International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 13, No. 1, 2026

A Case Report of Lynch Syndrome: Clinical Course and Literature Review

Di Wang [1], Xuyou Liu [2, *]

[1] Guangzhou Red Cross Hospital, Jinan University, Guangzhou Guangdong, 510235, China
[2] Department of Gastroenterology, Guangzhou Red Cross Hospital, Jinan University, Guangzhou Guangdong, 510235, China
*** Corresponding author:** Xuyou Liu (Email: liuxy717@163.com)

Abstract: Lynch syndrome (LS) is a hereditary cancer predisposition syndrome caused by germline defects in DNA mismatch repair (MMR) genes. While colorectal cancer is its most common manifestation, small bowel adenocarcinoma (SBA) remains a rare occurrence and often presents with nonspecific symptoms, contributing to delayed diagnosis. We present the case of a 76-year-old woman with Lynch syndrome who initially presented with anorexia, fatigue, and abdominal pain. Initial gastroscopy and colonoscopy were unrevealing. However, with progressive symptoms and rising tumor markers, further evaluation with positron emission tomography–computed tomography (PET-CT) and double-balloon enteroscopy led to the diagnosis of moderately differentiated duodenal adenocarcinoma. Immunohistochemical analysis confirmed microsatellite instability (MSI). Given her personal and family history of colorectal neoplasms, a clinical diagnosis of Lynch syndrome was established. The patient exhibited poor tolerance to platinum-based chemotherapy and was subsequently treated with a programmed cell death protein 1 (PD-1) inhibitor, resulting in transient clinical improvement. In the later course, her illness was complicated by exacerbation of pre-existing Sjögren's syndrome and severe opportunistic infections, culminating in acute respiratory distress syndrome and multiorgan failure, ultimately leading to death. This case highlights the elevated risk of multiple primary malignancies in Lynch syndrome, the diagnostic challenges associated with SBA, and the pivotal role of MSI status in guiding immunotherapy. It also underscores the need for careful monitoring of immune-related adverse events, particularly in patients with underlying autoimmune diseases.

Keywords: Lynch Syndrome; Small Bowel Adenocarcinoma; Microsatellite Instability; Immunotherapy.

1. Note

A 76-year-old woman was admitted to the Department of Gastroenterology at Guangzhou Red Cross Hospital on August 21, 2023, with a three-month history of anorexia, fatigue, and abdominal pain that had worsened over the preceding month, accompanied by low-grade fever.

2. Introduction

The patient's symptoms began in May 2023 with anorexia and generalized fatigue, without obvious precipitating factors, and intermittent dull pain predominantly in the upper abdomen. The abdominal pain was unrelated to food intake and was partially relieved by changes in body position. She denied abdominal distension, diarrhea, constipation, hematochezia, melena, nausea, or vomiting. Upper and lower gastrointestinal endoscopy performed at our hospital revealed duodenal bulb inflammation, chronic erosive antral gastritis, and multiple rectal polyps. Histopathological examination of the rectal polyps demonstrated tubular–villous adenoma and villous adenoma with focal high-grade intraepithelial neoplasia. Her symptoms transiently improved after symptomatic treatment. By July 2023, her anorexia, fatigue, and abdominal pain had progressively worsened and were similar in character to her previous symptoms but now accompanied by recurrent low-grade fever (maximum temperature 38.3°C), night sweats, and unintentional weight loss. Laboratory evaluation revealed elevated tumor markers: CA19-9 (97.1 U/mL), CA15-3 (27.8 U/mL), and CYFRA21-1 (6.4 ng/mL). Abdominal CT showed diffuse thickening of the descending and horizontal segments of the duodenum, raising suspicion for intestinal carcinoma or lymphoma. PET-CT revealed marked wall thickening of the duodenal descending and horizontal portions, with increased fluorodeoxyglucose uptake, apparent serosal involvement, pancreatic head invasion, and close proximity to the colonic wall. Multiple enlarged mesenteric and retroperitoneal lymph nodes, some with increased metabolic activity, were observed, raising concern for early lymph node metastasis. Mild thickening and increased metabolic activity of the pelvic peritoneum were also noted, suggesting possible peritoneal metastasis. Double-balloon enteroscopy revealed a large, irregular mass occupying nearly the entire circumference of the duodenal descending segment distal to the major papilla, measuring approximately 3.5 cm in diameter. The lesion had an ulcerated, rough surface with a firm consistency, bled on contact, and caused mild luminal narrowing, though the endoscope could still pass through.

