

CASE REPORT

DIAGNOSTIC CHALLENGE OF PRIMARY COLONIC POORLY COHESIVE ADENOCARCINOMA EXHIBITING GASTRIC-TYPE IMMUNOHISTOCHEMISTRY PROFILE AND FOCAL SIGNET-RING DIFFERENTIATION

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Colorectal adenocarcinoma infrequently exhibits a diffuse, poorly cohesive architecture and a gastric-type immunophenotype, closely resembling diffuse-type gastric carcinoma and posing a formidable diagnostic challenge. This report describes a 65-year-old woman who presented with non-specific abdominal discomfort and was found by colonoscopy to have a 6.5 cm ulceroinfiltrative lesion in the hepatic flexure. Histologically, the tumor comprised discohesive cells with focal signet-ring morphology, accompanied by extensive lymphovascular and perineural invasion, necrosis, and a marked peritumoral lymphoid response. Immunohistochemical analysis demonstrated a gastric-type profile (CK7+, CK20–, SATB2–, CDX2 weak/focal, MUC5AC+, MUC2–), whereas panels excluding breast, urothelial, Müllerian, neuroendocrine, and hematolymphoid differentiation were uniformly negative. Comprehensive imaging and endoscopic evaluation excluded an extra-colonic primary malignancy/carcinoma. Mismatch repair testing revealed loss of MLH1/PMS2 expression with preserved MSH2/MSH6. This case underscores that, in such uncommon colorectal variants, reliance on immunophenotype alone may mislead, and that definitive diagnosis necessitates integrated clinicopathologic correlation, exhaustive sampling, and exclusion of alternative primaries/primary malignancies/carcinomas to confirm a primary colonic poorly cohesive adenocarcinoma with focal signet-ring differentiation.

Key words: primary colonic poorly cohesive adenocarcinoma, gastric-type immunophenotype, signet-ring cell differentiation, MLH1/PMS2 deficiency, PD-L1 expression.

Introduction

Colorectal carcinoma remains a leading cause of cancer-related morbidity and mortality worldwide. The vast majority of cases present as conventional gland-forming adenocarcinomas [1]. However, a small subset of tumors exhibits uncommon histological patterns – such as medullary, micropapillary, mucinous, adenosquamous, and poorly cohesive (in-

cluding signet-ring cell) variants – that diverge from the classic morphology and immunophenotype [2]. These rare variants may closely resemble extra-colonic primaries/primary malignancies/carcinomas, particularly diffuse-type gastric carcinoma, and thus represent a serious diagnostic pitfall.

Secondary involvement of the colon by gastric, pancreatobiliary, urothelial or Müllerian tumors is well documented and often distinguished by serosal-

predominant invasion with minimal mucosal transition. In contrast, true primary colorectal neoplasms typically arise from areas of mucosal dysplasia with a continuous dysplasia-invasion sequence [3]. Poorly cohesive and signet-ring cell variants may lose conventional markers (CK20, CDX2, SATB2), necessitating extended immunohistochemical (IHC) panels (e.g. CK7, MUC5AC, GATA3, TRPS1, p63/p40) and thorough clinicopathologic correlation to exclude metastatic disease [4].

Herein, we present the case of a 65-year-old woman with a 6.5 cm hepatic-flexure lesion demonstrating diffuse discohesive architecture with focal signet-ring cells and a gastric-type immunoprofile. Comprehensive morphologic assessment, targeted IHC, and exclusion of extra-colonic primaries/primary malignancies/carcinomas were indispensable to establish a World Health Organization (WHO) concordant diagnosis of primary colonic poorly cohesive adenocarcinoma. This report underscores the need for an integrated diagnostic framework when confronting colorectal variants that phenotypically mimic gastric carcinoma.

Case report

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

A 65-year-old woman presented with altered bowel habits and abdominal distension. Contrast-enhanced computed tomography (CT) of the abdomen demonstrated a 6.5 × 5.0 cm (anteroposterior × mediolateral dimensions) ulceroinfiltrative mass at the hepatic flexure, markedly narrowing the lumen.

