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Primary peritoneal mucinous adenocarcinoma: Rarest of the rare?

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Abstract

Primary carcinomas of the peritoneum are an uncommon diagnosis which often present at an advanced stage with widespread peritoneal disease. They share histologic similarities to ovarian carcinomas and are often diagnosed once primary ovarian involvement has been ruled out. The most common histologic subtype reported of primary peritoneal carcinoma is the serous papillary variant. Another subtype reported, mucinous adenocarcinoma, yields less than 25 cases in the literature describing a primary mass within the retroperitoneum. Here, we report a novel case of an intra-peritoneal, cystic mass found to be primary peritoneal mucinous adenocarcinoma in an otherwise healthy 49-year-old female patient.

Keywords

peritoneal carcinoma; mucinous adenocarcinoma; serous papillary carcinoma

Abbreviations

CT: computed tomography; PET: positron emission tomography; PSPPC: primary serous papillary peritoneal carcinoma; ECOG: Eastern Cooperative Oncology Group, HIPEC: hyperthermic intraperitoneal chemotherapy; FDG: fludeoxyglucose

Introduction

Primary peritoneal carcinoma is an uncommon epithelial tumor arising from the peritoneal lining of the abdomen and pelvis. The most common histologic subtype reported is primary serous papillary peritoneal carcinoma (PSPPC) which often presents at an advanced stage at diagnosis. First reported in 1959 by Swerdlow [1], the etiology and pathogenesis still remain largely unknown. Because of its histologic similarity to serous ovarian carcinomas, it has been hypothesized that these carcinomas develop from the common embryonal epithelium from which the ovarian and peritoneal epithelium are derived; this epithelium is the coelemic epithelium [2].

PSPPC often presents at an advanced stage at diagnosis with widespread peritoneal disease. Interestingly, there are only three cases reported in the literature of PSPPC presentation as a localized pelvic mass without peritoneal dissemination at diagnosis [3,4,5]. To the best of our knowledge, there has been no documented cases in the literature of a primary peritoneal mucinous adenocarcinoma presenting as a localized, intra-peritoneal pelvic mass. The following case report describes a cystic mesenteric mass consistent with histologic and clinical findings of primary peritoneal mucinous

adenocarcinoma in a previously healthy 49-year-old female with no evidence of metastatic disease at presentation.

Case Presentation

A 49-year-old, para 3, African American woman was referred to the general surgery outpatient clinic for evaluation of an intra-abdominal,complex cystic mass that was incidentally discovered on imaging during workup of lumbago and radiculopathy. In addition to her chronic back pain and constipation, the patient experienced a four-month history of pain with bowel movements leading to anorexia and a 20-pound weight loss. One month prior to consultation, she noted abdominal fullness and a tender area of firmness in her right lower abdomen. Her colonoscopy the previous year showed no abnormal findings. Her past medical history was significant for depression and a 10-pack-year smoking history. Previous surgical history included an uncomplicated laparoscopic cholecystectomy and bilateral tubal ligation. Menopause occurred at the age of 47 and she was without hormone replacement therapy. Computed tomography of the abdomen and pelvis was significant for a 6.6 x 6.1 x 6.4 cm intermediate density, thin-walled complicated cyst in the right abdomen that closely approximated the ascending colon (Figure 1A). The cyst wall was scattered with calcifications (Figure 1B). Although there was mass effect on the adjacent colon, there was no evidence of obstruction. No free intraabdominal fluid or suspicious lymphadenopathy were present. The uterus contained multiple solid enhancing masses, most representing fibroids. Radiology suggested either a complex enteric duplication cyst, mesenteric cyst, endometrioma, or sequelae of prior infection in the differential for the cystic mass; they also recommended surgical evaluation.

The patient was taken to the operative theater for a diagnostic laparoscopy. The cystic mass was easily identified arising from the right mesocolon, deep to the posterior aspect of the anterior abdominal wall. Adherent omentum was divided off and the tumor was subsequently freed from the mesocolon and colon wall. Incision of the specimen produced a thick, purulent-like fluid which was sent for cultures. The specimen was sent for permanent section. A thorough inspection of the abdominal cavity did not reveal signs of liver or peritoneal metastasis.