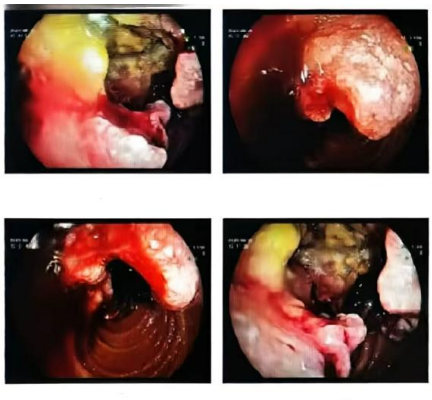

Figure 1. Findings on double-balloon enteroscopy

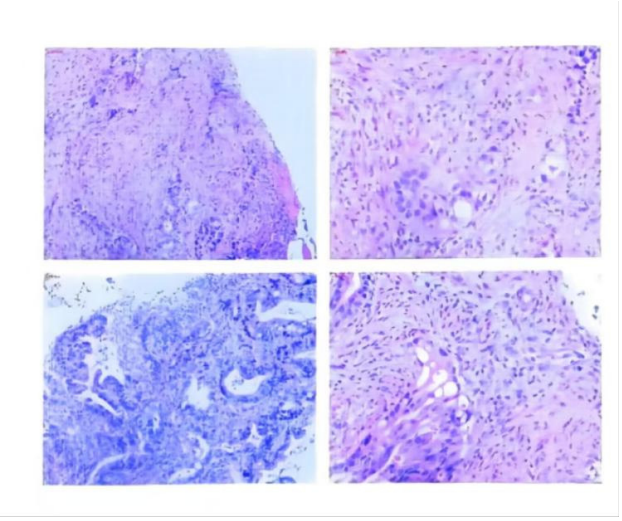

Figure 2. Histopathological findings on light microscopy

Histopathological analysis of biopsy specimens confirmed moderately differentiated adenocarcinoma of the duodenal mucosa with necrosis and inflammatory exudation. Immunohistochemical analysis showed loss of MSH2 expression, with retained MLH1, MSH6, and PMS2, and absence of the BRAF V600E mutation, indicating mismatch repair deficiency and microsatellite instability–high (MSI-H) status. Based on the patient's personal and family history, a clinical diagnosis of Lynch syndrome was established.

Past Medical History: Over 20 years earlier, the patient underwent curative resection for rectal cancer, followed by approximately six months of adjuvant chemotherapy (regimen details unavailable). On August 21, 2012, she underwent left hemicolectomy at our institution; postoperative pathology revealed high-grade tubular adenoma of the colonic mucosa. She received regular endoscopic surveillance thereafter, with repeated detection and removal of adenomatous polyps. The patient also had a longstanding history of hypertension requiring chronic antihypertensive therapy. Additionally, she reported persistent xerostomia and xerophthalmia over several years. Laboratory investigations demonstrated positivity for anti-SSA/Ro52, anti-SSA/Ro60, anti-SSB, and anti-U1RNP antibodies, along with decreased complement C3 and C4 levels. A labial salivary gland biopsy performed in 2023 showed lymphocytic infiltration with fibrotic changes, consistent with Sjögren's syndrome.

Family History: The patient's mother had a history of colorectal neoplasia.

Treatment and Clinical Course: After diagnostic confirmation, the patient began chemotherapy with oxaliplatin plus capecitabine on September 4, 2023, but treatment was discontinued due to poor tolerability. From September 2023 to February 2024, she switched to the PD-1 inhibitor tislelizumab, receiving seven cycles. The tumor showed sustained regression, with a partial response (PR) as the best response. However, she experienced recurrent immune-related cutaneous toxicities requiring corticosteroid therapy, ultimately leading to discontinuation of immunotherapy. In June 2025, tumor markers re-elevated and imaging revealed disease progression. Pembrolizumab was initiated as immune rechallenge therapy in July 2025. Shortly thereafter, she experienced an acute exacerbation of Sjögren's syndrome–related symptoms, which improved transiently with corticosteroids. By August 2025, her condition rapidly deteriorated with fever, dysphagia, altered mental status, and melena. Autoimmune antibody levels were markedly elevated, and rheumatological assessment suggested active Sjögren's syndrome. Cerebrospinal fluid analysis revealed significantly elevated protein and cell counts with negative cultures, raising suspicion for immune-related encephalitis. Cranial MRI showed acute infarction of the left corpus callosum. The clinical course was further complicated by severe pneumonia, respiratory failure, and acute kidney injury. Despite aggressive supportive care—including mechanical ventilation, continuous renal replacement therapy, high-dose vasopressors, corticosteroids, and immunomodulatory therapy—the patient developed ARDS and multiple organ failure. On September 30, 2025, she experienced persistent circulatory collapse and refractory hypoxemia. After discussion with her family, further resuscitative efforts were withdrawn, and the patient was pronounced dead at 14:16 on the same day.