Radiological features suggested extension beyond the serosa into the adjacent mesenteric adipose tissue (Figure 1). Additionally, multiple mesenteric lymph nodes were noted in the vicinity, with the largest measuring approximately 5 mm. Based on these CT findings, the clinical stage was suggested to be cT3 cN+ cM0. An upper endoscopy revealed erythematous antral mucosa; gastric biopsies showed intestinal metaplasia with active chronic gastritis. Colonoscopic examination revealed a stenosing, ulceroinfiltrative mass at the hepatic flexure, consistent with the CT findings; biopsies from this lesion were suggestive of adenocarcinoma. Additionally, synchronous sessile polyps identified at 15, 25, and 90 cm were removed *via* polypectomy. Histopathologic evaluation confirmed these as low-grade villous adenomas. Importantly, these polyps were anatomically distinct from the hepatic flexure carcinoma, with no macroscopic or histologic evidence of continuity.

The patient underwent right hemicolectomy with side-to-side ileocolic anastomosis. On gross examination, the right hemicolectomy specimen contained a 6.5-cm ulceroinfiltrative mass at the hepatic flex-

ure, causing marked luminal narrowing. The lesion was firm, tan-white, and poorly circumscribed on cut surface, with transmural wall thickening and extension into the subserosal adipose tissue. No additional polyps were identified in the resection specimen. Histologically, the neoplasm exhibited extensive necrosis and a diffuse, single-cell infiltrative pattern; signet-ring cells comprised approximately 8% of tumor cells per 10 high-power fields. At initial histologic evaluation, we specifically searched for a dysplasia-invasion transition zone in the mucosa overlying and adjacent to the lesion but could not identify a definite interface. This prompted extensive additional sampling: the entire grossly identifiable tumor, together with its interface with the adjacent mucosa, was submitted for histologic examination in multiple full-thickness blocks. In these additional sections, we observed stretches of normal-appearing colonic mucosa followed by ulcerated areas with an underlying poorly cohesive carcinoma; however, a distinct dysplasia-carcinoma transition could still not be unequivocally demonstrated (Figure 2).

Immunohistochemically, tumor cells were CK7-positive and CK20-negative; SATB2 staining was uniformly negative, and CDX2 exhibited only focal, weak nuclear positivity. Given this uncommon CK7+/CK20- profile, an extended panel was performed: GATA3, TRPS1, ER, PR, WT1, calretinin, PAX8, CD138, p63, uroplakin, CD45, chromogranin, and synaptophysin were all negative, whereas CK19 and MUC5AC were strongly positive and MUC2 was negative, indicating a gastric-type immunophenotype (Figure 3). Additional histochemical stains confirmed signet-ring cells in ~ 8% of fields and PAS/DPAS-positive cytoplasmic mucin. Comprehensive imaging (CT, positron emission tomography) and repeat endoscopic review excluded an extra-colonic primary malignancy/carcinoma (Figure 1C). The findings supported a diagnosis of primary colonic poorly cohesive adenocarcinoma with gastric-type immunoprofile and focal signet-ring differentiation. According to the American Joint Committee on Cancer 8th edition, the final pathological stage was pT3 pN1b (Stage IIIB).

Mismatch repair (MMR) analysis demonstrated loss of MLH1 and PMS2 with intact MSH2 and MSH6 (Figure 4). The patient's postoperative course was uneventful; she was discharged on day 8, initiated on adjuvant fluoropyrimidine-based chemotherapy, and remained disease-free at six-month follow-up.

Discussion

In the 2019 WHO Classification of Tumors of the Digestive System, colorectal neoplasms composed of single cells or loosely cohesive clusters without well-formed glandular structures are designated as "poorly cohesive carcinoma/signet-ring cell carci-