Histopathological examination revealed a cystic mass lined by malignant glandular epithelium with infiltrating malignant glands within fibrous tissue. Goblet cells were present in addition to abundant mucin production (Figure 2A). Immunohistochemical stains demonstrated the neoplastic cells to be diffusely and strongly positive for cytokeratin 7, with focal positivity for cytokeratin 20 and CDX2 (Figure 2B). The strong cytokeratin 7 staining was supportive of origin from a non-colorectal primary for the tumor, as colorectal adenocarcinoma is expected to be diffusely keratin 20 positive and keratin 7 negative (Figure 2C). The patient was diagnosed at that time with adenocarcinoma of unknown primary.

Colonoscopy was repeated without any noted abnormalities. Biopsy of multiple sessile polyps were negative for dysplasia or malignancy, which suggested the colon to be an unlikely source of adenocarcinoma. Baseline tumor markers were checked postoperatively with a mild elevation in CA-125 level to 67.9 U/mL (normal range < 35 U/mL); a normal carcinoembryonic antigen at <0.5 ng/mL (normal range < 5 ng/mL); and a normal CA 19-9 at 1 U/mL (normal range < 37 U/mL). Positron emission tomography (PET) imaging of her chest, abdomen, and pelvis showed no evidence of metastatic disease within her abdominal cavity due to the lack of FDG avidity. Computed tomography of her thorax showed

only two small pulmonary nodules within her right middle lobe and left upper lobe, both measuring less than four millimeters. After a prolonged discussion at a multidisciplinary tumor board, primary peritoneal adenocarcinoma was diagnosed with agreement that no adjuvant chemotherapy was recommended at that time. The patient was counseled regarding surveillance versus undergoing aprophylactic right colectomy. She ultimately chose to proceed forward with continued surveillance only.

Referral to gynecology for further workup of low pelvic pain and pressure with the possibility of a primary malignancy only revealed two large uterine fibroids on both pelvic and transvaginal ultrasound. Endometrium and cervix biopsies both were negative for dysplasia and malignancy. The patient underwent a laparoscopic hysterectomy with bilateral salpingo-oophorectomy five months after the index operation. The procedure was uncomplicated and she was discharged home on postoperative day one. Pathology again demonstrated benign tissues of the cervix, endometrium, myometrium, fallopian tubes, and ovaries.

She was noncompliant with her follow-up and presented approximately ten months later with obstructive gastrointestinal symptoms of abdominal pain, constipation, and emesis. Computed tomography of the abdomen and pelvis at that time demonstrated a new intraabdominal mass near the location of her previously resected adenocarcinoma, measuring approximately 4.5 cm in its greatest diameter (Figure 3A). PET confirmed a heterogeneously enhancing density within the aforementioned region, concerning for recurrence of her malignancy (Figure 3B). No evidence of metastatic disease was apparent at that time. She underwent exploratory laparotomy with excision of the intraabdominal tumor, right hemicolectomy, small bowel resection, and ileocolostomy. The tumor was metastatic to the terminal ileum and involved the peritoneum of the anterior abdominal wall, in addition to the retroperitoneum to the level of the right ureter which required resection. Histopathological examination demonstrated recurrent primary peritoneal carcinoma within the right colon, retroperitoneum, peritoneum, and small bowel with microscopically positive margins at the right ureter (Figure 4). Her CA-125 at that time was normal at 4.8 U/mL (normal range < 35 U/mL).

She was re-evaluated by medical oncology who began adjuvant systemic therapy with six cycles of carboplatin and paclitaxel. However, after only four cycles she began developing worsening chemotherapy-related grade two neuropathy and myalgia. Paclitaxel was discontinued and she proceeded with two more cycles of carboplatin. She presented several months later with worsening abdominal pain, vomiting, and fatigue. Abdominal computed tomography at that time showed findings consistent with peritoneal carcinomatosis (Figure 5). She developed obstructive symptoms shortly thereafter with feculent emesis and obstipation. Re-imaging demonstrated evidence of high grade small bowel obstruction with transition point in the right lower quadrant near an enhancing soft tissue mass along the peritoneal surface, extending into the right paracolic gutter and iliopsoas musculature (Figure 6). After failed trial of nonoperative management, the patient was taken to the operative theater for exploratory laparotomy, extensive enterolysis, and small bowel resection with end ileostomy. Innumerable peritoneal implants were noted throughout the abdomen with invasion into the abdominal wall and throughout the right lower quadrant. Distal small bowel was extremely adherent to multiple areas within the right lower quadrant and right retroperitoneum. Final postoperative histopathology revealed metastatic adenocarcinoma and tumor cell positivity for cytokeratin 7, cytokeratin 20, Pax8,

