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Clinical, endoscopic, histopathological, and molecular characteristics of lynch syndrome–associated colorectal cancer: a retrospective cohort study from a Mexican Tertiary Center

Abstract

Background: Lynch syndrome (LS) accounts for 3–5% of colorectal cancers and is characterized by mismatch repair (MMR) deficiency and microsatellite instability (MSI), leading to accelerated tumorigenesis[1–3]. Latin American data remain limited.

Aim: To characterize the clinical, endoscopic, histopathological, and molecular features of LS-associated colorectal cancer (CRC) in a Mexican tertiary referral center.

Methods: This retrospective cohort included 36 patients with confirmed LS-associated CRC identified within a registry of 117 individuals under LS surveillance. Clinical, endoscopic, histologic, molecular, and oncologic outcomes were analyzed descriptively.

Results: Mean age at CRC diagnosis was 42.9 years. Right-sided tumors predominated (58.3%). Common presentations included bleeding (66.7%) and anemia (66.7%). Most tumors were moderately differentiated adenocarcinomas; mucinous histology was present in 27.8%. dMMR was observed in 63.9%, MSI in 61.1%. MLH1 was the most frequent germline variant (58.3%). Extracolonic malignancies were documented in 47.2% of the overall Lynch syndrome cohort and in 36.1% of LS-CRC patients; additionally, 27.8% of LS-CRC patients developed metachronous CRC. Only one LS-related death occurred.

Conclusion: LS-associated CRC in this cohort exhibited early onset, right-sided predominance, high MSI/dMMR rates, and high metachronous and extracolonic cancer burden. These findings support intensified surveillance and genetic evaluation in LS populations.

Keywords: Lynch syndrome, colorectal cancer, mismatch repair deficiency, microsatellite instability, hereditary cancer, Mexico

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Introduction

Lynch syndrome (LS) is the most common hereditary colorectal cancer syndrome, caused by germline pathogenic variants in the mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2.[1-3] Defective MMR (dMMR) results in microsatellite instability (MSI), a hallmark of LS-associated tumors.[4,5] LS accounts for 3–5% of all colorectal cancers and exhibits early onset, proximal predominance, and accelerated adenoma-to-carcinoma progression.[6-9] LS is also associated with elevated lifetime risk of extracolonic cancers, including endometrial, gastric, ovarian, urothelial, pancreatic, biliary, brain, and sebaceous neoplasms.[10-12] Surveillance guidelines from NCCN,[13] the US Multi-Society Task Force,[14] and the InSiGHT consortium[15] emphasize early colonoscopic screening and individualized risk-based management.

Despite extensive characterization in Western populations, Latin American data remain scarce, with potential genomic and environmental differences affecting phenotype.[16-18] This study aims to provide a comprehensive characterization of LS-associated CRC in a major Mexican tertiary referral center, integrating clinical, endoscopic, histological, and molecular features.

Methods

Study design and setting

A retrospective cohort study was conducted at the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" (INCMNSZ), Mexico City.

Patient selection

From 117 individuals under LS surveillance, 36 patients with confirmed LS-associated CRC were included. LS diagnosis was established through germline pathogenic variant testing in MMR genes, and tumor dMMR/MSI results were reviewed as part of the molecular characterization.

Variables collected

Clinical data, endoscopic findings, histopathological features, molecular testing, and oncologic outcomes were extracted from electronic records.

Statistical analysis

Descriptive statistics were performed using IBM SPSS. Continuous variables were summarized as means and medians; categorical variables as counts and percentages.

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Ethics

Approved by the institutional ethics committee.

Results

Clinical characteristics

Among 117 LS patients, 36 (30.8%) developed CRC. Mean age at diagnosis was 42.9 years. The most common presenting features were lower gastrointestinal bleeding and anemia. A family history of LS-associated cancer was present in 86.1%. Early-onset disease was prominent, with 69.4% of patients diagnosed before the age of 50, with no relevant difference between sexes (70.6% in men vs. 68.4% in women) (Table 1).

