

Rectal Cancer Associated with Li-Fraumeni Syndrome.

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Abbreviations:

LFS: Li- Fraumeni Syndrome; MAPK: Mitogen-Activated Protein Kinase Pathway; PI3K/AKT: Phosphatidylinositol 3-kinase/Protein Kinase B Pathway; TP53: Tumor Protein p53;

ECOG: Eastern Cooperative Oncology Group Performance Status Scale; CA19-9: Carbohydrate Antigen 19-9;

CEA: Carcinoembryonic Antigen; APC: Adenomatous Polyposis Coli Gene; EGFR: Epidermal Growth Factor Receptor; BRAF V600E: Substitution Mutation at Codon 600 of the BRAF Gene (Valine to Glutamic Acid).

NRAS: Neuroblastoma RAS Viral Oncogene Homolog; KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog; NGS: Next-Generation Sequencing;

FOLFOX: Chemotherapy Regimen Based on Oxaliplatin; Leucovorin and 5-Fluorouracil; FOLFIRI: Chemotherapy Regimen Based on Irinotecan;

Leucovorin and 5-Fluorouracil; CAPEOX: Chemotherapy Regimen Based on Capecitabine and Oxaliplatin; H&E: Hematoxylin and Eosin staining;

MMR: Mismatch Repair System. MLH1: MutL Homolog 1 Gene; PMS2: Postmeiotic Segregation Increased 2 Gene; MSH2: MutS Homolog 2 Gene;

MSH6: MutS Homolog 6 Gene

1. Abstract

1.1. Background and Clinical Significance

Li-Fraumeni syndrome (LFS) is a rare hereditary cancer predisposition caused by germline TP53 mutations, associated with early-onset aggressive neoplasms. Although colorectal cancer is uncommon in LFS, its occurrence in young patients highlights the need for vigilance. This case report documents recto-sigmoid adenocarcinoma in a 19-year-old Latin American male, expanding the clinical spectrum of LFS in this population. Case Presentation: The patient, with a maternal history of breast carcinoma, was diagnosed with moderately differentiated adenocarcinoma of the

sigmoid colon. Molecular testing revealed a pathogenic TP53 variant consistent with LFS and a KRAS mutation. Imaging demonstrated locally advanced recto-sigmoid disease with bladder infiltration, bilateral hydronephrosis, and metastatic lymphadenopathy. Initial treatment with CAPEOX plus bevacizumab was followed by maintenance therapy. Due to progression and contraindication of radiotherapy in TP53 mutation carriers, therapy was escalated to FOLFIRI, achieving favorable clinical response. Tumor markers (CEA, CA 19-9) showed fluctuating elevations with subsequent decline, correlating with treatment efficacy. Conclusions: This case underscores the importance of considering LFS in young patients

with colorectal cancer and family history of multiple neoplasms. It highlights the need for personalized therapeutic strategies, avoidance of radiotherapy, and implementation of intensive surveillance protocols including colonoscopy and whole-body MRI. The report contributes novel evidence from Latin America, reinforcing the role of genetic counseling and multidisciplinary management in hereditary cancer syndromes.

2. Introduction and Clinical Importance

Li-Fraumeni syndrome (LFS) is a hereditary cancer predisposition syndrome caused by germline mutations in the TP53 gene, which encodes the p53 protein, a key regulator of the cell cycle and apoptosis. Affected individuals have an exceptionally high lifetime risk of developing cancer, approaching 100% in women and 75% in men by the age of 70 years. Disruption of the p53 molecular pathway leads to genomic instability, impaired cell-cycle regulation, and an increased susceptibility to multiple malignancies. Although the most characteristic tumors include sarcomas, breast cancer, and brain tumors, cases of colorectal and rectal cancer have also been reported in young patients with LFS, as well as leukemia, gastric cancer, lung cancer, and melanoma [1,2].

LFS is a rare disorder, with an estimated prevalence of approximately 1 in 20,000 individuals [2]. Colorectal cancer accounts for less than 5% of tumors associated with LFS; however, its incidence is significantly higher than that observed in the general population and typically occurs at an early age (<30 years) [3,4]. Isolated cases of rectal adenocarcinoma have been reported in Japan and Latin America [5,6].

