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Late-onset Microsatellite-Instable Colonic Cancer of a Housewife in a Li-Fraumeni Syndrome Family Whose Father and Son Died Young from Brain Tumor

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1. Abstract

An 80-year-old Japanese housewife was right hemicolectomized for Colorectal Cancer (CRC) at 69, mastectomized for breast cancer at 53 and hysterectomized for myoma uteri at 39. Since her father and son died at 47 and at 13 of meningioma and of large cell/anaplastic (LCA) medulloblastoma (MB), respectively, they satisfied the 2015 Chompret Criteria for Li-Fraumeni Syndrome (LFS). Given the way of inheritance of the syndrome, she is the obligate heterozygote who inherited the tumor-predisposing gene from her father, transferred it to her son, and developed breast cancer herself. It is considered logical that her CRC is engendered by the same LFS-specific gene as her father's, son's, and her probable core cancers. It was a sharply circumscribed ulcerating tumor exhibiting features of high microsatellite instability (MSI-H). Her CRC and family history were not contradictory to the Revised Bethesda Guidelines for Lynch Syndrome (LS). Immunohistochemistry (IHC) showed no expression of MLH1 or PMS2. Only few large-nuclear neoplastic cells were weakly stained with p53. Genetic testing detected no pathogenic germline mutations in MMR or TP53 genes. Notwithstanding the negative result, her family is considered afflicted with LFS because they are not necessarily proven even in the classic LFS family. This case shows that CRC should be included in the LFS tumor spectrum, and that strict screening should be performed for not only early- but for late-onset tumors in the family. It also implies that such tumors might account for a certain number of MSI-H proximal CRC in the elderly diagnosed as sporadic.

2. Introduction

LFS is a rare autosomal dominant hereditary cancer-prone condition characterized by familial aggregations of a diverse spectrum of children- and adult-onset malignancies, which are caused by mutation in the TP53 tumor suppressor gene [1, 2]. The definition of the classic LFS is as follows: a family with one proband diagnosed with a sarcoma before age 45 years, plus one first degree relative with any cancer before age 45 years, and another first or second degree relative with any cancer before age 45 years or a sarcoma at any age [3]. The malignancies include such characteristic core tumors, as follows: soft-tissue sarcomas (STS), osteosarcomas (OS), adrenocortical carcinomas (ACC), central nervous system (CNS) tumors, and very early-onset female breast cancers typically occurring at 30 years or younger. Thereafter Chompret et al. proposed other criteria defining the syndrome embracing broader core malignancy spectrum with less strict age limit [4] which were revised by Tinat et al. in 2009 [5] and further modified by Bougeard et al. in 2015 [6]. The most recent Chompret Criteria are as follows: Familial presentation: Proband with tumor belonging to LFS tumor spectrum (e.g., premenopausal breast cancer, STS, OS, CNS tumor, ACC) before age 46 years AND at least one first- or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 years or with multiple tumors. Multiple primitive tumors: Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 years. Rare tumors: Patient with ACC, choroid plexus tumor, or

rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history. Early-onset breast cancer: Breast cancer before age 31 years [6].

Many cases of LFS have recently been reported with more diversified, including gastrointestinal, cancers and with late-onset malignancies associated with certain TP53 genotypes [7-15]. A case of an LFS family fulfilling the 2015 version of Chompret Criteria is presented which will contribute to clarify the landscape of the syndrome

3. Case Report

An 80-year-old Japanese housewife underwent simple hysterectomy for myoma uteri at 39. She had her right breast resected for breast cancer at 53, as shown in Figure 1 which was solid tubular and papillotubular typed ductal carcinoma of no special type (NST) with the sclerotic stroma invading the adipose tissue but not the skin or fascia. Though revealed strong expression of human epidermal growth factor receptor 2 (HER 2) (score 3, 100%) as shown in Figure 2, IHC demonstrated no tumor cells positive for estrogen receptor (ER) or progesterone receptor (PgR). No lymph node metastases were detected. She underwent neither post-operative irradiation nor chemotherapy which would help provoke subsequent primary malignancies.

