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Case Report

Ovarian metastasis from adenocarcinoma of the rectosigmoid colon

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Abstract: Background: Approximately 12-14% of females affected with primary colorectal carcinoma have synchronous or metachronous metastatic ovarian lesions, i.e., metastatic colon carcinoma to the ovary (MCCO). MCCO most commonly affects both ovaries. Unilateral MCCO is a very unusual occurrence. Case Report: Here, we present a case of a 52-year-old postmenopausal woman with unilateral right ovarian metastases from a rectosigmoid adenocarcinoma. The patient had nonspecific symptoms at the diagnosis, including abdominal distension, malaise, and gradual weight loss. Radiology (CT and MRI) revealed a big tumor of the right ovary synchronous with the circumferential thickening of the rectosigmoid colon. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy together with anterior resection of the rectosigmoid colon were performed. The diagnosis of ovarian metastases from a primary rectosigmoid adenocarcinoma was confirmed by immunohistological examination of the ovarian mass and rectosigmoid thickening. We did not find any evidence of peritoneal deposits or metastases in the regional lymph nodes. The patient died shortly after surgery from a postoperative cardiac event. Conclusions: This paper presents a rare example of unilateral MCCO. The clinicopathological characteristics were discussed, and a brief review of the literature. Although unilateral MCCO is a rare occurrence, physicians should keep it in mind whenever ovarian, and colorectal tumors appear simultaneously.

Keywords: Ovaries, colon, carcinoma, metastasis, immunohistochemistry

Introduction

Ovarian metastases from colorectal adenocarcinoma

Colorectal cancer (CRC) represents the world's third most prevalent malignant tumor and the second most lethal human cancer. CRC is made up of two closely related cancers: colonic cancer and rectal cancer. While colon carcinoma is the fourth most frequent type of malignancy all over the world, rectal carcinoma is the eighth most common one [1, 2]. Pretzsch et al. have indicated that metastatic dissemination is the leading cause of death in CRC, with the liver and peritoneum being the most common sites [3]. Kim et al. have estimated that metastatic ovarian tumors account for 15-20% of all malignant ovarian tumors [4]. Rekhi et al. have reported that the ovaries are common sites of metastases from carcinomas of many organs [5]. In 1996, Friedrich Ernst Krukenberg (1871-1946) in Germany described a case of ovarian metastases from gastric carcinoma. Other gastrointestinal carcinomas also have been reported to metastasize to the ovary. For instance, there have also been reports of gastrointestinal carcinomas in other organs, such as the colon, small intestine, appendix, and pancreas, causing ovarian metastases simultaneously or metachronously [6]. Incredibly, between 10% and 33% of metastatic ovarian carcinomas have been attributed to CRC [7, 8].

It has been estimated that between 12-14% of women diagnosed with primary colorectal carci-

noma had synchronous (the second primary cancer is detected within a period of 6 months of the diagnosis of primary cancer) or metachronous (the second primary cancer is detected more than six months after the primary cancer is diagnosed) ovarian metastases. The term "metastatic colon carcinoma to the ovary" (MCCO) refers to metastatic colon carcinoma that has spread to the ovary [7, 8]. In general, MCCOs are grossly similar to primary epithelial ovarian carcinomas (PEOCs), especially mucinous and endometrial carcinomas of the ovary [5]. In most cases, MCCOs originate from the distal rectosigmoid region, and the size of metastatic ovarian tumors is often larger than primary colorectal cancer [9]. Patients with MCCOs are generally aged 19 to 87 years [8, 10]. Most MCCOs cases have histological features largely present in PEOCs, particularly endometrial or mucinous carcinoma. Primary CRCs are mostly Dukes stage B or C [11] and exhibit invasion of the muscularis propria. There are several ways malignant cells from the primary CRC can spread to the ovary, including direct spread, hematogenous spread, lymphatic invasion, and transperitoneal/transceolemic spread [12].

Clinical presentations of MCCOs

Several clinical features support the diagnosis of MCCOs, including a history of CRC, bilateral ovarian masses exceeding 10 centimeters in diameter, solid appearance, lack of ascites, and elevated levels of serum carcinoembryonic antigen (CEA) [13]. The clinical manifestations of MCCOs are nonspecific and consist of abdominal distension, malaise, and weight loss. MCCOs are generally accidentally diagnosed during autopsies, hysterectomies, and gastric, pelvic, or ovarian surgeries. Therefore, the actual high incidence of ovarian metastases from CRC is most likely to have been chiefly underestimated [8].

Gross and histological features of MCCOs

MCCOs appear as solid masses, cystic lesions, and complex cystic-solid masses, all with or without friable, necrotic, and hemorrhagic areas [14-16]. Seidman et al. have stated that all bilateral mucinous tumors and any unilateral tumors that are larger than 10 cm primarily represent metastatic ovarian carcinomas [17]. Alternatively, unilateral ovarian tumors smaller than 10 cm primarily represent PEOC [17]. PEOCs and MCCOs share several similar and overlapping morphological features, such as the presence of complicated tubular-glandular architecture, endometriotic-like glandular patterns, dirty necrosis (Garland or intraluminal necrosis), high-grade cytology, and desmoplastic reactions [5]. The histological characteristics of ovarian metastasis that support a colorectal origin include the presence of garland-like necrosis, segmental destruction of the mucosal glands, and the absence of squamous metaplasia [18].