The p53 protein, encoded by the TP53 tumor suppressor gene, plays an essential role in maintaining genomic integrity by acting as a key regulator of the cell cycle, DNA repair, and apoptosis. Its function as the “guardian of the genome” is reflected in its ability to induce cell-cycle arrest in response to genetic damage, thereby allowing DNA repair or, in cases of irreparable damage, promoting programmed cell death to prevent the propagation of potentially neoplastic cells [7].

In the context of LFS, an autosomal dominant hereditary disorder, germline TP53 mutations lead to a loss of p53 function. This dysfunction compromises genomic surveillance mechanisms, facilitating the survival and proliferation of cells harboring cumulative genetic alterations. As a result, the risk of developing malignant neoplasms in multiple organs is significantly increased, often at an early age and following a characteristic familial inheritance pattern [8].

Particularly within the rectal mucosa, p53 inactivation promotes the accelerated progression of precursor lesions, such as adenomas, toward invasive colorectal adenocarcinoma. This phenomenon is attributed to the inability of cells to arrest the cell cycle in response to genetic damage, thereby fostering increased genomic instability and the accumulation of additional somatic mutations. Recent studies have demonstrated that, in patients with LFS, this carcinogenic pathway may be significantly accelerated, highlighting the need for intensive surveillance strategies and early detection

protocols in this high-risk population [1,2,9].

The most common germline TP53 mutations associated with LFS include p.R175H, p.R248Q, and p.R273H, all of which are located within the DNA-binding domain, a region critical for the transcriptional function of the p53 protein. Additional alterations involving genes such as APC, EGFR, BRAF, and PI3K have also been reported [7,10].

These structural alterations impair the ability of p53 to activate tumor suppressor genes, resulting in genomic instability, defective apoptosis, and an increased propensity for the accumulation of somatic mutations. Furthermore, some of these variants have been reported to confer gain-of-function properties, promoting the aberrant activation of proliferative signaling pathways such as MAPK and PI3K/AKT, which enhance cell survival, angiogenesis, and evasion of cell-cycle control mechanisms [1].

Rectal tumors associated with LFS exhibit particularly aggressive behavior, characterized by rapid progression from precursor lesions to invasive adenocarcinomas, high recurrence rates, and a tendency toward early metastasis [11,12].

These findings explain the high morbidity and mortality observed in patients carrying TP53 mutations and underscore the need for intensive surveillance strategies, early detection protocols, and personalized therapeutic approaches that take into account the underlying molecular biology of these tumors. Approximately 95% of classic LFS cases result from heterozygous pathogenic germline variants in TP53, whereas the remaining 5% involve CHEK2 variants or remain genetically unexplained [1,2,4,7,11,12].

The clinical presentation of rectal cancer associated with LFS is characterized by digestive symptoms such as persistent rectal bleeding, changes in bowel habits (diarrhea, constipation, or alternating patterns), chronic abdominal pain, and signs of iron-deficiency anemia secondary to occult or overt gastrointestinal bleeding in young patients. Although these findings are common in colorectal disease, they acquire particular significance in individuals with a family history of multiple neoplasms, which should prompt clinicians to suspect an underlying hereditary cancer predisposition syndrome [5,13].

In numerous cases, rectal cancer constitutes the first clinical manifestation leading to the diagnosis of LFS, serving as a key indicator for the identification of germline TP53 mutations and the implementation of genetic and oncologic surveillance protocols in at-risk family members. Furthermore, these tumors exhibit aggressive biological behavior, characterized by rapid progression, high rates of local recurrence, and early development of systemic metastases, resulting in an unfavorable prognosis and underscoring the need for early detection strategies and intensive follow-up [2,4].

The treatment of rectal cancer in patients with Li-Fraumeni syndrome (LFS) is primarily based on oncologic surgical resection with adequate margins, which constitutes the cornerstone of initial therapy [5,14].

Systemic chemotherapy is administered according to standard colorectal cancer treatment protocols; however, it should be used with

caution due to the potential risk of inducing secondary primary malignancies. The most commonly used regimens include FOLF-
OX (oxaliplatin, leucovorin, and 5-fluorouracil), administered every 2 weeks for 8 to 12 cycles, and CAPEOX (oxaliplatin and oral capecitabine), administered every 3 weeks for 6 to 8 cycles, with treatment adjustments based on response and toxicity [2,8,15,16].