3. Discussion

Lynch syndrome (LS), one of the most common hereditary cancer predisposition syndromes in humans, is an autosomal dominant disorder that results from pathogenic germline mutations in DNA mismatch repair (MMR) genes—including MLH1, MSH2, MSH6, and PMS2—or from epithelial cell adhesion molecule deletions[1,2]. By impairing the DNA MMR system, these genetic alterations prevent the effective correction of replication errors and induce microsatellite instability (MSI)[3], thereby substantially elevating the risk of developing multiple malignancies. Prior research has shown that LS imparts an approximately 80% lifetime risk of developing colorectal cancer (CRC) and a 60% risk of endometrial cancer[4]. Furthermore, LS increases the incidence of several other cancers, including those of the stomach, small intestine, pancreas, urinary tract (renal pelvis, ureter, and bladder), prostate, biliary tract, ovary, brain, and skin[5]. Among the extracolonic malignancies associated with LS, small bowel adenocarcinoma (SBA) is of particular interest. Despite the fact that the small intestine occupies nearly 90% of the total surface area of the gastrointestinal tract, small bowel tumors are rare, accounting for only approximately 3.5% of newly diagnosed gastrointestinal cancers[6]. In China, cases of SBA occur at an incidence rate of 0.32 per 100,000 in men and 1.95 per 100,000 in women[7]. In patients with LS, the estimated lifetime risk of developing SBA is approximately 4%, 100-fold higher than the general population[8]. The occurrence of SBA consequently warrants consideration of an underlying diagnosis of LS. The median age at diagnosis for LS-associated SBA is approximately 52 years, and it most commonly appears in the duodenum, followed by the jejunum and ileum[9]. Histopathologically, these tumors often exhibit mucinous, signet-ring cell, or medullary differentiation, which is often complemented by prominent tumor-infiltrating lymphocytes and Crohn-like lymphoid reactions [10].

In the early stages, small bowel tumors often remain asymptomatic. With the progressive enlargement of the tumor, a range of gastrointestinal symptoms may arise: abdominal pain is the most common, frequently accompanied by diarrhea, nausea, vomiting, and dyspepsia. Gastrointestinal bleeding may occur when tumor growth involves or erodes adjacent blood vessels. There may also be recurrent episodes of chronic intestinal obstruction resulting from tumor-induced luminal narrowing and compression of surrounding bowel

segments. Cases complicated by intussusception or volvulus may develop acute intestinal obstruction. Additionally, nonspecific manifestations such as jaundice and unintentional weight loss may be observed[11].

The diagnostic criteria for LS have evolved from an initial reliance on family history–based clinical definitions to a comprehensive framework integrating molecular pathological evidence. This evolution has aimed primarily at enabling early identification of high-risk individuals and reducing cancer-related mortality through surveillance and timely intervention. The earliest Amsterdam I criteria, which focused exclusively on CRC, stipulated the following requirements: at least three family members with CRC, involvement of two or more successive generations, one diagnosis before the age of 50, and exclusion of familial adenomatous polyposis. Though they demonstrated high specificity, these criteria were limited in sensitivity. The Amsterdam II criteria, which were subsequently proposed, expanded the tumor spectrum to include endometrial, gastric, ovarian, small bowel, urinary tract, hepatobiliary, brain, and sebaceous tumors, thus enhancing the LS detection rate. Nevertheless, family history remained central to these criteria, which could still result in a failure to identify sporadic cases. Conversely, the Bethesda guidelines emphasize the integration of clinical and pathological features. These guidelines recommend MSI testing in individuals diagnosed with CRC before the age of 50, in those with synchronous or metachronous CRC or other LS-associated tumors, in individuals with MSI-high (MSI-H) histology diagnosed before the age of 60, in patients with at least one first-degree relative diagnosed with CRC or an LS-associated tumor before the age of 50, and in those with CRC or LS-associated tumors occurring at any age in two first- or second-degree relatives. The Bethesda guidelines offer higher sensitivity than the Amsterdam criteria, enabling the identification of more individuals with potential LS. Consequently, they are frequently employed in clinical practice, alongside MSI testing or immunohistochemical analysis of MMR proteins, and currently represent one of the most widely adopted screening strategies[12,13]. Notably, SBA exhibits a higher prevalence of MSI-H status than CRC[14].

