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Case Report

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Early-Onset Metachronous Colon Cancer in Probable Lynch Syndrome: Segmental Resection Followed by Total Colectomy

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ABSTRACT

Universal mismatch repair testing in colorectal cancer has reshaped modern surgical oncology because it influences hereditary cancer assessment, extent of resection, postoperative surveillance, and systemic treatment planning. We report the case of a 39- year-old man who presented with recurrent anemia and mild abdominal pain and was diagnosed with a transverse colon adenocarcinoma. He underwent open segmental colectomy with en-bloc small-bowel resection. Final pathology revealed a 12 × 8 × 6 cm mucinous adenocarcinoma with serosal invasion, lymphovascular invasion, 3 of 13 positive lymph nodes, and a positive radial margin, corresponding to pT4aN1bM0, stage IIIB disease. Immunohistochemistry demonstrated preserved MLH1/PMS2 and complete loss of MSH2/MSH6, strongly suggesting mismatch repair deficiency involving the MSH2 pathway. Due to the markedly high-risk pathologic features, he received six cycles of irinotecan-containing triplet adjuvant chemotherapy after multidisciplinary discussion. At 12 months, surveillance colonoscopy identified a second invasive adenocarcinoma in the cecum, interpreted as a metachronous second primary tumor. He then underwent total colectomy with ileorectal anastomosis. Pathology confirmed a well-differentiated pT4aN0 adenocarcinoma with negative margins and the same deficient mismatch repair pattern. In the context of early-onset disease, suggestive family history, duplication of the MSH2/MSH6-deficient phenotype in two anatomically distinct primary tumors, and rapid metachronous presentation, management as clinically probable Lynch syndrome was considered justified despite the absence of germline confirmation. This case highlights the practical value of tumor biology in guiding surgical strategy in resource-limited settings and supports early discussion of extended colectomy in young patients with highprobability Lynch syndrome.

KEYWORDS: Lynch syndrome, Colorectal cancer, Deficient mismatch repair, Metachronous colorectal cancer, Total colectomy, Ileorectal anastomosis.

ABBREVIATIONS: CRC: Colorectal Cancer; dMMR: Deficient Mismatch Repair; IHC: Immunohistochemistry; LS: Lynch Syndrome; CEA: Carcinoembryonic Antigen; ECOG: Eastern Cooperative Oncology Group; LVI: lymphovascular Invasion.

INTRODUCTION

Early-onset colorectal cancer should immediately raise concern for an inherited cancer predisposition syndrome, particularly Lynch syndrome, the most common hereditary cause of colorectal cancer.[1,2] Universal screening for mismatch repair deficiency or microsatellite instability is now recommended in all newly diagnosed colorectal cancers because it has direct diagnostic, prognostic, preventive, and therapeutic implications.[1,3]

Mismatch repair immunohistochemistry is especially valuable because it offers an accessible biologic surrogate for hereditary risk. Preserved MLH1/PMS2 with concomitant loss of MSH2/MSH6 is highly suggestive of Lynch syndrome and typically reflects dysfunction of the MSH2 axis, including possible EPCAM-associated MSH2 silencing.[1,3] In young patients, this information is not merely descriptive; it can materially influence the operative strategy, the intensity of postoperative surveillance, and the indication for counseling and screening of relatives.

The most difficult real-world scenarios arise when tumor biology strongly suggests Lynch syndrome but germline testing is unavailable, delayed, or unaffordable. In such settings, surgeons must often make definitive oncologic decisions based on clinical probability rather than molecular certainty. This tension is particularly relevant when the extent of resection may alter the risk of future metachronous colorectal cancer.

We present the case of a young man treated at the Instituto Nacional de Cancerología (INCAN), Guatemala, who developed a second metachronous colon cancer one year after resection of an initial dMMR transverse colon adenocarcinoma. Beyond its rarity, this case is clinically instructive because it shows how consistent tumor biology, family history, and disease behavior may justify management as probable Lynch syndrome and support escalation from segmental resection to total colectomy.