Table 1 Summarizes baseline clinical characteristics

Characteristic	Value
General	
Total LS patients in institutional registry	117
Patients with colorectal cancer (LS-CRC)	36
Age at CRC diagnosis, years	Mean 42.9 ± 12.2; Median 41 (range 17–74)
Sex	Female: 19 (52.8%); Male: 17 (47.2%)
Family history	
First-degree relative with LS-associated cancer	Yes: 31 (86.1%); No: 4 (11.1%); Not available: 1 (2.8%)
Presenting symptoms	
Lower GI bleeding	24 (66.7%)
Anemia	24 (66.7%)
Change in bowel habits	23 (63.9%)
Weight loss	17 (47.2%)
Abdominal pain	16 (44.4%)
Acute abdomen	5 (13.9%)
Positive fecal occult blood test	1 (2.8%)
Positive FIT	1 (2.8%)
Metabolic and cardiovascular comorbidities	
Metabolic syndrome components	13 (36.1%)
Overweight	3 (8.3%)
Obesity	5 (13.9%)
Dyslipidemia	4 (11.1%)
Hypertension	4 (11.1%)
Diabetes mellitus	4 (11.1%)
Lifestyle factors	
Current or former smoking	8 (22.2%)
Alcohol consumption	2 (5.6%)

Endoscopic characteristics

Right-sided CRC predominated (58.3%). Endoscopic morphology was heterogeneous, as summarized in Table 2. Therapeutic endoscopy was attempted in 30.6% of cases; however, complete resection was frequently limited by submucosal fibrosis.

Histopathological findings

Most tumors were moderately differentiated (58.3%), with mucinous features (27.8%) and poor differentiation in 25%. Vascular invasion was present in 36.1%, perineural invasion in 8.3%.

Table 2 Summarizes endoscopic features

Characteristic	Value
Tumor location	
Right colon	21 (58.3%)
Left colon	13 (36.1%)
Synchronous tumors	2 (5.6%)
Tumor size (mm)	
Right colon (n=17)	Height: mean 44 (median 54; range 10–83); Extension: mean 54 (median 54; range 10–100)
Left colon (n=10)	Height: mean 22 (median 23; range 10–30); Extension: mean 33 (median 25; range 10–80)
Endoscopic morphology (general)	
Obstructing	6 (16.7%)
Ulcerated	6 (16.7%)
Stenosing	6 (16.7%)
Infiltrative	5 (13.9%)
Friable	4 (11.1%)
Indurated	3 (8.3%)
Tubulovillous	3 (8.3%)
Adenomatous	2 (5.6%)
Irregular	2 (5.6%)
Circumferential	2 (5.6%)
Amorphous	2 (5.6%)
Nodular	1 (2.8%)
Giant pedunculated	1 (2.8%)
Paris classification	
0-Is	15 (41.7%)
0-Is + 0-III	4 (11.1%)
0-Ip	4 (11.1%)
0-Is + 0-Ip	1 (2.8%)
Not available	12 (33.3%)
Endoscopic therapy performed	
Yes	11 (30.6%)
No	22 (61.1%)
Type of endoscopic therapy	
Non-lifting due to fibrosis	5 (13.9%)
Complete endoscopic resection	4 (11.1%)
Positive margins / invasive	2 (5.6%)
Not attempted	25 (69.4%)

Molecular findings

Germline variants included:

MLH1: 58.3%,

MSH2: 27.8%,

MSH6: 11.1%,

PMS2: 2.8%.

dMMR was detected in 63.9%. MSI was positive in 61.1%. Concordance between genotype and IHC patterns followed classic associations.

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Extracolonic malignancies and outcomes

In the LS-CRC cohort, extracolonic malignancies were observed in 13 of 36 patients (36.1%), with a higher frequency in women compared to men (42.1% vs. 29.4%). Age distribution was comparable between sexes, with early-onset disease (<50 years) observed in 69.4%. Sex-specific patterns of extracolonic malignancies were observed. Women more frequently developed tumors within the classical Lynch syndrome spectrum, including endometrial and ovarian cancers, while men showed a predominance of non-classical extracolonic malignancies, particularly cutaneous and lymphoproliferative tumors. Gastric cancer was observed in both sexes, with a higher frequency in women (66.7% vs. 33.3%). In the overall institutional Lynch syndrome cohort, extracolonic malignancies were documented in 47.2% of patients, including endometrial, gastric, sebaceous skin tumors, lymphoma, thyroid, ovarian, pancreatic, brain, biliary, and renal cancers. Metachronous CRC developed in 27.8% (median 48 months). One LS-related death occurred (Table 3,4).