She was right hemicolectomized for CRC at 69 which was a sharply circumscribed ulcerating tumor measuring 25 x 25 mm in diameter surrounded by the low margin on the medial aspect of the proximal ascending colon just anal to the ileocecal valve accompanying no adenomas or polyps, as shown in Figure 3. No lymph node metastases were detected. It formed a solid tumor mass mainly composed of poorly differentiated adenocarcinoma cells invading in part into the muscularis propria infiltrated with numerous lymphocytes, as shown in Figure 4 and 5. Crohn's-like lymphocytic reaction was detected in the subserosa, suggesting high microsatellite instability (MSI-H) in the malignancy, as shown in Figure 6. No medullary growth pattern was observed neither detected were mucinous or signet ring cells, however. IHC, though showed strongly positive expression of MSH2 and MSH6 in the cancer, revealed no malignant cells immunoreactive with MLH1 antibody (Ab), as shown in Figure 7 or PMS2 Ab, as shown in Figure 8. The latter two proteins were expressed in the normal tissue around the lesion. Thus, it is suggested that this malignancy was induced by MSI due to loss of MLH1/PMS2 pair. Only few large-nuclear cancer cells were weakly stained with p53, indicating no clear somatic mutations, as shown in Figure 9.

Though her other history was noncontributory, her family history disclosed other malignancies, as shown in Figure 10. As far as she remembered, there was no consanguinity in her family. Her mother was diagnosed with gastric cancer at 75 and one of her three sisters died of hepatocellular carcinoma (HCC) with pulmonary metastasis due to hepatitis C Virus (HCV) infection at 64. Her father died of meningioma postoperatively at 47 in 1960, 9 years before LFS was first described [3] and 51 years before she was hemicolectomized under the diagnosis of CRC. His operation samples were said to have been destroyed by the Great Eastern Japan Earthquake in 2011. Her eldest son was diagnosed with LCA-MB at 12 and deceased at 13, as shown in Figure 11, 17 years after his grandfather's death and 18 years before his mother was mastectomized because of HER2-amplified ductal NST invasive carcinoma with the sclerotic stroma typical of the LFS core breast cancer [7, 8].

No pathogenic mutations were detected in the 19 exonic regions composed of ca 2,300 bases and their flanking intronic regions made up of ca 540 bases in her MLH1gene, in 16 exonic regions consisting of 2,800 bases and their flanking intronic regions composed of ca 450 bases in the MSH2 gene, in 10 exonic regions composed of ca 4,100 bases and their flanking intronic regions made up of 270 bases in the MSH6 gene, in 15 exonic regions consisting of 2,700 bases and their flanking intronic regions composed of 420 bases in the PMS2 gene by the Sanger sequencing method and in the exons of MLH1, MSH2, and EPCAM genes by the multiple ligation-dependent probe amplification (MLPA) method. Neither observed were pathogenic mutations in the exonic regions 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 consisting of ca 2,400 bases and their flanking intronic regions made up of ca 300 bases of her TP53 gene by the Sanger sequencing and the MLPA methods (FALCO Biosystems, Kyoto, Japan).

She had an uneventful course thereafter and neither had recurrence of both the cancers nor developed subsequent primary malignancies until age 80. Her remaining off-springs have been reported to be cancer-free.

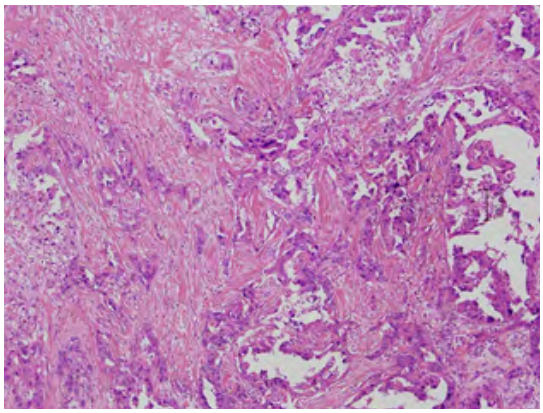

Figure 1: Microscopic picture showing NST invasive ductal breast cancer with the sclerotic stroma (H&E).

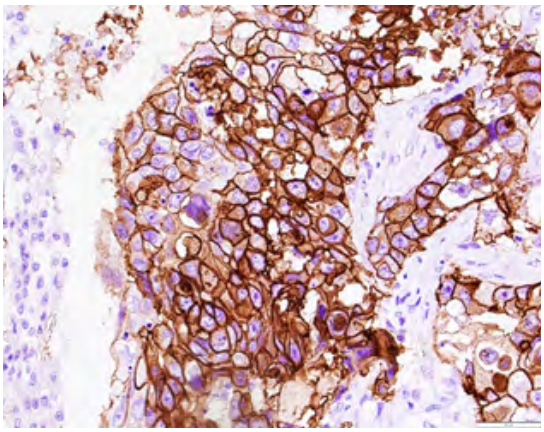

Figure 2: IHC revealing strong expression of HER2 (score 3, 100%) in the tumor (H&E).

Figure 3: Macroscopic picture of the hemicolectomized specimen showing ulcerating cancer.