CASE PRESENTATION

A 39-year-old man with ECOG performance status 0 and no major comorbidities presented with a 7-month history of recurrent anemia requiring transfusions, suspected blood in the stool, and mild abdominal pain. He denied bowel obstruction, perforation, or major alterations in bowel habits. Family history was notable for breast cancer in his mother at a very young age, two maternal relatives with colon cancer before 50 years of age, and an additional paternal family history of malignancy with an unspecified primary site. No previous germline genetic assessment had been performed.

On physical examination, a mobile palpable mass was identified in the left upper quadrant/left flank with mild tenderness. No peripheral lymphadenopathy was detected, and digital rectal examination was unremarkable.

Laboratory studies showed hemoglobin 10 g/dL and hematocrit 31%, with preserved renal and liver function. Preoperative CEA was 4.54 ng/mL.

Colonoscopy demonstrated a circumferential ulcerated lesion approximately 70 cm from the anal verge, with fibrin deposition, irregular borders, and approximately 40% luminal narrowing. The lesion was traversable. No synchronous lesions were identified, and no tattoo was placed. Biopsy revealed moderately differentiated adenocarcinoma without signet ring cells.

Cross-sectional staging showed no thoracic metastases. Abdominal imaging localized the lesion to the transverse colon near the splenic flexure without liver metastases or retroperitoneal adenopathy.

First Operation

The patient underwent open segmental resection of the transverse colon with en bloc resection of adherent small bowel, followed by hand-sewn end-to-end colocolic anastomosis and stapled side-to-side small-bowel anastomosis. Intraoperatively, the tumor measured approximately 15 cm, was mobile, adherent to the greater omentum, and tethered to a segment of small bowel. There was no ascites, carcinomatosis, or gross hepatic involvement.

Postoperative recovery was favorable, with only a minor complication consistent with Clavien-Dindo grade I, no requirement for intensive care, and discharge within one week (Figure 1).[6]

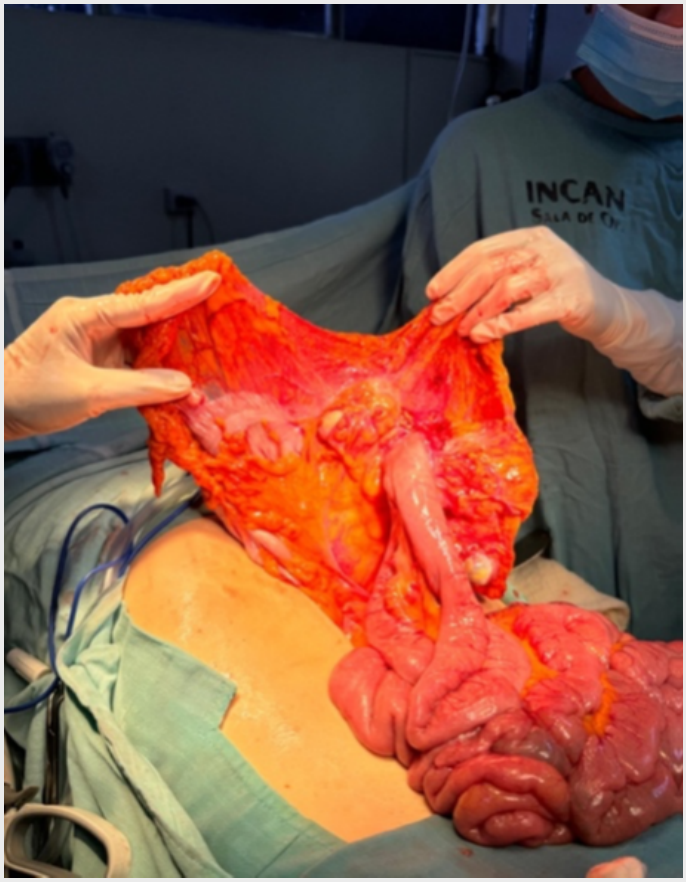

Figure 1. Intraoperative findings during the index segmental colectomy with en-bloc small bowel resection.