PEOCs and MCCOs are often difficult to separate from each other, so MCCOs continue to be misdiagnosed as PEOCs [4, 8, 16, 19]. PEOCs of the ovaries can be diagnosed based on histological features that include unilateral lesions, the expansile pattern of infiltration, papillary and Mullerian features, rarity of multiple nodules, rarity of signet ring cells, lymphovascular invasion or hilus involvement, and the presence of residual benign or borderline primary epithelial ovarian neoplasms [8, 9, 20]. In addition, both PEOCs and MCCOs exhibit similar immunohistochemical profiles, such as positive reactivity for CDX2 (mucinous carcinoma in the intestinal type of PEOC), CK7, pan-cytokeratin (AE1/AE3), and CAM5.2 expression [8, 16, 19]. To distinguish the PEOCs from MCCOs, several ancillary studies are used. For instance, serum levels of CEA and CA125 markers are usually measured. The former is typically high in CRCs, whereas the latter is usually elevated in MCCOs.

Immunohistochemical profile of MCCOs

If none of the above clinicopathologic and serologic studies resolve the colorectal origin of the tumor metastatic to the ovaries, immunomarker studies (immunohistochemistry) can be conducted to confirm a diagnosis of MCCOs. The standard panel used to distinguish between MCCOs and PEOCs is CK20/CK20. CK7 positivity/CK20 negativity is almost 100% specific for the colorectal origin of ovarian cancer [21]. Conversely, CK7-negative/CK20-positive tumors are almost 90% specific for the colonic origin of carcinoma [21]. Positive immunostainings for CK20, CDX2, SATB, and negative ones for CK7, PAX8, and CA125 support a diagnosis of MCCOs [8]. Tumor cells of PEOCs are usually positively stained by CK7, PAX8, and CA125 but

negatively stained by SATB2 [22]. On the contrary, features indicative of MCCOs include the involvement of both ovaries (bilaterally), the invasive infiltration pattern, the presence of multiple surface nodules of fibrous plaques containing invasive cancer cells, single-cell infiltration, multi-nodularity, desmoplastic reaction, lymphovascular invasion, and invasion of the hilar structures [22]. The presence of cribriform or garland-like patterns with dirty necrosis indicates colorectal origin. Tumor cells of CRC origin tend to stain positive for CK20, CEA, CDX2, and SATB2, and negative for PAX8 and CA125 [22].

Molecular mechanisms of MCCOs

Several molecular pathways contribute to the development of CRC, including microsatellite instability (MSI), chromosomal instability (CIN), and CpG methylator phenotype (CIMP) pathways. Colon cancer cells spread to the ovaries primarily via transceolemic and hematogenous spreads [3, 23-25]. Metastatic colorectal cancer cells spread hematogenously in several sequential steps. First, the cancer cells invade the tissue matrix surrounding them. This is followed by infiltration into blood vessels and lymph vessels, transport of malignant cells to various organs, and extravasation of tumor cells into new microenvironments. As the last step, metastatic tumor cells invade distant organs such as the ovaries [3, 25]. During the transport of tumor cells, protective shields of platelets (platelet-derived growth factor and transforming growth factor β) and extracellular traps of neutrophils protect them from immune cells and shear stress. Hematogenous spread is also impacted by the blood group antigens sLe^a and sLe^x, and the cytokines [3, 25]. The transceolemic spread results from the detachment of cancer cells from the primary CRC, the acquisition of tumor motility, escape from anoikis, and eventually the infiltration and attachment of tumor cells to the peritoneal surface and ultimately the formation of metastatic implants to the peritoneal surface and outer surface of the ovaries [3, 25].

Several types of cells and factors are involved in peritoneal spread. The key cells include peritoneal mesothelial cells, macrophages, and fibroblasts, together with subperitoneal fibroblasts. The key elements include adhesion molecules such as integrins and their ligands and epithelial cell adhesion molecule/EPCAM, immunoglobulin superfamily members such as L1CAM, VCAM1, and ICAM1, proteoglycans (such as CD44), and mucins such as MUC16 are involved in peritoneal dissemination [3, 25]. Metastatic colorectal cancer cells that have metastasized to the ovary have a protumor ovarian microenvironment consisting of immune cells (macrophages), inflammatory cells (neutrophils and lymphocytes), and carcinoma-related fibroblasts. The protumor microenvironment also includes extracellular matrix proteins, cytokines, soluble factors, hypoxia, and signaling molecules [3, 26].

Metastatic ovarian carcinoma to the colorectum versus MCCOs

Ovarian cancer is the sixth most common malignant disease in the world [27]. Metastatic colorectal cancer accounts for only 1% of the total number of malignant colon tumors [28, 29]. Metastatic colorectal carcinomas of an ovarian origin can develop from 1-22 years from the diagnosis of primary ovarian cancer, with a mean interval of 9 years [29, 30].