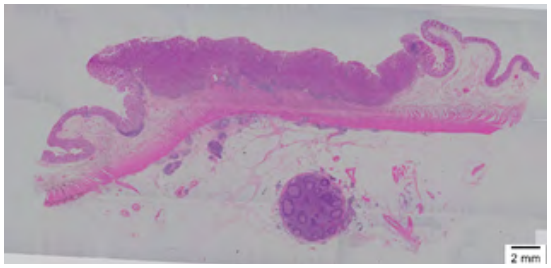

Figure 4: Low powered microscopic photograph showing the colonic cancer invading into the muscularis propria (H&E).

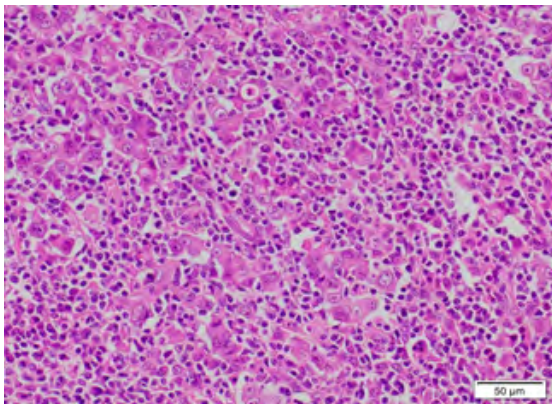

Figure 5: High powered view of poorly differentiated adenocarcinoma infiltrated with lymphocytes (H&E).

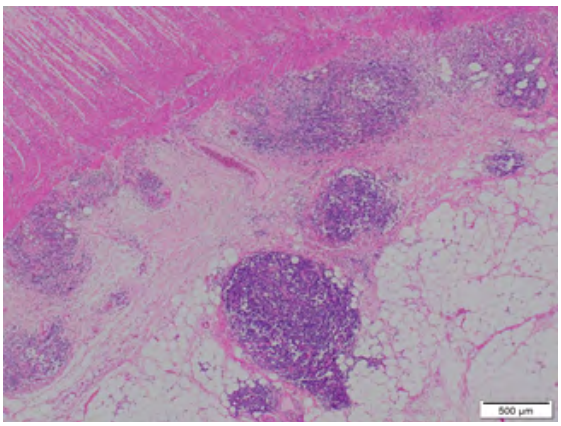

Figure 6: Microscopic photograph demonstrating Crohn's-like lymphocytic reaction (H&E).

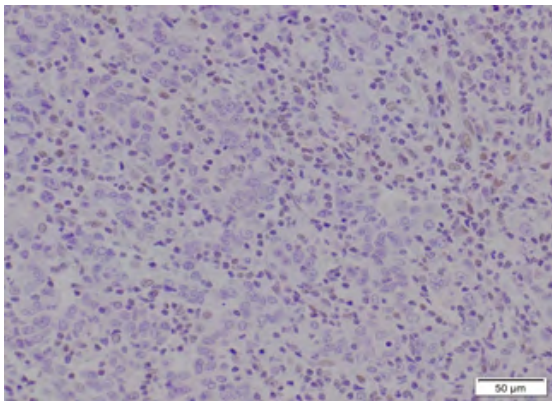

Figure 7: IHC showing no expression of MLH1 in the malignancy (H&E).

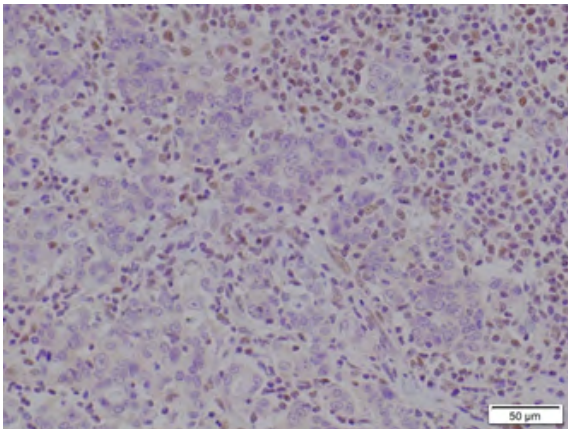

Figure 8: Microscopic photograph depicting colonic cancer without PMS2 expression (H&E).