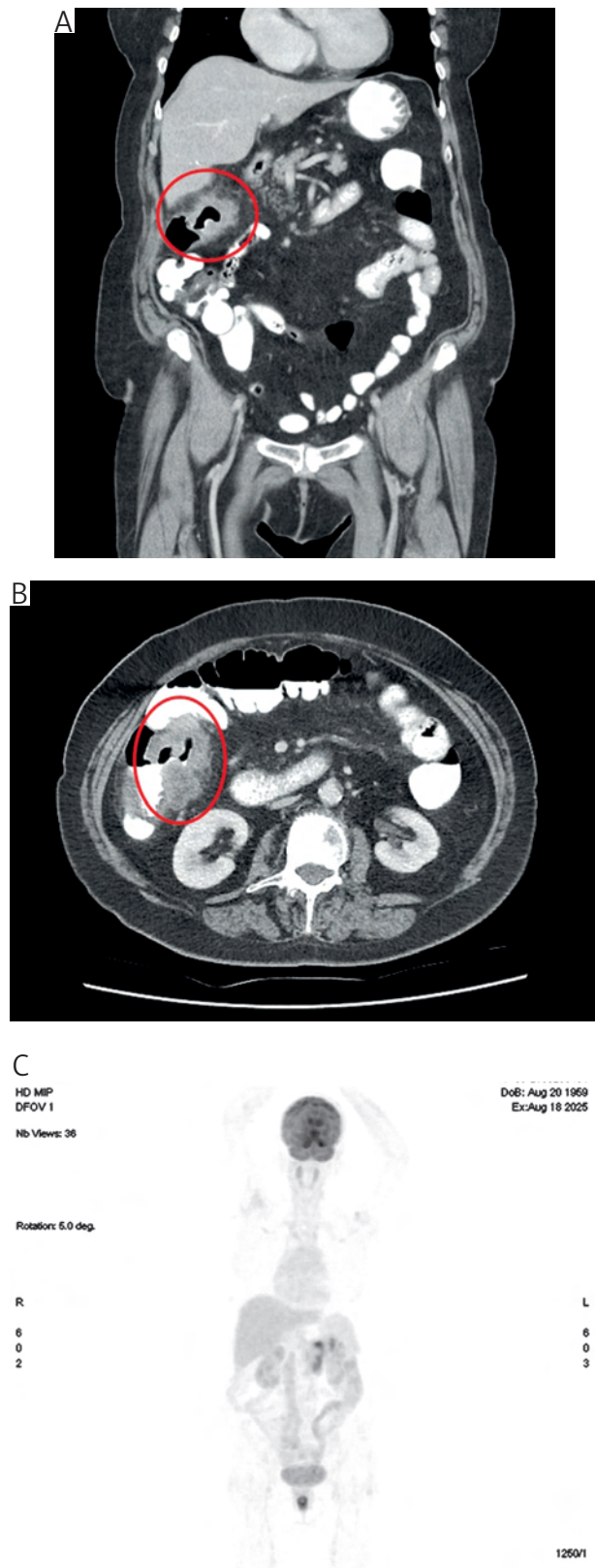


Figure 1. Coronal (A) and axial (B) contrast-enhanced computed tomography (CT) images demonstrate marked mural thickening and an ulceroinfiltrative mass at the hepatic flexure (highlighted with red circles), causing luminal narrowing. C) Postoperative whole-body positron emission tomography CT imaging reveals no abnormal FDG uptake, confirming the absence of distant metastasis

noma” (ICD-O 8490/3). Lesions in which over 50% of neoplastic cells exhibit signet-ring morphology are classified as signet-ring cell carcinomas, whereas those with fewer than 50% signet-ring cells but a diffuse, discohesive growth pattern are termed poorly cohesive adenocarcinomas with focal signet-ring differentiation [5]. Both entities are exceedingly rare – accounting for less than 1% of all colorectal adenocarcinomas – and share histologic hallmarks such as extensive lymphovascular and perineural invasion, tumor necrosis, and often a “bottom-up” submucosal infiltration pattern that replaces the usual dysplasia-invasion interface [5, 6]. Prior to 2019, these variants were subsumed under the broad “adenocarcinoma” category, and specific morphologic or immunophenotypic data remain limited [7].

Beyond nomenclature, the clinicopathologic spectrum of poorly cohesive tumors differs in several respects from conventional, gland-forming colorectal adenocarcinoma. Although they are enriched among younger patients, they span the full age range and may present in older adults as well [8, 9]. Sex distribution in colonic signet-ring carcinomas appears roughly balanced overall, whereas a male predominance has been reported in rectal counterparts [8]. Anatomically, there is a right-sided predilection, and the diffuse “bottom-up” pattern may lead to under-sampling at endoscopic biopsy, delaying definitive diagnosis. At presentation, many cases are already advanced (T3–T4), and there is a well-recognized propensity for peritoneal dissemination in addition to frequent lymphovascular and perineural invasion [8]. Our case aligns with this high-risk clinicopathologic profile despite the patient’s older age, reinforcing that the biology is not confined to early-onset disease.

