Case and Review

Right Colon Clear Cell Carcinoma of Müllerian Type

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Abstract
Clear cell carcinoma (CCC) is usually seen in tissues originating from the paramesonephric (Müllerian) ducts such as the kidneys, the ovaries, the cervix and the vagina. The pathogenesis has not yet been elucidated. The diagnostic hallmark is the clear cytoplasm. Primitive CCC of the colon is a very rare entity. There are two types of CCC of the colon; the intestinal type and the Müllerian type. The differential diagnosis arises mainly with secondary metastases of renal or ovarian origin. Immunohistochemistry allows retaining the primitive character. The treatment is not yet consensual. It depends on the type of tumor and its stage. The treatment is based on surgery and possibly chemotherapy. We report the case of a 75-year-old female patient who underwent surgery for a tumor of the ascending colon. Microscopic examination concluded an extensively necrotic carcinomatous growth which infiltrated all the layers of the intestinal wall and the peritoneum. The tumor was made of clusters and spans of clear cells which were separated by thin conjunctivo-vascular septa. The tumor cells were round to polygonal with a clear, optically empty, pseudo-vegetative (physaliferous) cytoplasm. Immunohistochemistry study showed a positive staining with CK7 and a negative staining with CK20, CDX2, PAX8, P63, CD10, chromogranin, and synaptophysin. We performed a Medical Literature databases (Pubmed and Google Scholar) research. Only forty-two cases were reported in English literature. The main age is 55.7 (25–89). The sex ratio is one, but female cases were younger (52 vs. 61). The rectum is the most involved site. The left colon location is more frequent than the right one. The Müllerian type was found only at the level of the left colon and rectum. There was no CCC in the right colon of Müllerien type. The case we report herein is the first right colon CCC which is positive in CK7 staining.
Introduction

Clear cell carcinoma (CCC) is usually seen in tissues originating from the paramesonephric (Müllerian) ducts such as the kidneys, the ovaries, the cervix and the vagina. Primary colic CCC is a very rare entity with only 41 cases reported in medical literature since 1964. It is characterized by cells with a clear cytoplasm associated with an adenoma or a component of an adenocarcinoma. The pathogenesis has not yet been elucidated, and the diagnosis is based on microscopic immunohistochemical study. There are two types of CCC; the intestinal CCC and Müllerien CCC. It was mostly described at the level of the left colon.

Objectives: we report herein a new case of colic CCC, and through a review of English literature, we studied the epidemiological and the immunohistochemical characteristics of this entity. Medical Literature databases (Pubmed and Google Scholar) were searched.

Primary CCC of the colon, rectum, anus, and small bowel were included. The statistical analysis was made with SPSS (Statistical Package for the Social Science version 21.0).

Observation

A 75-year-old female patient with a personal history of diabetes mellitus, hypertension and a laparoscopic cholecystectomy was admitted for right lower quadrant pain which had been present for 2 months. Physical exam found a right lower quadrant sensitivity. No other notable findings were recorded. In particular, the gynecological exam was normal. Laboratory studies showed a high white blood cell count at 20,300/mm³. An abdominal CT scan showed a suspicious thickening of the colonic wall with infiltration of the surrounding fat. No collection or free liquid was found. Lower GI endoscopy showed a circumferential, ulcerating, and burgeoning mass which prevented the optic to pass through. Biopsy examination was inconclusive (these involved the superficial leucocytic coating). The assessment for metastatic extension was negative. The patient was operated on by midline laparotomy. Intrasurgical observations found a 10-cm tumor which was perforated and covered by the lateral abdominal wall. The kidneys and the ovaries looked healthy. The patient underwent a right colectomy with an ileo-transverse anastomosis. Surgical follow-up was complication-free.

The gross examination of the surgical specimen showed an 8 cm, circumferential tumor which was highly necrotic (Fig. 1). Microscopic examination concluded an extensively necrotic carcinomatous growth which infiltrated all the layers of the intestinal wall and the peritoneum. The tumor was made of clusters and spans of clear cells which were separated by thin conjunctivo-vascular septa. The tumor cells were round to polygonal with a clear, optically empty, pseudo-vegetative (physaliferous) cytoplasm. The nucleolus was visible at low magnification (Fig. 2, 3). Immunohistochemistry study showed an intense and diffuse staining of tumor cells with CK7 and a negative staining with CK20, CDX2, PAX8, P63, CD10, chromogranin, and synaptophysin (Fig. 4).

