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Peritoneal Carcinomatosis of Primary Peritoneal Origin: A Short Review

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ABSTRACT

Primary peritoneal carcinoma is defined as an adenocarcinoma arising in the peritoneum, with or without minimum ovarian involvement. It was described for the first time by Martin A. Swerdlow in 1959 and since then it has been issue of investigation, but the knowledge we had about it is scant; however, the similarities with ovarian surface epithelial carcinoma are fascinating. Primary peritoneal carcinoma is a rare tumor with a frequency of about 10% with respect to ovarian carcinoma. The predominant histological subtype by far is serous adenocarcinoma. However, other subtypes have been reported and it is found almost exclusively in women but there are a few reports of cases in men. The known risk factors to date are age, feminine sex, and mutation of the breast cancer early onset 1 (BRCA1) gene.

The clinical presentation of primary peritoneal carcinoma is heterogeneous, and its diagnosis is based on the presence of a serous carcinoma with predominant peritoneal tumor load, with scant or no ovarian involvement. Generally it presents with disseminated peritoneal carcinomatosis with abdominal discomfort and ascites as the main symptoms. The lymph node dissemination has been a wide source of study; there is no characteristic spread pattern, but it has been observed that up to 63.9% of patients have retroperitoneal lymph node metastasis. It is always important to consider and search for a primary peritoneal carcinoma diagnosis in all patients with peritoneal carcinomatosis, because their clinical heterogeneity could distract the attention of the diagnosis and lead to a misdiagnosis with the consequent increase in mobility and mortality for a wrong treatment.

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INTRODUCTION

Diffuse peritoneal carcinomatosis is a heterogeneous clinical entity encountered in both male and female patients, where malignant deposits in the peritoneum may originate from tumors in the gastrointestinal tract, lung, breast, or genital system and tumor histology is serous, mucinous, signet ring, clear cell, or endometrioid, depending on the organ of origin[1]. Visceral metastases are present at frequencies that vary according to primary tumor, disease stage, bulk, and histological subtype. Still, the most common subset of peritoneal carcinomatosis includes patients with deposits of serous papillary carcinoma (60% of all peritoneal carcinomatosis cases). As serous carcinoma constitutes the majority of malignant tumors arising from the ovary or fallopian tube, a gynecologic diagnostic work-up should be promptly instituted in a female patient with serous peritoneal deposits or serous malignant ascites. In 80-90% of cases, a clinical, radiological, or pathological diagnosis of stage III-IV ovarian adenocarcinoma is established. However, in 10-15% of cases, no malignant pathology is evident in the ovaries, fallopian tubes, or uterus, in which case a diagnosis of primary peritoneal carcinoma (PPC) is made. This neoplasm was first described in Chicago by the American pathologist Martin Swedlow[2]. The Gynecologic Oncology Group has developed concise criteria for the diagnosis of PPC: (i) both ovaries must be either physiologically normal in size or enlarged by a benign process; (ii) the involvement in extra ovarian sites must be greater than the involvement on the surface of either ovary; (iii) microscopically, the ovarian component must be (a) nonexistent, (b) confined to the ovarian surface epithelium with no evidence of cortical invasion, (c) involving the ovarian surface epithelium and underlying cortical stroma with any given tumor smaller than 5 x 5 mm, or (d) a tumor less than 5 x 5 mm within the ovarian substance associated with or without surface disease; and (iv) the histological and cytological characteristics of the tumor must be predominantly of the serous type and either similar or identical to any grade of PPC[14].

A similar entity has been described as “normal-sized ovarian carcinoma syndrome”; this entity was first introduced by Feuer, et al. in 1989[15]. They subdivided this syndrome into several categories: mesothelioma, PPC, metastatic tumors from another primary origin, and primary ovarian carcinoma. Among those differential diagnoses, PPC should be considered first in female patients, especially, in the pelvic peritoneum. In this respect, Choi, et al. compared 20 ovarian serous carcinomas in patients with normal size ovary versus seven cases of PPC and they found no significant differences in the analyzed data such as clinical stage, ascites, symptoms, response to chemotherapy, histological grade and CA-125 serum levels; the only difference found was the median age of presentation, which was 52 vs. 64 years, respectively[16].