A series of Japanese autopsies estimated that only 5.97% of metastatic colorectal cancers were of ovarian origin [23, 31]. Conversely, metastatic ovarian tumors are common and MCCO is not a rare event. Koyama et al. studied the clinicopathological features of 19 cases of ovarian-derived metastatic colorectal cancer in Japanese patients ranging from 34 to 77 years. The lesions affected the rectum, sigmoid colon, descending colon (5 cases each), ascending colon (4 cases), and transverse colon (2 cases). These metastatic tumors to the colorectum were grossly similar to the primary CRC and appeared fungating, ulcerative, or submucosal masses. Therefore, separating ovarian metastases to the colorectum from the primary colorectal carcinoma was frequently difficult based on their gross appearance [32].

The clinical features of MCCOs

There is no specific clinical symptom, but weight loss, intestinal obstruction, melena, and anemia are the most common. Colorectal and ovarian cancers are usually treated differently, so separating these malignancies is critical for optimal treatment outcomes. Patients with ovarian adenocarcinoma respond well to plati-

num-based chemotherapy, while patients with colorectal adenocarcinoma respond well to 5-fluorouracil-based chemotherapy [33]. The transcoelomic, direct, and lymphovascular spread of malignant cells can occur in ovarian carcinomas to spread to the colorectum. However, most often, PEOC sends metastases to other organs via transcoelomic space, so metastatic colorectal cancer develops from serosal implants that invade the subserosal fatty tissue and muscularis propria to reach the submucosa. However, eventually, the tumor cells involve the mucosa, and the gross and histological separation from primary CRC is challenging. The morphological features of colorectal tumor indicative of metastasis of an ovarian origin include the absence of dysplasia in the mucosal glands together with the presence of heavy involvement of the submucosa, muscle layer or serosa, presence of cribriform pattern, intraluminal dirty necrosis, squamous metaplasia, and intraluminal dirty necrosis [5]. Preoperative analysis of serum CA125 levels (normal in CRCs), as well as CEA levels (normal in ovarian carcinomas), may prove helpful in these cases, but it is noteworthy that CA125 levels are expected in about 15% of ovarian malignancies [34].

The treatment of MCCOs

The management of MCOOs is planned according to the clinical scenario of the case. The management options include surgical resection of the metastatic ovarian masses, a prophylactic oophorectomy, hysterectomy, resection of the primary colonic tumor (colectomy or proctectomy), and chemotherapy using different agents. Shimazaki et al. described the treatment options in two cases with synchronous ovarian metastasis from colorectal carcinomas [35]. The first case was a 60-year-old lady who had a multilocular ovarian tumor and ascites (June 2014). A virtual colonoscopy revealed a sigmoid tumor and suspected ovarian metastases from the sigmoid colon. Immunohistological examination of the adnexectomy specimens revealed that the tumor cells were positive for CK20, and CDX2, and negative for CK7, inhibin, progesterone, and estrogen receptors. The patient received a modified FOLFOX6 chemotherapeutic regimen (oxaliplatin, leucovorin, and fluorouracil). Other components of the chemotherapy included 5-FU and anti-vascular endothelial growth factor monoclonal antibody (bevacizumab) for sigmoid carcinoma [35]. The patient was followed up until April 2016 and her condition was stable.

The second case was a 56-year-old lady who presented with ascites, multilocular pelvic mass, rectal tumor, and multiple peritoneal metastatic deposits (September, 2014). Colonoscopy identified a rectal mass and a left ovariectomy and transverse colostomy were done. The tumor cells were reactive for CK20 and CDX2 but had negative staining for CK7. Therefore, the diagnosis of ovarian metastasis from rectal adenocarcinoma was established. The patient received modified FOLFOX plus bevacizumab for the primary adenocarcinoma from the rectum. The patient was doing fine and her condition was stable on regular follow-up until April, 2016 (2016) [35]. Kemps et al. reported a case of MCCOs in a case of a 44-year-old lady who presented menorrhagia, a right ovarian mass, a transverse colon mass, and multiple hepatic hypodense lesions. The serum carcinoembryonic antigen (CEA) level was high whereas the level of serum CA125 level was low. Histological examination of the colonic biopsy established the diagnosis of colonic adenocarcinoma. The patient received palliative chemotherapy (Capecitabine, Oxaliplatin, and Bevacizumab/CapOx-B). Radiological examination following three courses of chemotherapy revealed an increase in the size of right ovarian metastasis associated with a decrease in the size of the transverse colon and hepatic tumors. Accordingly, bilateral salpingo-oophorectomy was done. Upon histology, there was a microscopic focus of metastatic adenocarcinoma in the left ovary. Mutational analysis revealed KRAS p.G12V mutations (both ovaries) and inactivating mutations in TP53 (p.R282W) and APC (p.K1350fs) genes. Therefore, five months after the surgical intervention, the chemotherapeutic regimen was modified to Folinic acid, Fluorouracil, Irinotecan, and Bevacizumab (FOLFIRI-B). A partial response to chemotherapy was found following four courses of FOLFIRI-B. After twelve courses of chemotherapy, the patient underwent laparotomy aiming at colectomy and metastasectomy of the liver metastases but unfortunately, they were not done due to the presence of multiple peritoneal metastatic deposits. The patient was doing well eighteen months after diagnosis (WHO performance score 0) [16].

