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Clear Cell Carcinoma of the Left Colon: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 69-year-old
Final Diagnosis: Clear cell carcinoma of the colon
Symptoms: Constipation • IBS like symptoms
Clinical Procedure: —
Specialty: Histology and Embryology • Oncology • Pathology • Surgery

Objective: Rare disease

Background: Primary clear cell carcinoma of the colon is an exceptionally rare condition. It is still uncertain whether this carcinoma represents a separate biological category or simply a variant of typical colorectal cancer. From a diagnostic standpoint, the presence of clear cell morphology introduces significant challenges, as similar features can be observed in various other carcinomas, including renal, ovarian, and endometrial carcinoma. Typically, primary colorectal tumors demonstrate positivity for markers such as CK20 and CDX2, supporting intestinal origin.

Case Report: We present a case of primary clear cell carcinoma of the sigmoid colon, with no adenoma component, in a 69-year-old woman. The tumor was detected on routine bowel screening colonoscopy, and the patient underwent anterior resection of a pT3N2b sigmoid tumor with prophylactic oophorectomy and salpingectomy. In contrast to the positivity for intestinal-origin markers typically seen in primary colorectal tumors, in this case, the histopathological and immunohistochemical analyses revealed that the tumor was positive for AMACR, CK7, and PAX 8 and negative for WT1, ER, PR, P16, CD10, CDX2, and CK20. These results were consistent with colonic clear cell carcinoma.

Conclusions: Specific data on colorectal clear cell carcinoma in Ireland and worldwide are limited. In academic literature, few cases have been documented. The presence of clear cell morphology in colon tumors presents significant diagnostic challenges, necessitating careful radiological and histopathological evaluation, which should be correlated with the patient's clinical history. This case was documented due to the extreme rarity of this condition and the diagnostic difficulties it poses, particularly in distinguishing clear cell carcinoma of the colon from conventional adenocarcinoma.

Keywords: clear cell carcinoma • colonoscopy • colorectal neoplasms • sigmoid neoplasms

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Introduction

Clear cell carcinoma of the colon is an exceedingly uncommon type of colorectal cancer. It was first identified by Hellstrom and Fisher in 1964 in a 67-year-old male patient who presented with melena and was diagnosed with an atypical colonic carcinoma exhibiting clear cell morphology [1]. While clear cell carcinoma is well recognized in organs such as the kidney and female reproductive system, its occurrence in the colon is extremely rare and remains poorly understood.

To date, approximately 30 to 40 cases of primary colorectal clear cell carcinoma have been reported, highlighting its rarity, uncommon presentation, and diagnostic challenges [2].

In this report, which we believe to be the first documented instance in the Republic of Ireland, we present a case of de novo sigmoid clear cell carcinoma and provide an updated review of the literature.

Case Report

A 69-year-old woman with essential hypertension, high cholesterol, diverticular disease, and irritable bowel syndrome (IBS), had undergone a hysterectomy 40 years earlier due to uterine fibroids complicated by severe menorrhagia. She had attended our institution's endoscopy unit in late 2023 for routine bowel cancer screening following a positive fecal occult blood test and intermittent constipation, which was initially attributed to IBS. She denied abdominal pain, palpable masses, melena, or other symptoms commonly associated with abdominal cancer. She also reported no previous history of endometriosis and no known family history of hereditary carcinoma or other gastrointestinal disorders.

Laboratory Investigations

The colonoscopy revealed a large circumferential sigmoid tumor that the endoscopist was unable to traverse despite using a pediatric endoscope (**Figure 1**). Contrast-enhanced computed tomography (CT) and pelvic magnetic resonance imaging (MRI) revealed a 7-cm circumferential solid sigmoid colon mass with luminal narrowing and T3 extension, along with multiple enlarged mesenteric lymph nodes (**Figure 2**). Imaging also revealed no concerning renal or ovarian pathologies.

At the time of diagnosis, all of her blood results, including complete blood count, liver function tests, renal profile, and the tumor markers CEA and CA 19-9, were within normal limits. Ten biopsies obtained during colonoscopy were reported as invasive, moderate to poorly differentiated adenocarcinoma (**Figures 1, 2**).