First Pathology and Molecular Profile

Gross and microscopic examination demonstrated a 12 × 8 × 6 cm mucinous adenocarcinoma invading the visceral peritoneum (pT4a), with lymphovascular invasion and no perineural invasion. Proximal and distal margins were negative; however, the radial margin was positive. Three of thirteen lymph nodes were positive for metastatic disease, resulting in pN1b status. Final pathologic stage was pT4aN1bM0, stage IIIB.

Mismatch repair immunohistochemistry showed preserved MLH1 and PMS2 expression with complete loss of MSH2 and MSH6 expression, supporting a dMMR phenotype highly suggestive of MSH2 pathway dysfunction (Figures 2-4).

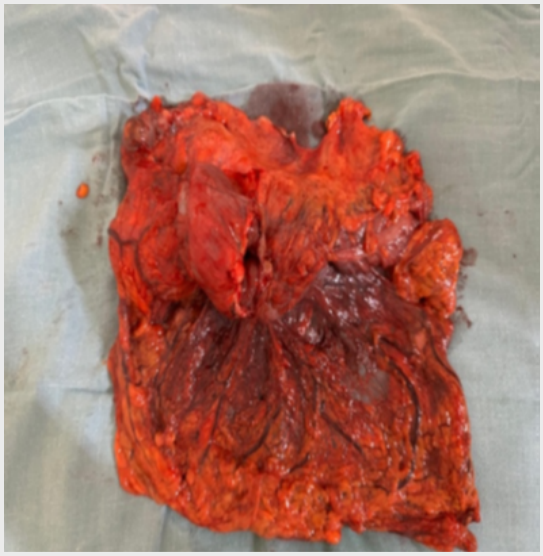

Figure 2. Gross specimen from the first resection showing the primary mucinous adenocarcinoma of the transverse colon.

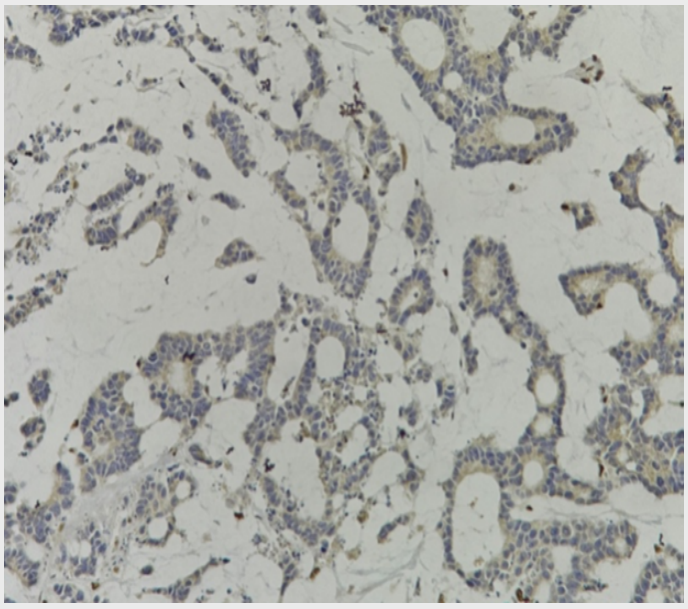

Figure 3. Immunohistochemistry from the first primary tumor demonstrating loss of MSH2 expression.