The FOLFIRI regimen (irinotecan, leucovorin, and 5-fluorouracil) is also used, particularly in advanced disease or as an alternative following disease progression, with a typical duration of 8 to 12 cycles, although treatment may be extended depending on patient tolerance and tumor control. The use of radiotherapy remains controversial because it may increase the risk of secondary malignancies due to the inability of cells harboring TP53 mutations to adequately repair DNA damage. Therefore, radiotherapy should be employed with caution, given the elevated risk of radiation-induced secondary neoplasms in carriers of germline TP53 mutations [17-19].

Finally, genetic counseling is essential for both patients and their family members, enabling the implementation of intensive surveillance protocols and personalized prevention strategies [20].

The prognosis of rectal cancer in patients with Li-Fraumeni syndrome (LFS) is generally unfavorable due to the high rate of local recurrence and the frequent occurrence of new primary tumors in different organs, resulting from the genomic instability associated with germline TP53 mutations [1].

Histopathological examination reveals, at low magnification, colonic mucosa with complex glandular architecture transitioning into an infiltrative neoplastic proliferation, characterized by irregular glands embedded within a desmoplastic stroma, intraluminal mucinous content, and an associated fibroinflammatory stromal reaction. At higher magnification, neoplastic glands lined by columnar epithelium with moderate to marked nuclear atypia, hyperchromasia, and pseudostratification can be identified [25,26,27,30,33].

Immunohistochemical analysis demonstrates loss of expression of mismatch repair (MMR) proteins, including MLH1, PMS2, MSH2, and MSH6 [28,29,31,32].

Compared with patients without a genetic predisposition, overall survival is lower, reflecting both the biological aggressiveness of these tumors and the multiplicity of neoplasms that may develop throughout life. This clinical scenario underscores the need for intensive surveillance strategies, early detection protocols, and a multidisciplinary approach integrating oncologic surgery, systemic therapies, and genetic counseling for affected patients and at-risk family members [2,11,18,20,21].

International guidelines for the management of Li-Fraumeni syndrome (LFS) recommend intensive and multidisciplinary surveillance because of the high risk of multiple and early-onset malignancies. In the context of colorectal cancer, colonoscopy is recommended every 2–3 years beginning at 25 years of age, or earlier in the presence of a family history of early-onset colorectal cancer, with the aim of detecting precursor lesions and tumors at an early stage [2,22,23].

In addition, the incorporation of annual whole-body magnetic resonance imaging (MRI), a noninvasive and radiation-free technique, is recommended for the detection of synchronous or metachronous tumors in different organs. This approach has been shown to improve survival through earlier diagnosis [23]. Additionally, genetic counseling and predictive testing in family members are essential for identifying carriers of germline TP53 mutations, establishing personalized surveillance protocols, and providing prevention strategies tailored to each individual case [23,24].

3. Presentación de Caso Clínico

A 19-year-old male patient with a history of sigmoid colon adenocarcinoma, without known comorbidities or toxic habits, presented with a significant family history of cancer. His mother had died from breast carcinoma, although the age at diagnosis and death was unknown.

The clinical course began with a diagnosis of sigmoid colon adenocarcinoma, which was surgically treated in November 2023 with a sigmoidectomy and end colostomy. The patient did not receive initial adjuvant chemotherapy due to a family decision. Subsequently, he was readmitted for oncologic evaluation, where clinical and radiological evidence of tumor progression was identified. He was assessed by the surgical oncology team, which determined the presence of an unresectable tumor mass located approximately 6 cm from the anal verge. Consequently, systemic therapy was initiated.

At admission, the patient was clinically stable and asymptomatic, with an ECOG performance status of 0 and a Glasgow Coma Scale score of 15. He had a functioning colostomy and patent bilateral percutaneous nephrostomy tubes. Tumor markers demonstrated temporal variation, with intermittent elevations in carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9). Peak values reached 16.9 ng/mL for CEA (Figure 2) and 102 U/mL for CA 19-9 (Figure 1), followed by a subsequent decline during treatment (Figure 1, Table 1).