The majority of patients with this PCC present with few and unspecific symptoms over time, and because of that, two thirds of the patients are diagnosed in FIGO stages III and IV at the disease presentation; this is the main reason for the low five-year overall survival. Some studies have suggested that women with PPC are significantly older, have later menarche, and are less likely to have used perineal talc powder[3]. The most common symptom present in up to 85% of the patients is abdominal distention and discomfort, caused by massive ascites caused by widespread diffuse peritoneal carcinomatosis. However, the clinical suspicion of the diagnosis should be higher to lead to the correct diagnosis, because this diagnosis is very difficult, especially in the preoperative setting.

Lavazzo, et al. in 2008 reported the results of nine patients in clinical stage III and IV with PPC; they diagnosed preoperatively only 66% of the patients based on image studies like computed tomography and vaginal ultrasound[17].

Moreover, there are unusual clinical presentations[7-9,12,14]. Yonemura, et al.[11] reported a case with a serous peritoneal carcinoma arising in the pelvic peritoneum with supraclavicular, para-aortic, obturator and iliac lymph node metastasis without evidence of peritoneal dissemination. However, the diagnosis of this case report is not well supported because the ascites fluid cytology was negative and the lymph node disease diagnosis was not pathologically confirmed.

The lymph node dissemination has been source of extensive study. Steinhagen, et al. in 2011 made a literature review to determine the pattern of lymphatic dissemination in PPC. They evaluated four studies

(three retrospective and one prospective) where retroperitoneal lymphadenectomy was made in patients with stage III and IV disease. They found that 63.9% of the woman diagnosed with PPC had positive retroperitoneal lymph nodes, 72% had para-aortic positive lymph nodes (upper to lower mesenteric vein), and 59.5% para-aortic pelvic lymph nodes. They did not find a particular dissemination pattern, but the studies reviewed had a small number of patients and they were heterogeneous in the limits of lymphatic dissection[10].

The CA-125 antigen is elevated in patients with PPC and it could be a tumoral marker of value in the follow-up of the patient. The CA-125 antigen is expressed in the tissue derived of the coelomic *epithelium* (mesothelium cells of the pleura, pericardium, and peritoneum) and in the Müllerian *epithelium* (salpinx, ovary, endometrium, and endocervix). It is of special value in differentiating between a carcinoma and a mesothelioma, with 100% specificity for carcinoma, and its values correlate with clinical stage of PPC[18]. It is not a tumor-specific antigen as it is also elevated in approximately 1% of healthy control subjects; in patients in the first trimester of pregnancy; in patients with liver cirrhosis, endometriosis, or infectious processes such as tuberculosis or pancreatitis; and in 40% of patients with advanced intraabdominal non-ovarian malignancy[19].

TREATMENT

The standard treatment for PPC has not been well established. However, due to the clinical, histological, and biological characteristics being similar to those of ovarian carcinoma, the current treatment of PPC is cytoreductive surgery and chemotherapy (adjuvant or intraperitoneal normothermic or hyperthermic) based on platin and taxanes[20]. Pentheroudakis and Pavlidis made a critical review about the treatment up to 2010[21].

Management of patients with PPC generally consisted of surgical debulking and cytotoxic chemotherapy. As emphasized above, optimal debulking at surgery was often problematic: in chronologically older series, the rate of minimal residual disease (maximum deposits < 2 cm) was as low as 30-50%. The efficacy of combination chemotherapy (response rates > 60%) did not prevent the emergence of chemoresistant clones in residual metastatic deposits, resulting in a rather poor median survival of 15-25 months. In most recent series after 1995, acknowledgement of the importance of surgery led to management in reference centers and in a 60-80% reported incidence of optimal debulking (residual lesions < 1 cm). However, in some series, debulking status was not prognostic for outcome, though the small sample size and often heterogeneous surgical management in terms of expertise and aggressiveness make it unsafe to draw firm conclusions[22-36].