and CDX2 (Figure 7). Tumor cells were negative for ER, PR, mammaglobin, gata 3, WT1, and TTF1. These findings were similar to her previous immunohistochemical results from her prior operations. Tumor studies revealed negativity for PD-L1 expression; amplification of CCND1, FGF19, FGF3, FGF4, and RBM10. Due to her performance status measured at an ECOG of 3, she was not a candidate for off-label treatment or clinical trials. Palliative care and hospice were ultimately consulted for her medically and surgically refractory disease. She was admitted to inpatient hospice 77 days after her final surgery and expired 18 days after being placed on hospice due to widely metastatic disease and associated cancer cachexia.

Discussion

Primary peritoneal carcinoma and its histologic variants are a rare diagnosis, with estimated incidences of primary serous papillary peritoneal carcinoma (PSPPC) in the United States as 6.78 cases per 1,000,000 individuals [6]. Common presenting symptoms include abdominal discomfort, distention, pressure associated with ascites, loss of appetite, and a palpable abdominal mass [7,8,9]. Pathologic values of serum CA-125 (> 35 U/mL) are also a common finding at presentation and diagnosis, similar to epithelial ovarian serous papillary carcinomas [2].

PSPPC is treated using the same chemotherapeutic and surgical approach as serous ovarian carcinomas due to its similar biological and clinical behavior. The diagnosis of PSPPC can be made with the criteria defined by the Gynecologic Oncology Group in 1993:

1) Both ovaries must be either physiologically normal in size or enlarged by a benign process.

2) The involvement of extra-ovarian sites must be greater than the involvement on the surface of either ovary.

3) The ovarian tumor involvement must be either nonexistent, confined to the ovarian surface epithelium without stromal invasion, or involving the cortical stroma with tumor size less than 5 × 5 mm.

4) The histological and cytological characteristics of the tumor must be predominantly of the serous type that is similar or identical to ovarian serous papillary adenocarcinoma, any grade [10].

Although the Gynecologic Oncology Group has assigned these specific criteria for the diagnosis of extra-ovarian serous papillary peritoneal carcinoma, these criteria may not extend to the diagnosis of other histologic subtypes such as extra-ovarian mucinous peritoneal carcinoma.

Review of the literature reveals most, if not all, case reports describing the papillary serous subtype of primary peritoneal carcinomas. Theoretically, if the germinal epithelium of both the peritoneum and ovary develop from the same embryologic origin and retain the multipotentiality of the Müllerian system, other histologic subtypes of epithelial ovarian carcinomas are also capable of presenting as a primary peritoneal carcinoma. Less than 25 cases of retroperitoneal mucinous cystadenocarcinoma, a similar variant to our patient's subtype, have been reported in literature [11-19]. These tumors also share similar morphological and immunohistochemical profiles of ovarian mucinous tumors. However, this is in stark contrast from our patient's presentation as these tumors are reported to grow within the retroperitoneum; our patient's tumor originally presented as aperitoneal mass. Diagnosis of retroperitoneal location in the aforementioned cases were made primarily intraoperatively

or by computed tomography. Our patient did not share those similar findings on imaging or intraoperatively during her first operation to remove the mass. Hence, to our knowledge there has yet to be a case published that describes a primary peritoneal carcinoma that is not only mucinous in histology but cystic in morphology within the peritoneal cavity. In addition, immunohistochemical studies in the current case resulted in tumor positivity for cytokeratin 7, focal positivity for cytokeratin 20, and focal positivity for CDX2. Interestingly, this is identical to the markers expressed by ovarian mucinous carcinomas of the ovary [20-22].