The morphologic differential diagnosis hinges on recognizing a genuine discohesive epithelial neoplasm and separating it from mimics. Diffuse-type gastric carcinoma, plasmacytoid urothelial carcinoma, classic lobular carcinoma of the breast, and certain lymphomas can emulate a single-cell or sheet-like infiltrate in colorectal sites. Accordingly, accurate classification relies on integrating histology with a judicious IHC panel and clinicoradiologic correlation, particularly when endoscopic sampling is scant or the lesion is right-sided and ulceroinfiltrative.

Immunophenotypically, these tumors may deviate from the canonical colonic profile (CK7–/CK20+/CDX2+/SATB2+). A subset acquires a “gastric-type” signature characterized by de novo CK7 expression with reduced or negative SATB2 and CDX2 and expression of gastric-type mucins (e.g., MUC5AC), sometimes accompanied by loss of CK20 [9, 10]. This discordant phenotype can complicate the diagnostic work-up by blurring the distinction from an extracolonic primary malignancy/carcinoma; however, when it aligns with the morphology and clinical con-

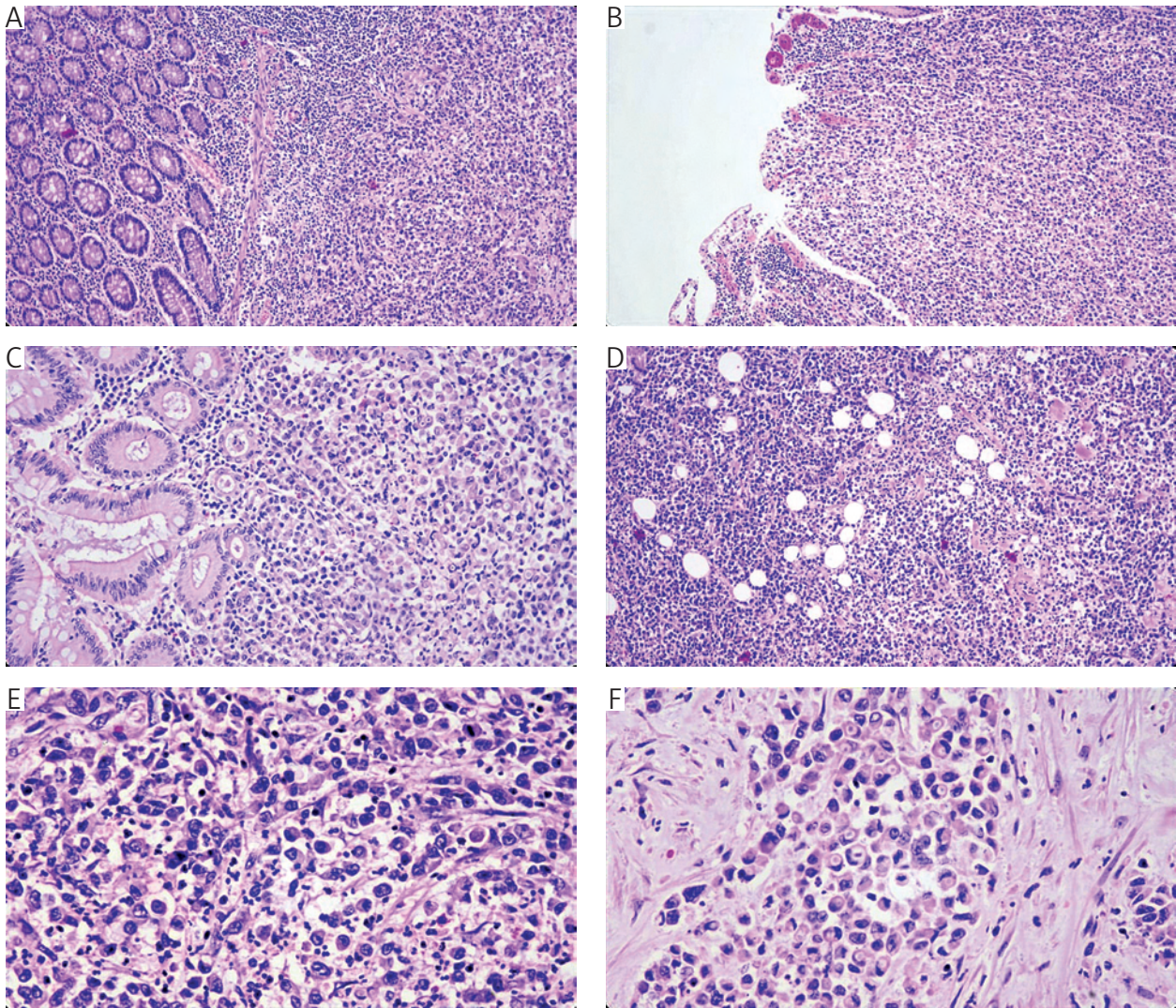


Figure 2. A) Intact colonic mucosa overlying a subepithelial infiltrate composed of isolated single tumor cells, without surface dysplasia or an *in situ* component. B) Superficial portion of the ulceroinfiltrative mass in which the surface mucosa is completely effaced and replaced by poorly differentiated, discohesive carcinoma, representing the most luminal aspect of the lesion. C) Area where poorly cohesive tumor cells infiltrate between and around non-neoplastic colonic glands, highlighting the intermingling pattern with preserved native crypts. D) Deeper tumor infiltration composed of diffuse sheets of poorly cohesive cells accompanied by a mixed inflammatory infiltrate. E, F) Higher magnification showing marked nuclear pleomorphism, irregular chromatin distribution, and focal signet-ring-like morphology

