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Ovarian metastases from right colon cancer treated with systemic cancer chemotherapy, a case report

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ABSTRACT

BACKGROUND: The progression of cancer from its primary site has been the focus of study of surgeons and oncologists for many decades. Why the primary disease goes on to take the life of some patients while others live out their normal lives after a surgical procedure is only partially understood.

METHODS: In a patient with caecal cancer metastatic to the right ovary the clinical, radiologic, surgical and histopathologic findings are presented. Efforts were made to confirm that the disease process was from a single primary site (colon cancer) and not two primary sites (colon cancer and ovarian cancer).

RESULTS: In this patient there was progression of ovarian metastases from a right colon cancer simultaneous with near complete disappearance of the primary malignancy. The marked difference in control of the metastatic disease as compared to the primary cancer occurred as multiple treatments of systemic chemotherapy were administered over one year. The specimens of disease removed by surgery showed profound histologic differences at the two sites of cancer.

CONCLUSIONS: The primary colon cancer regressed to a small nodule while the ovarian metastases progressed. Efforts to understand and interpret the pathobiology of these observations were made.

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1. Introduction

Cancer chemotherapy is usually delivered by a venous access device into a central vein. Whether by bolus or by long-term infusion, the drug or drugs distribute themselves as a result of continuous mixing of the blood and chemotherapy agent to the tissues of the body. The brain and spinal cord are excluded because of the blood brain barrier. Also, as a result of fibrosis, ischemia or actual necrosis, some tissues are exposed to a different amount of chemotherapy than others. Some highly vascularized tissues, such as the liver, may have increase exposure to cancer chemotherapy because of a portal venous and arterial blood supply. Perhaps it is not surprising that different sites of organ metastases have a variable response to systemic chemotherapy.

Although these observations are not well documented, variable responsiveness to repeated doses of cancer chemotherapy is a frequent clinical observation. Liver metastases are observed to respond more robustly than peritoneal metastases, for example [1]. Perhaps the most overt disparity of chemotherapy response occurs in young women with ovarian metastases from gastrointestinal cancer. The Krukenberg tumor may be a manifestation of gastric,

colorectal, or appendiceal cancer [2]. A frequent observation is the continued expansion of an ovarian mass despite remarkable response of cancer at other sites. The incidence of this phenomenon has not been reported.

In this case report the continued progression of ovarian masses to a giant size that occurred with a near complete response of a caecal cancer is documented radiologically, clinically with cancer resection, and histopathologically. To our knowledge, this is the first manuscript to document this heterogeneous chemotherapy response of a primary colon cancer and its ovarian metastases. Some thoughts regarding the pathobiology of this phenomenon are offered.

2. Methods

In a single patient with caecal cancer and ovarian metastases, the clinical information over her first year of treatment was accumulated. This involved original pathology and radiology reports, records of the patient's cancer chemotherapy treatments, radiologic workup prior to cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC), and then a histopathologic study of the specimens resected at the time of cytoreductive surgery. Efforts were made using immunostains to determine whether the ovarian masses were from the primary colon tumor or were from a second primary ovarian malignancy.

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Fig. 1. Coronal cut of abdominal and pelvic CT with oral and intravenous contrast. Despite optimal CT technology with maximal intracolonic contrast the caecal cancer is no longer visible. Calcified nodules immediately adjacent to the superior mesenteric vein are shown by the arrow. A large multicystic and solid right ovarian mass is attached to the uterus.

Permission from the patient to publish these clinical findings was obtained. Clearance from the Institutional Review Board for publication of this case report was not required. This manuscript was constructed in compliance with consensus-based surgical report guidelines (SCARE) [3]. A PubMed search was performed to find other manuscripts that concerned the response of ovarian metastases to systemic chemotherapy.

2.1. Patient presentation

A 49-year-old woman complained of abdominal pain in November of 2015. A diagnosis of large uterine fibroid was made and a myomectomy from within the uterus was performed. No malignancy was associated with the specimens recovered. In December of 2016, the abdominal pain persisted and a mass was palpable in the area of the right colon. Colonoscopy was performed and biopsy showed a moderately differentiated adenocarcinoma.

CT was performed in December of 2016 and bilateral ovarian metastases were imaged. Percutaneous biopsy of the right ovarian mass showed well-differentiated adenocarcinoma consistent with a colonic primary. From December of 2016 through December of 2017, the patient was maintained on chemotherapy. Initially, she was treated with FOLFOX and then after four cycles because of neuropathy, the oxaliplatin was stopped. The patient was maintained on 5-fluorouracil and Avastin.

