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CASE REPORTS

Clear Cell Colon Adenocarcinoma with Enteroblastic Differentiation: A Rare Case Report with Literature Review

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Abstract

Introduction Primary clear cell adenocarcinoma of the colon is an exceptionally rare malignancy, with an incidence reported between 0.086 and 2.05%. Furthermore, enteroblastic differentiation in colorectal adenocarcinoma has been documented in approximately 4% of cases. Given the rarity of these conditions, additional data are necessary to elucidate their clinicopathological characteristics and potential interrelations. This report presents a rare case accompanied by a review of relevant literature.

Case A 31-year-old female patient presented with symptoms indicative of ileus. A right hemicolectomy revealed an annular colonic lesion, histologically consistent with clear cell adenocarcinoma. Immunohistochemical analysis demonstrated enteroblastic differentiation and confirmed the colonic origin of the tumor. Molecular analysis identified wild-type RAS and BRAF genes, but a p.Glu545Lys mutation in the PIK3CA gene was noted. During the treatment course, the patient developed distant metastasis.

Conclusion While enteroblastic differentiation has been described in gastric clear cell adenocarcinomas, no established definition exists for its colonic counterparts. The number of case reports and studies exploring the clinical and molecular features of these tumors is limited. The available evidence suggests that these tumors may exhibit a more aggressive clinical course compared to conventional colorectal adenocarcinomas. Larger case series are required to enhance our understanding of the biological behavior and therapeutic implications of this rare tumor subtype.

Keywords Colorectal adenocarcinoma · Clear cell adenocarcinoma · Enteroblastic differentiation

Introduction

Primary clear cell adenocarcinoma of the colon (CCA) remains exceedingly rare [1–3]. Most CCA have been identified in the left colon, predominantly affecting males, with a mean age of 56.5 years [3–5].

Gastric adenocarcinoma with enteroblastic differentiation (GAED) is typically diagnosed based on positivity for AFP, glypican-3, and SALL4, and is often associated with clear cell morphology [6]. In contrast, colorectal adenocarcinoma with enteroblastic differentiation (CAED) is poorly understood, with only a limited number of case reports available [7]. Due to its rarity, the clinicopathological and epidemiological features have not been clearly defined. This report describes an uncommon case of enteroblastic CCA in a young female patient, with the tumor localized in the right colon.

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Case

A 31-year-old female presented with periumbilical cramps and nausea. The patient was discharged after receiving an enema under emergency conditions. However, due to persistent pain, she presented again the following day. As her symptoms did not respond to symptomatic treatment, an abdominal CT was performed, which was evaluated in favor of ileus, and emergency surgery was planned. There were no notable features in the medical history and family history. The development of ileus prompted an exploratory laparotomy, which revealed a 3-cm circumferential mass in the hepatic flexure. Since a tumor was not initially suspected, no tumor markers or clinical tumor staging evaluations were performed preoperatively. In the post-operative blood tests, CA-15-3 (14.8 U/ml; reference range 0–25 U/ml), CA-19-9 (14 U/ml; reference range 0–27 U/ml), and CEA (0.508 ng/ml; reference range 0–3.8 ng/ml) were within normal limits, whereas CA-125 was elevated at 53.7 U/ml (reference range 0–35 U/ml). The patient underwent right hemicolectomy. Gross examination revealed a $4 \times 3.5 \times 1.4$ cm annular, stenosing mass infiltrating the full thickness of the wall (pT4a). Histologically, the tumor exhibited tubular-glandular adenocarcinoma with extensive clear cell morphology. Lymphovascular invasion, perineural invasion, and high tumor budding were observed. Immunohistochemical analysis indicated that both the conventional and clear cell components were CK7-negative and CK20, CDX2, and CEA positive (Fig. 1). A comprehensive immunohistochemical panel was employed to exclude the possibility of metastatic disease (Table 1). PAS staining was positive and cleared after diastase, indicating glycogen-rich cytoplasm (Fig. 1). Given the clear cell morphology, enteroblastic differentiation was considered. SALL4, AFP, and Glypican-3 were evaluated, revealing that approximately 30% of tumor cells exhibited strong nuclear SALL4 positivity (Fig. 1), whereas AFP and Glypican-3 were negative, thereby supporting the diagnosis of enteroblastic differentiation. HER2 was negative. The tumor was microsatellite stable, as evidenced by intact expression of MLH1, MSH2, MSH6, and PMS2. After the pathological diagnosis, serum AFP and HCG levels were tested and found to be unremarkable. Molecular analysis demonstrated wild-type NRAS, KRAS, and BRAF genes. Among 33 reactive lymph nodes, two displayed metastasis with extracapsular extension, and additional tumor nodules were identified (pN1b). The patient was diagnosed with locally advanced colon cancer (pT4aN1bM0)

Table 1 Immunohistochemistry results of the case

Stain	Result
Cytokeratin 7	Negative
Cytokeratin 20	Positive
CDX2	Positive
mCEA	Positive
MUC1	Positive
MUC2	Negative
MUC5AC	Negative
MUC6	Negative
AMACR	Negative
PAX8	Negative
Synaptophysin	Negative
Chromogranin A	Negative
SALL-4	Positive
AFP	Negative
Glypican-3	Negative