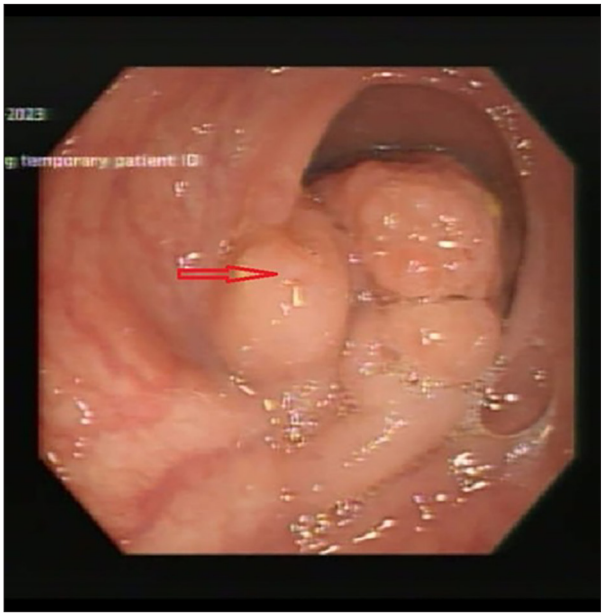

Figure 1. Screening colonoscopy image taken using a pediatric endoscope revealing a stenotic tumor in the sigmoid colon.

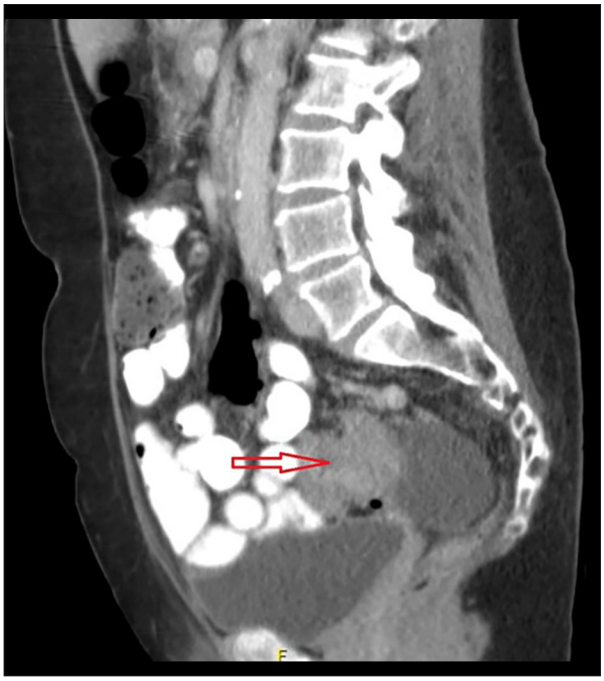

Figure 2. Computed tomography scan revealing a stenotic tumor in the sigmoid colon.

Management

After discussion in a multidisciplinary meeting, the patient subsequently underwent low anterior resection of the sigmoid tumor. Intraoperatively, no pelvic abnormalities were identified apart from a longstanding benign left ovarian cyst.

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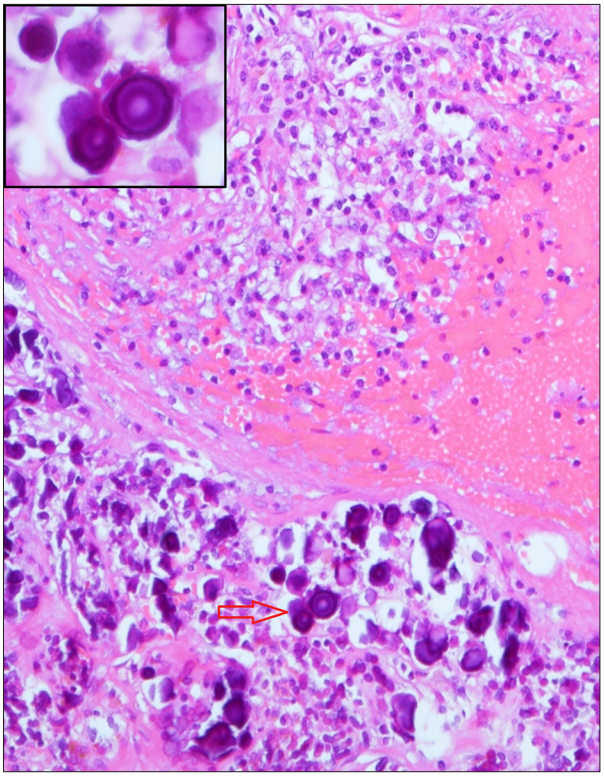

Figure 3. Lymph node showing tumor involvement with extensive psammomatous calcifications (inset). Hematoxylin and eosin, original magnification 100×, inset magnification 600×.

Consequently, prophylactic left salpingo-oophorectomy was performed concurrently.

