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Gastric/pancreatobiliary-type differentiation in colorectal adenocarcinoma: a rare and aggressive case in a young adult

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Abstract

Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality worldwide. Although most CRCs exhibit a characteristic immunohistochemical profile, rare variants with unusual differentiation patterns can pose significant diagnostic challenges and carry an adverse prognosis. We report a case of an aggressive colorectal adenocarcinoma with gastric/pancreatobiliary-type differentiation in a young adult. A 29-year-old woman presented with a 2-year history of melena, constipation, fatigue, and weight loss. Imaging and colonoscopy revealed a circumferential stenosing sigmoid colon mass with suspected peritoneal involvement. Histopathological examination demonstrated a moderately to poorly differentiated adenocarcinoma. Immunohistochemistry showed an atypical profile for colorectal origin, with positivity for CK7, MUC1, and MUC5AC, and negativity for CK20, CDX2, SATB2, and MUC2. Mismatch repair proteins were intact, indicating microsatellite stability. Surgical exploration revealed locally advanced disease with direct invasion of adjacent small bowel, appendix, and abdominal wall. *En bloc* resection was performed, and final pathology confirmed pT4bN2b disease with lymphovascular invasion and extranodal extension. This case highlights a rare immunophenotypic subtype of colorectal adenocarcinoma that mimics gastric or pancreatobiliary differentiation. Recognition of this entity is essential to avoid misclassification as metastatic disease from an extraintestinal primary and to ensure accurate staging and management. Awareness of such aggressive variants is particularly important given their association with poor prognostic features despite young patient age.

Key words: locally advanced colorectal cancer, *en bloc* resection, gastric differentiation, pancreatobiliary differentiation, immunohistochemistry.

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and a major cause of cancer-related mortality. In 2020, more than 1.9 million new CRC cases and approximately 930,000 deaths were estimated globally. The burden of CRC is projected to increase substantially, reaching 3.2 million new cases and 1.6 million deaths by 2040, with the majority of cases expected to occur in countries with high or very high Human Development Index levels.[1] Early diagnosis is critical for achieving a favorable prognosis.

Definitive diagnosis of CRC is established through pathological examination of tissue specimens. Immunohistochemistry plays a crucial role in differentiating primary CRC from metastatic disease involving the colon. Gastric/pancreatobiliary-type differentiation in CRC is a rare immunohistochemical pattern that poses significant diagnostic challenges and is associated with a poorer prognosis. Awareness of this entity is essential for accurate diagnosis and the formulation of an appropriate and definitive management plan.

Although CRC commonly presents electively, a subset of patients require urgent surgical management because of obstruction, perforation, or impending obstruction. Circumferential stenosing tumors that prevent complete endoscopic evaluation represent a clinically important presentation requiring prompt surgical assessment. In the present case, the inability to traverse the lesion endoscopically, together with radiological evidence of locally advanced disease, supported urgent operative management.

Case Report

A 29-year-old woman was referred to our Department by her primary care physician for surgical management after an initial diagnostic work-up for a 2-year history of melena and constipation, accompanied by fatigue and unintentional weight loss. Her past medical history and family history were unremarkable. The patient denied alcohol consumption and smoking.

The initial work-up included laboratory investigations, which revealed elevated tumor markers, with cancer antigen 19-9 meas-

uring 38 U/mL (reference range 0-37) and cancer antigen 125 measuring 86 U/mL (reference range 0-35). Contrast-enhanced computed tomography (CT) of the abdomen and pelvis demonstrated edematous thickening of the sigmoid colon with blurring of the adjacent small-bowel wall. Approximately four solid nodular lesions measuring up to 1.5 cm were identified adjacent to the primary tumor, raising suspicion for metastatic mesenteric lymph nodes and possible peritoneal implants.

Pre-referral colonoscopy demonstrated a circumferential stenosing lesion located 16 cm from the anal verge, characterized by friable, protruding, edematous mucosa with focal ulceration. Further advancement of the endoscope was not possible because of the marked luminal narrowing, and targeted biopsies confirmed a moderately differentiated adenocarcinoma.

Histopathological examination of the biopsy specimens showed moderately differentiated adenocarcinoma of the colon. Immunohistochemical analysis demonstrated intact expression of MLH1, MSH2, MSH6, and PMS2, indicating microsatellite stability.