Molecular profiling revealed a KRAS mutation in codons 12/13, while BRAF V600 and NRAS were found to be wild type. A next-generation sequencing (NGS) panel for hereditary cancer predisposition identified a likely pathogenic variant in the TP53 gene, consistent with autosomal dominant Li-Fraumeni syndrome. Copy number variant (CNV) analysis could not be performed.

Histopathological review (Figure 3, Figure 4) confirmed a moderately differentiated sigmoid colon adenocarcinoma with mucinous areas and ulceration, measuring 6 × 3 cm, causing 95% luminal obstruction. The tumor extended into the subserosa and was associated with tumor perforation. Lymphovascular invasion was present, while perineural invasion was absent. Four negative lymph nodes and four tumor deposits were identified, resulting in a pathological stage of pT3 pN1c. Microsatellite instability was considered unlikely.

Imaging studies, including computed tomography (CT) and magnetic resonance imaging (MRI), revealed a large rectosigmoid mass with infiltration of the mesorectal fascia, bladder involvement,

metastatic mesorectal and extramesorectal lymphadenopathy, and bilateral hydronephrosis secondary to tumor infiltration. These findings were consistent with advanced, unresectable locoregional disease, without clear evidence of hepatic metastases. Small non-specific pulmonary nodules were also identified. The patient initially received CAPEOX chemotherapy (capecitabine and oxaliplatin) for eight cycles. Bevacizumab was added

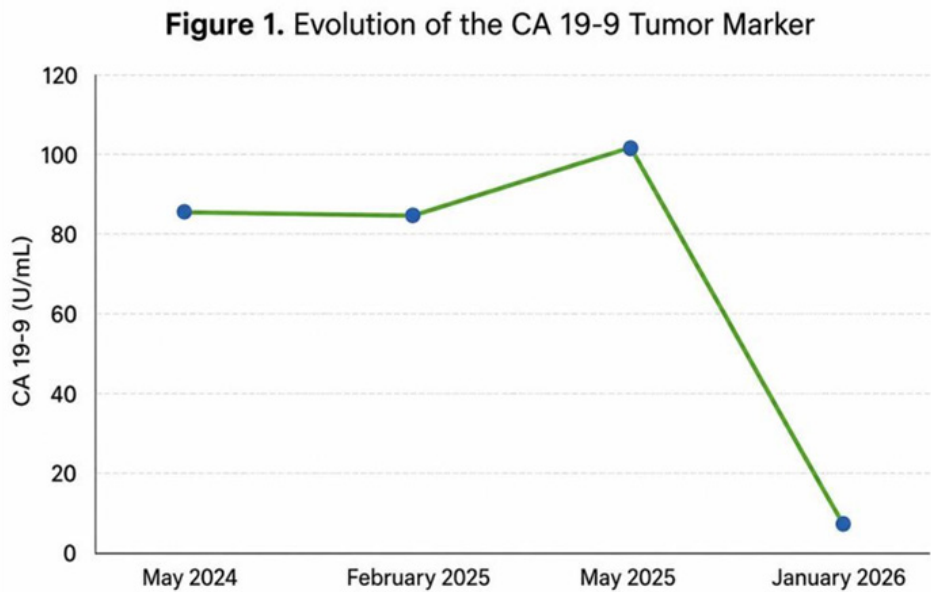


Figure 1: Evolution of the CA 19-9 tumor marker between May 2024 and January 2026. Initial stability was observed, followed by an increase in May 2025 and a marked decline in January 2026.