Histopathological Findings

The final histopathological analysis of the resected colon revealed a pT3N2b clear cell carcinoma with focal calcification, and notably, there was no evidence of colorectal adenoma or adenocarcinoma, which is an unusual finding for this location. However, based on the anatomical distribution of the lesion, the tumor was initially considered most consistent with a primary colorectal carcinoma.

Additionally, the analysis of the resected ovary and fallopian tube identified a benign simple ovarian cyst and a normal fallopian tube. Furthermore, the examination of 11 nearby lymph nodes revealed a metastatic tumor characterized by psammomatous calcification, which is a nonspecific feature more commonly associated with tumors with Müllerian differentiation (**Figure 3**).

Immunohistochemistry

Following surgery, immunohistochemistry was conducted to determine whether the tumor originated from colorectal, renal, or gynecological sources. The immunohistochemistry results showed that the excised tumor tested positive for AMACR, CK7, and PAX 8, while it was negative for WT1, ER, PR, P16, CD10, CDX2, and CK20 (**Figure 4**). This result aligns more closely with clear cell carcinoma of the gynecological tract lineage. Generally, the absence of CDX2 and CK20 excludes a colorectal origin for the tumor, while the presence of PAX8 and CK7 suggests a clear cell carcinoma with Müllerian differentiation [3].

Considering the hypothesis that the tumor might have originated from an endometriosis site, thorough sampling of the resected bowel wall immediately adjacent to the tumor, as well as the excised left ovarian cyst and fallopian tube, was conducted. This procedure was carried out by the pathologist on 2 separate occasions, and neither revealed any evidence of endometriosis (**Figure 5**).

The case was discussed during a second multidisciplinary meeting. A diagnosis of Müllerian-origin clear cell carcinoma was made. This conclusion was based on the patient's immunohistochemical profile (PAX8+, CK7+, CDX2-, CK20-), and was further supported by the presence of psammoma calcification (concentrically laminated calcifications often associated with Müllerian tumors). Following a surgical consultation with the medical oncology team, the patient received postoperative adjuvant chemotherapy with carboplatin and paclitaxel, rather than opting for 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX), which is typically the standard adjuvant regimen for colorectal carcinoma.

The patient successfully completed 6 cycles of chemotherapy without experiencing significant complications. Follow-up imaging and colonoscopy conducted 1 year postoperatively revealed no evidence of disease recurrence. She remains under active surveillance with laboratory follow-up testing every 6 months, annual CT scans of the thorax, abdomen, and pelvis, and a repeat colonoscopy planned for 3 years after the surgery.

Discussion

Overview and Epidemiology

Clear cell changes in colorectal tumors are extremely rare. Clear cell carcinomas are well documented in organs that are derived from the Müllerian system such as the kidneys, ovaries, female genital tract, and lower urinary tract [4-6]. While these tumors share the characteristic clear cell cytoplasm, they differ in their histogenesis, immunohistochemical profiles, and clinical behavior depending on the organ of origin. For example, Müllerian and renal clear cell carcinomas demonstrate PAX8 expression in immunohistochemical analyses, whereas colorectal clear cell tumors are more likely to express CDX2 and CK20, supporting intestinal differentiation.