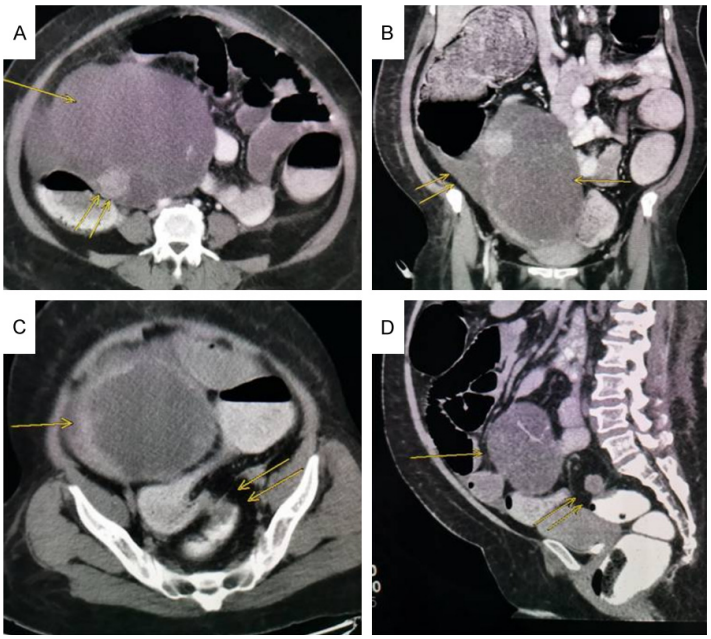

Figure 1. Photomicrographs of the radiological features of right ovarian metastases from adenocarcinoma of the rectosigmoid colon. The post-contrast CT scan of the abdomen and pelvis with intravenous, oral, and rectal contrast revealed a cystic mass lesion with internal septations and solid components (single arrow in all images) noted at the right ovary anatomy. (A) Small solid component (double arrow), (B) Ascites (double arrow), (C, D) Soft tissue mass with marked lumen narrowing at the rectosigmoid junction.

Here, we investigated the clinicopathologic features of a case of unilateral ovarian metastases from rectosigmoid carcinoma. Our study provides insights into the clinicopathologic features, pathogenesis, diagnosis, treatment, and prognosis of MCCOs.

Case presentation

Clinical findings

An obese 52-year-old woman (para 6+0, all were vaginal deliveries), post-menopausal for the last six months, was referred from the Secondary Health care center to the Emergency section of the Gynecology and Obstetrics Department. She complained of insidious onset and progressive course of abdominal distension for one year with chronic intermittent abdominal pain for more than one month associated with on and off constipation. This constipation became persistent for one week before reporting to OB-GYN ER with passing flatus, associated with recurrent non-projectile vomiting. Her medical history was noteworthy for medications for insulin-dependent diabetes, hypertension, and dyslipidemia.

On general examination, the patient was fully conscious with normal vital signs. Abdominal examination revealed an asymmetrically distended abdomen with a large, easily palpable right pelviabdominal firm to hard mass with limited mobility. The upper border of the mass was midway between the umbilicus and xiphisternum. Bimanual examination showed a slightly bulky uterus (± 12 weeks gestation in volume) that was compressed by the pelviabdominal mass with obliteration of vaginal fornices. The patient was admitted to the Gynecology ward for further workup, including imaging and tumor markers. A General Surgery consultation was requested to exclude the possibility of intestinal obstruction.

Radiological and laboratory findings

Ultrasound's assessment revealed the presence of a multicystic, pelviabdominal mass measuring 20 × 12 cm, with internal septations and focal areas of calcification. Post-contrast CT scan of the abdomen and pelvis with intravenous oral and rectal contrast showed a well-defined multilocular complex cystic lesion in the pelvis and lower abdomen, likely originating from the right adnexal region. The lesion was about 21 × 18 in maximum dimensions. The lesion had a complex appearance, irregular thick enhancing septa, and enhancing soft tissue components suggestive of malignant ovarian neoplasm of the right ovary: adjacent mildly enlarged mesenteric lymph nodes and mild fluid collection in the lower abdomen and pelvis. The uterus appeared enlarged, with diffuse thickening of the endometrium for further assessment. A circumferential soft tissue density mass lesion was noted at the rectosigmoid junction measuring about 2.6 × 1.6 × 2.7 cm opposite the S1 vertebral body and L5-S1 disc level; it was associated with per-rectal fat stranding. A summary of the radiological findings is shown in **Figure 1**.