Table 3 Summarizes age distribution and extracolonic malignancies by sex in LS-CRC patients

Characteristic	Overall (n=36)	Female (n=19)	Male (n=17)
Age <50 years	25 (69.4%)	13 (68.4%)	12 (70.6%)
Extracolonic malignancies	13 (36.1%)	8 (42.1%)	5 (29.4%)

Table 4 Details the distribution of extracolonic malignancies by sex in LS-CRC patients

Tumor type	Total (n)	Female n (%) within tumor type	Male n (%) within tumor type
Endometrial	3	100%	0%
Ovarian	1	100%	0%
Gastric	3	66.70%	33.30%
Skin	3	33.30%	66.70%
Lymphoma	3	33.30%	66.70%
Thyroid	2	100%	0%
Pancreatic	1	100%	0%
Biliary	1	100%	0%
Renal	1	0%	100%
Brain	1	0%	100%

Discussion

This study provides a detailed characterization of LS-associated CRC in a Mexican tertiary referral cohort. The findings align with international patterns of early-onset disease, proximal predominance, and molecular signatures of dMMR/MSI.[3-8] The high proportion of extracolonic cancers observed in the overall Lynch syndrome cohort (47.2%) reflects the multisystemic nature of LS, consistent with global data.[10-12] In the LS-CRC subgroup, extracolonic malignancies were identified in 36.1% of patients, suggesting a substantial burden even among individuals already affected by colorectal cancer. Rates of metachronous CRC (27.8%) further emphasize the importance of intensive surveillance, consistent with recommendations from NCCN[13] and USMSTF[14] advocating 1–2 year colonoscopy intervals.

The predominance of MLH1 and MSH2 mutations parallels global registries[15-18] but also reflects regional founder variants described in Mexican cohorts.[19] Histologically, mucinous and poorly differentiated patterns reflect classical LS tumor biology.[20,21] The proportion of early-onset CRC in our cohort (69.4% <50 years) exceeds previously reported rates of approximately 58% in Mexican-Mestizo populations,[19] reinforcing the aggressive and early presentation of LS-associated malignancies. No significant differences were observed between sexes.

Extracolonic malignancies were more frequent in women than in men, and distinct sex-related patterns were observed. Women more frequently developed tumors within the classical Lynch syndrome spectrum, whereas men showed a higher proportion of non-classical extracolonic malignancies, including cutaneous and lymphoproliferative tumors. These findings are consistent with those reported by Arteaga et al. in a Mexican-Mestizo population,[19] suggesting a reproducible sex-associated variation in tumor distribution within Latin American Lynch syndrome cohorts. This pattern supports the need for individualized surveillance strategies beyond standard organ-based risk models.

The molecular landscape of LS-associated CRC has important therapeutic implications, particularly given the high prevalence of MSI/dMMR tumors, which are associated with increased tumor mutational burden and enhanced responsiveness to immune checkpoint inhibitors, as demonstrated in pivotal trials such as KEYNOTE-177 and CheckMate-142.[23,24] This has transformed the management of advanced disease, positioning immunotherapy as a cornerstone treatment in this molecularly defined subgroup.

Beyond mismatch repair deficiency, several emerging molecular pathways are currently under investigation and may further refine the understanding of colorectal carcinogenesis in LS. Among these, Sirtuin 1 (SIRT1), a NAD^+-dependent deacetylase involved in DNA repair, apoptosis, and cellular senescence, has been proposed as a potential modulator of tumor biology through interactions with key regulators such as p53.[25] However, its role in LS-associated CRC remains incompletely understood and warrants further investigation. Broader theoretical models have also suggested a role for SIRT1 in systemic disease regulation,[26] although its direct relevance in this context remains unclear.

Strengths of this study include detailed phenotyping and molecular correlation. Limitations include its retrospective design, single-center scope, and relatively small sample size.

Conclusion

LS-associated CRC in this Mexican cohort demonstrated early onset, proximal predominance, characteristic histopathological patterns, and high extracolonic and metachronous cancer burden. These findings support intensified, risk-adapted surveillance strategies and reinforce the importance of early genetic evaluation in LS populations.

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