Diagnostic Dilemma: A Case Report on Primary Peritoneal Carcinoma in a Patient with Suspected Ovarian Malignancy

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ABSTRACT

Introduction. Primary peritoneal carcinoma (PPC) is an uncommon malignancy and is often misdiagnosed as peritoneal carcinomatosis from metastatic gastrointestinal carcinoma and more frequently from ovarian carcinomas due to a common embryonic origin of the ovary and the peritoneum. Its diagnosis is a challenge for clinicians. Herein, we report a rare case of PPC in a 72-year-old woman who was initially suspected with metastatic ovarian malignancy, and emphasizes points that help differentiate PPC from primary ovarian cancer.

Case. This a case of a 72-year-old female with abdominal discomfort and distension, initially diagnosed with ovarian carcinoma, with abdominal CT scan revealing thickening of the omentum multiple enhancing nodules in the left adnexa, within the pouch of Douglas and subdiaphragmatic region compatible with malignancy such as metastases from carcinoma. Cancer antigen (CA) 125 (3476 u/mL) and CA 15-3 (45.94 u/mL) were elevated. The patient underwent dilation and curettage and diagnostic laparoscopy and biopsy with frozen section, which revealed metastatic clear cell adenocarcinoma, favoring primary ovarian carcinoma. The patient then underwent exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy with bilateral lymph node dissection, and omentectomy. Further histopathological findings later confirmed that the patient had carcinoma primarily from the peritoneum instead of from the ovary. The patient was discharged, improved and underwent chemotherapy post-operation.

Conclusion. This report emphasizes how to distinguish primary malignancy from the peritoneum from that in the ovary, preventing misdiagnosis. The emphasis in considering primary peritoneal cancer as a differential diagnosis in patients with abdominal symptoms suspected due to malignancy should be noted.

Keywords: primary peritoneal carcinoma; ovarian cancer; peritoneal carcinomatosis; case report

INTRODUCTION

Primary peritoneal carcinoma (PPC) is a rare tumor with an estimated incidence in the United States of 6.78 cases per million individuals. [1] It may present with symptoms similar to other primary malignancies involving the organs of the female reproductive system, particularly the ovaries. PPC in its advanced form, presents nonspecifically with abdominal distension, abdominal pain, and obstructive symptoms such as constipation and urinary difficulties. Moreover, primary peritoneal carcinoma is histologically identical to epithelial ovarian carcinoma as they have a common embryonic origin.[2] Hence, its diagnosis may be difficult and possibly missed when the patient presents with nonspecific symptoms, and when tumors are seen not just in the peritoneum but also elsewhere.

In this report, a case of a 72-year-old female patient manifesting with the nonspecific symptom of abdominal discomfort with tumors in the peritoneum, ovary, and fallopian tubes, is presented. This report emphasizes how to diagnose and differentiate primary malignancy from the peritoneum from that in the ovaries, or fallopian tubes, so that its diagnosis would not be missed. The peritoneum must be considered as a focus in patients with an abdominal problem suspected to have a malignancy. The management and prognosis of primary peritoneal carcinoma are also discussed.

CASE PRESENTATION

This is a case of a 72-year-old female, who sought consultation due to hypogastric discomfort. She sought consultation due to a 4-month history of recurrent tolerable hypogastric discomfort and constipation. Patient was initially referred to a gynecologist. Transvaginal ultrasound was done and revealed an enlarged uterus with thick endometrium with uterine myoma. Symptoms persisted and were tolerated until a