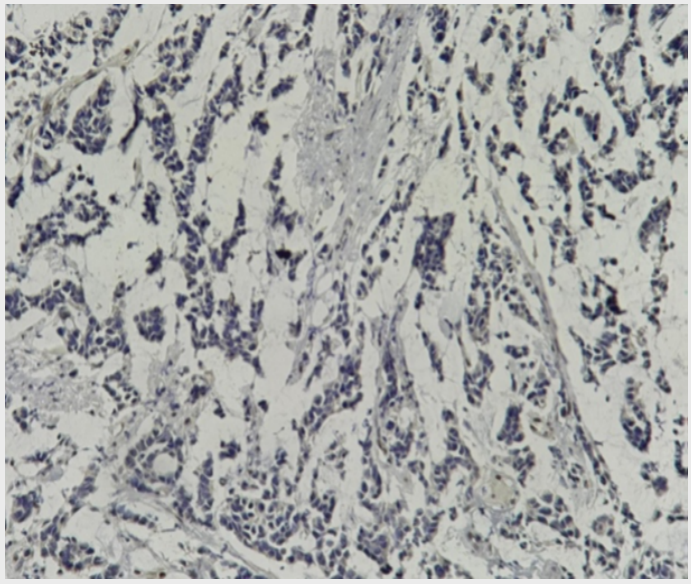

Figure 4. Immunohistochemistry from the first primary tumor demonstrating loss of MSH6 expression.

Adjuvant Therapy

Given the patient's young age, excellent performance status, T4 disease, nodal positivity, lymphovascular invasion, and positive radial margin, he received six cycles of irinotecan containing triplet adjuvant chemotherapy consisting of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan after multidisciplinary discussion. Although standard adjuvant therapy for stage III colon cancer is fluoropyrimidine-oxaliplatin doublet therapy, this intensified regimen was selected institutionally because of the markedly high-risk pathologic profile and after discussion with the patient regarding the balance between potential benefit and increased toxicity.[7,8]

Surveillance and Diagnosis of a Metachronous Second Primary

At 12 months, surveillance imaging showed no evidence of recurrence and CEA remained within normal range. However, surveillance colonoscopy identified a new lesion in the cecum. Biopsy confirmed invasive adenocarcinoma. Because the initial colonoscopy had been complete and had shown no synchronous lesions, and because the new lesion appeared more than 6 months after the initial diagnosis in a distinct colonic segment, this lesion was interpreted as a metachronous second primary colorectal cancer rather than local recurrence.

Second Operation

The patient subsequently underwent total colectomy with ileorectal anastomosis as definitive oncologic treatment and colorectal risk-reducing surgery.

Pathology from the second operation demonstrated a 2 × 1 cm well-differentiated adenocarcinoma with mucinous features invading the visceral peritoneum (pT4a) (Figure 5).

No perineural invasion or tumor deposits were identified, tumor budding was low, and all 11 examined lymph nodes were negative. Proximal, distal, and radial margins were free of tumor.

Repeat mismatch repair immunohistochemistry again demonstrated preserved MLH1/PMS2 with loss of MSH2/MSH6, reproducing the molecular phenotype of the first primary tumor (Figures 6-8).

Current Management

The patient was referred again to medical oncology to evaluate the role of additional postoperative systemic therapy after the second primary tumor. Germline multigene testing was strongly recommended, with particular attention to MSH2 and EPCAM, together with genetic counseling and surveillance planning for first-degree relatives.