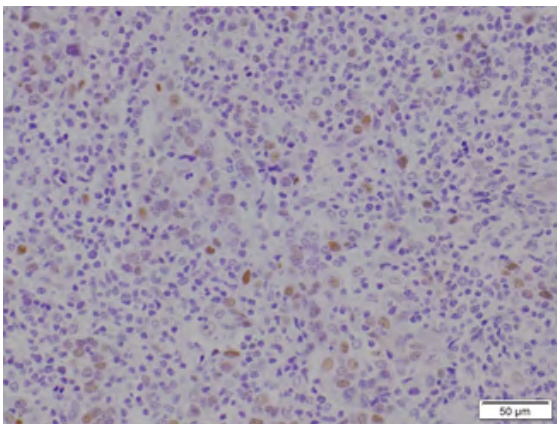

Figure 9: IHC demonstrating only few large-nuclear cancer cells weakly stained with p53 (H&E).

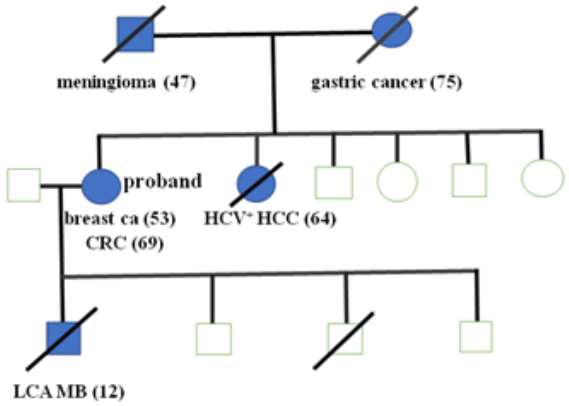

Figure 10: Pedigree of the LFS family. (age at diagnosis) ca: cancer: male: female blue: cancer-bearing white: cancer-free/: deceased

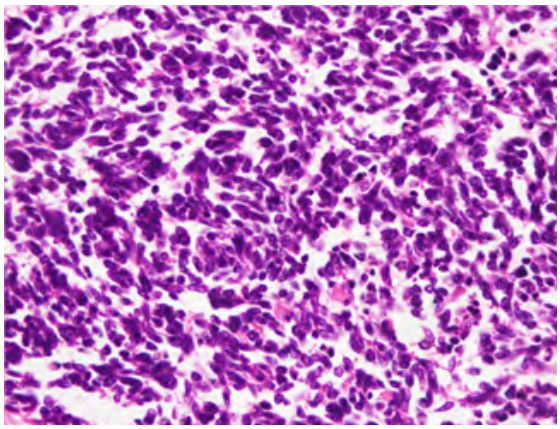

Figure 11: Microscopic picture of the autopsied brain from her son showing solidly proliferating LCA MB (H&E).

4. Discussion

LFS is an autosomal dominant cancer complex characterized by early-onset tumors, including core, in multiple affected relatives and multiple tumors in individuals, which are caused by mutation in the TP53 tumor suppressor gene [1, 2]. The syndrome which strictly fulfills the original criteria is designated the classic LFS [3] whereas Chompret proposed other criteria defining the syndrome embracing broader core malignancy spectrum with less strict age limit [4] which were thereafter revised twice [5, 6], so far. Many cases of LFS have recently been reported with more diversified, including gastrointestinal, cancers and with late-onset malignancies associated with certain TP53 genotypes [7-15].

The eldest son of the proband patient was diagnosed with CNS tumor at age 12 (before age 46 years), his maternal grandfather, second-degree relative, died of meningioma, another CNS tumor, at 47 (before age 56 years) and the proband, his mother, first-degree relative, suffered from multiple tumors one of which is probably premenopausal breast cancer coming under LFS core tumor spectrum. Her breast cancer is not only probably premenopausal but HER2-amplified, ductal NST invasive carcinoma with the sclerotic stroma typical of the malignancy detected in germline TP53 pathogenic carriers [7, 8].

Apart from the patient's mother and sister suffering from non-core cancer of LFS and virus-induced malignancy at their 8th and 7th decade, respectively, given LFS inheritance, the three-remaining cancer-afflicted family members including the proband herself must have the same cancer-predisposing gene, satisfying the first criterion, the "familial presentation", of the 2015 version of Chompret Criteria [6]. She is the obligate heterozygote LFS gene carrier who inherited the brain tumor-producing gene from her father and transferred it to her eldest son. His rapidly deteriorating tumor with LCA histology suggests childhood Sonic Hedgehog (SHH)-activated MB which shows much greater genomic instability and is characterized by frequent amplifications of oncogenes most likely due to undergoing chromothripsis and strongly associated with germline TP53 mutations [16]. It is, therefore, considered logical that her colonic cancer was engendered by the same LFS-specific genetic abnormalities as her father's, eldest son's, and her own probable (though shows histologic character typical of LFS [7, 8], uncertain whether her breast cancer is precisely premenopausal or not because of her previous hysterectomy) core cancer was.