HE; original magnifications: 100× (A–D), 200× (E, F).

text, a primary colonic origin can be secured through a broad immunopanel and exclusionary imaging [11, 12]. Our case exemplifies this pattern (CK7 positive, CK20 negative, weak/focal CDX2 with SATB2 loss and MUC5AC positivity), and the extended negative panel for non-colorectal lineages supported a primary colonic diagnosis.

Furthermore, gastric-type immunophenotypic shifts are not restricted to poorly cohesive carcinomas but have also been documented in mucinous and signet-ring cell subtypes of colorectal adenocarcinoma – entities already associated with aggressive clinical behavior and poor outcomes [9, 10]. In large retrospective analyses, *de novo* CK7 expression in colorec-

tal tumors has emerged as an independent predictor of reduced overall survival, reflecting a loss of enteric differentiation and acquisition of a more undifferentiated phenotype [10]. Concurrently, SATB2 loss correlates with higher tumor grade, deeper invasion, advanced nodal stage, and diminished disease-specific survival. Taken together, these findings highlight that immunophenotypic discordance – characterized by CK7 positivity, SATB2 negativity, and ectopic gastric mucin expression – not only complicates the diagnostic work-up but also identifies a biologically distinct, high-risk subset of colorectal carcinomas. Consequently, recognizing this phenotype should prompt both meticulous pathologic evaluation and consideration

