The Features of Colorectal Tumors in a Patient with Li-Fraumeni Syndrome

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Abstract

A young woman with Li-Fraumeni syndrome (LFS) was referred to our hospital. On examination, multiple flat neoplasms were detected in addition to semi-pedunculated polyps. Restorative proctocolectomy was performed; one submucosal invasive cancer, two mucosal cancers, and several adenomas with high-grade dysplasia were detected. On immunohistochemical staining with p53, every part of all neoplasms, even the small adenomas, showed strong positive staining. Multiple flat neoplasms may be characteristic of patients with LFS and may have a much higher risk of rapid progression to invasive carcinomas than sporadic neoplasms. Thus, careful and frequent colonoscopy surveillance may be needed for patients with LFS.

Key words: Li-Fraumeni syndrome, TP53, laterally spreading tumor, colorectal cancer, colorectal polyps

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Introduction

Li-Fraumeni syndrome (LFS) is a hereditary syndrome with a high risk of various neoplasms, such as sarcomas of soft tissues and bone, breast cancer, brain tumor, adrenocortical carcinoma, and leukemia, in children and young adults (1). The underlying genetic defect in the majority of LFS families has been identified as a germline mutation in the p53 tumor-suppressor gene (2). Although the proportion of colorectal adenocarcinoma is low among LFS-associated tumors, the relative risk of colorectal cancer in LFS is 2.8 times that of the general population (3). An analysis of 397 patients in 64 families with classic LFS performed by Wong et al. showed that 16 patients (4.0%) from 15 different families (23.4%) had colorectal cancer. They concluded that LFS patients may have an increased susceptibility to colorectal cancer that presents up to several decades earlier than usual (4). LFS should be considered when a relatively young patient presents with colorectal cancer. However, the clinicopathological features of colorectal tumors in LFS are not well known. In this report, a case of LFS with multiple colorectal adenomas and adenocarcinomas is described.

Case Report

A 34-year-old woman was suspected of having LFS because she had a history of osteosarcoma of the left leg in her teens and right breast cancer in her 30s, both of which are representative tumors of LFS. Although she did not meet the clinical criteria for classic LFS because she had no family history of malignancy at a young age, she met the 2009 Chompret criteria (5). In addition a TP53 missense mutation at exon7 c.743G>A;p.Arg248Gln was detected during a detailed genetic examination, so she was diagnosed with LFS. Two years before visiting our hospital, she had undergone total colonoscopy at another hospital because of a positive fecal occult blood test. Two polyps were resected, and the
pathological findings showed tubular adenomas. One month prior, she had undergone a second colonoscopy for a positive fecal occult blood test at the same hospital, and four polyps at the cecum, and ascending, transverse, and descending colon were detected. Two of them were removed by endoscopic mucosal resection (EMR), but one was considered difficult for EMR and one was suspected of harboring mucosal cancer. Therefore, she was referred to our hospital for further examination and treatment, including endoscopic submucosal dissection (ESD).

On colonoscopy, we found more than 10 laterally spreading tumors—nongranular (LST-NGs), some of them >20 mm in size, and countless small (<10 mm), flat neoplasms in every part of the colorectum (Fig. 1). Some were suspected of being adenocarcinoma in situ based on magnifying colonoscopy findings, and one tumor located in the lower rectum, which had not been pointed out on previous colonoscopy, was strongly suspected of being invasive cancer (Fig. 2). Because multiple colorectal tumors were located in every part of the colorectum with a hereditary basis, restorative proctocolectomy was recommended. However, from the perspective of quality of life, the patient wanted to preserve the rectum. Therefore, ESD was performed for the lower rectal neoplasm as total biopsy first. Histology showed moderately differentiated adenocarcinoma with vascular and submucosal invasion (2,200 μm in depth) (Fig. 2). Finally, proctocolectomy with ileal pouch-anal anastomosis was performed (Fig. 3). The surgically resected specimen showed dozens of LST-NGs, some of which were pathologically diagnosed as well-differentiated intramucosal adenocarcinomas, and the rest were diagnosed as adenomas with high-grade dysplasia (Fig. 3). Strong positive immunohistochemical staining of p53 was found in every part of all neoplasms, including both adenocarcinomas (Fig. 4a) and adenomas (Fig. 4b). Some parts of the ductal epithelium of mucosa without elevation or depression and that were apparently normal by Hematoxylin and Eosin (HE) staining (Fig. 5a and b) also had positive p53 staining (Fig. 5c and d).