To facilitate the early identification of individuals with LS, the National Comprehensive Cancer Network recommends molecular testing for all patients with SBA. Such testing is also significant for therapeutic decision-making in patients with stage IV disease[15]. MSI testing and immunohistochemical (IHC) analysis of MMR proteins represent two cornerstone approaches. IHC, which uses antibodies to assess the expression of the four key MMR proteins (MLH1, MSH2, MSH6, and PMS2), is generally favored as the initial method in the evaluation of suspected LS-associated tumors. Equivocal IHC results necessitate molecular confirmation, with polymerase chain reaction (PCR)–based assays serving as the first-line approach. Currently, a panel of five polyadenine mononucleotide repeat markers—BAT-25, BAT-26, NR-21, NR-24, and NR-27—is recommended, as it offers superior sensitivity and specificity. Next-generation sequencing is an alternative molecular diagnostic strategy that incorporates MSI assessment within tumor mutational burden analysis, thus enabling the identification of potentially actionable genetic alterations[16]. In cases of suspected duodenal or small bowel malignancy, esophagogastroduodenoscopy is performed as part of the initial diagnostic evaluation and staging to facilitate early lesion detection and histopathological sampling. Endoscopic ultrasonography, which may be used for preoperative staging of proximal small bowel tumors, assists in differentiating secondary involvement from pancreatic, biliary, or other intra-abdominal malignancies. For lesions in the distal small bowel, particularly when conventional imaging modalities are inadequate, double-balloon enteroscopy (DBE) and small bowel capsule endoscopy (SBCE) provide valuable adjunctive diagnostic options. Although SBCE is a safe and noninvasive modality enabling detection of primary lesions, it is not suitable for patients with suspected strictures or obstruction because it cannot obtain tissue samples and carries a risk of capsule retention[17]. Conversely, DBE allows for tissue biopsy, lesion localization, marking, and the retrieval of retained capsules. Local tumor invasion and the presence of distant metastases are routinely assessed using computed tomography (CT) or magnetic resonance imaging (MRI)[15]. At present, positron emission tomography–CT does not appear in clinical guidelines as a recommended tool for routine diagnostics; however, growing evidence indicates that it has substantial value in the initial diagnosis, staging, treatment response assessment, and restaging of SBA, particularly when CT or MRI findings are inconclusive[18].

Research has shown that MSI tumors are associated with a more favorable prognosis than microsatellite-stable tumors and respond well to immunotherapy[19]. In recent years, substantial advances have been made in cancer immunotherapy—regarded as the “fourth major treatment modality” after surgery, chemotherapy, and radiotherapy. Its primary mechanism consists of employing the patient’s own immune system to recognize and eliminate tumor cells while inducing durable immune memory that reduces recurrence and improves long-term survival and quality of life[20,21]. Among immunotherapeutic agents, immune checkpoint inhibitors (ICIs)—specifically those that target the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway—are currently standard treatment options for multiple solid tumors, including non–small cell lung cancer, melanoma, and esophageal cancer[22]. MMR deficiency (dMMR) and MSI-H status cause an exceptionally high tumor mutational burden, rendering LS-associated tumors particularly sensitive to ICIs[23]. Emerging evidence suggests that patients with SBA exhibiting features of dMMR or MSI-H greatly benefit from PD-1 inhibitor therapy, especially in circumstances involving advanced or metastatic disease that warrant immunotherapy as an important therapeutic option[24]. Pembrolizumab, a monoclonal antibody that targets PD-1, was approved by the U.S. Food and Drug Administration in May 2017 for the treatment of various advanced MSI-H or dMMR solid tumors, including SBA[25].