The most common therapies used for PSPPC, maximal cytoreduction combined with platinum-based chemotherapy, are based upon proven effectiveness in serous ovarian carcinomas. This was the treatment modality used in our patient. Although this produces comparable response rates of 79% [23,24], it is unclear whether this treatment for PSPPC is as effective against the mucinous histologic variant.

Figures

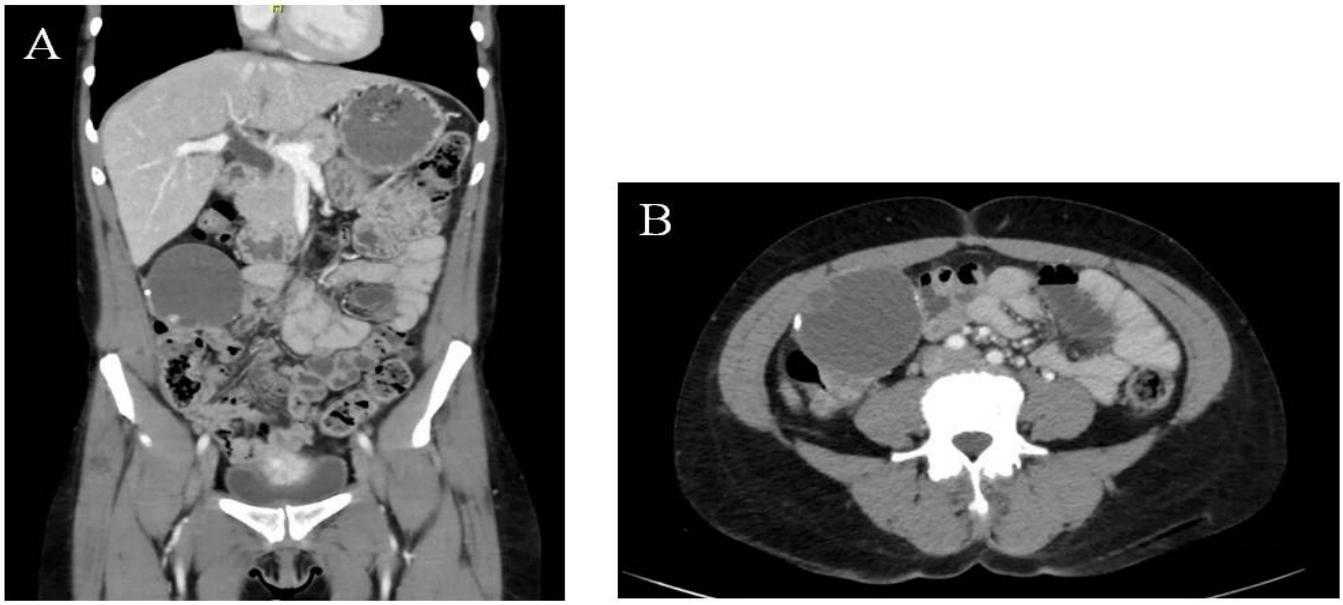

Figure 1: Computed tomography of the abdomen demonstrated a complicated cystic mass in the right lower quadrant with scattered calcifications.