Fifty-two cases of primary colon CCC are reported in the literature. The mean age is 55.7 years (25–89). There is no difference between the two sexes. The mean age of onset in men is 59.38 years and 52.85 years in women.

The digestive tract from the small bowel down to anal canal can be concerned (Table 1). The rectum and the left colon are the most concerned parts (33.3% and 21.4%, respectively). The right colon is affected in 19% of cases, the sigmoid in 9.5%, the transverse and the small intestine both in 7.1%, and only one case of CCC of the anus is described (i.e., 2.4%). Other results are detailed in Table 1.

In gross and microscopic examination, all the tumors show cells with clear cytoplasm. PAS staining was positive in 8 patients. Other markers are detailed in Table 2.
Fig. 1. Gross examination of the surgical specimen showing an 8 cm, circumferential tumor (arrow) which was highly necrotic.

Fig. 2. Microscopic examination (×4 objective) showing clusters and spans of clear cells, separated by thin conjunctivo-vascular septa.

Fig. 3. Microscopic examination (×10 objective) showing the tumor cells, which were round to polygonal with a clear, optically empty, pseudo-vegetative (physaliferous) cytoplasm.
Two types of CCC have been described: the Müllerian type and the intestinal type. The typing was based on immunohistochemistry data in 23 cases (56.09%) or in front of the association with other lesions in 2 patients (histological evidence of endometriosis in close proximity to the tumor).

The Müllerien type was found in 9 patients (36%) and the intestinal type was found in 16 patients (64%). The latter is found in the right colon in 5 cases (31.25%) and in the left colon in 9 patients (56.25%), while the Müllerian type characterizes the left colon (88.89%). Only one case of Müllerian type is found in the right colon. All cases of Müllerian CCC are found in female patients. In 2 patients (22.2%), the Müllerian-type diagnosis was retained in the presence of other associated lesions (histological evidence of endometriosis in close proximity to the tumor).

Discussion

The primitive colon CCC is a rare entity. Described for the first time in 1964 by Hellstrom and Fisher [1].

Since then, 41 cases have been reported in the literature (see Tables 1, 2), the last of which dates back to 2019. At the colonic level, the incidence of this pathology remains low [2] and is usually seen in tissues of Müllerian origin such as the kidneys, the ovaries, the cervix, and the vagina.

After a review of the literature, colic CCC occurs at an average age of 55.7 years, equally in both sexes. The woman is affected at a younger age (52.85 vs. 59.38 years). The rectum and left colon are the two most concerned sites (63.41%).

The positive diagnosis of this entity is based on the microscopic and immunohistochemical study of the specimen. Microscopically, the tumor shows cells with a clear cytoplasm. Some authors require the presence of at least 50% of the clear cell contingent to consider the diagnosis of CCC [3]. The tumor can be well differentiated defined by cells arranged in columns with an eccentric nucleus, or undifferentiated with polygonal cells, central nucleus, and solid architecture [3].

The nature of “clear” cytoplasmic inclusions is still controversial. They could be due to an accumulation of mucin, lipid, or to an enteroblastic or glycogen differentiation which justifies the positivity of PAS [4]. The lipidic nature seems the most probable etiology. This finding was confirmed by immunohistochemical studies and by electron microscopy [2, 5–9].
Table 1. Main characteristics of patients, tumor site, size, and TNM state