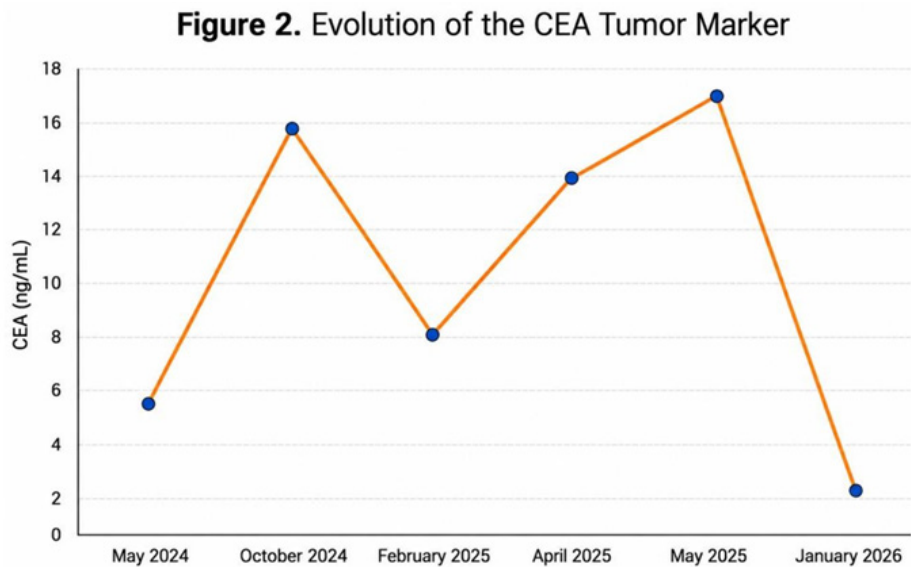


Figure 2: Evolution of the CEA tumor marker between May 2024 and January 2026. A fluctuating pattern was observed, with peaks in October 2024 and May 2025, followed by a significant decline in January 2026.

Table 1: Temporal evolution of tumoral markers CA 19-9 y CEA from may 2024 to january 2026.

	CEA	CA 19.9
May 2024	5,62	85,5
October 2024	15,7	Not measured
February 2025	8,03	84,5
April 2025	14,1	Not measured
May 2025	16,9	102
January 2026	2,18	8,29

In table 1, Temporal evolution of tumoral markers CA 19-9 y CEA from may 2024 to january 2026, it is evidenced the progressive elevation of the markers throughout time, with peaks at 2025 followed by a marked fall in 2026.

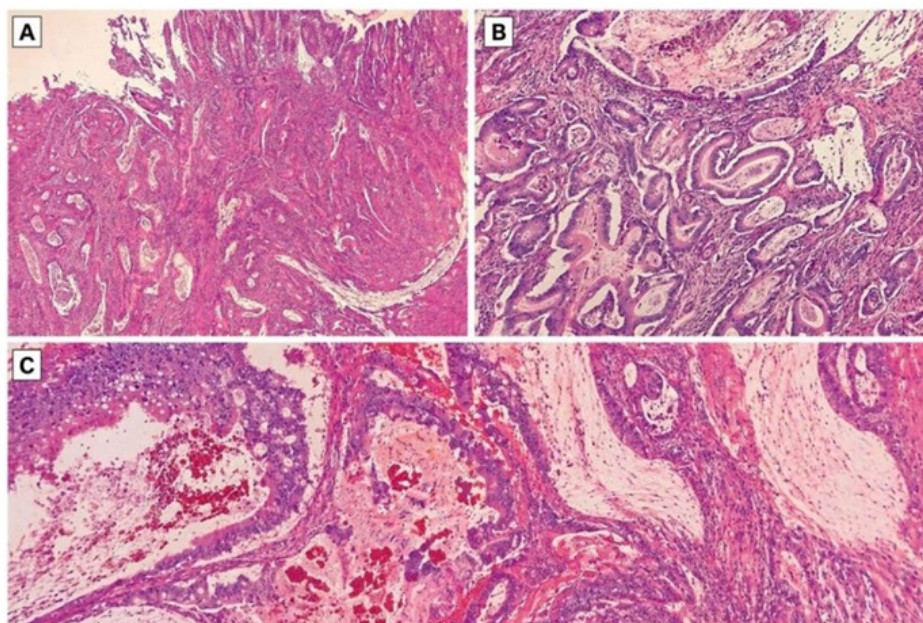


Figure 3: Microscopic description. (A) Panoramic view showing colonic mucosa with complex glandular architecture and transition toward an infiltrating neoplastic proliferation, characterized by irregular glands embedded in a desmoplastic stroma. (H&E, low magnification). (B) Intermediate field demonstrating a complex glandular pattern with irregular lumina, intraluminal mucinous content, and associated fibroinflammatory stromal reaction. (H&E, intermediate magnification). (C) At higher magnification, neoplastic glands lined by columnar epithelium with moderate to marked nuclear atypia, hyperchromasia, and pseudostratification are identified. (H&E, high magnification). Detail of tumor invasion with glands infiltrating the stroma (MUCIN), in whose dilated lumina necrotic debris and foci of intratumoral hemorrhage accompanied by mucin are observed. (H&E, high magnification).