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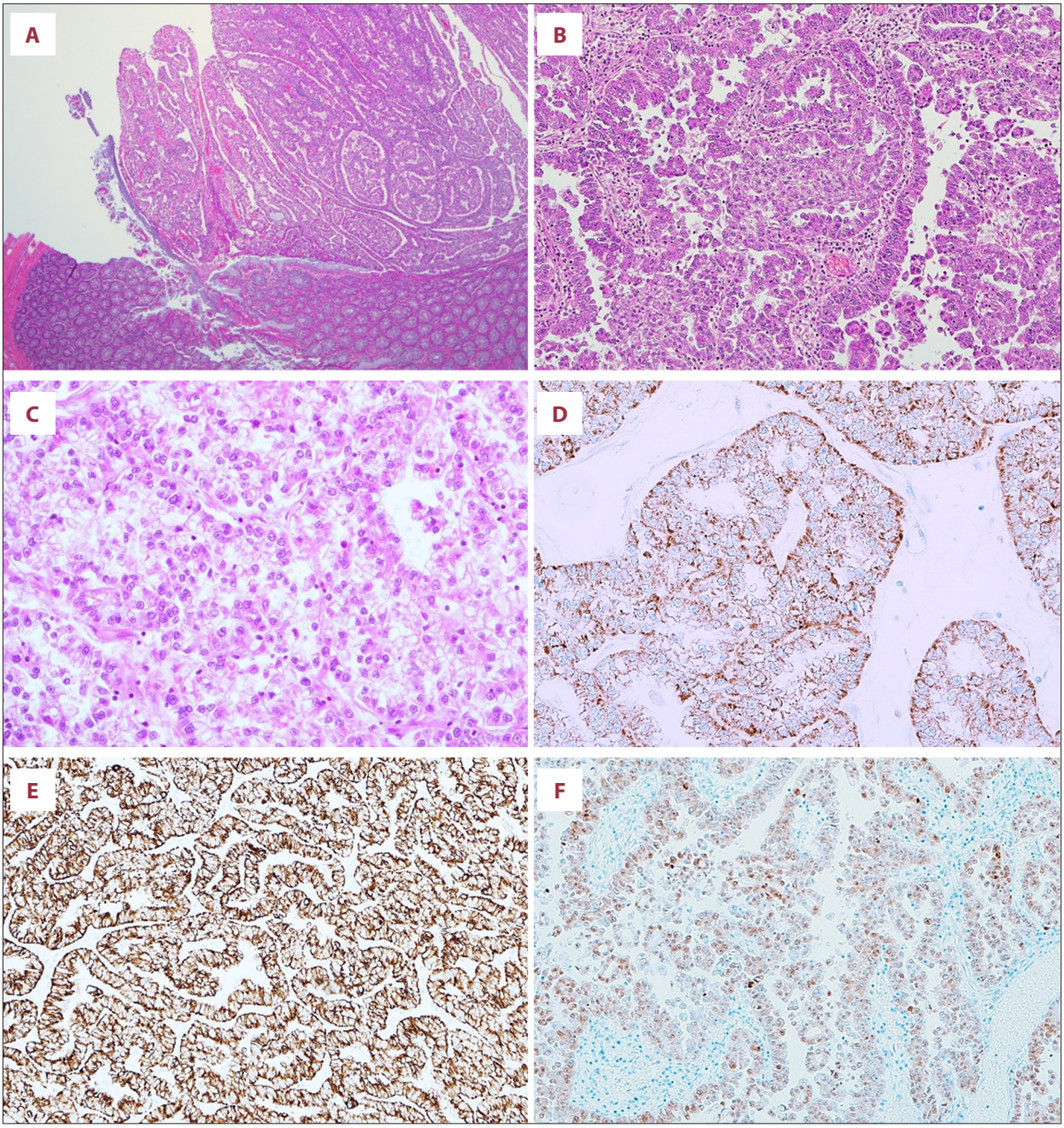

Figure 4. Anterior resection of the sigmoid tumor. (**A**) Section showing normal colonic mucosa with adjacent tumor, with no adenomatous edge; hematoxylin and eosin, original magnification 20×). (**B**) Papillary areas of tumor with fibrovascular cores (hematoxylin and eosin, original magnification 40×). (**C**) Tumor cells showing clear cytoplasm with prominent cell borders (hematoxylin and eosin, original magnification 200×). (**D**) Positive immunohistochemistry staining with AMACR. (**E**) Positive immunohistochemistry staining with CK7. (**F**) Positive immunohistochemistry staining with PAX8.

Unlike primary colorectal cancers, clear cell carcinomas of the colon present with nonspecific and often subtle symptoms that may delay diagnosis. The most reported symptoms include abdominal pain or discomfort, anemia and fatigue, lower gastrointestinal bleeding or melena, and bowel obstruction [2]. In our case, the cancer went undetected until it had grown large enough to cause stenosis of the sigmoid colon, primarily because most clinical signs were absent, except for intermittent constipation. This situation is both rare and atypical for primary colonic adenocarcinomas.

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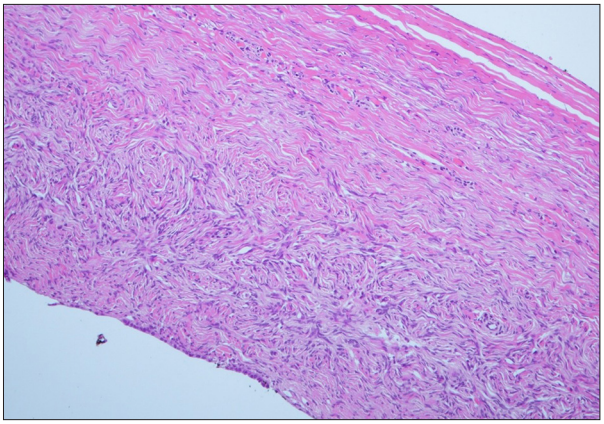

Figure 5. Pelvic side wall mass, showing a simple cuboidal-lined cyst with ovarian stroma (hematoxylin and eosin, original magnification 100×).