In December of 2017, she again became symptomatic. A CT scan documented marked regression of the primary tumor. It was not visible by CT. CT did show 2 cm in greatest diameter calcified lymph nodes immediately adjacent to the superior mesenteric vein (Fig. 1).

In the same CT, a pelvic mass showed a right ovary approximately 15 cm in greatest diameter (Fig. 1).

Over the course of approximately 1 month, the patient rapidly became more symptomatic. Her abdomen was distended with ascites. A large mass was palpable in the right lower quadrant arising from the pelvis. The mass was thought to be compatible with an enlarged right ovary. On February 1, 2018, the patient underwent to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in a specialized center for management of peritoneal surface malignancy. At the time of surgery she underwent a greater omentectomy, hysterectomy, bilateral salpingo-oophorectomy, complete pelvic peritonectomy, right colon resection, and small bowel resection. An end-to-side colo-enteric anastomosis was performed after HIPEC. Intraperitoneal mitomycin C and doxorubicin with systemic 5-fluorouracil was used for HIPEC. After a 3-week hospitalization the patient was discharged eating well and having normal bladder and bowel function.

At the time of surgery the tumor nodule in the area of the right colon was 2 cm in greatest diameter. By gross inspection the ovarian tumor at the time of surgery was 20 cm in greatest diameter. Both right and left ovaries were involved by metastatic disease.

Histopathologic study of the tissue adjacent to the primary cancer showed extensive fibrosis with small infiltrating glands. The response of the primary cancer to chemotherapy was judged to be “extensive”. There were a small number of residual well-differentiated infiltrating glandular structures (Fig. 2). Also, photomicrographs of the ovarian tumors were produced (Fig. 3). This tissue from the right ovary showed large infiltrating glands moderately differentiated and some areas of tumor necrosis. No histologic response of ovarian metastases to cancer chemotherapy was observed.

Immunocytochemistry was performed on both the small primary tumor and the large ovarian tumor. The CK-20 and CDX-2 immunostains were positive on both the residual primary cancer and the large ovarian tumor. PAX-8, ER and CK7 were negative on the primary tumor and on the ovarian metastases. The immunoprofile is consistent with colonic metastasis. The conclusion was that the ovarian tumor was metastatic from the primary right colon metastases but had markedly progressed with cancer chemotherapy as compared to the primary tumor which had undergone extensive regression.

Tumor markers were obtained preoperatively and decreased over the first 3 weeks of her postoperative course. CEA over a 3-week time period went from 29.4 to 2.2, CA19-9 from 448.3 to 66.2, and CA125 from 405.0 to 52.2.

3. Discussion

3.1. Krukenberg metastases

The oncologic literature regarding ovarian metastases from gastrointestinal cancer began with the observations of Friedrich Krukenberg in 1896 [4]. He reported large ovarian fibromas associated with the diagnosis of a primary gastric cancer. Schlagenhauser suggested that these two cancerous sites were related [5]. Although the original case report showed a gastric cancer causing the ovarian focus of malignancy, other primary gastrointestinal cancers have been reported to give rise to concomitant ovarian malignancy. Colorectal cancer, small bowel adenocarcinoma, pancreas cancer, and appendiceal cancer all can cause ovarian metastases [2]. Initially it was postulated that the route of metastatic spread was hematogenous or lymphatic. However, the frequent association of ovarian metastases with simultaneous peritoneal metastases has convinced most oncologists that the route for metastatic spread is