This case underscores the considerable diagnostic and therapeutic complexities inherent to Lynch syndrome–associated small bowel adenocarcinoma (SBA). As a rare malignancy, SBA often presents with nonspecific symptoms, such as anorexia, fatigue, and abdominal pain—manifestations that are easily mistaken for benign gastrointestinal conditions. In this patient, initial upper and lower gastrointestinal endoscopies failed to detect malignant lesions, highlighting the limitations of conventional endoscopic techniques in identifying small bowel tumors. Despite persistently elevated tumor markers, including CA19-9, a definitive diagnosis remained elusive in the absence of pathological confirmation, underscoring the

limited specificity and diagnostic utility of serum biomarkers in the context of SBA. The initial differential diagnosis was broad, encompassing primary duodenal carcinoma, intestinal lymphoma, secondary duodenal involvement from pancreatic malignancy, and inflammatory bowel disease–related strictures. Cross-sectional imaging revealed diffuse thickening of the duodenal wall, raising suspicion for malignancy, but was insufficient for definitive etiological delineation. Ultimately, a combination of PET-CT and double-balloon enteroscopy facilitated direct visualization, tissue sampling, and histological confirmation of the lesion. This diagnostic trajectory illustrates the vital importance of advanced endoscopic modalities in the evaluation of suspected small bowel neoplasms, particularly when standard endoscopic approaches are inconclusive. Lynch syndrome, an autosomal dominant disorder caused by germline mutations in DNA mismatch repair (MMR) genes, is most commonly associated with colorectal and endometrial cancers. However, SBA is a well-recognized extracolonic malignancy in Lynch syndrome, with affected individuals facing a substantially elevated lifetime risk relative to the general population. The patient's personal history of multiple colorectal neoplasms, relevant family history, and loss of MSH2 expression provided strong evidence for Lynch syndrome. This case reinforces the necessity of considering Lynch syndrome in patients with SBA, especially those with a background of colorectal cancer or multiple adenomatous polyps. Microsatellite instability (MSI) and MMR deficiency (dMMR) are central to the pathogenesis and behavior of Lynch syndrome–associated tumors. MSI-H/dMMR tumors typically exhibit a high mutational burden and increased immunogenicity, which underpin their favorable responses to immune checkpoint inhibitors (ICIs). Consistent with current evidence, our patient demonstrated a sustained partial response to PD-1 blockade following intolerance to platinum-based chemotherapy, supporting the preferential use of immunotherapy in advanced MSI-H SBA. Nevertheless, the use of ICIs introduces a unique risk of immune-related adverse events. In this case, prolonged immunotherapy was complicated by recurrent immune-mediated cutaneous toxicity and, following immune rechallenge, a dramatic exacerbation of Sjögren's syndrome. This culminated in suspected immune-related encephalitis, severe opportunistic infection, and ultimately, multiorgan failure. These complications illustrate the delicate balance between therapeutic efficacy and immune toxicity, particularly in patients with underlying autoimmune diseases. Careful patient selection, vigilant monitoring, and early multidisciplinary intervention are imperative when considering ICI therapy in this high-risk population. Compared with previous reports, this case exemplifies both the significant efficacy and the potential lethality of immunotherapy in Lynch syndrome–associated SBA. While prior studies have highlighted the durable responses and survival benefits of ICIs in MSI-H tumors, fewer reports have detailed severe autoimmune flares and fatal infectious complications following immune rechallenge. This variability underscores the heterogeneity of immune responses and the necessity for individualized risk assessment.

In summary, this case offers several key clinical insights. First, SBA should be actively considered in Lynch syndrome patients with unexplained abdominal symptoms, even when initial endoscopic evaluations are unremarkable. Second, MSI/MMR testing is essential not only for establishing etiology but also for guiding therapeutic decision-making. Finally, while immunotherapy provides significant benefit in MSI-H SBA, clinicians must remain vigilant for immune-related complications, particularly in patients with pre-existing autoimmune conditions. The main limitations of this report include its nature as a single case and the inability to definitively attribute the patient's fatal complications to immunotherapy. Nonetheless, this case adds valuable evidence to the evolving understanding of Lynch syndrome–associated SBA and highlights the ongoing need for research aimed at optimizing immunotherapy strategies in this unique patient population.

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