| Authors                        | Age | Sex | Tumor site   | Size (cm) | T  | N  | M  |
|--------------------------------|-----|-----|--------------|-----------|----|----|----|
| Hellestrom and Fisher [1] 1964| 67  | M   | Rectum       | 2         | NM | +  | 0  |
| Reed et al. [9] 1983           | 71  | M   | Transverse colon | 7     | NM | NM | NM |
| Jewell et al. [10] 1988        | 75  | M   | Rectum       | 2         | NM | 0  | 0  |
|                               | 56  | F   | Left colon   | 6         | NM | 0  | 0  |
| Watson [11] 1990               | 53  | M   | Anal canal   | 3.5       | NM | +  | 0  |
| Hitti et al. [29] 1990         | 39  | F   | Sigmoid      | 6.5       | NM | 0  | 0  |
| Young and Hart [12] 1998       | 27  | F   | Small intestine | 4       | NM | +  | 1  |
|                               | 33  | F   | Transverse colon | NM   | NM | NM | NM |
|                               | 33  | F   | Left colon   | NM        | NM | NM | NM |
|                               | 49  | F   | NM           | NM        | NM | NM | NM |
|                               | 71  | F   | NM           | NM        | NM | NM | NM |
| Rubio [13] 1995                | 68  | M   | Left colon   | 6         | 4  | 2  | 1  |
| Sasaki et al. [30] 1996        | 49  | F   | Rectum       | NM        | NM | NM | NM |
| McCluggage et al. [28] 2001   | 65  | F   | Rectum       | NM        | 3  | NM | 1  |
| Mallik and Katchy [14] 2005    | 36  | F   | Rectum       | 5         | 3  | 1  | 0  |
| Braumann et al. [15] 2004      | 89  | M   | Left colon   | 2.2       | 2  | 0  | 0  |
| Ko et al. [16] 2007            | 62  | M   | Left colon   | 1.5       | In situ | 0  | 0  |
| Hao et al. [17] 2007           | 37  | M   | Rectum       | 3         | 3  | +  | NM |
| Sawai [35] 2007                | 56  | F   | Rectum       | NM        | NM | NM | NM |
| Houma 2007 [27]                | 50  | F   | Rectum       | NM        | NM | NM | NM |
| Eloy et al. [5] 2009           | 48  | F   | Transverse colon | 2.5     | In situ | 0  | 0  |
| Soga et al. [18] 2008          | 71  | F   | Right colon  | NM        | In situ | 0  | 0  |
| Authors                        | Age | Sex | Tumor site | Size (cm) | T | N | M |
|--------------------------------|-----|-----|------------|-----------|---|---|---|
| Barisella et al. [19] 2008     | 54  | M   | Right colon| 0.9       | 2 | 0 | 0 |
| Bressenot et al. [20] 2008     | 84  | F   | Left colon | 3.5       | 4 | 0 | 0 |
| Finkelstein et al. [21] 2010   | 41  | F   | Rectum     | 5         | 2 | 0 | 0 |
| Shi et al. [6] 2010            | 52  | M   | Rectum     | 0.9       | 1 | NM| NM|
| Finkelstein et al. [21]        | 51  | M   | Sigmoid    | 1.4       | 1 | 0 | 0 |
| Furuya et al. [22] 2011        | 81  | M   | Right colon| 10        | 3 | 2 | 1 |
| Bakshi et al. [23] 2012        | 42  | M   | Right colon| 4         | 3 | 0 | 0 |
| Kanstrup et al. [24] 2012      | 69  | M   | Sigmoid    | NM        | 3 | 0 | 0 |
| Barrera-Maldonado et al. [25] 2014 | 41  | F   | Rectum     | 5         | 4 | 2 | 1 |
| Min et al. [33] 2013           | 82  | M   | Left colon | NM        | 2 | 1 | 0 |
| Gureru et al. [32] 2014        | 50  | F   | Rectum     | 2.5       | 2 | 0 | 0 |
| Wang et al. [31] 2014          | 83  | M   | Rectum     | 4         | 4 | 0 | 0 |
| Okazawa et al. [27] 2014       | 25  | M   | Right colon| 3         | NM| NM|NM|
| Thelin et al. [34] 2014        | 58  | M   | Right colon| 7         | 4 | 2 | 0 |
| Remo et al. [3] 2017           | 79  | M   | Right colon| 4.5       | 4 | 0 | 0 |
| Tochio et al. [8] 2018         | 48  | M   | Left colon | 2.5       | NM| NM|NM|
| Oyama et al. [4] 2019          | 58  | M   | Sigmoid    | 2.5       | 1 | NM|NM|
| Current case                   | 75  | F   | Right colon| 8         | 4 | 0 | 0 |