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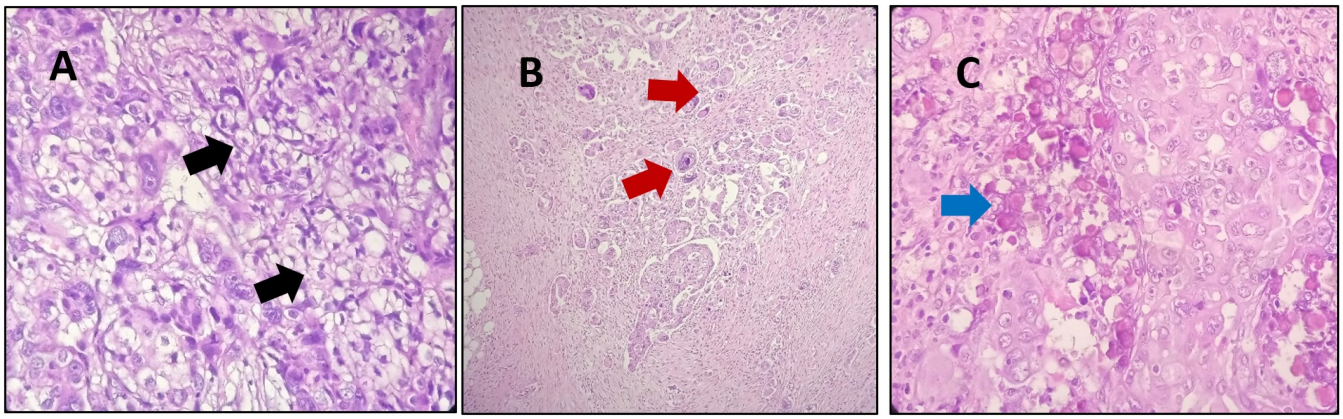

Figure 1. Histopathological findings. **(A)** peritoneal tumor revealed predominance of clear cells (black arrows; H&E stain, 40x magnification), **(B)** cells showing severe atypia with high size variation, irregular chromatin, with or without macronucleoli consistent with peritoneal high-grade serous adenocarcinoma (red arrows; H&E, 10x), and **(C)** numerous psammoma bodies (blue arrow; H&E, 40x)

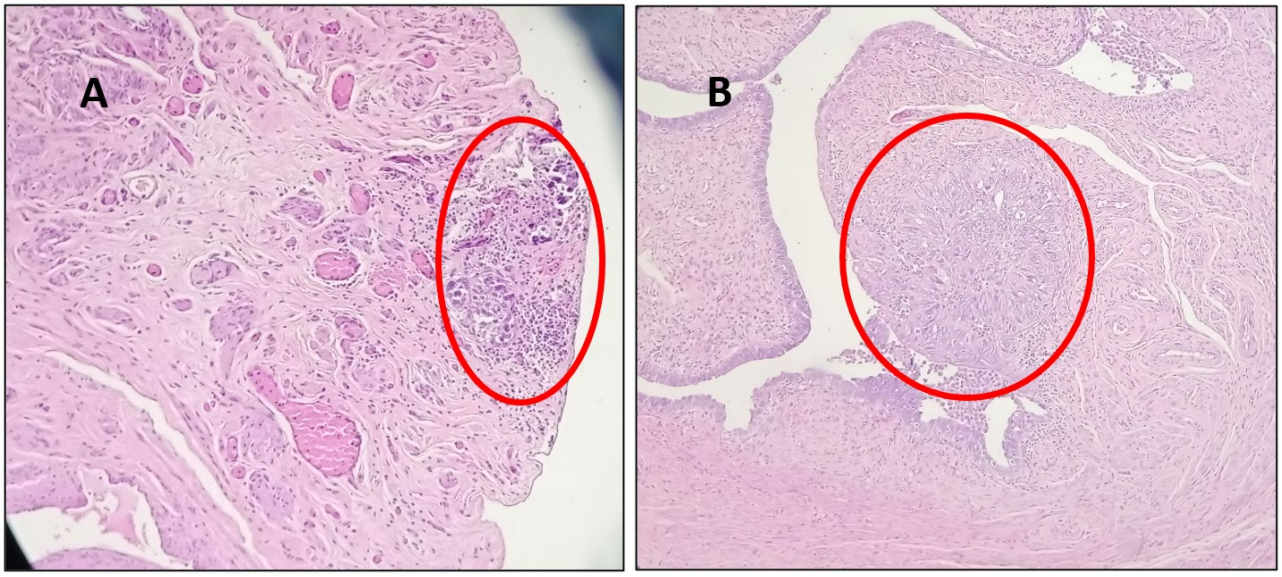

Figure 2. Histopathological findings. **(A)** Ovarian implant limited in the superficial area (open red circle) (H&E, 10x), **(B)** Tubal in situ (open red circle) (H&E, 10x)

month prior to admission when the hypogastric discomfort and constipation worsened. At this point, a colonic obstruction was considered, likely a colorectal mass, or a metastatic peritoneal carcinomatosis from a gynecologic malignancy. She was then referred to a gastroenterologist for further work-up and was then admitted.

