REVIEW

Pseudomyxoma Peritonei Associated with Ovarian Tumor

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Pseudomyxoma peritonei was first described by Werth as the presence of gelatinous ascites and implants that involve the peritoneal surfaces and omentum. This condition is rare, usually accidentally found during an operation for ovarian tumor. Moreover, the origin of the disease and how to treat it are still obscure and researchers are still searching for the best treatment options for the best outcome. This article reviews current clinical profiles, and best current options for the management of patients with pseudomyxoma peritonei.

Terminology

The term pseudomyxoma peritonei means “false mucinous tumor of the peritoneum”. It is most commonly applied to a slowly progressive disease process characterized by copious amounts of mucus that, over time, fill the peritoneal cavity. Usually, such a tumor is not considered biologically aggressive because it does not invade or metastasize, although it is a deadly process. The space required within the abdomen or pelvis for nutritional function eventually becomes replaced by the mucinous tumor. It always results in death of the patient unless properly treated.

Most oncologists and many pathologists apply the term to any condition that leads to extensive mucus accumulation within the abdomen and pelvis. Thus, a clear understanding of the natural history of pseudomyxoma has been hampered by the fact that tumors of various primary sites with significantly different biologic behaviors have been lumped together as one clinical entity. The nomenclature of this disease should be distinguished as its origin from aggressive mucin-producing tumors of gastrointestinal origin, appendiceal mucinous adenoma, mucinous low-malignant-potential tumors or carcinomas of ovarian origin.

As in benign of malignant tumor of the appendix, pseudomyxoma peritonei that originate from the primary tumor of appendiceal adenoma was named disseminated peritoneal adenomucinosis, in contrary to the more biologically aggressive primary mucinous carcinoma of the appendix named peritoneal mucinous carcinomatosis. Therefore, pseudomyxoma peritonei of ovarian origin should also be classified as either benign or malignant, either for appropriated prognostic evaluation or adjuvant treatment decision using ovarian cancer regimen or gastrointestinal cancer regimen.

Incidence

Pseudomyxoma peritonei is a rare condition, with most reports showing an incidence of approximately 1-2 in 10,000 laparotomies, and it is three to four times more common in women than in men. Commonly, pseudomyxoma peritonei occurs in the fifth to sixth
decade of life, and it occurred in approximately 2.5% of ovarian mucinous neoplasms.\(^5\)

**Pathogenesis**

The origin of the disease is a subject of considerable disagreement. Pseudomyxoma peritonei is most commonly associated with benign, borderline or malignant mucinous tumors of the ovary and appendix.\(^6-9\) The primary lesion has also been found in association with mucinous tumors of the urachus, bowel, pancreas and common bile duct.\(^4,10,11\) Some investigators believe that the appendix is the primary origin in most cases of pseudomyxoma peritonei, while the peritoneal and ovarian lesions are metastatic lesions, despite the fact that metastatic appendiceal carcinoma of the ovaries is rare.\(^12\) However, there are still some reports on the appearance of pseudomyxoma peritonei in the presence of a normal appendix,\(^13,14\) or a history of prior appendectomy remote from initiation of the symptoms.\(^15,16\) There has also been much discussion concerning whether pseudomyxoma peritonei might originate from implants of a primary mucinous tumor or as part of a multifocal neoplastic process.\(^17\)

The pathogenesis of this entity remains elusive, but simple rupture of a mucinous lesion is not sufficient to cause pseudomyxoma peritonei.\(^18\) However, the redistribution phenomenon, as in the rupture of an appendiceal adenoma, would explain the wider distribution of mucinous tumor cells from their origin.\(^19\) The tumor cell surfaces do not have the adhesion molecules to stick randomly to peritoneal surface, therefore, the tumor cells have tendency to “redistribute” around the peritoneal cavity. Usually, the portions of the peritoneum that are in motion, such as the visceral peritoneum on the bowel surface, are only sparsely seeded. The abdominal surfaces that absorb peritoneal fluid (such as the greater omentum and the undersurface of the diaphragm) are coated by tumor cells, as fluid is pulled to these anatomic sites. Although the tumor cells spread widely throughout the peritoneal cavity, they do not usually invade past the peritoneal surface. In contrast, the tumor cells do progress exuberantly on the surface. This hypothesis could explain why the ascites and implants can be extensive but a visceral invasion is uncommon.\(^4\)

The other hypothesis has been described as an agent in the mucinous ascitic fluid, which induces a mucinous metaplasia in the peritoneal mesothelium.\(^20\)

**Presentation and Investigation**

The most common presenting symptoms are symptomatic pelvic or abdominal mass and an increase in abdominal girth.\(^21\) Some reports also note symptoms of painful sensation in the abdomen, fever, anorexia, nausea, vomiting and weight loss may be associated with pseudomyxoma peritonei.\(^22\)

Diagnosis is seldom absolute until a laparotomy is performed, despite the presence of a distended abdomen with non-shifting ascites on physical examination. Laboratory studies are also of little help but fortunately, over the past few years, there have been many reports based on radiological imaging techniques, which are proving to be extremely useful in forming a correct preoperative diagnosis. For example, in the later stages of the disease, plain films used when the abdomen is distended with mucus show central displacement of the bowel with obliteration of the psoas muscle border.\(^23\) Occasionally, small calcific lesions can be seen widely disseminated throughout the abdomen. As the disease progresses, plain films become invaluable in following inevitable bowel obstruction and assessing the need for emergency debulking.\(^24\) Furthermore, when used in conjunction with barium studies, the proximal extent of the disease can be assessed and a possible extrinsic tumor causing large bowel obstruction can be ruled out.