In most series, the survival of patients with serous peritoneal cancer is comparable to that of sub-optimally debulked serous ovarian cancer[22-36]. The scarce high-quality data from rare prospective trials, especially the GOG138 and GOG111 trials, further support this conclusion[23].

In a retrospective review of 22 patients, Liu, et al. reported the results of the patients who were treated with surgery with hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendicectomy, and extrapelvic lymph node dissection. In five patients, perioperative intraperitoneal chemotherapy with cisplatin in one or two cycles to relieve the ascites was made. Before the surgery, adjuvant chemotherapy was continued. The reported five-year overall survival was 34.4%[20]. In the series of nine patients of Lavazzo, et al. only 33% were lead to complete cytoreduction and only one patient showed complete response. The average disease-free survival was seven months and overall survival was 2.5 years. In this study, the cytoreductive surgery included hysterectomy, bilateral salpingo-oophorectomy, and omentectomy; however, a para-aortic lymphadenectomy was not performed[17]. The use of Hypertermic Intraperitoneal chemotherapy during the debulking surgery is a promessing treatment, founded in the mesothelial origin and the pattern of disemination of PPC.

Recent advances in the field of targeted antibodies has allowed the development of drugs against serous carcinoma. Recently, selumetinib, a strong and selective MEK1/2 inhibitor, was tested by Farley, et al. who treated 52 patients (47 with ovarian cancer and five with PPC); 15% had complete or partial response, the average response time was 4.8 months, and the duration of response was 10.5 months. Of the 52 patients,

63% had median disease-free survival of six months. They gave an average of 4.5 cycles of treatment to the patients, but 25% had to leave the study due to high toxicity. The response seen to selumetinib is not related with activation of BRAF or KRAS[37].