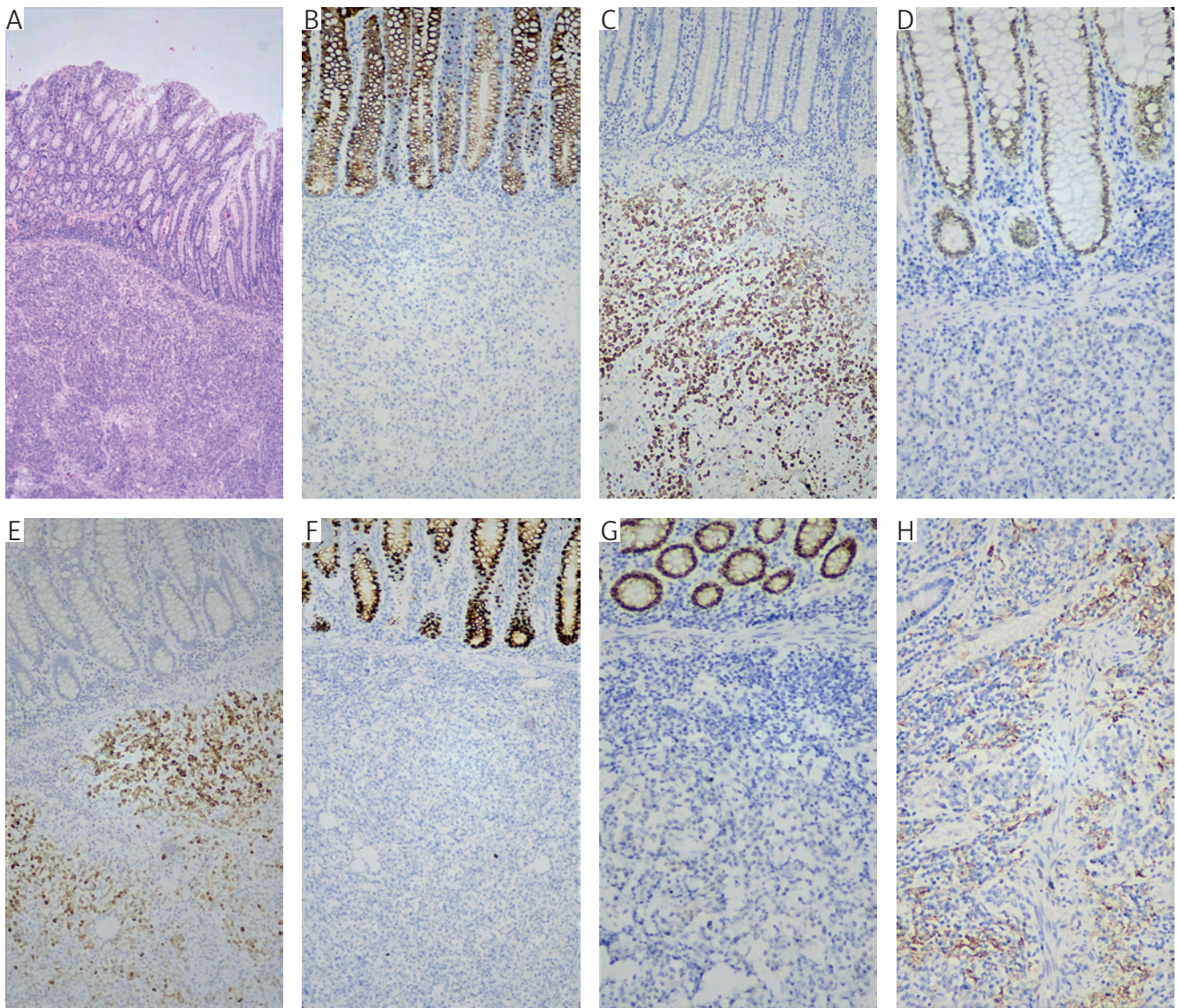


Figure 3. Hematoxylin and eosin staining (A) demonstrates infiltration of tumor cells located directly beneath an intact colonic mucosal surface. Immunohistochemical analysis reveals that CK20 (B), SATB2 (D), CDX2 (F), and MUC2 (G) are positively expressed in the native colonic epithelium but are completely negative in the underlying tumor, indicating loss of typical colorectal differentiation markers. In contrast, CK7 (C) and MUC5AC (E) show positive staining in the tumor component, while being absent in the surface colonic mucosa, suggesting an aberrant immunophenotypic profile. PD-L1 immunostaining (H) reveals membranous positivity in tumor and/or immune cells, with a combined positive score estimated at approximately 10%

of intensified surveillance or adjunctive therapeutic strategies.

The coexistence of synchronous colonic neoplasms in this patient provided a valuable morphological counterpoint. Although three low-grade villous adenomas were identified and removed, they were anatomically distant from the hepatic flexure mass and showed no histologic continuity with the carcinoma. Their presence implies that while the patient retained the propensity for the classic adenoma-carcinoma sequence, the poorly cohesive carcinoma likely arose *via* an alternative, rapid de novo pathway. This distinction is critical; the main tumor lacked a precursor adenoma and exhibited a ‘bottom-up’ growth pat-

tern, a feature that sharply contrasts with the conventional polypoid progression seen in the synchronous lesions. This divergence in tumorigenesis directs attention towards a distinct molecular driver, specifically the MMR pathway [13, 14].