She has been hypertensive for more than 10 years with fair compliance to medications – Losartan 50mg + Amlodipine 5mg/tablet 1 tablet once daily in the morning. She had cholelithiasis with cholecystitis about 20 years ago and underwent open cholecystectomy. She is a non-smoker and a non-alcoholic beverage drinker. She is a Gravida 3 Para 3 (3003) with unremarkable obstetric and gynecologic history. Heredofamilial diseases include hypertension. No family history of malignancy.

Upon admission, vital signs were stable, and the patient was noted to have moderate ascites. There were no palpable masses on abdominal palpation and direct rectal examination. Other physical examination findings were normal. Ultrasound of the whole abdomen was unremarkable, except for the ascites. Computed tomography (CT) scan of the whole abdomen with contrast revealed diffuse thickening of the omentum with multiple enhancing nodules in the left adnexa, within the pouch of Douglas and subdiaphragmatic region. The findings were compatible with malignancy such as metastases from carcinoma elsewhere in the body. Full workup for primary malignancy was then done. Chest radiography, breast mammography, and breast sonogram were all unremarkable, as well as the upper gut endoscopy and colonoscopy. The following tumor markers were within normal limits: Alpha-fetoprotein, Beta HCG II, Carcinoembryonic antigen, and Cancer Antigen (CA) 19-9. CA 125 (patient: 3476 u/mL; Normal

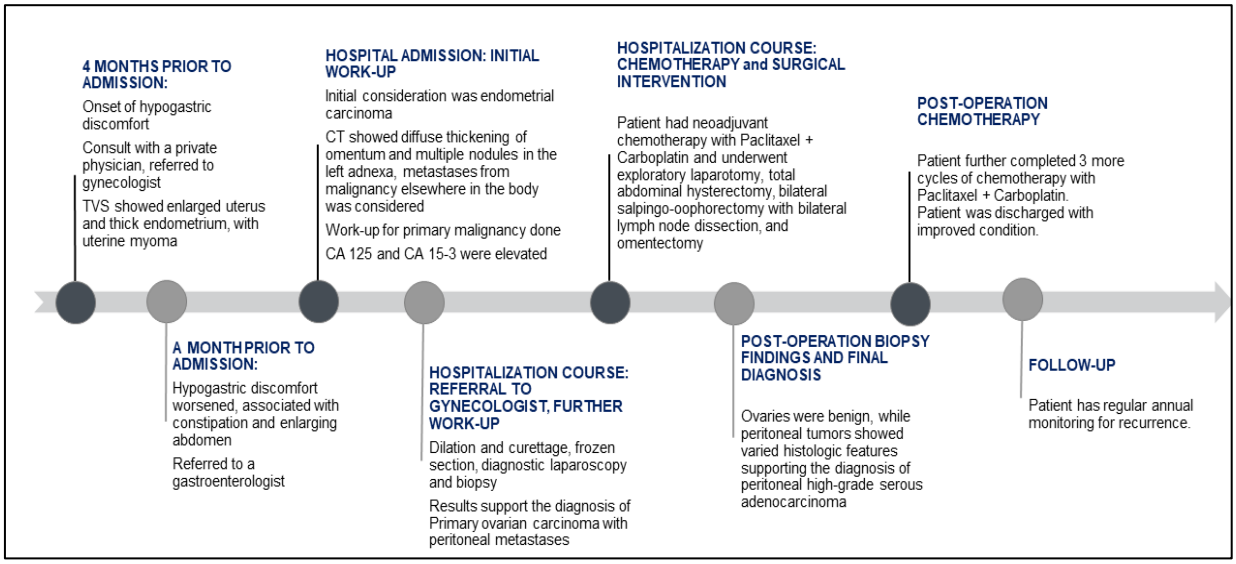

Figure 3. Timeline of the patient's course from the onset of symptoms until discharge and follow-up.

value: 0-35 u/ml) and CA 15-3 (patient: 45.94 u/mL; Normal value: of 0-32 u/ml) were elevated.