M, male; F, female; NM, not mentioned.
| Authors                  | Coloration (positivity) | Immunohistochemistry (positivity) | Associated lesion | Type (intestinal/Müllerien) |
|-------------------------|-------------------------|-----------------------------------|-------------------|----------------------------|
| Hellestrom and Fisher [1] 1964 | PAS, D-PAS, Alcian blue| CEA, EMA, low-molecular weight keratin |  | Intestinal                |
| Jewell et al. [10] 1988  |                         | CEA, EMA, low-molecular weight keratin |  | Intestinal                |
| Watson [11] 1989         | PAS                     | CEA, EMA, low-molecular weight keratin | Adenoma           | Intestinal                |
| Hitti et al. [29] 1990  |                         |                                   | Endometriosis     | Müllerien                 |
| Rubio [13] 1995          | PAS                     | CEA, TPA                          | –                 |                           |
| Sasaki et al. [30] 1996  |                         |                                   | Endometriosis     | Müllerien                 |
| Young and Hart [12] 1998 |                         |                                   | Crohn’s disease   |                           |
| McCluggage et al. [28] 2001 | PAS, laminin type IV collagen | CA125, CK7, Ber-EP4 | Endometriosis     | Müllerien                 |
| Braumann et al. [15] 2004 |                         | CEA, EMA, CK18, CK20              | Hyperplastic polyps | Intestinal                |
| Mallik and Katchy [14] 2005 | PAS, Alcian Blue       | CEA, EMA                          | –                 | Adenoma                   |
| Ko et al. [16] 2007      |                         |                                   | Endometriosis     | Müllerien                 |
| Hao et al. [17] 2007     | PAS                     | CEA, EMA                          | –                 |                           |
| Swai [35] 2007           |                         | CK7                               | Endometriosis     | Müllerien                 |
| Houma [27] 2007          |                         | CK7                               | Endometriosis     | Müllerien                 |
| Soga et al. [18] 2008    | PAS                     | CD10, CK20, p53, Ki67             | Adenoma           | Intestinal                |
| Barisella et al. [19] 2008 |                         | CEA, CK20, p53, hMLH1, hMSH2, B-catenin | Adenoma           | Intestinal                |
| Bressenot et al. [20] 2008 |                         | CEA, CK20, Ki67                   | –                 | Intestinal                |
| Authors                | Coloration (positivity) | Immunohistochemistry (positivity) | Associated lesion | Type (intestinal/Müllerien) |
|------------------------|-------------------------|-----------------------------------|-------------------|-----------------------------|
| Eloy et al. [5] 2009   | CK20, CDX2, CEA, p53    | Adenoma                           | Intestinal        |
| Finkelstein et al. [21] 2010 | CK7, p53, ER, PR, CD10 | Endometriosis                     | Müllerien         |
| Shi et al. [6] 2010    | CK20, CDX2              | Adenoma                           | Intestinal        |
| Furuya et al. [22] 2011 | PAS, D-PAS             | CEA, EMA, CK AE1/3, CK20, c-kit, B-catenin | Intestinal        |
| Kanstrup et al. [24] 2012 |                        | Adenoma                           | Intestinal        |
| Min et al. [33] 2013   | CK7, ER, CD10           | Endometriosis                     | Müllerien         |
| Barrera-Maldonado et al. [25] 2014 | CK20, CK10, CDX2, villin |                                    | Intestinal        |
| Gurzu et al. [32] 2014 | AE1/AE3, CK20, CK7, EMA, CEA, CD10, maspin |                                    | Intestinal        |
| Wang et al. [31] 2014  | Cytokeratin, EMA        |                                    | Intestinal        |
| Okazawa et al. [27] 2014 |                        |                                    | Mülleren          |
| Remo et al. [3] 2017   | CK20, CEA, MUC2, CDX-2  | Endometriosis                     | Intestinal        |
| Tochio et al. [8] 2018 | CK20, CDX-2, MUC2, CEA, Ki67, p53, B-catenin | Prostate carcinoma               | Intestinal        |
| Oyama et al. [4] 2019  | CK20, CDX2, MUC2, CEA, CD10, COX2, APC, Ki67 | Adenoma                           | Intestinal        |
| Current case           | CK7                     |                                    | Mülleren          |