The prevalence of clear cell colorectal cancer has not been adequately documented. In a study encompassing 3486 cases of colon cancer, just 0.086% demonstrated clear cell changes [7]. As of now, the number of reported cases remains limited, with the tumor being more frequently observed in males, who constitute 70% of the documented cases [7-10]. Additionally, the tumor is reported more commonly on the left side of the colon and almost exclusively in the sigmoid and rectum, which is consistent with our case.

Pathogenesis and Classification

The pathogenesis of colonic clear cell carcinoma is not yet fully understood. Current literature broadly categorizes these tumors into 2 subtypes: Müllerian- type and intestinal-type clear cell carcinoma. The defining feature of both types is the distinct clear cytoplasm [11]. For the Müllerian type, the proposed hypotheses suggest that it might arise from endometriosis patches, residual embryological Müllerian tissues, or through the process of Müllerian metaplasia [12-14]. However, the most credible hypothesis regarding intestinal type is that it may originate in dysplastic colonic mucosa or in proximity to adenomas or carcinomas [1,12,15,16].

Diagnostic Criteria and Histopathological Features

Currently, no guidelines exist for the pathological or clinical staging of these tumors. In 2017, a group of Italian pathologists conducted a European study aimed at defining the diagnostic criteria for colorectal clear cell carcinoma [13]. This study aimed to distinguish between intestinal- and Müllerian-derived clear cell carcinomas. The diagnostic criteria for Müllerian-type clear cell carcinoma are as follows: (a) the presence of histological or immunohistochemical analysis confirming a Müllerian origin; and (b) the absence of an identifiable primary malignancy site. The same study indicated that the expression of Müllerian markers can be an excellent substitute for the histological proof of endometriosis, as large tumors might sometimes entirely obscure existing endometriotic foci. This aligns with our findings, as the tumor was notably large, and 5 blocks of colon samples tested negative for endometriosis.

The diagnostic criteria for intestinal-type clear cell carcinoma are described as: (a) the presence of an adjacent adenoma component or composite carcinoma; (b) the absence of endometriosis in proximity to the tumor; and (c) immunohistochemical expression indicative of intestinal differentiation, such as CEA, CK20, and CDX-2 [6,10,13]. This does not align with our findings, as the lack of CDX2 and CK20 expression in immunohistochemistry in our case argue against an intestinal origin. Importantly, the CT and MRI scans showed no indications of an extracolonic primary site that would suggest endometriosis or other Müllerian origins. Moreover, neither the histopathology sampling of the resected colon adjacent to the tumor nor that of the resected left ovary and fallopian tube showed any such indications either.

Treatment and Prognosis

The management and prognosis of clear cell carcinoma of the colon remain challenging due to its rarity and the absence of standardized guidelines. Surgical resection remains the primary treatment approach, while adjuvant chemotherapy derived from conventional colorectal cancer is often considered [2]. Considering the heterogeneity of clear cell carcinomas and their shared characteristics with non-colorectal tumors, the role of adjuvant chemotherapy remains insufficiently defined, and may require customization based on histopathological and immunohistochemical findings. In our case, the choice to administer carboplatin and paclitaxel instead of FOLFOX was influenced by the tumor's atypical immunophenotype (PAX8+, CK7+, CDX2-, CK20-), which does not align with typical colorectal adenocarcinoma.

Limitations and Future Directions

We believe that larger studies are necessary to enhance our understanding of the pathology, evaluation, and treatment of these tumors. A notable limitation of this report is the absence of molecular and genomic profiling. Integrating these analyses would have enriched the understanding of the tumor's genetic composition, clarified potential pathogenic pathways, and highlighted therapeutic targets.

Conclusions

This case is noteworthy because of its rarity and atypical presentation. This tumor manifested as an extensive stenotic

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intraluminal colonic mass with minimal symptoms, which is unusual for primary cancer of the colon. Furthermore, this case underscores the critical importance of employing a comprehensive diagnostic strategy that integrates histopathology, immunohistochemistry, and clinicopathological correlation to accurately determine the tumor's origin. Increased awareness of such rare entities is crucial to prevent misdiagnosis. It also highlights the importance of early detection and routine colorectal cancer screening, even in asymptomatic individuals, particularly in settings where screening programs are not universally established.

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Institutions Where Work Was Done

Roscommon University Hospital, Roscommon, and Galway University Hospital, Galway, Ireland.

Informed Consent

The patient provided informed consent for writing and publication of this case report.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest related to this study.

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