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Colon Pathology Characteristics in Li–Fraumeni Syndrome

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Li–Fraumeni syndrome (LFS) is a rare autosomal-dominant hereditary cancer syndrome associated with germline mutations in the *TP53* tumor-suppressor gene. The lifetime risk of cancer is up to 70% in men and almost 100% in women.[1] Studies continue to show that the tumor spectrum of *TP53* mutation carriers is wider than previously thought and includes early onset colorectal cancer (CRC).[2–4]

Several studies have reported that LFS accounts for a small portion of early onset colon cancer.[5,6] However, extensive descriptions of the number, size, location, and histology of lesions encountered in screening colonoscopies preformed in LFS patients is lacking. Understanding the colorectal pathology associated with LFS will help clinicians understand the CRC risk in this population and define the best screening measures.

Materials and Methods

We identified all subjects with pathogenic *TP53* mutations enrolled in the Cancer Genetics Study at Huntsman Cancer Institute at the University of Utah (Institutional Review Board 41211). Medical records were reviewed to determine demographic and clinical data from colonoscopies.

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Conflicts of interest

These authors disclose the following: Kory Jasperson is an employee of Ambry Genetics; and Joshua Schiffman holds an Edward B. Clark, MD, Chair in Pediatric Research at the University of Utah and is a member of the Primary Children's Hospital Pediatric Cancer Program, funded by the Intermountain Healthcare Foundation and the Primary Children's Hospital Foundation. The remaining authors disclose no conflicts. The Genetic Counseling Shared Resource is supported by the National Cancer Institute of the National Institutes of Health uncer Award number P30CA042014.

Results

Among 66 individuals with pathogenic *TP53* mutations, 31 (47%) underwent a colonoscopy evaluation, with their first colonoscopy at an average age of 28 years (range, 11–53 y). Thirty-five of 66 patients (53%) did not have a colonoscopy evaluation; 22 (63%) did not have a colonoscopy because they were younger in age (age, <25 y). Because some patients had more than 1 colonoscopy evaluation, a total of 72 procedures were reviewed.

In the 31 patients with a colonoscopy evaluation, no abnormalities were found in 16 patients (52%). The remaining 15 patients (48%) were found to have a total of 42 abnormal lesions found in 28 biopsy procedures. Tubular adenomas (TAs) were the predominant finding (N = 23; 55%), followed by hyperplastic polyps (HPs) (N = 8; 19%), CRC/high-grade dysplasia (HGD) (N = 6; 14%), and sessile serrated polyps (SSPs) (N = 5; 12%). TAs were found most frequently in the descending colon, whereas all other lesions were most prominent in the sigmoid colon and absent in the ascending colon. The average size of the lesions was 3.9 mm (range, 2–6 mm) for TAs, 4.4 mm (range, 3–6 mm) for HPs, 6.6 mm (range, 4–15 cm) for SSPs, and 17.6 mm (range, 3–70 mm) for CRC/ HGD. Lesions were predominantly in the left colon: 67% of TAs, 88% of HPs, 80% of SSPs, and 83% of CRC/HGD.

The mean age of patients at diagnosis with CRC/HGD was 25.4 years (range, 19–43 y), with 4 of 5 diagnosed before age 25. Three CRCs were identified on baseline colonoscopy, 1 CRC was detected on a screening colonoscopy performed more than a decade since the patient's prior examination, and the HGD was detected 2 years after a normal colonoscopy. Two patients were siblings who shared a mutation (deletion exon 1), and the other 3 patients were unrelated with *TP53* mutation variability (P117R, I125L, and R248W). The precursor lesions were TAs for 2 cases, tubulovillous adenomas for 2 cases, and SSP for 1 case. Two cancers had micro-invasion and 2 cases presented with lymph node metastasis (Table 1).

Discussion

Current guidelines for LFS patients recommend CRC screening with colonoscopy every 2 to 5 years, initiated at age 25.[7] In our series of individuals with *TP53* mutations, 16% of those undergoing colonoscopy screening were diagnosed with CRC/HGD. Four colon cancers were diagnosed at much younger ages (ages, 19, 21, 22, and 24 y), while another case was diagnosed at 41 years, exemplifying the early onset of colon malignancies and the importance of early colonoscopy evaluation.

The average size of CRC/HGDs was only 7.2 mm (after excluding the 1 outlier large cancer). Malignant transformation was observed in polyps as small as 3 mm. This malignant transformation in small polyps poses special challenges to the clinician performing the colonoscopy because these lesions are considerably smaller than the 4.5-cm average colon tumor size reported in the general population.[8] To avoid missing a small lesion that may carry malignant potential, the following colonoscopy parameters may be considered: longer withdrawal time during the procedure, careful and thorough examination with special attention to small lesions, retroflexion in the cecum, and the use of snare polypectomy rather

than piecemeal with forceps. Limitations of our study included the retrospective nature and the small number of patients and procedures.

In summary, we recommend beginning colonoscopy screening at an earlier age for patients with LFS. Colonoscopy evaluation should be performed to detect small lesions regardless of patient age, owing to the possibility of early onset, malignant transformation in smaller polyps in patients with a *TP53* mutation.

Abbreviations used in this paper

CRC	colorectal cancer
HGD	high-grade dysplasia
HP	hyperplastic polyps
LFS	Li–Fraumeni syndrome
SSP	sessile serrated polyp
TA	tubular adenoma.

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Table 1

Colorectal Cancer/High-Grade Dysplasia Features in Li–Fraumeni Patients

Indicator	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	M	M	M	F	F
Age, *y*	21	19	22	24	41
Mutation	P177R	I251L	Del exon 1	R248W	Deletion exon 1
FH of CRC	No	No	Yes	No	Yes
Additional primary	Sarc/osteo	GBM	Sarc/oligo	None	Breast/lung
Cancer/HGD details					
Location	Sigmoid	Sigmoid	Sigmoid	Sigmoid	Rectum
Type	CRC	CRC	CRC	HGD	CRC
Precursor lesion	TVA	TVA	TA	SSP	TA
Cancer size, *mm*	70	3	9	8	6
Invasion	LN (T3N2)	Submucosa	LN (T4N2)	None	Submucosa Transverse HGD TA 10 mm None Transverse

Del, deletion; F, female; FH, family history; GBM, glioblastoma multiforme; LN, lymph node; M, male; osteo, osteosarcoma; oligo, oligodendroglioma; Sarc, sarcoma; TVA, tubulovillous adenoma.