The results of the tumor markers revealed elevated levels of CA125 (42.7 μ/ml, normal range: 0-35 μ/ml), and CEA (4.20 ng/ml, normal level:

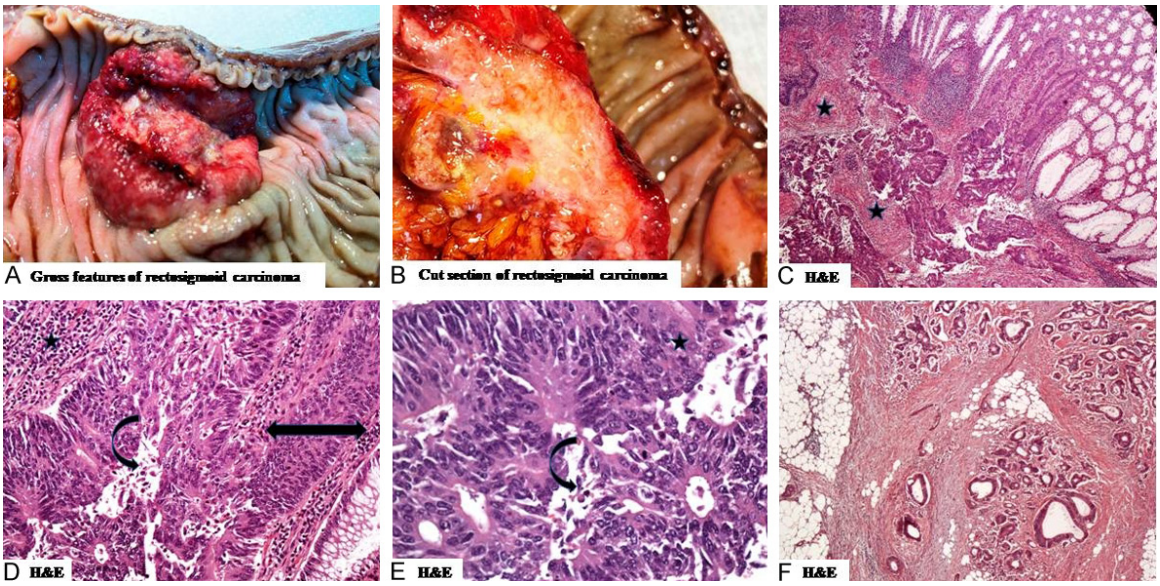

Figure 2. Photomicrographs of the gross and histological features of the rectosigmoid adenocarcinoma. (A) Theenface view of the opened rectosigmoid colon with an ulcerative mass with elevated, heaped-up edges and necrotic floor. The tumor is well-demarcated from the normal colonic mucosa. (B) The cross-section of the opened rectosigmoid colon shows a tumor that extends through the colonic wall into the pericolic adipose tissue. (C-E) The low power magnification (C) shows glandular structures with architectural abnormalities amid desmoplastic stroma(stars). There is dysplasia of the mucosal glands (left-right arrow). The malignant cells are arranged in complicated back-to-back glands (D, E), and dirty necrotic materials inside the lumens of the glands (curved arrow, D, E). (F) The malignant glands invade the subserosal fatty tissues (Original magnifications: C: ×40, D: ×200, E: ×400 and F: ×40).

3 ng/ml). The levels of AFP (1.9 ng/mL, normal range: 10-20 ng/mL), and hCG (1.1 mIU/mL, normal range: 5 mIU/mL) were normal. The risk of the Malignancy Index was 378. Intestinal obstruction was excluded following clinical evaluation by the General surgeon. The patient and her family were counseled. The plan of referral to a specialized Gynae-oncology center for further management of the ovarian tumor was discussed. The patient preferred to go home until the completion of the referral process.

Intraoperative findings

Two days later, the patient presented with manifestations of intestinal obstruction. The patient underwent exploratory laparotomy. Intraoperative findings included the presence of a bulky uterus (equal 10 weeks gestation), a large right ovarian multilocular mass with a smooth surface, partially solid, partially cystic, and ascites. There were no peritoneal seedlings, no calcifications, and no peritoneal nodules. The left ovary was unremarkable. Ascitic fluid was obtained and sent for cytological evaluation. Total hysterectomy, salpingo-oophorectomy, and omentectomy were performed. Also, a resection of the rectosigmoid colon was done by the colorectal surgeon.

Pathological findings

Gross examination revealed a 21 × 18 × 16 cm encapsulated, solid-cystic right ovarian mass with a smooth outer surface (without surface implants). The mass had a multilocular, partly cystic, partly solid cut section with extensive hemorrhage, necrosis, and degenerated materials. The rectosigmoid colon showed a circumferential thickening (mass) measuring 2.8 × 2.0 cm that invaded the subserosal fatty tissues. Postoperative histological examination of the rectosigmoid colon revealed moderately colorectal differentiated adenocarcinoma arising in a background of colorectal mucosa with high-grade dysplasia/intramucosal adenocarcinoma, without metastasis in the regional lymph nodes. Postoperative immunohistological examination of the ovarian mass revealed adenocarcinoma that was similar to colorectal carcinoma (CK20+, SATB2+, CDX2+, PAX8-, CK7-, ER-, WT-1-, and Vimentin-) on immunohistochemistry. A summary of the pathological changes is shown in **Figures 2-5**. Molecular analysis of the colorectal carcinoma revealed