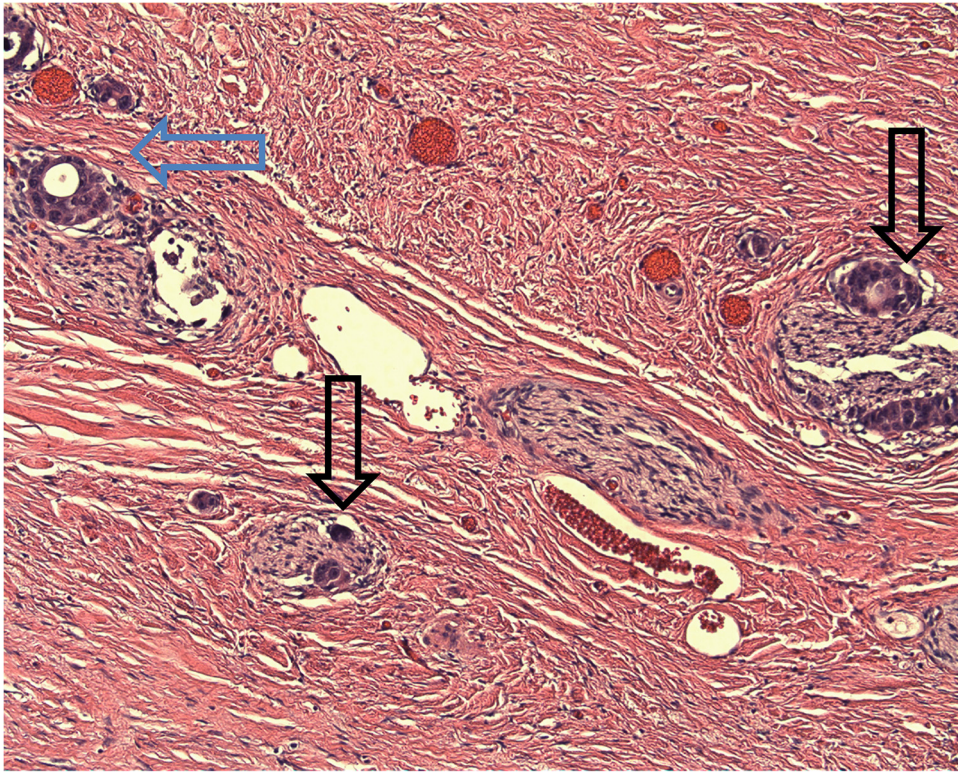


Fig. 2. Photomicrograph of the calcified mass immediately adjacent to the primary tumor shows extensive fibrosis throughout the field of view with small infiltrating glands (black arrows) and small infiltrating glands with perineural invasion (blue arrow). The gross tumor was 2 cm in greatest dimension (Hematoxylin and Eosin stain, 10 \times).

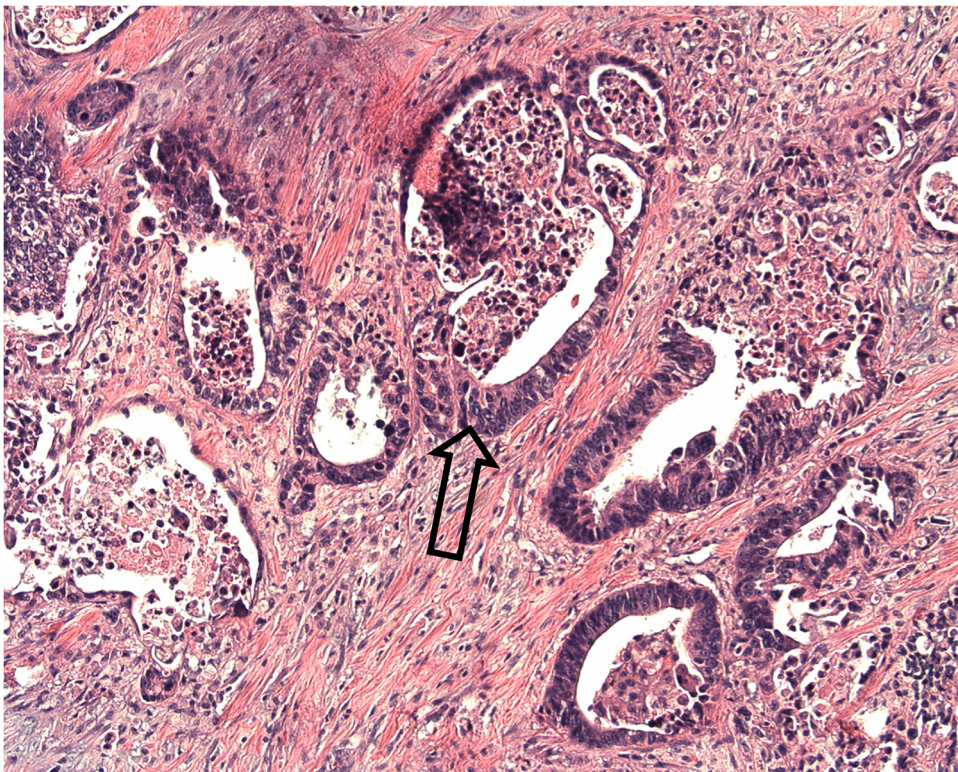


Fig. 3. Photomicrograph of the right ovarian metastases shows abundant large infiltrating glands (black arrow) filled with necrotic debris (dirty necrosis). The gross tumor was 20 cm in greatest diameter. Both ovaries were involved by metastatic disease (Hematoxylin and Eosin stain, 10 \times).

Table 1
Comparison and contrast of liver and ovarian metastases from colorectal cancer.