Discussion

LFS is a hereditary cancer syndrome that was first described as an autosomal dominant familial syndrome with soft tissue sarcoma, breast cancer, and other neoplasms in children and young adults by Li and Fraumeni in 1969 (1). However, TP53 is now known as the causal gene (2), and patients who have a germline mutation in TP53 regardless of family history are also diagnosed as having LFS (5). The Chompret criteria for selection of individuals for TP53 testing enable the identification of individuals at high risk of carrying a germline mutation in TP53, independent of family history (5).

TP53 is known as “the guardian of the genome” because the product of TP53, p53 protein, has multiple functions to prevent tumorigenesis, such as activation of DNA repair, production of proteins that control cell cycles, and promotion of apoptosis of cells with irreversibly injured DNA. The
Figure 2. (a) White-light views of the rectal tumor. Type 0-Ia+IIa. (b) Chromoendoscopy view using indigo carmine. (c) Magnified view of narrow band imaging showing irregular thick vessels. (d) Magnified view with crystal violet dye showing Type VN. (e) Histological findings of the rectal tumor resected by endoscopic submucosal dissection (×20), which show well-differentiated adenocarcinoma in adenoma, pT1b (SM 2,200 μm), LY1, V1, HM0, VM0.

Figure 3. Views of the resected specimen of the colorectum showing multiple flat neoplasms in each section (red circles contain LST-NG): (a) Ascending colon, (b) transverse colon to descending colon, and (c) sigmoid colon to rectum.
major part of the mutated TP53, including the Arg248Gln mutation in the present case (6), is known to produce mutant (mt) p53 protein, which is slowly degenerated compared with wild (wd) p53 protein. Therefore, accumulated mutant p53 protein can be detected by immunohistochemistry for p53 protein. The mt p53 protein interferes with the activity of p53 by forming inactive tetramers with wd p53 protein (7) in a process known as dominant negative effect, which leads to tumorigenesis. Therefore, TP53 germline mutations cause various tumors, in addition to the representative “LFS tumors” (1). Colorectal cancer is one of the LFS tumors, and one report noted that 2.8% of people with TP53

Figure 4. Immunohistochemical staining for p53. (×20) (a) Rectal adenocarcinoma with submucosal invasion, as in Fig. 2e, (b) one of the LST-NGs in the transverse colon showing tubular adenoma with severe atypia.

Figure 5. Hematoxylin and Eosin (H&E) staining and immunohistochemical staining for p53 of apparently normal mucosa (a), H&E staining (×20); mucosa without depression or elevation (b), H&E staining (×40); the ductal epithelium is apparently normal for H&E staining (c), (d) immunohistochemical staining for p53. (c): (×20) (d): (×40); Some parts of the ductal epithelium had positive p53 staining.
mutations had colorectal cancer, with a mean age of diagnosis of 33 years (4). It is well known that TP53 mutation plays an important role in sporadic colorectal cancer. About 40% of colorectal adenocarcinomas have a TP53 mutation (8), with a higher frequency of TP53 mutations reported with malignant progression of adenoma. These reports indicate the central role of TP 53 mutation in malignant progression of colorectal neoplasms, as well as its role in the latter phase of carcinogenesis compared to adenomatous polyposis coli (APC) mutation or K-ras mutation.