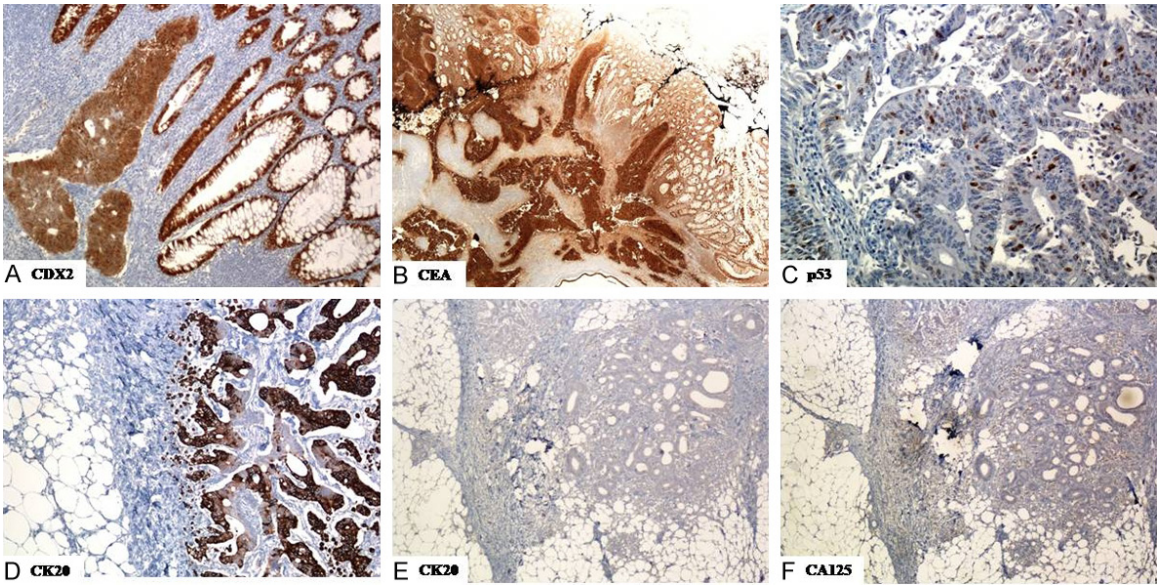

Figure 3. Photomicrographs of the immunohistological features of the rectosigmoid adenocarcinoma. (A-F) The tumor cells are reactive for CDX2, p53 (nuclear staining), and CEA (cytoplasmic staining). The tumor cells invading the muscle layer and the subserosal fatty tissue are reactive for CK20 (cytoplasmic staining, D). The tumor cells are negative for CK7 (E) and CA125 (F) (Original magnifications: A: ×100, B: ×20, C: ×200, D: ×40, E: ×40 and F: ×40).