Though did not meet the Amsterdam Criteria II for Lynch syndrome (LS) excluding brain tumor from the specific malignancies in the syndrome [17], her CRC and her eldest son's and father's CNS tumors were not contradictory to the Revised Bethesda Guidelines [18]. The possibility emerged that her tumor was induced by MSI-H due to co-abnormality in MLH1 and PMS2. The genetic testing showed no definite pathogenic mutations in the 19 exonic and their flanking intronic regions in MLH1 and in the 16 exonic and their flanking intronic regions in PMS2 by the Sanger sequencing and the MLPA methods as well as in other MMR genes, as described above. The MSI-H is, therefore, considered due to inactivation of the two through MLH1 promotor hypermethylation (19) or BRAF mutation (20, 21), as quite commonly found in sporadic CRC [19-21].

Though TP53 germline mutation was not detected in this patient, her family is considered afflicted with LFS because the mutation is not always detected even in the classic LFS family [12, 22]. This is a grand saga of an LFS family extending 51 long years in which the center of the direct lineage, the obligate heterozygote proband, developed breast cancer and CRC 35 and 51 years, respectively, after her father died of brain tumor 9 years before the first article on LFS was published [3] and 18 and 34 years, respectively, after her son died of childhood brain cancer. Such cases of LFS family as the mother developed cancer, particularly breast cancer, after her children suffered from malignancies have been reported, so far [13, 23].

Paucity of cases of CRC detected in LFS patients has rendered extensive description of the precise characteristics of the malignancy next to impossible. Yurgelun et al. reported early-onset CRCs detected in 6 germline TP53 mutation carriers in the colon cancer family registry who did not satisfy either the classic or the revised Chompret LFS criteria: the cancer in 4 cases was left sided, while

the remaining 2 carriers' tumor was undefined and the histology of all the malignancies was not described [24], whereas CRC/High Grade Dysplasia (HGD) detected in individuals with LFS having pathogenic TP53 mutations which were derived from tubulovillous and tubular adenomas and sessile serrated polyps are reported to be predominantly located in the left side colon and absent in the ascending colon [25]. Given the precursor lesions, these malignancies are considered well differentiated. On the contrary, the tumor in the present case resided in the proximal ascending colon and mainly consisted of poorly differentiated adenocarcinoma cells, showing MSI-H features, which has not yet been described in LFS, so far. Though 10% of subjects developing CRC at 40 or younger without the known hereditary cancer syndrome are reported to show MSI/abnormal MMR IHC [24], in sporadic CRC, epigenetic gene inactivation by hypermethylation of the MLH1 promotor is reported to be associated with increasing age and proximal tumor location in the bowel [19, 26]. If it had not been for very precise history taking, the present case would have simply been diagnosed as such MSI-H proximal CRC in the elderly. The accumulation of the cases of LFS CRC is expected to precisely characterize the malignancy.

LFS patients are recommended to undergo CRC screening from age 25 or 10 years prior to the first familial case of CRC [27], but such recommendations are called in doubt by some researchers [28]. Among the classic LFS registry 12.5% of the family was reported to have CRC at age younger than 50 years with a documented germline TP53 mutation, so that the classic LFS patients with the mutations are considered to have an increased susceptibility to CRC, especially early-onset one [11] and CRC is considered one of the core malignancies in LFS [11-14, 22]. The incidence of early-onset (50 years or younger) CRC/HGD is reported to be 8.6% with 3.2% diagnosed prior to age 25 in LFS patients with a confirmed pathogenic germline mutation in TP53 in a clinically well annotated cohort so that it is suggested that, considering the improved outcomes with early detection, a subset of LFS patients, especially pediatric ones who received abdominal irradiation, at an increased risk to develop CRC at a young age should undergo earlier CRC screening [15].

A case in the LFS registry is reported of a confirmed TP 53 mutation carrier with a history of pancreatic cancer and non-Hodgkin lymphoma who was diagnosed with documented gastric cancer at age as old as 74 [14]. The present case shows that colonic cancer should be included in the LFS core tumor spectrum and that strict screening should be performed for not only early- but for late-onset tumors in the cancer family. It also implies the possibility that certain cases of LFS CRC might be entailed among MSI-H right side colon cancer in the elderly hitherto erroneously regarded as sporadic.

5. Conclusion

The late-onset MSI-H CRC presented above is a malignancy occurring in an obligate heterozygote of LFS. It shows that CRC should be included in the LFS core tumor spectrum, implying the possibility that MSI-H CRC in the elderly like hers would have erroneously been diagnosed as simply sporadic right side colon cancer but for very precise examination and that strict screening should be performed for not only early- but for late-onset tumors in the cancer family.

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