The patient was then referred back to the gynecologist and endometrial carcinoma with distant metastases was considered and the patient then underwent dilation and curettage and diagnostic laparoscopy and biopsy with frozen section. The frozen section revealed scanty and tiny fragments of benign endometrium. Biopsy of the endometrial scrapings revealed scant fragments of benign endometrial tissue with no tumor cells found. Tumor implants revealed metastatic clear cell adenocarcinoma, favoring primary ovarian carcinoma. The cell block of the peritoneal fluid revealed malignant tumor cell clusters. Adenocarcinoma of the ovary was highly considered and the patient underwent neoadjuvant chemotherapy with Paclitaxel + Carboplatin for 3 sessions prior to the second operation. Patient thereafter underwent exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy with bilateral lymph node dissection, and omentectomy.

Microscopic findings of the peritoneal tumor revealed a predominance of clear cells (*Fig. 1A*) and cells showing severe atypia with high size variation, irregular chromatin, with or without macronucleoli (*Fig. 1B*), consistent with peritoneal high-grade serous adenocarcinoma. Numerous psammoma bodies were also noted (*Fig. 1C*). Immunohistochemical staining with calretinin was negative. There was an ovarian implant seen (*Fig. 2A*), however, it only involved the superficial layer. Moreover, there was a tumor seen in the fallopian tube, however, it was in situ (*Fig. 2B*) and thus was less likely to be a primary tumor. Prior to these histopathologic findings, the initial diagnosis was a primary ovarian carcinoma with peritoneal carcinomatosis. However, the presence of small-sized benign ovaries bilaterally with only a finding of a nonspecific implant on the superficial layer without the involvement of the deeper layers, in addition to the varied histologic features of the tumors found in the omentum and peritoneum dominated by numerous micropapillae, clear cells, calcifications, and bizarre tumor cells, supported the diagnosis of primary peritoneal high-grade serous adenocarcinoma, superseding the diagnosis of primary ovarian carcinoma, in accordance with the specific guidelines for the diagnosis of peritoneal carcinoma by the Gynecologic Oncology Group (1993). The diagnosis of primary peritoneal carcinoma, therefore, is difficult to establish pre-operatively as this presents similarly with other malignancies, especially that of ovarian malignancy.

Treatment of PPC is similar to epithelial ovarian cancer – cytoreductive surgery including surgical staging, which is based on the CA-125 level normalization with platinum-based chemotherapy. Patient already underwent hysterectomy, bilateral salpingo-oophorectomy with bilateral lymph node dissection, and omentectomy, as well as the removal of the peritoneal tumor implants. Patient was advised continued chemotherapy and therefore, completed 3 more cycles of chemotherapy with Paclitaxel + Carboplatin post-operation. The patient was fully compliant with the plans, and was discharged improved, and currently has regular annual monitoring including CT scan of whole abdomen and CA 125. There were no major adverse reactions to the treatment except for the expected effects including decreased appetite and hair loss after chemotherapy. She tolerated the medications and she complied with the regimen.

Figure 3 shows the timeline of the patient's course from onset of symptoms until discharge from the hospital. Informed consent was provided by the patient.