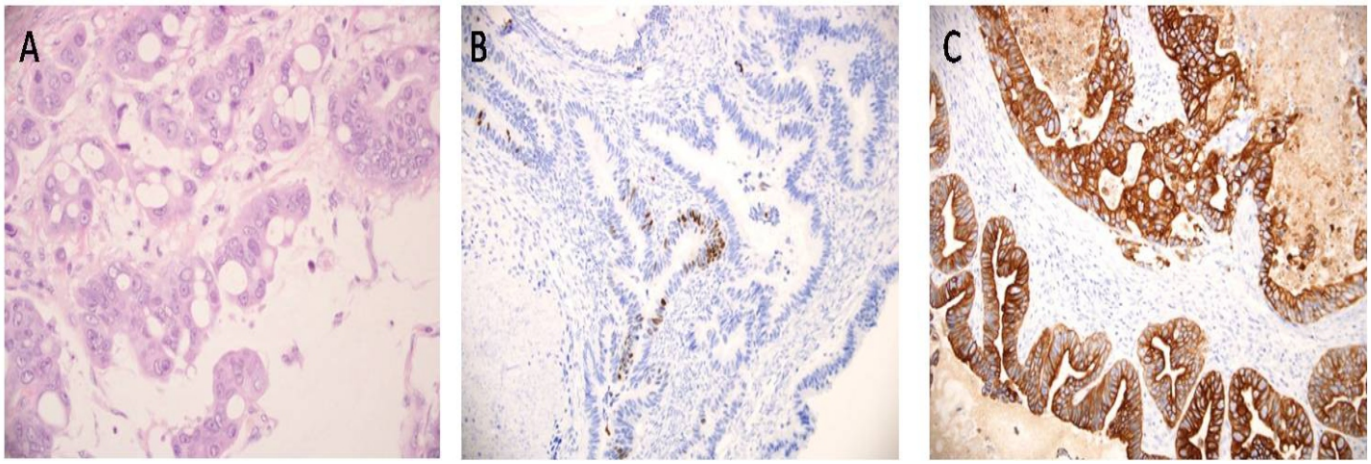

Figure 2: Pathology from the first operation showed findings consistent with mucinous adenocarcinoma. (A) H&E stain demonstrated glandular epithelium with infiltrating malignant glands and goblet cells with abundant mucin production. (B) Immunohistochemical staining revealed focal CDX2 positivity. (C) Cells stained diffusely and strongly for cytokeratin 7, supportive of origin from a non-colorectal primary.

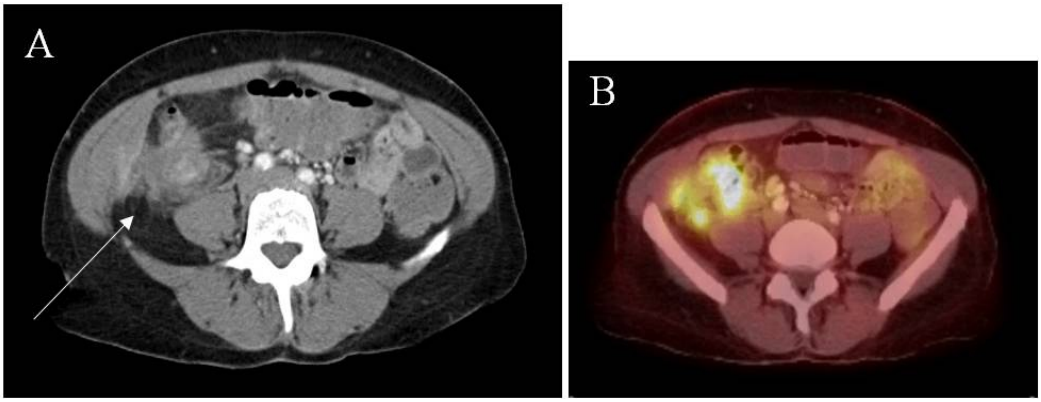

Figure 3: Imaging obtained approximately 15 months after index operation to remove cystic mass. (A) Computed tomography of the abdomen and pelvis demonstrated a new intraabdominal mass near the location of her previously resected adenocarcinoma. (B) Positron emission tomography confirmed a heterogeneously enhancing density within the right abdomen, concerning for recurrence of her malignancy.