Subsequent ^18F-fluorodeoxyglucose positron emission tomography-CT revealed increased tracer uptake in the known large sigmoid colon mass as well as in five additional solid nodular lesions, interpreted as peritoneal implants and/or metastatic lymph nodes. These included one lesion measuring 1 cm anterior to the right iliac vessels, two lesions measuring 7-8 mm adjacent to the left iliac vessels, and two lesions measuring 12-13 mm bilaterally adjacent to the sigmoid lesion within the lesser pelvis.

Although imaging suggested possible peritoneal involvement, the findings remained equivocal. Because the patient had a nearly obstructing circumferential sigmoid tumor that precluded complete colonoscopic evaluation and there was no definitive evidence of unresectable disseminated disease, surgical resection was considered the most appropriate management strategy.

The patient underwent exploratory laparotomy. Intraoperatively, a sigmoid colon mass was identified with direct contiguous invasion of an adjacent loop of small bowel, the tip of the appendix, and the abdominal wall. An *en bloc* resection was performed, consisting of sigmoid colectomy, segmental small-bowel resection, appendectomy, and resection of the involved portion of the abdominal wall with the parietal peritoneum.

The postoperative course was uneventful, and the patient was discharged on postoperative day 7. Gross pathological examination revealed a neoplastic mass measuring 6.5 cm in greatest dimension, located 3.5 cm from the proximal resection margin. The tumor infiltrated the adherent loop of small intestine, the appendiceal tip, and extensively involved the resected portion of the abdominal wall. Thirty lymph nodes ranging from 0.2 to 1.5 cm in size were retrieved.

Microscopically, the tumor was a moderately to poorly differentiated adenocarcinoma measuring approximately 6 cm, arising predominantly from the wall of the sigmoid colon and associated with extensive mucosal ulceration. The neoplasm demonstrated transmural invasion with direct extension into the adjacent small bowel, the appendiceal tip, and the abdominal wall by contiguity.

Immunohistochemical analysis showed tumor cell positivity for CK7, MUC1, and MUC5AC, with retained expression of SMAD4. The tumor cells were negative for CK20, CDX2, SATB2, MUC2, thyroid transcription factor 1, estrogen receptor, PAX8, WT1, p16, GATA3, glypican-3, HepPar-1, CD56, synaptophysin, and chromogranin. p53 exhibited a wild-type staining pattern. The Ki-67 proliferation index was approximately 30%. Mismatch repair protein analysis confirmed microsatellite stability, with a low probability of microsatellite instability-high status.

All surgical resection margins were free of neoplastic infiltration. Metastatic carcinoma was identified in 8 of the 30 examined lymph nodes, with evidence of extranodal extension. The remaining segments of the colon and small intestine submitted separately were unremarkable and showed no neoplastic involvement.

Following recovery from surgery, the patient was referred to the oncology service for evaluation and initiation of adjuvant therapy based on the final pathological staging. Although preoperative imaging suggested possible peritoneal disease, diffuse peritoneal carcinomatosis was not confirmed intraoperatively. Therefore, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were not performed.

Discussion

Metastatic adenocarcinoma from an unknown primary site represents a common clinical challenge. Immunohistochemical phenotyping of tumors plays a critical role in determining the site of origin. Among available markers, evaluation of CK7 and CK20 expression patterns is particularly useful, as the CK7−/CK20+ immunophenotype is characteristic of colorectal adenocarcinomas.

In the present case, the tumor demonstrated an unusual immunohistochemical profile (CK7+, MUC1+, MUC5AC+, CDX2−, CK20−, SATB2−, MUC2−), which is not typical of conventional colorectal adenocarcinoma. This profile is consistent with gastric/pancreatobiliary-type differentiation. Given that no extraintestinal primary tumor was identified and the lesion originated predominantly from the sigmoid colon, the findings support a diagnosis of primary colorectal adenocarcinoma rather than metastatic disease. The tumor was classified as pT4bN2b (8/30), with lymphovascular invasion and negative surgical margins (R0 resection), according to the 8th edition (2017) of the American Joint Committee on Cancer Tumor-Node-Metastasis staging system. This immunophenotypic profile represents a rare and highly aggressive variant of CRC.