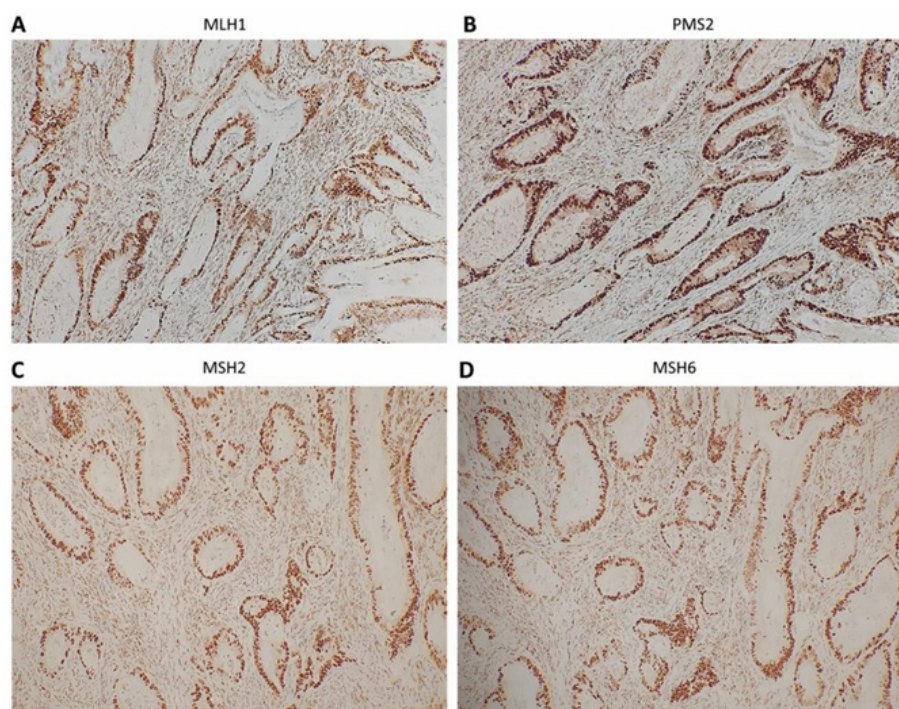


Figure 4: Immunohistochemical study. Immunohistochemistry for mismatch repair (MMR) proteins in sigmoid colon adenocarcinoma. (A) MLH1, (B) PMS2, (C) MSH2, and (D) MSH6 show preserved nuclear expression in tumor cells, with appropriate positivity in non-neoplastic cells serving as an internal control. These findings are consistent with mismatch repair proficiency (pMMR).

during the ninth cycle due to the presence of a KRAS mutation, followed by maintenance therapy with capecitabine plus bevacizumab until April 2025. The patient had also previously undergone radiotherapy. Following multidisciplinary reassessment, considering both tumor progression and the diagnosis of LFS, further radiotherapy was contraindicated, and treatment was escalated to the FOLFIRI regimen (irinotecan, leucovorin, and 5-fluorouracil). Bevacizumab was subsequently discontinued because of the development of a rectovesical fistula. The patient completed 12 cycles of FOLFIRI chemotherapy with favorable clinical evolution. Final staging was established as T3N1cM0, corresponding to clinical stage IIIB disease.

4. Discussion

The present case describes a 19-year-old male patient with a history of sigmoid colon adenocarcinoma and rectosigmoid tumor progression in the context of a hereditary cancer predisposition syndrome confirmed by the identification of a likely pathogenic TP53 variant, consistent with Li-Fraumeni syndrome (LFS). The early age at presentation, together with the family history of breast carcinoma, reinforces the clinical suspicion of LFS and underscores the importance of genetic counseling and intensive surveillance in at-risk family members.

