further information should be gathered by prospectively following LFS cancer patients to further elucidate cancer-specific outcomes and to assess the impact of screening, surveillance, and therapeutic protocols.

CONCLUSIONS

LFS is an autosomal dominant predisposition for early onset of cancers, some of which may involve the GU tract. Although definitive associations between common GU malignancies and LFS have not been elucidated to date, the concomitant presence of TP53 mutations, environmental carcinogens, and other genetic factors might increase the risk of developing GU malignancies in carriers. There should be continued efforts to define optimal screening, management, and surveillance protocols in order to provide LFS families with more efficacious cancer treatment options, including chemoprevention or TP53-targeted therapies, and longer survival expectations.

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Fig. 1.

MRI of rectoprostatic space of 27-year old male with Li-Fraumeni Syndrome Axial (A) and sagittal (B) T2-weighted, axial apparent diffusion coefficient (ADC) map (C) and sagittal dynamic contrast-enhanced MR (D) images showing a heterogeneously enhancing, diffusion-restricting tumor in the rectoprostatic space. Subsequent axial T2-weighted image (E) and ADC map (F) after 6 cycles of chemotherapy (gemcitabine and docetaxel) shows near-complete resolution of rectoprostatic space tumor.

Fig. 2.
Limited family pedigree of our Li-Fraumeni Syndrome patient with pelvic angiosarcoma.

Table 1.

Characteristics of Li-Fraumeni patients with genitourinary malignancies

Patient#	Gender	First Malignancy			Urologic Malignancy		
		Type of malignancy	Year of diagnosis	Age at diagnosis (year)	Type of malignancy	Year of diagnosis	Time from first malignancy (year)
1	Male	Osteosarcoma	1977	14	Pelvic sarcoma	1998	21
2	Male	Diffuse large B cell lymphoma	2004	17	Pelvic angiosarcoma	2014	10
3	Female	Acute lymphoblastic leukemia	2000	7	Sarcomatoid carcinoma of the bladder	2006	6
4	Female	Breast (cystosarcoma phyllodes and intraductal)	1990	31	Pelvic mesenchymal leiomyosarcoma	2008	18
5	Female	Choroid plexus carcinoma	2007	4	Adrenocortical carcinoma	2010	3
6	Male	Rectal adenocarcinoma	1980	40	Leiomyosarcoma of spermatic cord	1990	10
7	Male	Upper extremity embryonal rhabdomyosarcoma	1965	2	Leiomyosarcoma of bladder	1994	29

Multidisciplinary management and outcomes of Li-Fraumeni patients with genitourinary malignancies

Table 2.

Patient#	RT prior to GU malignancy	Site and dose of radiation	Type of GU malignancy	Surgical intervention	Chemotherapy	RT for GU malignancy	Follow-up since GU malignancy (yr)	Status
1	No	NA	Left parasacral angiosarcoma	Yes	No	Yes	3	Died of disease
2	Yes	Abdomen and pelvis, 4,140 cGy	Pelvic angiosarcoma	No	Yes	No	1.2	Died of disease
3	No	NA	Sarcomatoid carcinoma of the bladder	Yes	No	No	NA	Unknown
4	No	NA	Pelvic mesenchymal leiomyosarcoma	Yes	No	No	6.3	Alive with disease
5	No	NA	Adrenocortical carcinoma	Yes	Yes	No	3	Alive without disease
6	Yes	Pelvis; unknown dosage	Leiomyosarcoma of spermatic cord	Yes	No	No	23	Died, unknown cause
7	No	NA	Leiomyosarcoma of bladder	Yes	No	No	14	Died of disease

GU, genitourinary; RT, radiation therapy

Table 3.

Cancer family tree of Li-Fraumeni patients with genitourinary malignancies

Patient#	No. of family members diagnosed with LFS-related malignancies	No. of family members with a GU malignancy
1	3	0
2	2	0
3	NA	NA
4	5	0
5	2	0
6	2	0
7	2	0

GU, genitourinary; LFS, Li-Fraumeni Syndrome