Most colorectal adenocarcinomas lack CK7 expression; however, aberrant CK7 positivity has been associated with poorer prognosis and more aggressive biological behavior.[2,3] Similarly, MUC1 is commonly over-expressed in pancreatic and gastric cancers, and its expression in CRC has been linked to worse clinical outcomes.[4] Loss of CDX2 expression is uncommon in CRC and has been associated with decreased disease-free survival.[5] In one study, the CDX2−/CK20− phenotype was associated with older age (>56 years), advanced tumor stage (stage III or IV), deep tumor invasion (pT3 or pT4), lymph node metastasis (pN1 or pN2), poor differentiation (nonmedullary/non-signet ring cell type), *BRAF* mutation, and CpG island methylator phenotype-high status among microsatellite instability-high CRC.[6]

Low MUC2 expression in CRC tissues has been identified as an independent poor prognostic factor, regardless of tumor stage or other established markers of advanced disease.[7] Furthermore, decreased expression of SATB2, a highly specific marker for colorectal differentiation, has been correlated with regional lymph node metastasis, lymphovascular invasion, and higher tumor grade – features associated with unfavorable prognosis.[8] In a study of 130 colon adenocarcinomas, SATB2 expression was observed in

73.85% (96/130) of cases and was significantly higher in well-to-moderately differentiated tumors compared with poorly differentiated tumors ($p<0.05$).[9]

Unlike loss of SMAD4, which has been associated with tumor progression, metastatic potential, and poorer survival in CRC, retained SMAD4 expression in the present case suggests preservation of transforming growth factor-β signaling. Nevertheless, despite retained SMAD4, the tumor demonstrated highly aggressive clinicopathological features, indicating that other molecular mechanisms likely contributed to its biological behavior.

MUC5AC expression has been reported in 261 (15.7%) of 1,667 analyzed CRCs and was not associated with pT or pN status; however, it was also found to be unrelated to tumor aggressiveness in that cohort.[10] In contrast, another study suggested that differential expression of the secretory mucin MUC5AC may enhance tumorigenesis and confer chemoresistance.[11]

These apparently conflicting findings may reflect differences in patient populations, tumor molecular subtypes, and the biological role of MUC5AC at different stages of tumor progression. While large cohort studies have not consistently associated MUC5AC with adverse pathological features, experimental studies suggest that MUC5AC may contribute to tumor progression and chemoresistance. In the present case, MUC5AC positivity occurred in conjunction with multiple adverse pathological features, including locally advanced disease, lymphovascular invasion, and extensive nodal metastasis, supporting the concept that its biological significance may depend on the broader molecular context rather than its isolated expression.

In a comparative immunohistochemical study including 118 colorectal, 59 gastric, and 32 pancreatic adenocarcinomas, the CK7−/CK20+ phenotype was observed in 64% (75/118) of colorectal tumors, 5% (3/59) of gastric tumors, and none of the pancreatic tumors. The CK7+/CK20+ phenotype was identified in 20% (24/118) of colorectal, 48% (28/59) of gastric, and 22% (7/32) of pancreatic adenocarcinomas, whereas the CK7+/CK20− pattern was found in only 2% (2/118) of colorectal carcinomas. CDX2 expression was present in 97% (114/118) of colorectal, 61% (36/59) of gastric, and 16% (5/32) of pancreatic adenocarcinomas.[12] Recognition of this rare gastric/pancreatobiliary-type immunophenotype in primary colorectal adenocarcinoma is essential, as it has important diagnostic, prognostic, and therapeutic implications and may warrant closer clinical surveillance and tailored management strategies.

Reports of primary colorectal adenocarcinomas exhibiting a gastric/pancreatobiliary immunophenotype remain exceedingly uncommon. Published cases have highlighted the diagnostic challenge posed by CK7 positivity, loss of conventional colorectal markers such as CK20, CDX2 and SATB2, and expression of gastric mucins, which may closely mimic metastatic upper gastrointestinal or pancreatobiliary adenocarcinoma.[13] Similar to these reports, our case demonstrated an aggressive clinicopathological profile with locally advanced disease and extensive lymph node metastases, but occurred in a remarkably young patient.

Limitations

This report describes a single case and therefore cannot establish clinicopathological associations. Extended molecular profiling beyond mismatch repair status was unavailable, limiting further biological characterization. In addition, postoperative oncological follow-up was limited, precluding assessment of treatment response and long-term outcome.

Conclusions

This case highlights a rare and diagnostically challenging subtype of primary colorectal adenocarcinoma with gastric/pancreatobiliary-type differentiation occurring in a young adult. Recognition of this uncommon immunophenotype is essential to distinguish it from metastatic upper gastrointestinal or pancreatobiliary malignancies and to ensure appropriate staging and management. Despite its rarity, this variant appears to be associated with aggressive clinicopathological features, emphasizing the importance of comprehensive immunohistochemical evaluation and awareness among clinicians and pathologists. Further studies are needed to better define its molecular characteristics, biological behavior, and optimal therapeutic approach.

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