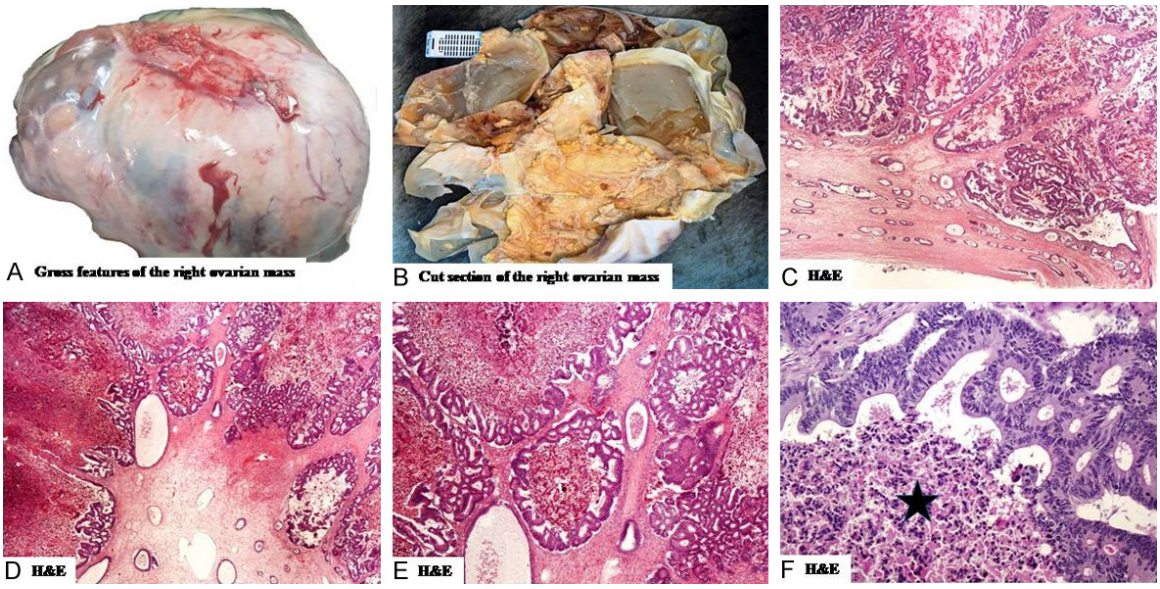

Figure 4. Photomicrographs of the right ovarian metastases diagnosed synchronously with the rectosigmoid adenocarcinoma. (A, B) The right ovarian mass is large and has a smooth outer surface (no implants), and the cut section shows cystic and solid areas that contain mucinous and necrotic materials. (C-F) The metastatic colorectal carcinoma to the right ovary consists of malignant glands arranged in a complicated pattern. Their lumens are filled with abundant necrotic materials (garland necrosis, E, F, star) and lined by malignant epithelial cells. The tumor cells are patently malignant and have hyperchromatic columnar nuclei, eosinophilic cytoplasm, and inconspicuous nucleoli (Original magnifications: C: ×20, D: ×40, E: ×100 and F: ×200).

the absence of mutations (K-Ras, N-Ras, BRAF, and PIK3CA), microsatellite stable colon cancer with a regular expression of the repair enzymes (0/4 enzyme damaged, MLH1, MSH2, MSH6, and PMS2). Unfortunately, five days after the surgery, the patient developed sudden onset of

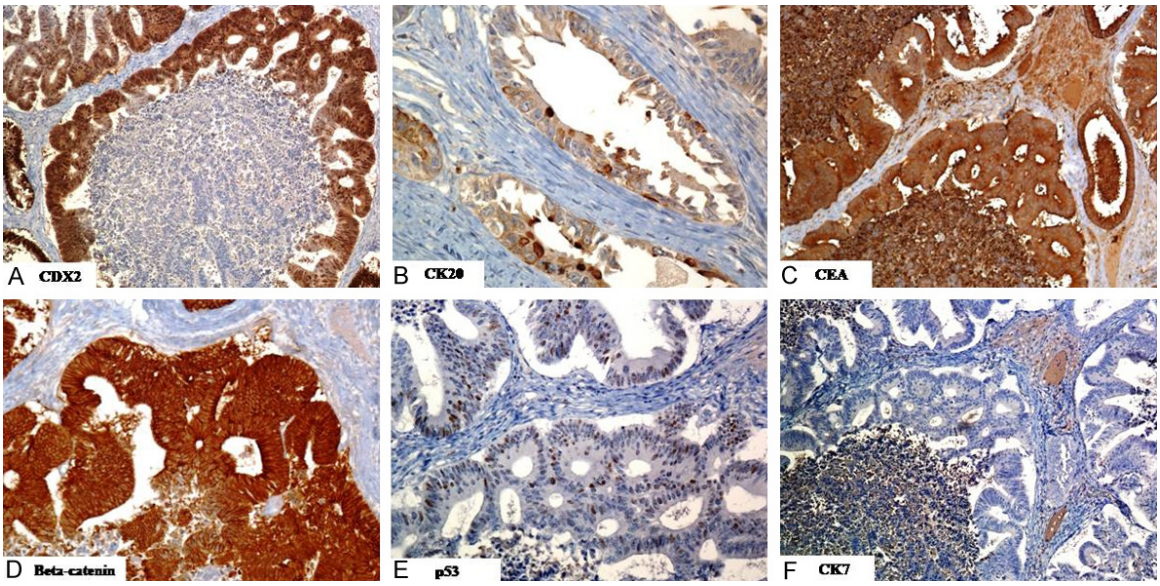

Figure 5. Photomicrographs of the immunohistochemical features of the right ovarian metastases diagnosed synchronously with the rectosigmoid lesion. (A-E) The metastatic tumor cells were positive for CDX2, CK20, CEA, Beta-catenin, and p53. They are negative for CK7 (F) (Original magnifications: A: ×100, B: ×100, C: ×100, D: ×100, E: ×200 and F: ×200).

chest pain and shortness of breath, which deteriorated rapidly in the intensive care unit. The Cardiology team evaluated the patient, and an emergency cardiac catheterization was performed. The patient died shortly from cardiorespiratory failure. Molecular analysis of the colorectal carcinoma revealed the absence of mutations (K-Ras, N-Ras, BRAF, and PIK3CA), microsatellite stable colon cancer with a regular expression of the repair enzymes (0/4 enzyme damaged, MLH1, MSH2, MSH6, and PMS2).

