

Peritoneal metastases from mucinous endocervical adenocarcinoma



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Introduction

Pseudomyxoma peritonei is a clinical condition characterized by mucinous tumors and mucinous ascites that accumulates in large volume and over time will interrupt gastrointestinal function. Pseudomyxoma peritonei most commonly arises from a mucinous neoplasm of the appendix (Sugarbaker et al., 1996). Also, occasionally this syndrome may arise from the colon or rectum, gallbladder, small intestine, ovarian teratoma, lung, breast, pancreas, fallopian tube, and urachus (Sugarbaker, 2012a). Described here are three patients presenting with mucinous peritoneal metastases arising from an adenocarcinoma of the endocervix. This cause of this rare condition is unclear; it may be caused by retrograde menstruation. Evaluation of these patients for cytoreductive surgery (CRS) and hyperthermic perioperative chemotherapy (HIPEC) at a peritoneal surface oncology treatment center early in the natural history of the disease is recommended.

Patient presentation 1

A 33 year old woman presented in May of 2011 with chief complaints of abdominal distention and pain. A past history of cone biopsy of the cervix in 2002 showed pre-cancerous cells with no invasive malignancy. CT of the chest, abdomen, and pelvis showed a large volume of intraabdominal fluid consistent with combined mucinous and serous ascites (Fig. 1). Laparoscopy was performed showing bilateral adnexal masses, copious mucinous fluid, and peritoneal metastases on the abdominal wall, the right hemidiaphragm, and greater omentum. Pathology showed mucinous adenocarcinoma and immunostains suggested a cervical origin with P16 and CK7 positive and CK20 negative.

Upper and lower gastrointestinal endoscopy was not revealing of a cancerous process. She underwent a 9-hour complete CRS with greater omentectomy, appendectomy, right upper quadrant peritonectomy, lesser omentectomy, pelvic peritonectomy, hysterectomy, and bilateral salpingo-oophorectomy (Sugarbaker, 2012b).

Pathology showed in-situ and invasive mucinous adenocarcinoma of the endocervix with metastases to ovaries, fallopian tubes, omentum, and peritoneum. The appendix was normal except for overlying extracellular mucin. She was treated with HIPEC and early postoperative intraperitoneal chemotherapy (EPIC) (Sugarbaker, 2012b). The patient was treated with a single cycle using cisplatin (50 mg/m²) and doxorubicin (15 mg/m²) by intraperitoneal administration at 42 °C. Continuous infusion intravenous ifosfamide was given over the 90 min of HIPEC. Fifteen minutes prior to infusion 2-mercaptoethane sulfonate NA (MESNA) at 260 mg/m² was given as a bolus. The MESNA was repeated at 4 and 8 h after initiation of the HIPEC. Early postoperative intraperitoneal chemotherapy (EPIC) with paclitaxel at 20 mg/m² in one liter of 1.5% dextrose peritoneal dialysis solution was used postoperative days one through five (Sugarbaker, 2012b). Systemic chemotherapy was given over five months using paclitaxel at 135 mg/m² administered over 24 h on day one plus cisplatin 50 mg/m² administered on day two. Treatment was every 21 days for six cycles.

She remains asymptomatic on 6 monthly CT follow-up at 3 years.

Patient presentation 2

In February of 2012, this 27 year old woman reported her first symptom as increasing inability to eat or drink. CT showed high jejunal obstruction, a pelvic mass thought to be an enlarged ovary, and ascites. Laparoscopy and dilatation and curettage with endocervical biopsy showed adenocarcinoma from an invasive endocervical primary cancer.