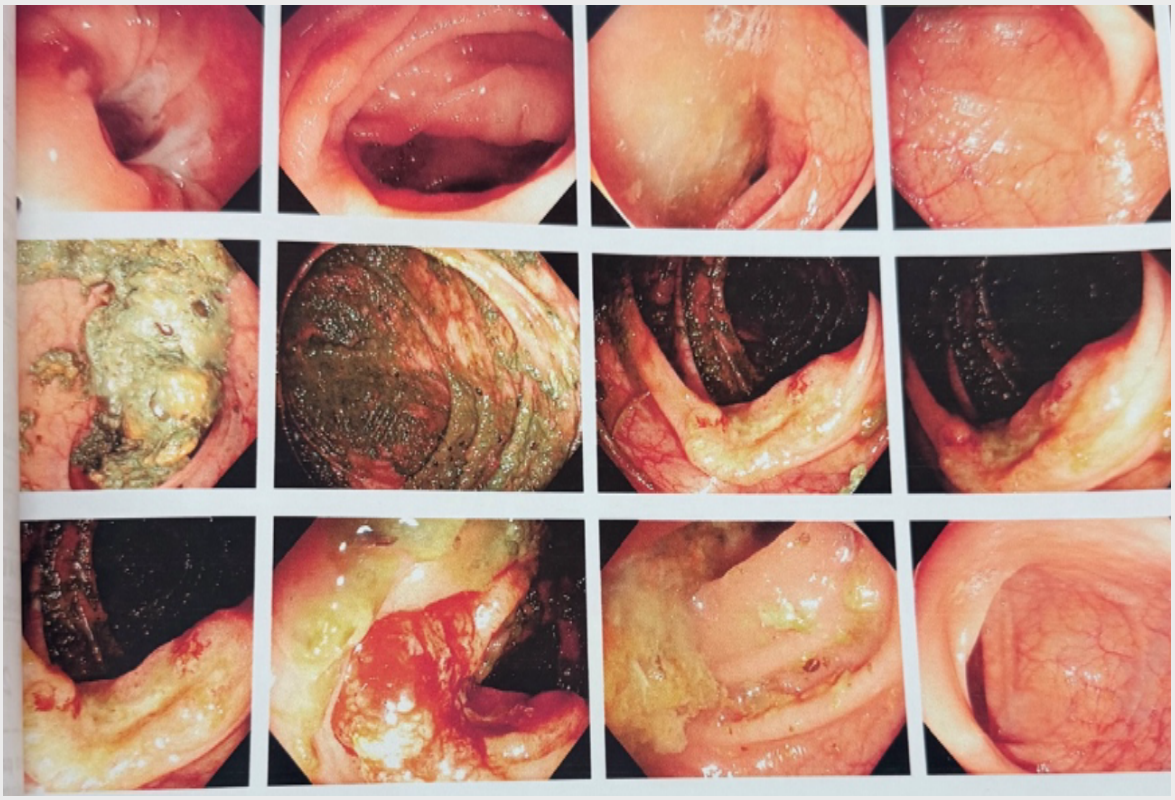

Figure 5. Surveillance colonoscopy demonstrating the metachronous cecal lesion detected 12 months after index treatment.

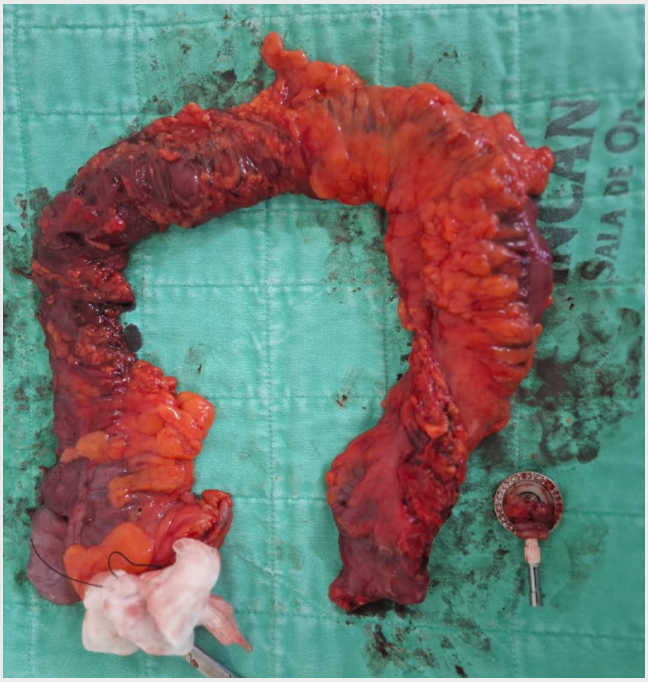

Figure 6. Gross specimen from total colectomy performed for the second primary tumor and colorectal risk reduction.