CK, cytokeratin; CDX2, caudal type homeobox 2; CEA, carcinoembryonic antigen; CD, cluster differentiation; MUC, mucin; COX2, cyclooxygenase 2; APC, adenomatous polyposis coli; PAS, periodic acid-Schiff; D-PAS, periodic acid-Schiff with diastase treatment; EMA, epithelial membrane antigen; TPA, tissue polypeptide antigen; p53, p53 protein; Ki67, Ki67 labeling index.
There are currently two types of CCCs; the intestinal type and the Müllerian type. Three diagnostic criteria are necessary to retain the intestinal type: the presence of colonic adenoma near the tumor or a composite tumor with a classic adenocarcinoma component, the absence of endometriotic lesions, and immunohistochemical expression of intestinal differentiation (CEA, CK20, CDX-2) [1, 6, 10–25].

The pathogenesis of intestinal-type clear cell colon carcinomas has not yet been elucidated. Two hypotheses are suggested. The first reports the classic evolution from clear cell adenoma to carcinoma of the same type [4, 6], the other reports a degeneration of inflammatory diseases such as Crohn’s disease [12].

Three diagnostic criteria are also recommended to retain the Müllerian type: presence of endometriosis lesions (with histological evidence) in close proximity, absence of other primitive clear cell tumors, and a histological appearance of the tumor compatible with endometriosis [26–28]. In this case, the tumor cells express CK7 and CA125 [26–28].

This type affects young women in the 4th and 5th decade with an average age of 56.44 years and has a more negative prognosis than the intestinal type [21]. Almost all (88.89%) of cases of Müllerian colonic CCC described in the literature siege at the level of the left colon [27–31]. To the best of our knowledge, the case described above is the first case of CCC of Müllerian type described at the level of the right colon.

This predominance at the level of the left colon is explained by the embryological hypothesis: an inducing role of the primordial germ cells which appear in the mesoderm of the yolk sac near the allantoic diverticulum could be at the origin of extra ovarian endometriosis. Another hypothesis suggests that ovarian migration during fetal life leaves ectopic foci of Müllerian cells which degenerate secondarily. This hypothesis seems more plausible for our patient to explain the right involvement [21].

The differential diagnosis arises mainly with secondary metastases of renal or ovarian origin. There are several histological and immunohistochemical means to retain the primitive character. The clear histological boundary between clear cells and dysplastic lesions is a means of retaining the primitive character [32].

Treatment will depend on the type of tumor and its stage. CCCs of the intestinal type join colorectal adenocarcinoma and respond to the same indications for adjuvant treatment. Some offer targeted therapy associated with the immunohistochemical profile [32]. On the other hand, the treatment of the Müllerian type is based on surgical resection of the affected segment associated with adjuvant treatment which remains nonconsensual, and the treatment of associated lesions.

CCC of the colon is a very rare entity. Its ontology remains unclear. There are two types: the intestinal type and the Müllerien type. The latest, exclusively described in the sigmoid, the rectum and the anal canal, is identified for the first time in the right colon. Further studies are needed to gain a better knowledge of this entity.

**Statement of Ethics**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

**Conflict of Interest Statement**

The authors have no conflicts of interest to disclose in association with this study.
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Author Contribution

The authors’ contribution was as follows: Fahd Khefacha and Wissem Triki participated in the conception, interpretation of data, drafting of the work, and final approval of the version to be published. Imed Abbassi and Abdelmajid Baccar participated in the acquisition of data, analysis of data, and final approval of the version to be published. Karim Ayed, Oussema Baraket, and Sami Bouchoucha participated in the analysis of data, critical revising of the work, and final approval of the version to be published. All authors agree to be responsible for all aspects of the work ensuring that questions relating to the accuracy or integrity of any part of the work are investigated and resolved appropriately.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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