Discussion

Here, we report a unilateral MCCO from synchronous rectal sigmoid adenocarcinoma. The nonspecific clinical manifestations and immunohistochemical profiles of the case presented here are consistent with previous studies [5, 8, 10, 11]. Rekhi et al. examined the clinicopathological features of 9 cases of MCCOs. The average age of the patients was 55 years. The diagnosis of MCCOs was synchronous with CRC in 6 cases and metachronous in 3 cases. Four patients had bilateral MCCOs, and two patients had unilateral involvement. Ovarian metastatic masses had both solid and cystic components (4 cases). The origin of colorectal carcinomas was located in the sigmoid colon (five cases) and ileocaecal region (one case) in 1 (16.6%) case. The level of CEA levels was high in 4 cases. The origin of CRC was sigma (5 cases) and ileocecal region (1 case) in 1 case (16.6%) [5]. The CEA level was high in 4 cases [5]. Histologically, a complicated glandular pattern (tubule-glandular or endometrioid-like patterns) was evident in 6 cases. The remaining three cases had an either mucinous type of signet ring cell appearance. In this series, the most important histological features indicative of MCCOs were the presence of Garland necrosis, stromal desmoplastic reaction, lymphovascular invasion, and CK20 positivity. Most cases (7 cases) were CEA positive. In addition, 6 cases were positive for CK7 [5]. In addition, 6 cases were positive for CK7 [5].

In our case, the size of the ovarian metastasis was much larger than the size of the primary rectal sigmoid adenocarcinoma. This observation (large-sized ovarian metastatic tumor) may be due to loss of contact inhibition of metastatic cancer cells in the ovarian and peritoneal tissues. In addition, early transplantation of malignant cells into follicles may lead to the accumulation of cancer cells in ovarian tissue [36, 37]. The large size of MCCOs may also be reasoned to the release of some pro-inflammatory cytokines with continuous upregulation of NF-κB

and STAT3 signaling pathways [38] and some cytokines with growth factor activity such as TNF-α [39].

The metastatic tumor cells of MCCO in the ovarian microenvironment may release several angiogenic factors, such as vascular endothelial growth factor (VEGF). Angiogenesis is a process in which new blood vessels form a network of arteries that supplies nutrients and oxygen to the malignant cells [40, 41].

Cytokeratin 7 (CK7) is a type II cytokeratin encoded by the KRT7 gene and normally expressed by glandular, transitional, and ductal epithelia. CK20 is a type I cytokeratin encoded by the KRT20 gene and is normally expressed by the urothelium, Merkel cells, and gastrointestinal epithelium. These two cytokeratins provide helpful directions for identifying ovarian and colorectal carcinomas [42]. CDX2 is a transcription factor that plays a vital role in the proliferation and differentiation of intestinal epithelial cells. It is expressed by the vast majority of colorectal carcinomas but may also be seen in lung, ovarian, bladder, and pancreaticobiliary carcinomas [43, 44].

Although CK20, CDX2, CEA, and MUC2 are sensitive epithelial markers for carcinomas of colorectal origin, these immunostains lack specificity and can be positive in some PEOC, especially the mucinous type. The combined use of CK7 and 20 allows for separating most metastatic MCCOs (most cases are CK7-/CK20+) from non-mucinous PEOCs (most cases are CK7+/CK20+). However, a few cases of CRC are CK7+/CK20+ [8, 45]. Alternatively, some cases of PEOC (mucinous adenocarcinoma) are DX2+/CEA [8, 46, 47]. In 2002, Special AT-rich sequence-binding protein 2 (SATB2) was first identified as a gene involved in cleft palate defects [48, 49]. SATB2 is a nuclear matrix-associated transcription factor that selectively binds adenine and thymine (AT)-rich regions [48, 49]. The SATB2 is a nuclear marker that is selectively expressed by the epithelium of the lower gastrointestinal tract. It has selectively preserved expression in colorectal and appendiceal carcinomas. Therefore, it is a highly sensitive and specific immunostain that can differentiate colorectal adenocarcinoma from other carcinomas (pulmonary, gastric, pancreaticobiliary, mammary, neuroendocrine, and urothelial origins). SATTB2 can separate ovarian metastases of colorectal and appendiceal origin (SATB2 positivity) from primary mucinous or endometrioid ovarian carcinomas (SATB2 negativity) [48-50].

Taken together, here we report a case of unilateral MCCO. It is difficult to separate these lesions from PEOCs. Immunohistochemistry's differential expression of CK7 and CK20 helps solve these dilemmas. CK7 negativity and CK20/SATB positivity are indicative of colonic adenocarcinoma, whereas CK7 positivity and CK20 negativity is indicative of PEOCs. Additionally, frequent CEA positivity in colorectal tumors vs. CA125 expression in ovarian tumors improves diagnostic accuracy.

Take-home messages

The following lessons can be gathered from our study:

- Approximately 1.2-14% of females diagnosed with primary CRC have synchronous or metachronous MCCOs.

- Approximately 5.97% of metastatic colorectal cancers were of ovarian origin (according to a series of Japanese autopsies).

- MCCOs can present as unilateral ovarian tumors and their clinical manifestations are nonspecific.

- The features that support the diagnosis of MCCOs are bilaterality of the tumors, 'garland-like' necrosis, and desmoplasia.

- The PEOCs, primary CRC, MCCOs, and colorectal cancers of ovarian origin are usually treated differently.

Disclosure of conflict of interest

None.

Abbreviations

MCCO, metastatic colon carcinoma to the ovary; PEOC, primary epithelial ovarian carcinoma; CRC, colorectal carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; ER, estrogen receptor; CK, cytokeratin.

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