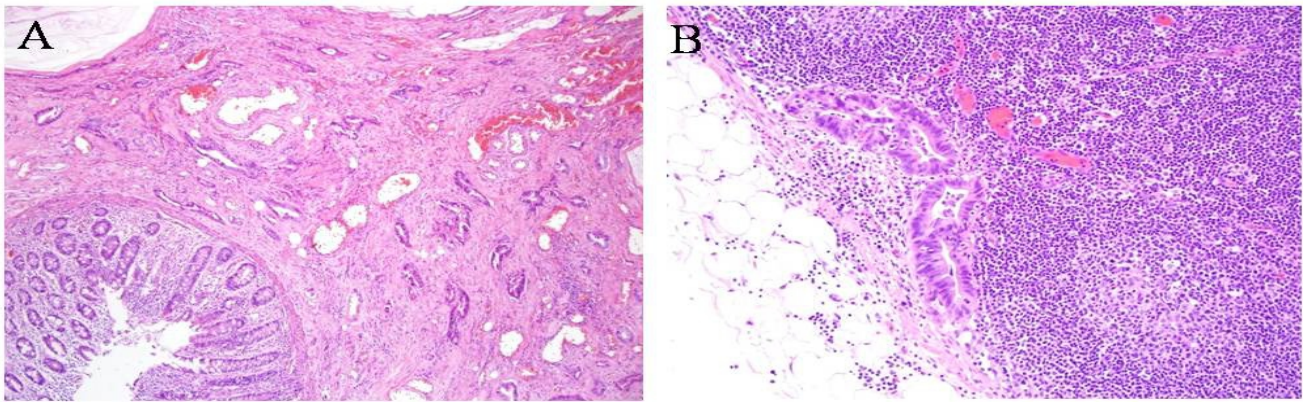

Figure 4: Histology of her second operation to remove the recurrent mass showed recurrent primary peritoneal carcinoma.(A) Tumor cells approach the colonic mucosa. (B) Tumor cells within a pericolonic lymph node.

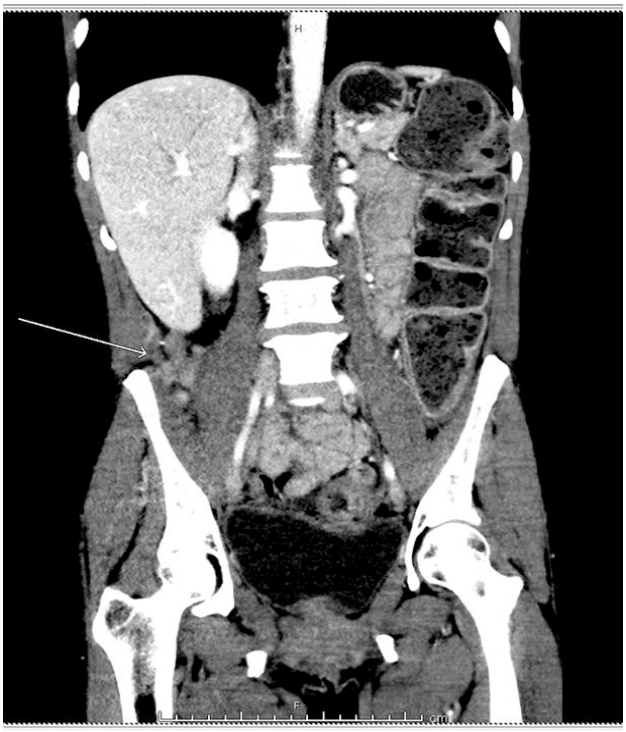

Figure 5: Abdominal computed tomography revealed findings consistent with peritoneal carcinomatosis more than two years from her original operation and after six cycles of carboplatin and four cycles of paclitaxel.

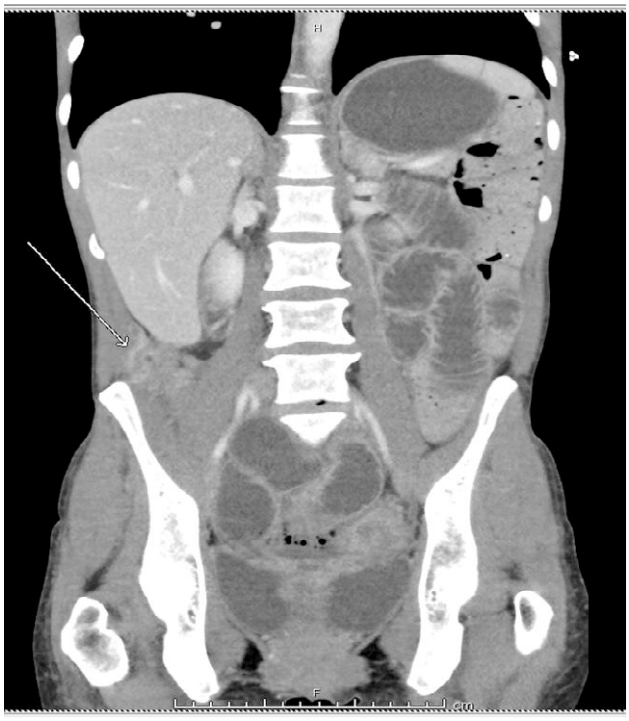

Figure 6: CT enterography showed evidence of a high grade small bowel obstruction anda soft tissue mass along the peritoneal surface extending into the right paracolic gutter and iliopsoas musculature.