Mismatch repair deficiency is enriched across discohesive and mucinous colorectal carcinoma phenotypes, supporting a distinct biology relative to conventional, gland-forming tumors. In unselected colorectal adenocarcinoma, mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) is identified in a meaningful minority ($\approx 15\%$), but rates are higher in specific histotypes: medullary carcinomas frequently demonstrate MSI-H (often $> 40\%$ across series),

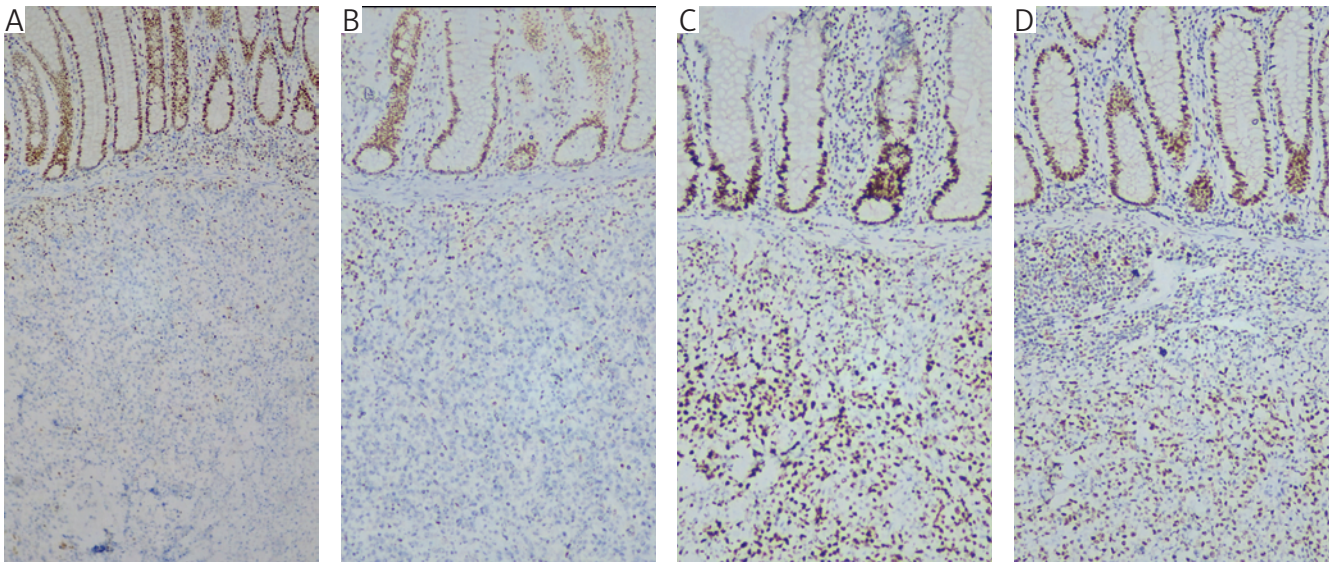


Figure 4. Immunohistochemical evaluation of DNA mismatch repair proteins demonstrates loss of nuclear expression for MLH1 (A) and PMS2 (B) in tumor cells, while the internal positive control (colonic mucosa) retains intact staining. In contrast, nuclear expression of MSH2 (C) and MSH6 (D) is preserved in both tumor and non-neoplastic epithelium

mucinous adenocarcinomas show enrichment (commonly ~ 20–30%), and signet-ring cell variants also exhibit variable association [13]. Although dedicated cohorts of poorly cohesive carcinomas remain limited, their overlap with mucinous and signet-ring morphologies provides a plausible framework for dMMR enrichment [14]. In our case, loss of MLH1/PMS2 with intact MSH2/MSH6 places the tumor squarely within this spectrum and underscores the rationale for universal MMR screening in colorectal cancer to refine diagnosis, stratify prognosis, and guide downstream multidisciplinary decision-making.

Collectively, these observations emphasize that recognition of this morphological spectrum is not merely descriptive but carries direct implications for patient management and therapeutic stratification.

Conclusions

Rare colorectal carcinoma variants – including poorly cohesive and focal signet-ring cell subtypes – may lack the standard CK7-/CK20⁺/CDX2⁺/SATB2⁺ immunophenotype, instead exhibiting a “gastric-type” profile (CK7⁺, CK20⁻, SATB2⁻, and MUC5AC⁺). This immunophenotypic discordance, together with their diffuse, single-cell growth pattern, right-sided predilection, advanced stage at diagnosis, and frequent MMR deficiency, identifies a biologically distinct and aggressive subset. Accurate diagnosis therefore requires vigilant recognition of atypical morphologic features, comprehensive IHC panels to exclude non-colonic primaries/primary malignancies/carcinomas, and incorporation of MMR testing to inform prognostic assessment. Awareness of this pheno-

type is essential to avoid misclassification and to guide appropriate clinical management.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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