DISCUSSION

This report described a case of an elderly female diagnosed with primary peritoneal carcinoma, presenting with nonspecific abdominal symptoms of constipation and hypogastric pain. Consideration after initial work-up which included a CT scan of the abdomen, was an ovarian malignancy with peritoneal carcinomatosis. Histopathological findings post-operation were consistent with primary peritoneal carcinoma, and not ovarian carcinoma. The ovaries were benign, and the peritoneal tumor showed high-grade serous adenocarcinoma. The nonspecific and overlapping symptoms of PPC with ovarian malignancy and other abdominal malignancies presenting as obstruction, makes it difficult to consider PPC as initial diagnosis, and hence, usually the diagnosis is based on surgical and histopathologic findings. The most common presenting symptoms include abdominal distension due to ascites, pain, nausea, vomiting, dyspepsia, or change in bowel habits. [2] Although a rare event, it could also initially present with pleural effusion. [3] Other unusual presentations include dysmenorrhea, dyspareunia, together with chronic lower abdominal pain, which are signs typical for endometriosis in young women. [4] In this current case, the presentations include hypogastric discomfort and constipation.

Primary peritoneal carcinoma (PPC), also known as serous surface papillary carcinoma, primary peritoneal papillary serous adenocarcinoma, and extraovarian peritoneal serous papillary carcinoma, is a rare malignancy that arises from the peritoneum lining the abdomen. It is characterized by disseminated intraperitoneal carcinomatosis involving the peritoneum and omentum, and has been implicated in many cases of carcinomas of unknown primary origin. It occurs almost exclusively in menopausal and post-menopausal women. [2,5] But, Shmueli et al (2001) and Canbay et al (2013) each reported very rare cases of PPC in men, who presented with abdominal pain, changes in bowel habits, weight loss, ascites, and cough. [6,7] In the case by Shmueli et al (2001), the patient was initially diagnosed with metastatic adenocarcinoma with pancreatic or pulmonary origin, and was later confirmed with a diagnosis of PPC histologically and immunohistochemically.[6]

Initial imaging done in the patient highly suggested a peritoneal carcinomatosis from a distant malignancy. With the frozen section of the tumor implants revealing a metastatic clear cell adenocarcinoma, primary ovarian carcinoma was the diagnosis preoperatively, and primary peritoneal carcinoma was less suspected as a differential diagnosis. This diagnostic challenge reasonably happens as primary peritoneal carcinoma is similar to serous ovarian carcinoma in several aspects including clinical presentation, histologic features, and treatment pattern. [5,8] Histologically, the appearance is similar to both types of carcinomas, as they originate from the embryonic Mullerian cells in the peritoneum. [2] Hence, primary peritoneal carcinoma may account for about 10% of the cases with a presumed diagnosis of ovarian cancer. In 1993, the Gynecologic Oncology Group established specific guidelines for the diagnosis of peritoneal carcinoma: 1) ovaries are of normal size or enlarged only as a result of a benign process, 2) extraovarian involvement is greater than surface ovarian involvement, 3) ovarian involvement does not show evidence of cortical invasion and is confined to the ovarian surface epithelium and cortical stroma and the ovarian surface penetration is less than 5×5 mm, and 4) histologically, the cancer is primarily of serous type, appearing similar or identical to ovarian serous adenocarcinoma of any grade. [5,10] In this case, although there is an abnormal cellular growth noted in the ovary, it only involved the superficial area, hence it could not be considered the primary area of the malignancy. It may be considered a metastasis from the peritoneal malignancy instead. Moreover, the tumor growth found in the fallopian tube was an isolated lesion rather than a source of metastasis. Hence, fulfilling the guidelines, the diagnosis of primary peritoneal carcinoma was made.

In the current case, CA 125 and CA 15-3 were elevated. In terms of tumor markers, diagnosis between a primary peritoneal carcinoma and serous ovarian carcinoma is also a challenge. Both stain positive for estrogen receptor (ER), CK7, Wilm's tumor suppressor gene (WT1), and cancer antigen 125 (CA 125), but stain negative for cytokeratin 20 (CK 20), progesterone receptor (PR), calretinin, carcinoembryonic antigen (CEA), gross cystic disease fluid protein (BRST-2), and thyroid transcription factor 1 (TTF1). Immunochemical overlap can occur between different cell types but the pattern of positive and negative antigenicity reveals a unique immunochemical "fingerprint" that determines cellular origin. [10,11] CT findings in PPC includes predominantly ascites, omental caking, and peritoneal nodules or enhancement, with or without ovarian enlargement, and these findings are similar with serous ovarian carcinoma.[12] However, imaging is still important in the diagnosis of PPC as its treatment and prognosis differ with other peritoneal disorders such as mesothelioma, and tuberculosis, which are other differential diagnoses in patients with disseminated peritoneal tumors.