CLINICAL AND IMAGING DIFFERENTIAL DIAGNOSIS

The main differential diagnoses of peritoneal carcinomatosis are: infectious diseases and tumors. The images can help to differentiate infectious diseases like peritoneal tuberculosis. Peritoneal tuberculosis occurs predominantly in patients aged 20-40 years. Drug abuse, alcoholism, acquired immunodeficiency syndrome, cirrhosis, and steroid therapy are the usual risk factors for peritoneal involvement in patients with tuberculosis. Peritoneal infection can appear as the wet type, with ascites or pockets of loculated fluid; as the dry type, with bulky mesenteric thickening and lymphadenopathy; as the fibroadhesive type, with mass formation due to omental thickening; or as a combination of types. It is usually seen in association with widespread abdominal disease that includes lymphadenopathy, organomegaly, ascites, or bowel involvement[38]. The peritoneal thickening associated with tuberculosis is usually mild and smooth; however, nodular irregular thickening with large omental cakes was seen in this patient. Ovarian carcinoma is the most frequent cause of metastatic disease of the omentum. The features of primary malignant ovarian epithelial tumors include a diameter of more than 4 cm, varying proportions of a solid component with necrosis, a thick irregular wall, thick septum, papillary projections, and the presence of ascites and invasive characteristics such as peritoneal disease or lymphadenopathy[39]. In this case, the ovaries were normal in size but showed surface nodularities similar to the pelvic peritoneal omental cakes on CT scans and magnetic resonance images; this finding was indicative of metastasis in the left ovary and made a diagnosis of primary ovarian carcinoma less likely. Other tumors that frequently spread to the peritoneum include primary tumors arising from the stomach, colon, breast, pancreas, kidney, bladder, or uterus. No identifiable primary tumor was detected in this patient. The differential diagnosis of malignant primary tumors of the peritoneum with omental involvement and a variable amount of ascites includes malignant peritoneal mesothelioma, peritoneal lymphomatosis, and primary serous papillary carcinoma of the peritoneum. Malignant peritoneal mesothelioma is a tumor that arises from mesothelium cells lining the peritoneal cavity. The peritoneal form represents approximately 30% of all mesotheliomas. Previous exposure to asbestos is an important risk factor, but about half of the patients with this abnormality do not have a history of asbestos exposure. This tumor has a clear male predominance, with a 7:1 male-to-female ratio. Imaging features include: (i) diffuse or nodular thickening of the peritoneum, (ii) peritoneal or omental masses mainly in the upper abdomen, (iii) local invasion of adjacent abdominal organs, (iv) thickened mesentery and serosal ligaments, and (v) ascites. The organs most commonly involved are the colon and liver. Pleural effusion and pleural plaques are also sometimes observed[40]. Given the imaging studies performed in this patient, malignant peritoneal mesothelioma was not the most likely diagnosis. Primary non-Hodgkin's lymphoma may rarely involve the peritoneum, omentum, and mesentery[41]. Although the involvement pattern of omentum and ascites without any loculation or septation matches the findings in this patient, the absence of enlarged lymph nodes in the retroperitoneum and mesentery without primary gastrointestinal lesions argues against a diagnosis of peritoneal lymphomatosis. *Pseudomyxoma peritonei* can also be considered in the differential diagnosis. This disorder represents a form of intraperitoneal spread of mucin-secreting tumors. This condition usually arises from tumors in the appendix (adenoma or adenocarcinoma) and ovaries (benign or malignant mucinous tumors). Typical imaging features include widespread heterogeneous peritoneal fluid collections that displace and distort the hollow viscera or produce a scalloping effect on solid organs[42]. Mucinous implants on the peritoneal surfaces and omentum may contain linear or septal calcifications. The absence of a primary tumor and mucinous ascites with the mucinous involvement of peritoneal surfaces, omentum, and bowel loops made a diagnosis of *pseudomyxoma peritonei* unlikely.

The imaging features of PPC, much like the imaging features of papillary serous ovarian carcinoma, include ascites and focal or diffuse peritoneal nodules. However, the size of the ovaries is usually normal, even though implants may occur on the surface of the ovaries in patients with PPC. Diffuse omental involvement ranged from lacelike infiltrations to large masses and irregular nodular peritoneal thickening of the lower abdominal cavity that was caused by pelvic ascites in this elderly postmenopausal woman with normal-sized ovaries; these findings were most compatible with a diagnosis of PPC[38]. Calcifications of the omental masses and peritoneum, lymphadenopathy, focal bowel wall thickening, and large adnexal masses are the other reported imaging findings associated with PPC[43].

Pathological differential diagnosis

The pathological differential diagnosis is limited and includes endometriosis, endosalpingiosis and, more important, mesothelioma and borderline serous ovarian tumor[44]. The distinction between peritoneal mesotheliomas and serous carcinomas diffusely involving the peritoneum can be challenging because of the overlapping morphological features that exist between these two malignancies. The differential diagnosis, however, can be facilitated by the combined use of markers that are either commonly expressed in mesothelioma, but not in carcinoma (positive mesothelioma markers) or in carcinomas, but not in mesotheliomas (positive carcinoma markers). Thrombomodulin, calretinin, and podoplanin were the best positive mesothelioma markers, and MOC-31 and Ber-EP4 were the best positive carcinoma markers for discriminating between peritoneal epithelioid mesotheliomas and serous carcinomas. The current recommendation is to do four markers at least, two in favor of mesothelioma and two in favor of carcinoma. In the study of Ordoñez in 2012, PAX8 and PAX2 nuclear positivity was demonstrated in 42 (93%) and 25 (56%) of the serous carcinomas, respectively, whereas none of the mesotheliomas expressed either marker. Forty-four (98%) of the serous carcinomas exhibited claudin-4 reactivity along the cell membrane, whereas none of the mesotheliomas were positive for this marker. No absolutely specific marker for Müllerian lineage has yet been identified. The results of this investigation indicate that, because of their sensitivity and specificity, claudin-4 and PAX8 should be considered to be the best positive carcinoma markers, and PAX8 and PAX2 suggests Müllerian origin in a neoplasm[45].

