Clear cell adenocarcinoma of the colon is rare, with only a handful of cases reported after the first description by Helstrom in 1964.1 There have been reports attributing at least some of these cases to endometriotic involvement of the colonic wall; however, a presence of the clear cell adenocarcinoma and endometriotic glands with dysplastic clear cell changes in the colonic wall has not been compellingly demonstrated. Here we describe a case of clear cell adenocarcinoma of rectosigmoid in a 41-year-old woman, where we have been able to document endometriotic glands with dysplastic clear cell transformation in the background. The presence of the endometriotic glands and the endometrial stroma is confirmed with immunohistochemical stains. The diagnostic approach and immunohistochemical characteristics of these neoplasms are discussed along with difficulties in staging of these tumors.

Case Report

A 41-year-old woman presented with rectal bleeding and diarrhea. A mass in the upper rectum was visualized by colonoscopy. The biopsy showed a high grade adenocarcinoma with clear cell differentiation, consisting of back to back glands formed by clear cells with high grade nuclei, invading into the submucosa. The tumor cells were CK-7 positive, CK 20, CDX 2, WT 1, and TTF-1 negative. Scattered nuclei showed p53 positivity, while the ER and PR stains were noncontributory. Based on the morphologic appearance and immunohistochemical phenotype of the tumor, the neoplasm was interpreted as metastatic to the colon with a possible primary tumor in the ovaries or uterus. A follow-up segmental resection of the sigmoid colon and proximal rectum with total abdominal hysterectomy and bilateral salpingo-oophorectomy revealed a 5 cm ulcerated fungating mass in the sigmoid colon and upper rectum. Histologically the tumor appeared similar to the biopsy specimen (Image 1). The colonic wall was extensively involved by ER and PR positive endometriotic glands surrounded by CD10-positive endometrial stroma extending from the serosa to the muscularis propria. The endometriotic glands demonstrated prominent dysplastic changes with few cells undergoing clear cell transformation (Image 2). No evidence of a tumor was found in the uterus or ovaries. Sixteen lymph nodes were free of tumors. A temporary loop ileostomy was placed with an ileostomy reversal in 2 months. Carboplatin and Taxol were administered and were well tolerated.

Discussion

Clear cell adenocarcinoma of the colorectum is extremely rare. In a study involving 3,486 cases of colon cancer, only 0.086% had clear cell changes.2 Clear cell adenocarcinomas usually develop in the organs of Müllerian origin.3 An occurrence of an isolated clear cell carcinoma of the colon is unclear. However, malignant transformation of gastrointestinal (GI) endometriosis, also known as endometriosis-associated intestinal tumors (EAIT), is well documented with approximately 50 cases reported in the literature. These neoplasms include
primarily endometroid and squamous tumors arising in the background of endometriosis as well as clear cell carcinoma, carcinosarcoma, Müllerian adenosarcoma, endometrial stromal sarcoma, and endometroid adenofibroma.4,5 Despite the well-established link between GI endometriosis and Müllerian-type adenocarcinomas, no direct evidence of dysplastic clear cell transformation within the endometriotic glands coexisting with the nearby clear cell carcinoma in the colon has been convincingly observed.6-11 The presence of a cystic structure suggestive of endometriosis at the deep aspect of the tumor with possible transition within the epithelial lining cells from cells with eosinophilic cytoplasm to cells with abundant clear cytoplasm similar to the cells of the main tumor was demonstrated after multiple re-cuts by McCluggage and colleagues. However, no unambiguous endometrial glands and/or endometrial type stroma were identified in close proximity to the tumor according to the authors.7 In our case, we have documented dysplastic clear cell changes within the endometriotic glands in the colonic wall present simultaneously with a nearby clear cell carcinoma of the colon.

Of clinical importance is that more than 40% of endometriosis-associated intestinal neoplasms arise in relatively young women in their late 30s to early 50s, which is 1 to 2 decades earlier than primary adenocarcinoma of the colon. The rectosigmoid colon is reported to be the most common site of involvement by EAIT with abdominal/pelvic pain, pelvic mass, bowel obstruction, and GI bleeding symptoms.4,5 In this case, the patient presented with GI bleeding and diarrhea.

Recognizing the neoplasms associated with intestinal endometriosis is also clinically significant since the chemotherapy for the Müllerian origin tumors is different from the treatment for the primary intestinal malignancies. If no dysplastic endometriotic glands are present within the vicinity of the intestinal tumor demonstrating clear cell changes, immunohistochemistry can help to distinguish the origin of the tumor. Generally, 75%–95% of primary colonic adenocarcinomas are CK20 positive and CK7 negative, whereas 80%–100% of Müllerian origin adenocarcinoma are CK20 negative and CK7 positive.12,13 CDX2 is expressed in the majority of primary colonic adenocarcinomas and is negative in the Müllerian origin neoplasms. CD10 stain can help verify the presence of the adjacent endometrial stromal cells.14 In this case, the tumor cells were positive for CK7 and negative for CK20 and CDX2. The presence of adjacent dysplastic endometriotic glands with clear cell changes and CD10 positive stromal cells helped establish the diagnosis of clear cell adenocarcinoma of the Müllerian origin (Table 1).

One of the challenges in these cases is the classification and staging of EAIT. Currently, there are no guidelines for pathological or clinical staging of these tumors. Considering they arise within the endometriotic glands in the colonic wall but not in the colonic mucosa, and the treatment of these tumors is similar to other Müllerian adenocarcinomas, there is a thought to classify these tumors as primary peritoneal adenocarcinomas. However, when the colonic wall (including the mucosal lining), is the primary site of involvement by these neoplasms, the biological behavior of these tumors is close to mucosal colon cancer.

Image 1. Microscopic findings. (A) Low-power view showed invasive adenocarcinoma with clear cell areas with back to back glands in the colonic mucosa and submucosa (H&E, ×40). (B) Medium-power view showed invading glands formed by clear cells with high grade nuclei (H&E, ×100). (C) High-power view demonstrated cells with clear cytoplasm, high N/C ratio, and large nucleoli (H&E, ×400).
We feel that prognostically it would be more appropriate to approach these cases similarly to primary colon cancer.

In summary, we present a case of clear cell adenocarcinoma arising in the background of intestinal endometriosis with clear cell dysplastic transformation and clinical and pathological features similar to primary colonic carcinoma, including GI bleeding, diarrhea, and extensive involvement of the colonic

<table>
<thead>
<tr>
<th>Stain</th>
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<tr>
<td></td>
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<td>CK7</td>
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<tr>
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</tr>
<tr>
<td>PS3</td>
<td>Scattered positivity</td>
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**Table 1: Summary of Immunohistochemical Stains**

**Image 2** Microscopic findings. (A) Low-power view showed endometriotic glands in the submucosa and muscularis propria (H&E, ×40). (B) High-power view demonstrated dysplastic clear cells with high N/C ratio, and prominent nucleoli similar to the cells in the malignant glands (H&E, ×400). (C) The stromal cell surrounding the endometriotic glands in the colonic wall showed strong positive staining with CD10 (DACO CD 10, ×100). (D) The endometriotic glands demonstrated positive staining with ER (DACO, ER, ×100). (E) The endometriotic glands demonstrated positive staining with PR (DACO PR, ×100).
mucosa and surface epithelium. Endometriosis associated intestinal tumors should be suspected in relatively young female patients with clinical and pathological presentation of colonic malignancies, and a clinical history and histological finding of endometriosis should be explored. Careful histological and immunohistochemical (CK7, CK20, CDX2, CD10) examination is warranted to establish a correct diagnosis.