	Liver	Ovary
Pattern of spread from primary tumor	Hematogenous	Coelomic
Progression in comparison to primary tumor	More rapid	More rapid
Response to systemic chemotherapy in comparison to primary tumor	More responsive	Less responsive
Architecture of metastatic focus	Nodular	Multicystic
Contact inhibition of metastatic focus	Present because of surrounding liver parenchyma	Absent because of expansion into peritoneal space
Chemotherapy access to metastases	Arterial and portal venous	Arterial only

the peritoneal space [2]. Also, the greater of proportion of young (premenopausal) women with ovarian metastases from gastrointestinal cancer is suggested to be caused by extrusion of an ovum through the ovarian capsule, a site for cancer cell adherence at the corpus hemorrhagicum, and then implantation [2].

3.2. Contrast of the rate of disease progression with different anatomic sites of cancer

Clinicians have repeatedly observed that cancer metastases often grow much more quickly than the primary tumor. A small appendiceal mucinous neoplasm, a few cm in greatest dimension, can cause the formation of an “omental cake” that weighs more than 10 kg. Rectal cancer may result in bilateral ovarian metastases with each gland many centimeters in diameter and much larger than the primary rectal cancer [6]. Also, liver metastases from colon cancer may be many times the size of the primary tumor. Clearly, there is a heterogeneous rate of progression of cancer in different environments or different organs. No clear pathophysiologic explanation for the rapid progression of an ovarian metastasis as compared to the primary cancer site has emerged. Sugarbaker and Averbach hypothesized that an early implantation of cancer cells within the Graafian follicle resulted in an early accumulation of intraperitoneal cancer cells within the ovarian tissue [2]. The ovary was considered a favored site for intracoelomic metastases. A second factor may be the loss of contact inhibition noted as cancer progresses within the free peritoneal space. A liver metastasis will grow in a nodular fashion and have contact inhibition from the surrounding liver parenchyma. In contrast, metastatic disease within an ovary will not be limited by contact inhibition. A multicystic and solid mass can progress into the free abdominal and pelvic spaces in an uninhibited manner (Table 1).

3.3. Heterogeneous response to systemic chemotherapy at different anatomic sites

The continued rapid progression of ovarian metastases in our patient compared to the primary tumor is the focus of this manuscript. Most oncologists accept that cancer chemotherapy in repeated doses over time achieves a response because chemotherapy-induced cell kill is more active than tumor progression. This may explain the mechanism whereby giant ovarian metastases occur. With the total lack of containment of the ovarian metastasis, it is progressing at a rapid rate. Although some initial response may occur, the rapid proliferation of ovarian tumor between cycles of cancer chemotherapy will predominate. Whereas other more slowly progressing cancer sites (the primary

tumor) may respond, ovarian metastases do not. Another rapid progressing cancer sites, the liver metastases, may respond remarkably well to cancer chemotherapy because of bidirectional blood flow. Again, it is the intrinsic rate of cancer progression as compared to the extent of cell kill by repeated doses of chemotherapy that determines response. The incidence of heterogeneous responses to repeated cycles of systemic chemotherapy as occurred in this case report has never been determined. It is possible that a molecular analysis of the primary colon cancer as compared to the ovarian metastasis may, in the future, reveal different mutations that would explain different responses to cancer chemotherapy (Table 1).

Kammar and colleagues studied 25 patients with ovarian metastases of colorectal origin [7]. All patients received chemotherapy and they observed that 66% of patients showed progression of their ovarian metastases while on chemotherapy. They suggested that treatment of ovarian metastases of colorectal origin has a consistently poor outcome and a majority of ovarian metastases progress while on chemotherapy. In contrast, Briau and colleagues studying 35 patients with ovarian metastases from gastric cancer found that the ovarian metastases were not more resistant than extraovarian metastases in their responses to systemic chemotherapy [8].

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

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Ethical approval

Local IRB-approval for this case report was not required: MedStar Health Institutional Review Board has determined that a case report of less than three (3) patients does not meet the DHHS definition of research (45 CFR 46.102(d)(pre-2018)/45 CFR 46.102(1)(1/19/2017)) or the FDA definition of clinical investigation (21 CFR 46.102(c)) and therefore are not subject to IRB review requirements and do not require IRB approval.

This case report is only of 1 patient.

Consent

Written and signed consent was obtained from the patient.

Author contribution

Paul H. Sugarbaker, MD: study concept or design, data collection, data analysis or interpretation, writing the paper
John Liang, MD: study concept or design, data collection, data analysis or interpretation, writing the paper

Registration of research studies

Not applicable.

Guarantor

Paul H. Sugarbaker, MD

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