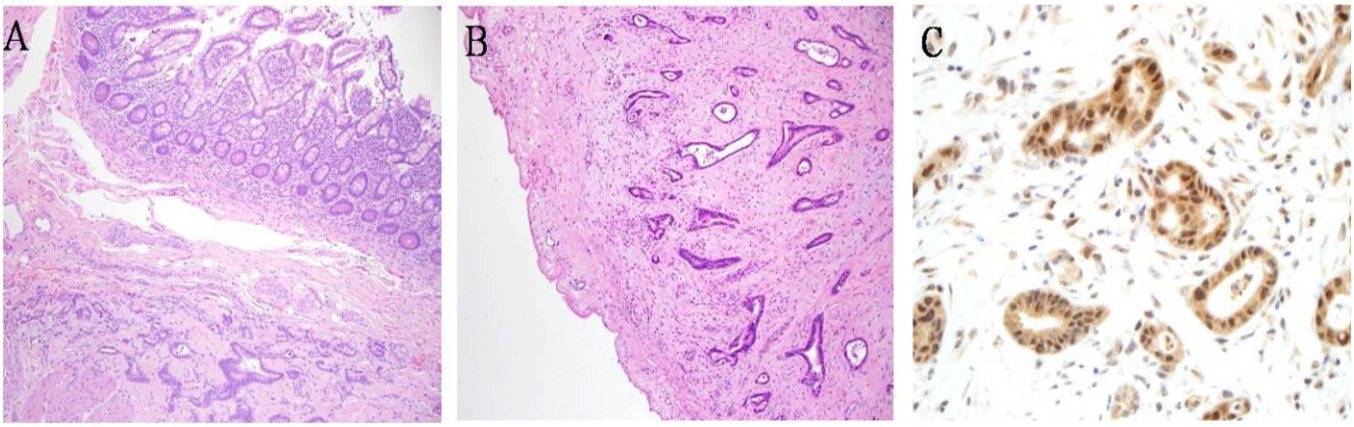

Figure 7: Pathology from her third recurrence demonstrated again metastatic adenocarcinoma. (A) Tumor cells within the muscularis propria of the small intestine. (B) Tumor cells present at the serosal surface. (C) Immunohistochemical staining showed tumor cell positivity for Pax8.

Conclusion

In summary, primary peritoneal carcinomas are a rare diagnosis that histologically and biologically resembles that of epithelial ovarian carcinomas. One hypothesis for this similarity stems from the common embryonal heritage that the ovarian and peritoneal epithelium share in embryonic life. As such, other varieties of Müllerian differentiation of ovarian epithelial carcinomas are theoretically possible for primary peritoneal carcinomas. These include serous, endometrioid, mucinous, and clear cell. The optimal treatment for PSPPC, maximal cytoreduction followed by platinum-based chemotherapy, was used in our patient despite the difference in histologic subtype. Like the histological sub-classification of epithelial ovarian carcinoma, sub-classification of primary peritoneal carcinoma and its subtypes is important. Each subtype is a biologically different disease with distinct precursor lesions, patterns of spread, molecular biology, response to therapy, and ultimate prognosis [25]. Further investigation into these other histologic variants of primary peritoneal carcinomas is needed to determine if comparable efficacy and survival rates are expected with the cytoreduction and chemotherapy regimen. Other therapies such as hyperthermic intraperitoneal chemotherapy (HIPEC), commonly used in appendiceal mucinous cystadenocarcinoma and pseudomyxoma peritonei, should be considered and evaluated for the treatment of mucinous peritoneal carcinomas to possibly improve response and prognosis of residual and/or disseminated disease.

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