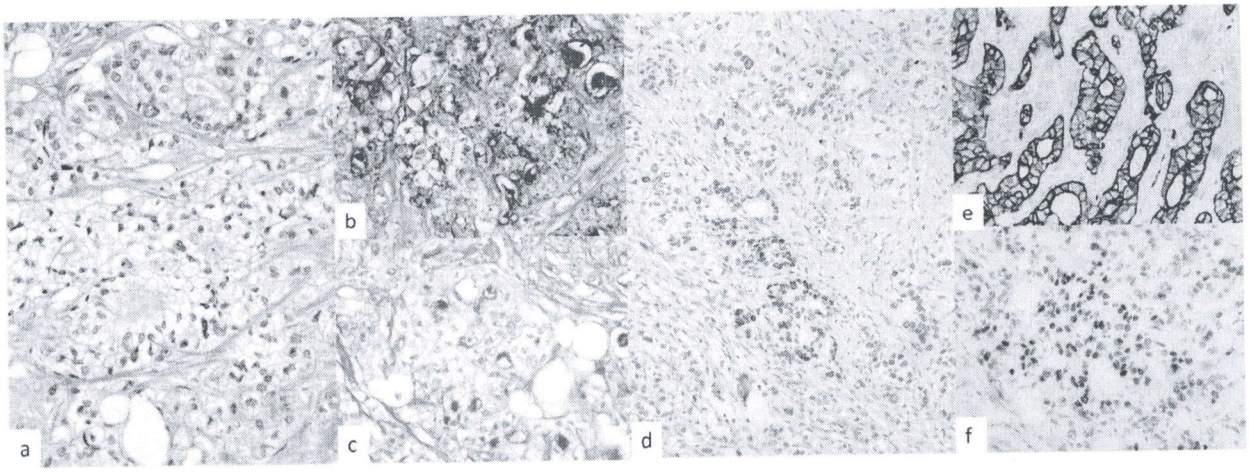


Fig. 1 Adenocarcinoma with clear cell morphology, H&E×400 (**a**). Cytoplasmic PAS positivity of clear cell component,×400 (**b**). PAS-D negativity, showing the glycogen rich nature of the clear cells,×400 (**c**). Focal strong nuclear staining of SALL4,×400 (**d**). Strong, diffuse CK20 positivity,×400 (**e**). Diffuse CDX2 positivity,×400 (**f**)

and subsequently received adjuvant FOLFOX4 chemotherapy for six months. Six months following treatment, the patient presented with abdominal pain. CT imaging revealed bilateral ovarian masses. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed, which confirmed metastatic colonic adenocarcinoma and malignant cells in peritoneal washings. The tumor in the metastatic lesion also exhibited clear cytoplasm and showed enteroblastic differentiation with SALL4 positivity. The patient was subsequently diagnosed with pT4N2M1 metastatic colon cancer and was treated with FOLFIRI-Bevacizumab. Next-generation sequencing (NGS) of the ovarian metastasis revealed four mutations: PIK3CA (p.Glu545Lys), PBRM1 (p.Arg1160Ter), TP53 (p.Trp91Ter), and AR (p.Asp223Tyr). The PIK3CA p.Glu545Lys mutation is associated with poorer outcomes regarding recurrence and metastasis [8]. The patient then commenced FOLFOX4-Cetuximab chemotherapy.

Ten months into therapy, ileus symptoms recurred. CT imaging indicated widespread metastatic lesions in the liver, peritoneum, and sigmoid colon, prompting diagnostic laparotomy and loop ileostomy. At this stage, serum tumor marker levels were markedly elevated: CA-125 (118 U/ml), CA-15-3 (29.3 U/ml), CA-19-9 (1349 U/ml), and CEA (9.5 ng/ml). Four months later, the patient presented with fever, dyspnea, confusion, diarrhea, and fatigue. Despite supportive care, she succumbed to sepsis and cardiopulmonary failure 32 months after diagnosis.

Discussion

Reports indicate that clear cell colorectal epithelial tumors are rare, with a reported prevalence of approximately 0.086% [2, 3]. Due to its rarity, a comprehensive immunohistochemical panel is also necessary to rule out metastasis [2, 5].

The detection of AFP-producing gastric adenocarcinoma has led to the identification of GAED, a subtype known for its aggressive clinical behavior [6]. CAED is typically diagnosed based on positivity for at least one of the following markers: AFP, Glypican-3, or SALL4, and is often associated with clear cell morphology and a poor prognosis. In fact, approximately half of CAED cases display features such as vascular invasion, lymph node metastasis, distant metastases, or peritoneal dissemination, all of which are linked to a worse prognosis [9]. Yamashiro et al. identified enteroblastic differentiation in 4.58% ($n=42$) of 917 colorectal carcinoma cases. Among these 42 CAED cases, only 23.8% ($n=10$) showed clear cell morphology. Enteroblastic cases were found to correlate with adverse outcomes, independent of clear cell features [10].

Molecular profiling has revealed similar mutation rates in CAED and conventional colorectal cancers, including KRAS (27.6%) and TP53 (52.4%). Microsatellite stability was also comparable, although ERBB2 amplification was more prevalent in CAED (9.5% vs. 5%). Notably, clear cell CAED displayed a higher rate of TP53 mutations [10].

Data on targeted therapy is still limited. HER2 overexpression may occur more frequently in CAED; however, the presence of enteroblastic markers, regardless of clear cell morphology, appears to be a key factor in determining aggressive behavior. In a large case series, the 3-year survival rate for colorectal carcinoma cases positive for enteroblastic markers was reported as 66%, compared to 85% in conventional cases. In the same study, CAED was associated with significantly poorer overall and progression-free survival ($p<0.01$ and $p<0.05$, respectively) [10]. Although routine screening for enteroblastic differentiation may not be cost-effective, it is recommended for tumors that demonstrate clear cell morphology. Although studies on this rare tumor subtype have shown a worse prognosis compared to conventional colorectal carcinoma, no effective difference has yet been identified in terms of targeted therapeutic strategies. However, identifying these cases may help refine treatment strategies and improve prognostic accuracy due to their more aggressive clinical course.

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Declarations

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Informed consent Informed consent was obtained.

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