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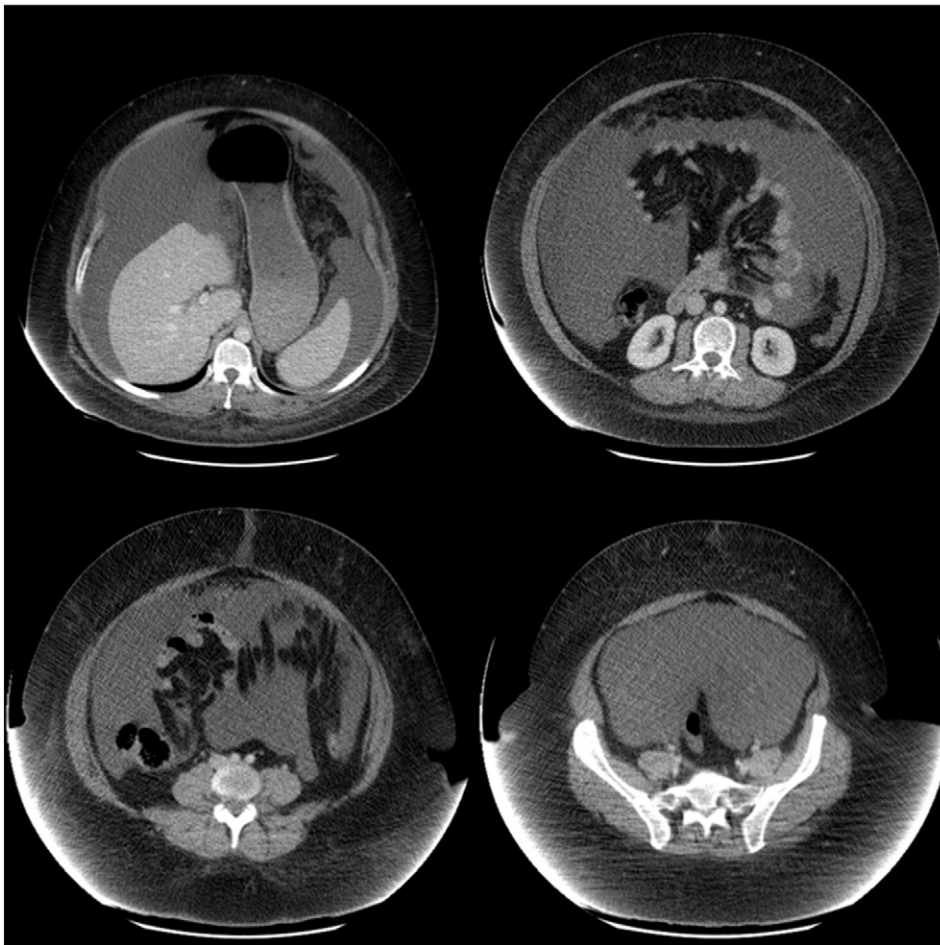


Fig. 1. Abdominal and pelvic CT on a patient with adenocarcinoma of the endocervix. Paracentesis resulted in the drainage of 10 l of ascites.

A jejunostomy was placed for nutritional support. Systemic carboplatin AUC 4–7.5 was given every 21 days together with paclitaxel 175 mg/m² also every 21 days. Treatment was for six cycles with good symptomatic benefit and a resumption of oral nutrition. In July of 2013, the patient again became unable to eat and recurrent high jejunal obstruction was confirmed. At this time she underwent palliative surgery to bypass jejunal and colonic obstructions. Greatly enlarged omentum and ovaries were resected (Fig. 2). HIPEC was used in an attempt to control debilitating ascites (Sugarbaker, 2012b). HIPEC used cisplatin (50 mg/m²) and doxorubicin (15 mg/m²) by intraperitoneal administration at 42 °C. Continuous infusion intravenous ifosfamide was given over the 90 min of HIPEC. Fifteen minutes prior to infusion 2-mercaptoethane sulfonate NA (MESNA) at 260 mg/m² was given as a bolus. The MESNA was repeated at 4 and 8 h after initiation of the HIPEC. Early postoperative intraperitoneal chemotherapy (EPIC) with paclitaxel at 20 mg/m² in one liter of 1.5% dextrose peritoneal dialysis solution was used postoperative days one through five (Sugarbaker, 2012b). All biopsies and resected specimens were compatible with endocervical adenocarcinoma. The left upper quadrant mass was not resected. She was not thought to be a candidate for further systemic chemotherapy. She died in October of 2013.

Patient presentation 3

This patient had Peutz–Jeghers syndrome and carried an STK-11 mutation. In January 2012 at age 44, she presented with vaginal discharge. A hysterectomy showed a well differentiated mucinous adenocarcinoma of the endocervix that fulfilled the criteria for minimal deviation adenocarcinoma ('adenoma malignum') (McCluggage, 2013).