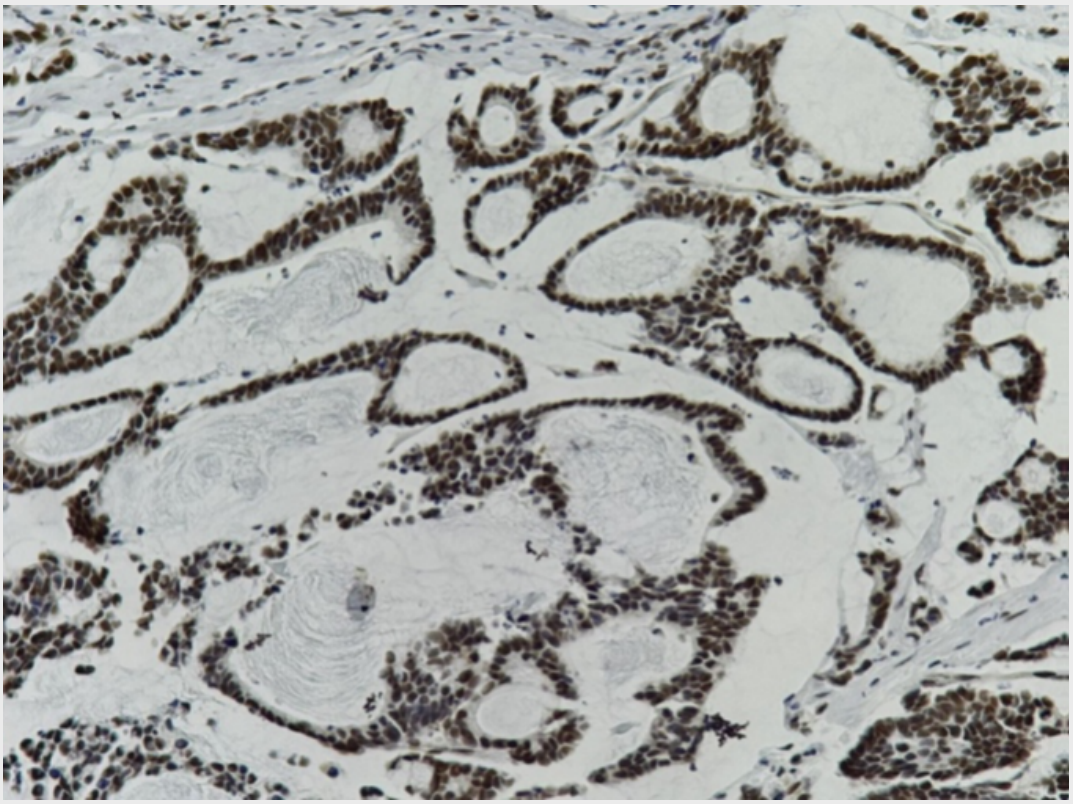

Figure 7. Surveillance colonoscopy demonstrating the metachronous cecal lesion detected 12 months after index treatment.