Tumor molecular profiling revealed a KRAS mutation in codons 12/13, while BRAF and NRAS were wild type. These findings influenced therapeutic decision-making and supported the incorporation of bevacizumab into the treatment regimen. Histopathological examination confirmed a moderately differentiated adenocarcinoma with lymphovascular invasion and a pathological stage of pT3 pN1c, findings that explain the aggressive clinical behavior characterized by bladder infiltration, bilateral hydronephrosis, and metastatic lymphadenopathy. These observations are consistent with reports in the literature, where rectal tumors associated with LFS exhibit rapid progression, high recurrence rates, and a tendency toward early metastasis.

The therapeutic management included standard regimens such as CAPEOX and later FOLFIRI, with a favorable clinical response, demonstrating the utility of conventional treatment protocols adjusted to the tumor's molecular biology. However, the contraindication of radiotherapy in carriers of germline TP53 mutations highlights the need to adapt therapeutic protocols to genetic predisposition, in order to avoid the risk of radiation-induced secondary malignancies.

This case provides relevant evidence by documenting the presentation of rectosigmoid cancer in a young Latin American patient with LFS, expanding the description of the clinical manifestations of this syndrome in populations from the region. It also emphasizes the importance of early clinical suspicion, the implementation of intensive screening strategies such as periodic colonoscopy and annual whole-body magnetic resonance imaging, as well as mandatory genetic counseling for patients and their relatives. This report contributes to scientific knowledge by highlighting the need for personalized therapeutic approaches and multidisciplinary surveillance in individuals carrying germline TP53 mutations.

Cancer surveillance for individuals with a pathogenic TP53 variant is a fundamental pillar in the management of this condition. Protocols such as the "Toronto Protocol," implemented in Canada and the United States, have established that continuous surveillance improves survival rates in affected individuals. Subsequently, several countries-initiated cancer surveillance programs, and currently, six countries are using 12 cancer surveillance programs. These surveillance strategies would be beneficial if implemented in our region.

Regarding treatment, although the risks of primary or treatment-induced malignancies resulting from exposure to diagnostic or therapeutic radiotherapy, or genotoxic chemotherapy, have not been definitively established, they are likely related to factors beyond the mutation itself, such as the therapeutic dose used, the field of exposure, the specific TP53 variant, the tissue being targeted, and even the age at the time of exposure. Therefore, exposure should be avoided whenever possible; however, necessary diagnostic imaging and therapies should not be omitted if they are required to achieve better patient survival. (Hyperfractionated doses versus conventional fractionation, stricter constraints, or smaller doses per fraction during radiotherapy do not protect normal tissues with dysfunctional p53.)

5. Conclusions

Li-Fraumeni syndrome (LFS) should be considered as a differential diagnosis in young patients with colorectal cancer, particularly when there is a family history of multiple neoplasms. The identification of a likely pathogenic TP53 variant, together with the presence of a KRAS mutation, helped guide the therapeutic approach and underscored the need for personalized strategies that integrate tumor molecular biology into clinical decision-making.

The patient's clinical course, with a favorable response to conventional chemotherapy regimens such as CAPEOX and FOLFIRI, demonstrates that management must be flexible and multidisciplinary, adapting to tumor aggressiveness and to the inherent limitations of LFS, such as the contraindication of radiotherapy due to the risk of secondary malignancies. This scenario reflects the inherent uncertainty in treating patients with genetic predisposition syndromes and highlights the need for individualized treatment protocols.

This case provides scientific novelty by documenting the presentation of rectosigmoid cancer in a Latin American patient with LFS, expanding the evidence on the clinical manifestations of this syndrome in the region. It also clarifies debatable aspects such as therapeutic selection in the presence of specific mutations and the relevance of intensive surveillance programs.

This report emphasizes the need for mandatory genetic counseling, the implementation of periodic colonoscopy and annual whole-body magnetic resonance imaging as early detection strategies, and the integration of multidisciplinary teams in the management of patients with hereditary cancer predisposition. Finally, it looks toward the future, recommending the development of research lines aimed at optimizing personalized therapies and evaluating the effectiveness of intensive surveillance programs in carriers of germline TP53 mutations.

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