Mucinous lesions were noted on the peritoneal surfaces, and a biopsy showed metastatic mucinous adenocarcinoma that was morphologically similar to the cervical lesion. Immunohistochemistry showed expression of CK7 and CA125, but CK20 and CDX-2 were negative. Adjuvant treatments with cisplatin at 40 mg/m² for 5 weeks plus radiation therapy to 45 Gy were given.

In 2013 she presented with pelvic pain and radiological features of pseudomyxoma peritonei. There was significant respiratory compromise as a result of a pulmonary embolism combined with massive abdominal distention from ascites. It was decided to proceed to laparotomy following insertion of a vena cava filter and anticoagulation. Laparotomy released 20 l of watery ascitic fluid leading to improved ventilation. Nodules of mucinous tumor were found on the small bowel, on the under-surface of both diaphragms, in the paracolic gutters, on the jejunum and the terminal ileum, and there was a massive omental cake. Complete cytoreduction was not possible and a debulking procedure was performed, including total colectomy with end ileostomy. HIPEC with mitomycin C at 20 mg/m² at 42 °C for 90 min was administered to help alleviate further ascites accumulation. Histology of the tumor confirmed metastatic mucinous adenocarcinoma (Fig. 3).

Her postoperative course was complicated by further deep venous thromboses and she died on the 31st postoperative day.

Discussion

It is extremely uncommon for cervical cancer to be associated with peritoneal metastases. Gatalica, Foster, and Loggie reported on low-grade mucinous peritoneal metastases eight years after hysterectomy in a patient who had cervical adenocarcinoma (Gatalica et al., 2008).

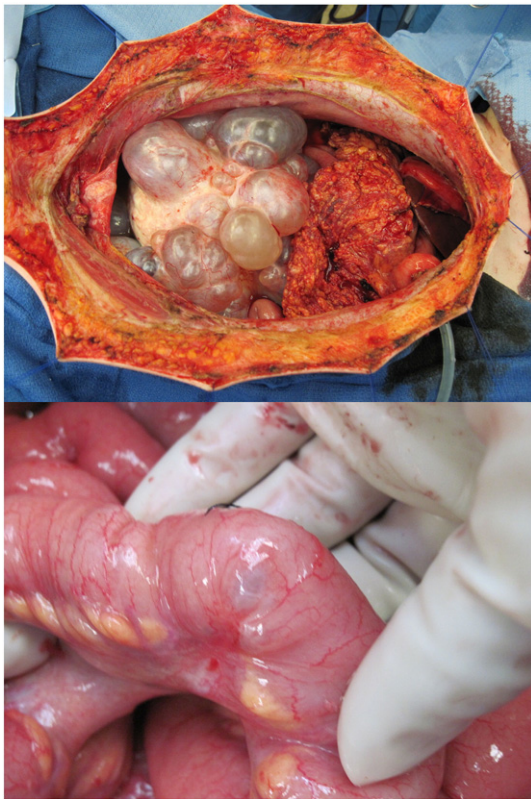


Fig. 2. Findings at the time of exploratory laparotomy in a patient with endocervical adenocarcinoma. Top. The cystic left ovary was enlarged to 20 cm. The omentum was diffusely infiltrated by tumor nodules. Bottom. Although a majority of the small bowel was free of mucinous adenocarcinoma, mucinous cancer nodules at the junction of small bowel and its mesentery caused partial obstruction at several sites.

No primary mucinous tumors to serve as a primary site for the peritoneal metastases were identified. The peritoneal lesions tested positive for high risk human papilloma virus, strongly suggesting abdominal and pelvic cancer contamination at the time of hysterectomy as a cause of the patient's peritoneal metastases.

The pathophysiology of cervical adenocarcinoma dissemination to the peritoneal surfaces is not readily apparent. Recently, retrograde menstruation from the fallopian tubes has been suggested to cause what was previously identified as serous ovarian cancer (Kurman & Shih, 2011). It is possible that adenocarcinoma cells from the endocervix could likewise, in unusual patients, spread into the free peritoneal space through a process of retrograde menstruation. Two of our three patients