The relationship between TP53 mutation and the morphology of colorectal neoplasms is still unsettled. Some case reports have been published on LFS patients with colon cancer (9, 10), but no detailed data on the shape or size or concomitant colon neoplasms have been collected. Miyaki et al. reported a case of a patient with a germ line TP53 mutation who had advanced colon cancer with multiple early adenocarcinomas and adenoma (11). However, their report lacked details about the morphology of the synchronous early tumors; the locus of the mutation was A189Y, which is not common in LFS; and the patient’s age was 73 years with no past or present history of malignancies. Therefore, this case does not seem to be typical LFS.

In contrast, the endoscopic findings in the present case were very characteristic, as most colorectal tumors are flat type, known as LST-NGs. This is in contrast to familial adenomatous polyposis, in which the tumors are pedunculated or semi-pedunculated. Recently, Konda et al. reported that the frequency of TP53 mutations was higher in LST-NGs and depressed neoplasms than in polyoid neoplasms, while K-ras mutations were less frequent (12). Furthermore, some reports have noted that the frequency of K-ras mutations is lower in LST-NG than in LST-G and polyoid adenomas. In LFS patients, in contrast to the classic adenoma-carcinoma sequence, TP53 mutations occur earlier than K-ras mutations, which may explain the difference in morphological features between these tumors.

In the present case, even adenomas less than 5 mm in size showed strongly positive immunohistochemical staining for p53, and some parts of the mucosa that appeared normal on H&E staining were also positive, reflecting widespread dysfunction of TP53. However, in the present case and in other case reports of LFS patients (10, 13), a large part of the normal mucosa was negative on immunohistochemical staining for p53. Furthermore, in many cases of TP53 germ-line mutation, loss of function or deletion of the wild type allele is needed for phenotypic manifestation and the initiation of tumor development (14). These present and previous findings suggest that the preserved wild type p53 allele interferes in some way with the mt p53 protein activity.

Nagata et al. reported that mt p53 protein is rapidly degraded via the ubiquitin-proteasome proteolytic pathway, which is promoted by wt p53 protein. When the wt p53 allele is also mutated, the ubiquitin-proteasome proteolytic pathway is inactivated, and non-ubiquitinated mt p53 protein accumulates (15). It is likely that mucosa that is apparently normal but shows positive immunohistochemical staining for p53 has loss of function of the wild type TP53 allele with accumulation of mt p53 protein. Other parts of the mucosa that are negative for p53 likely have a preserved wild type TP53 allele, so that the mutant p53 protein is broken down.

We found high-grade dysplasia even with small tumors, and hence even small adenomas in LFS may have a high risk of rapid progression to invasive carcinoma. The small, flat neoplasms and sometimes even larger counterparts such as LST-NG are difficult to detect, and therefore careful and frequent.

LSTs-some of which were early colon cancer-were missed during colonoscopy at the previous hospital one month prior. In addition, even if no neoplastic lesions are detected, underlying genetic changes may be present in mucosa that appears normal. There are some studies that suggest that, in inflammatory bowel disease patients, immunohistochemically detected p53 protein in mucosa without polyps indicates precancerous lesions (16, 17). On extrapolating these findings to the present case, even mucosa that appears normal with p53 positive immunohistochemistry can be a precancerous lesion. However, at present, there are no data on the frequency with which an apparently normal, but genetically abnormal mucosa will become malignant and how long such a transformation can take.

Recently, McBride et al. reviewed the cancer risk and clinical management of LFS (18). In their review, with respect to proposed evidence-based screening for colorectal cancer, they recommended colonoscopy every 2-5 years from 25 years of age, or, in cases with a known family history of this disease, from the age of 10 before the earliest onset of colorectal cancer in the family. However, as in the present case, colonoscopy might need to be more frequent and performed carefully and attentively, given concerns about missing LSTs and the potential risk of relatively rapid progression to advanced carcinoma from apparently normal mucosa.

The authors state that they have no Conflict of Interest (COI).

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