Primary peritoneal neoplasms showed significantly less expression of estrogen receptor and progesterone receptor than ovarian primary tumors did. Conversely, primary peritoneal neoplasms demonstrated increased expression of Ki-67 and HER-2/neu when compared to primary ovarian tumors. The data suggested that different molecular events triggered these clinically distinct tumors. In a study that compared the molecular profiles between the two groups, PPC demonstrated almost double the rate of HER-2/neu overexpression without any difference in p53 protein overexpression, p53 gene mutations, and abnormal DNA content compared with ovarian carcinoma[46].

Finally, the primary peritoneal borderline serous tumor, also called “micropapilomatosis of low malignant potential”, is a rare epithelial proliferation. Their characteristics are similar to their ovarian counterpart and the distinction is based on the tumor burden in peritoneum vs. ovarium[44].

MOLECULAR AND GENETICS

Of the molecular studies published to date, the Müllerian phenotype of serous peritoneal tumors is well documented and exhibited no evidence of significant pathogenic differences from the carcinogenic events leading to ovarian cancer. The Müllerian markers CA-125, S100, LN1, LN2, EMA, and MB2 were present in 70-100% of serous PPC, in keeping with the reported expression profile of ovarian cancer. Peritoneal tumors harbored similar rates of tumor suppressor gene dysfunction (p53, BRCA1, WT1) as the ovarian counterparts and exhibited similar angiogenic activity, as witnessed by immunohistochemical CD34 endothelial clusters and thymidine phosphorylase activity[23,47-60].

The first clue that p53 aberrations appear early in carcinogenesis came when investigators identified segments of normal-appearing epithelia of the ovaries and fallopian tubes that have strong p53 nuclear

immunostaining. This phenotype was termed "p53 signature" and led to carcinogenesis when additional genetic lesions caused genome-wide DNA damage, increased proliferation (Ki67), and suppression of apoptosis (BCL2)[61].

An interesting finding reported by several investigators is the 35-55% incidence of HER2 overexpression in serous peritoneal cancer, consistently higher than the 5-30% overexpression rate seen in ovarian cancer, though criteria were not standardized as in breast tumors. HER2 overexpression/amplification is considered an early tumorigenic event in a proportion of serous carcinomas of the ovary and endometrium, leading to evasion of apoptosis, angiogenesis, cellular proliferation, and invasion. Its frequent occurrence in serous papillary peritoneal cancer along with the availability of established targeted therapies warrants pilot clinical studies to evaluate its clinical utility as a therapeutic target[62,63].

Women with germline mutations in the DNA damage repair BRCA1/BRCA2 genes carry a 35-75% lifetime risk of developing ovarian cancer and a 5% risk of developing peritoneal cancer even after prophylactic oophorectomy. The published series reported an incidence of germline BRCA mutations in patients with PPC similar to that of patients with serous ovarian cancer (5-10%)[64,65]. An interesting observation by Schorge, et al. is the frequent emergence of multifocal peritoneal tumors in patients carrying germline BRCA1 mutations, in keeping with the two-hit model of hereditary carcinogenesis: the second hit inactivating the normal BRCA1 allele occurs in parallel in several peritoneal loci, giving rise to tumors with distinct clonal origin[66].

In summary, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy may achieve long-term survival in patients with PPC. In experienced multidisciplinary teams, the combined treatment is associated with relatively high morbidity, but no mortality. The high rates of node involvement, the pattern of diffuse peritoneal spread, and the theoretical assumption that the PPC could be a multicentric disease in the peritoneum would support the systematic use of parietal peritonectomy and pelvic/retroperitoneal lymphadenectomy. These data warrant confirmation in prospective trials.

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