In a study by Killackey and Davis (1993), the clinicopathologic characteristics of PPC were compared with papillary serous ovarian carcinoma. Clinical presentation of PPC was very similar to ovarian cancer, that is, abdominal pain and distension were the two most common presenting symptoms. Both also had a similar chronological course of the disease, with respective intervals from symptom onset to date of primary surgery of 3.1 and 4.6 months. Mean CA 125 levels at diagnosis were elevated and were not significantly different between both types of carcinomas. Moreover, in this study, patients with PPC have more limited cytoreduction with the platinum-based chemotherapeutic regimen, shorter disease-free interval, and shorter overall survival time. [3,13] This emphasizes the importance of proper recognition and differentiation of PPC with ovarian carcinoma. Moreover, as shown in the study by Komiyama et al (2018), some patients with PPC may be asymptomatic, and PPC was only detected upon

endometrial cytology. This might be resulting from an intraperitoneal carcinoma cell reaching the uterine cavity transtubally. This therefore suggests that endometrial cytology is an important test for early detection of PPC. [14] Further, PPC spreads primarily transperitoneal, but lymphatic and blood-borne metastases have also been reported. It predominantly metastasizes to the liver, brain, lung, and lymph nodes and rarely to the breast. [8,15] When presented with metastatic lesions in these areas with unknown primary, PPC should be one of the considerations.

In primary peritoneal carcinoma, clinical status of the disease and response to therapy correlate well with the level of increase in CA 125. The treatment PPC is similar to epithelial ovarian cancer -- cytoreductive surgery including surgical staging based on CA-125 level response to platinum-based chemotherapy. [2] Chemotherapy includes Carboplatin or Cisplatin along with Paclitaxel or Docetaxel. Chemotherapy may be given intravenously or intraperitoneally. The patient received Carboplatin + Paclitaxel, and with normalization of CA 125 after completing 6 cycles. The prognosis of PPC is usually poor with extensive cancer spread at the initial diagnosis. The median survival is approximately 24 months, and the 5-year survival rate is 18%. [16] This highlights the significance of early detection and correct diagnosis of PPC, consequently, increase in the diagnostic rate with proper approach as considering PPC in patients with nonspecific abdominal symptoms, including ascites and peritoneal disseminated tumors, and the suspicion of ovarian or other primary organs with benign or absent lesions after histopathologic examination, will establish other aspects of the disease as to the risk and prognostic factors and treatment.

CONCLUSION

Primary peritoneal carcinoma is a rare malignancy and is often difficult to distinguish from primary ovarian carcinoma in several aspects including clinical presentation, immunohistochemistry, and peritoneal imaging findings. Histopathologic findings distinguish the two diseases, and therefore diagnosis is often established after surgery. The current study presented a case of primary peritoneal carcinoma, initially diagnosed with ovarian malignancy with peritoneal carcinomatosis, managed with debulking surgery and platinum-based chemotherapy. This report emphasizes the significance of the correct diagnosis of PPC as it has an aggressive clinical course. Its management differs from that of gastrointestinal cancers; and although it is treated using the same chemotherapeutic approach as primary ovarian cancer, it has a poorer prognosis when compared to the latter.

REFERENCES

1 Goodman MT, and Shvetsov YB; Incidence of Ovarian, Peritoneal, and Fallopian Tube Carcinomas in the United States, 1995-2004. Cancer Epidemiology Biomarkers & Prevention, 18(1), 132–139, 2009.