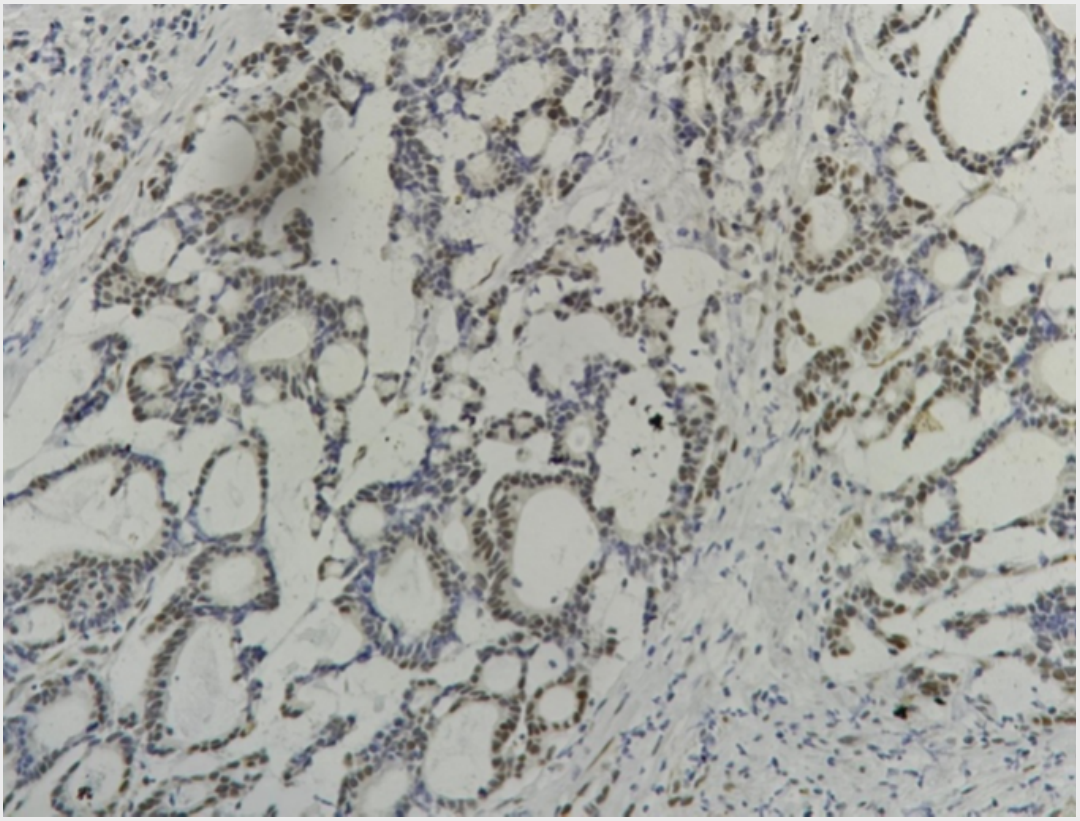

Figure 8. Gross specimen from total colectomy performed for the second primary tumor and colorectal risk reduction.

DISCUSSION

This case is publishable and clinically meaningful not simply because it presents metachronous colorectal cancer, but because it documents a coherent hereditary-oncology phenotype with direct surgical consequences. Four elements strongly converge toward probable Lynch syndrome: diagnosis at 39 years of age, a suggestive family history of early malignancy, complete loss of MSH2/MSH6 in the first tumor, and reproduction of the same immunophenotype in a second anatomically distinct primary tumor that appeared only one year later. The consistency of these findings makes a sporadic explanation substantially less convincing.

The duplicated MSH2/MSH6-deficient pattern is the strongest biologic argument in the case. Loss of MSH2 and MSH6 with preserved MLH1 and PMS2 is far more typical of Lynch syndrome than of sporadic dMMR colorectal cancer.[1,3] In daily practice, this profile should immediately trigger the assumption of an MSH2-pathway abnormality until proven otherwise, including the possibility of EPCAM-associated MSH2 silencing. The fact that the same pattern was demonstrated in two separate primary tumors materially strengthens the hereditary hypothesis and reduces the likelihood that the first result represented an isolated tumor-specific event.

The differential diagnosis deserves consideration. Sporadic dMMR is less likely because both tumors retained MLH1/PMS2 expression. Constitutional mismatch repair deficiency is improbable given the age at presentation and the absence of the broader childhood-onset phenotype typically seen in that syndrome. Polyposis syndromes are not supported by the reported endoscopic findings. An initially missed synchronous cecal lesion must always be entertained; however, the index colonoscopy was reportedly complete, no synchronous lesion was identified, and the second lesion emerged in a biologically concordant context.