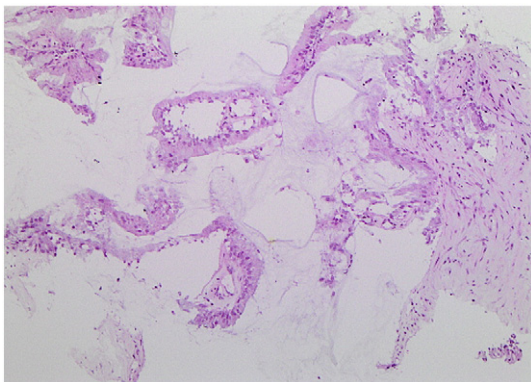


Fig. 3. Peritoneal metastases from a patient with Peutz–Jeghers syndrome and endocervical adenocarcinoma. The specimen was taken at the time of the surgery.

were young and nulliparous. This is the patient who is most likely to develop endometriosis, which is a manifestation of normal endometrial tissue entering the peritoneal space through the process of retrograde menstruation. Also, in all three of our patients there was extensive mucus and serous fluid produced by the malignancy leading to profound abdominal distention in all three patients. The demonstrated ability of endocervical adenocarcinoma to produce such copious amounts of fluid seems well documented by our three patients. Copious slippery fluid discharged into the uterus may be forced into the fallopian tubes and be expressed into the free peritoneal space. Of course, the fluid would be contaminated by mucinous cancer cells and would soon lead to the extensive peritoneal metastases present in our patients.

Uterine perforation can result in direct inoculation of cancer cells into the free peritoneal space. Anecdotal reports from the gynecologic oncology literature document this fact. In 1981, Mills, Sugg, and Mahnesmith reported the direct extension of a uterine adenocarcinoma through the wall of the uterus and growing out as a pelvic mass attached to the uterine serosa (Mills et al., 1981). The cancer inside and outside of the uterus was histologically identical. They identified this clinical situation as the first reported example of direct inoculation of a cancer into the peritoneal space following myometrial perforation. Levine et al. noted trophoblastic tissue spread to the surface of the sigmoid colon following uterine perforation during dilatation and curettage. A laparotomy showed trophoblastic tumor implants at the perforation site, anterior uterine wall, and appendix epiploica of the sigmoid colon. Surgical removal and treatment with methotrexate enabled the patient to recover (Levin et al., 2004). A possible mechanism of dissemination of endocervical adenocarcinoma into the free peritoneal cavity would be uterine perforation at the time of a cervical dilatation and curettage. However, no surgical record of uterine perforation was present in our patients and the patients were not aware that such an event had occurred.

The applications of CRS and HIPEC have been evolving and expanding over the last 30 years. This combined treatment has been shown to be of benefit in the management of intraabdominal malignancies, especially those having a high propensity for peritoneal metastases (Glehen et al., 2010). Current data suggests that CRS and HIPEC should be considered for appendiceal mucinous neoplasms with peritoneal dissemination, colon and rectal cancer with a small extent of peritoneal metastases, and peritoneal mesothelioma. Also, patients with ovarian cancer may be benefited by complete CRS plus HIPEC as a first line of treatment or treatment for recurrent disease (Chua et al., 2009). In this manuscript an uncommon application of CRS and HIPEC for pseudomyxoma peritonei originating from endocervical adenocarcinoma was presented. To our knowledge this is the first report of CRS and HIPEC for endocervical adenocarcinoma with ovarian and peritoneal metastases with the pseudomyxoma peritonei syndrome. Further clinical studies are required to assess the durability of this approach to this unusual manifestation of endocervical adenocarcinoma.

A survey of the surgical literature reveals that CRS and HIPEC have been used to treat a variety of rare malignancies with peritoneal surface dissemination (reviewed in Sugarbaker, 2012a). Usually, low malignant potential (LMP) ovarian tumors carry an excellent prognosis. Unfortunately, with long-term follow-up, a small spill of the minimally aggressive tumor cells may progress within the peritoneal space to an extreme size and become a terminal condition. Dermoid cysts of the ovary may cause gliomatosis peritonei or mucinous peritoneal metastases and the pseudomyxoma peritonei syndrome. A urachal mucinous adenocarcinoma may cause pseudomyxoma peritonei successfully treated by CRS and HIPEC. Malignant pararectal hamartoma and perforated malignancy mesenteric cysts may cause pseudomyxoma peritonei and be successfully treated by CRS and HIPEC. As a result of our successful management of at least one patient, we suggest that patients who have peritoneal metastases from endocervical adenocarcinoma be evaluated by a center experienced in the treatment of peritoneal surface malignancy.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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