2 Kim JW, Lee HS, Shin KS, Gam YH, & Baik KD; Primary peritoneal serous papillary carcinoma presenting as a large mesenteric mass mistaken for ovarian cancer: A case of primary peritoneal carcinoma. Obstetrics & Gynecology Science, 58(3), 246-250, 2015.

3 Killackey MA, Davis AR; Papillary Serous Carcinoma of the Peritoneal Surface: Matched-Case Comparison with Papillary Serous Ovarian Carcinoma. Gynecologic Oncology, 51(2), 171-174, 1993.

4 Banz C, von Otte S, Noack F, Diedrich K, Hornung D; Primary peritoneal carcinoma in a young woman with suspected endometriosis. Fertility and Sterility, 92(1), 390.e5–390, 2019.

5 Shameem M, Akhtar J, Baneen U, Bhargava R, Ahmed Z, Sharma P, Hassan MJ; Primary peritoneal adenocarcinoma causes pleural effusion. North American Journal of Medical Sciences, 2(6), 281–284, 2010.

6 Shmueli E, Leider-Trejo L, Schwartz I, Aderka D. & Inbar M; Primary papillary serous carcinoma of the peritoneum in a man. Annals of Oncology, 12(4), 563–567, 2001.

7 Canbay E, Ishibashi H, Sako S, Kitai T, Nishino E, Hirano M, Mizumoto A, Endo Y, Ogura S, Yonemura Y; Photodynamic detection and management of intraperitoneal spreading of primary peritoneal papillary serous carcinoma in a man: report of a case. Surgery Today, 44(2), 373–377, 2013.

8 Sun J, Sun J, Gebre W, Dong Y, Shaun X, Robbins R, Podrumar A; Primary peritoneal carcinoma metastasizing to breast: A single case report and literature review from clinic to biology. Cancer Biology & Medicine, 13(3), 389-395, 2016.

9 Cobb LP, Gaillard S, Wang Y, Shih I, Secord AA; Adenocarcinoma of Mullerian origin: Review of pathogenesis, molecular biology, and emerging treatment paradigms. Gynecologic Oncology Research and Practice, 2(1), 2015.

10 Riedenauer WB, Janjua SA, Kwon DS, Zhang Z, Velanovich V; Immunohistochemical identification of primary peritoneal serous cystadenocarcinoma mimicking advanced colorectal carcinoma: A case report. Journal of Medical Case Reports, 1(1), 2007.

11 Barnetson RJ, Burnett RA, Downie I, Harper CM, Roberts F; Immunohistochemical Analysis of Peritoneal Mesothelioma and Primary and Secondary Serous Carcinoma of the Peritoneum. American Journal of Clinical Pathology, 125(1), 67-76, 2006.

12 Morita H, Aoki J, Taketomi A, Sato N, Endo K; Serous Surface Papillary Carcinoma of the Peritoneum: Clinical, Radiologic, and Pathologic Findings in 11 Patients. American Journal of Roentgenology, 183(4), 923–928, 2004.

13 Mills SE, Andersen WA, Fechner RE, Austin MB; Serous Surface Papillary Carcinoma. The American Journal of Surgical Pathology, 12(11), 827-834, 1988.

14 Komiyama S, Nishijima Y, Kondo H, Nomura H, Yamaguchi S, Futagami M, Arai H, Yokohama Y, Suzuki N, Mikami M, Kubushiro K, Aoki D, Udagawa Y, Nishimura R; Multicenter Clinicopathological Study of High-Grade Serous Carcinoma Presenting as Primary Peritoneal Carcinoma. International Journal of Gynecological Cancer, 28(4), 657–665, 2018.

15 Watson G; A Rare Case of Metastatic Primary Peritoneal Adenocarcinoma presenting as Breast Cancer. International Journal of Cancer and Oncology, 3(2), 1-4, 2016.

16 Insabato L, Natella V, Somma A, Persico M, Camera L, Losito NS, Masone S; Primary Peritoneal Clear Cell Carcinoma Versus Ovarian Carcinoma Versus Malignant Transformation of Endometriosis. International Journal of Surgical Pathology, 23(3), 211–216, 2015.