Accordingly, the most parsimonious interpretation is that this patient developed a true metachronous second primary colorectal cancer in the setting of probable Lynch syndrome. The surgical lesson of this case is central. In young patients with likely Lynch syndrome, the question is not only how to remove the index tumor, but how to reduce the substantial future risk of additional colorectal primaries. Current literature supports individualized discussion regarding the extent of colectomy, particularly in patients with suspected MLH1-, MSH2-, or EPCAM-related disease, in whom the risk of metachronous colorectal cancer is meaningful enough to justify more extensive resection.[1,4,5] This case illustrates that principle with unusual clarity. Following segmental resection for the first cancer, the patient developed a second primary lesion within 12 months, thereby validating the subsequent choice of total colectomy with ileorectal anastomosis as both definitive cancer treatment and rational risk-reducing surgery.

Importantly, the case should not be interpreted as a criticism of the initial segmental resection. Rather, it reflects the real constraints of oncologic practice in many settings. When a patient presents with locally advanced colon cancer and germline testing is not available in a timely manner, it is understandable that treatment may begin with resection of the primary tumor, especially when the hereditary diagnosis remains strongly suspected but not molecularly confirmed. The present case demonstrates how rapidly disease evolution can clarify the biology and compel escalation to extended colectomy. In that sense, it is not merely a case of metachronous cancer; it is a case of staged hereditary-risk surgical decision-making under imperfect information.

The adjuvant treatment strategy also warrants candid discussion. Standard evidence-based adjuvant treatment for stage III colon cancer remains fluoropyrimidine plus oxaliplatin, most commonly FOLFOX or CAPOX.[7,8] Therefore, the irinotecan-containing triplet regimen administered after the first operation should be described as a nonstandard intensification selected because of the extraordinarily high-risk pathologic profile, including T4 disease, nodal involvement, lymphovascular invasion, and a positive radial margin, in a young and fit patient. Explicitly acknowledging this departure from standard practice strengthens the manuscript because it shows critical appraisal rather than overstatement.

This report also has value beyond the individual patient because it reflects a common challenge in low- and middle-resource environments: hereditary cancer management often depends first on tumor-based surrogates rather than immediate germline confirmation. In such contexts, clinicians still need to make real decisions about resection extent, surveillance intensity, and family counseling. This case supports a practical principle: when age, family history, tumor biology, and disease behavior all align strongly, management as probable Lynch syndrome is reasonable and clinically responsible while confirmatory germline testing is pursued.

The main limitation is the absence of germline testing, which prevents definitive molecular classification. A second limitation is the use of a nonstandard adjuvant regimen after the first primary tumor. Nonetheless, these limitations do not weaken the relevance of the report. On the contrary, they highlight the exact circumstances in which real-world oncologic judgment is most necessary. The strength of this case lies in the concordance between clinicopathologic suspicion and subsequent disease behavior.

CONCLUSIONS

This case demonstrates that a clinically actionable diagnosis of probable Lynch syndrome can be established even in the absence of germline confirmation when the cumulative evidence is compelling. Early-onset colorectal cancer, suggestive family history, repeated loss of MSH2/MSH6 in two separate primary tumors, and rapid development of a metachronous second colon cancer created a highly coherent hereditary-risk profile.

The second operation, total colectomy with ileorectal anastomosis, was not only appropriate oncologic management for the new cancer but also an evidence-based risk reducing strategy. This case strongly supports early and explicit discussion of extended colectomy in young patients with high-probability Lynch syndrome, particularly when the tumor immunophenotype suggests MSH2/EPCAM pathway involvement.

More broadly, this report emphasizes that tumor biology should meaningfully influence surgical planning when hereditary testing is

delayed or inaccessible. In resource constrained settings, rigorous interpretation of available pathology can still lead to sound oncologic and preventive decisions for both patients and their families.

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None

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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