Conversely, ultrasonography is more useful and generally has similar features to computed tomography images showing abdominal echogenic masses with ascites, multiple septations, and scalloping of the liver.\(^25,26\) Computed tomography usually shows four basic patterns:

1. posterior displacement of the intestines with
numerous low density masses and calcifications, (2) diffuse peritoneal infiltration appearing similar to ascites with septated fluid pockets filling the pelvic cavity, (3) intrahepatic low density attenuated lesion, and (4) scalloping of intra-abdominal organs due to extrinsic pressure of adjacent peritoneal implants.

Scalloping of the liver has been widely described, and in 1987 Parikh et al. reported the first case of splenic scalloping in pseudomyxoma peritonei. Treatment
The mainstay of treatment for pseudomyxoma peritonei remains cytoreductive surgery, removing the primary disease, ie, oophorectomy and/or total abdominal hysterectomy, followed by removal of mucinous nodules from the omentum and peritoneal surfaces. Appendectomy must be done and submitted for through sampling by microscopic analysis.

To perform radical operations in the past, a ball-tip electrode at a high cutting current was used to destroy tumor implants but also produced large intraperitoneal burns, resulting in prolonged ileus and requiring total parenteral nutrition (3-4 weeks). Newer technologies such as the argon beam coagulator conduct electrical current to the tissue in a beam of inert argon gas. The beam spreads over the tissue surface with a more homogenous distribution of energy and less tissue injury than with standard electrocautery. The reason why the argon beam coagulator was applied to pseudomyxoma was possibly due to the nature of minimally invasive coat parietal peritoneal surfaces.

And, because the mucinous tumors associated with pseudomyxoma peritonei are minimally invasive and yet extensively coat parietal peritoneal surfaces, a series of peritonectomy procedures has been developed. These involve stripping the parietal peritoneum and resecting structures at fixed sites that contain visceral peritoneum with the use of electro-surgery to obtain maximal cytoreduction in peritoneal carcinomatosis. The six different peritonectomy procedures, greater omentectomy-splenectomy, right upper quadrant peritonenectomy, lesser omentectomy-cholecystectomy with stripping of the omentum bursa, pelvic peritonenectomy with sleeve resection of the sigmoid colon and antrectomy, can be performed separately or all together. Also, an objective method to score the presence and size of macroscopic tumors in 13 different abdominal regions was developed by Sugarbaker (Peritoneal cancer index) before and after cytoreductive surgery. This score helps in estimating the likelihood of complete cytoreduction in peritoneal surface malignancy to prevent unnecessary surgery in high risk patients, thus decreasing postoperative morbidity.

Adjuvant treatment
Mucolytic agent
Although surgical debulking and removal of the mucinous ascites may be attempted, complete removal of the material is sometime impossible. Many regimens have been initiated to prevent reaccumulation of the mucus, including intraperitoneal and systemic chemotherapy. Several authors have also found that intraperitoneal irrigation or percutaneous larvage with dextrose and water will expedite the removal of mucus and prevent its reaccumulation but the exact mechanism has not been determined. Beller et al. in 1986 also reported the instillation of intraperitoneal mucolytic such as dextran sulphate, in concentrations of up to 5%, and plasminogen activators such as urokinase might be useful in preventing and treating recurrence of the mucus. Unfortunately, dangerous levels of hyperglycemia have been reported after instillation of 10% dextrose in water even through dwell times are very short. Therefore, glucose monitoring during and after irrigation with dextrose should be carefully done, and all personnel aware of potential dangerous complications of this procedure.

Chemotherapy
Postoperative intraperitoneum chemotherapy and intravenous chemotherapy are also reasonably effective, particularly for ovarian carcinomas.
Until the 1980s melphalan was the agent chosen most often to treat pseudomyxoma originating from an ovarian neoplasm.\(^4\) Cisplatin-based regimens have become the standard of treatment in cases of ovarian epithelial neoplasms and some articles have reported using single cisplatin or cisplatinum-based regimens to treat pseudomyxoma.\(^4,13,14\) Nevertheless, there also are controversies in the response to the chemotherapeutic agent and the regimens of the chemotherapy used.

### Radiotherapy

Postoperative radiotherapy was reported by Fernandez et al., who suggested that postoperative radiotherapy may be better at prolonging survival than chemotherapy (75% versus 44% at five years), but the differences were not statistically significant.\(^7\)

### New modalities in treatment technique

Intraoperative heated chemoperfusion of the abdominal cavity has been used in the prevention and treatment of peritoneal surface malignancy. Hyperthermia itself has a direct cytotoxic effect caused by impaired DNA repair, denaturation of proteins, introduction of heat-shock proteins which may serve as receptors for natural killer-cells, induction of apoptosis and inhibition of angiogenesis.\(^24,35\) Eventually, increased cell-membrane permeability at higher temperatures can also increase drug uptake by tumor tissues.\(^96\) Clinical experiences with aggressive surgical cytoreduction in combination with hyperthermic intraperitoneum chemotherapy have been reported, with some clinical response in pseudomyxoma peritonei\(^37,38\) and advanced ovarian cancer.\(^99\) Although there has been a tendency to improved outcome in those receiving both cytoreduction and intraperitoneal chemotherapy, there have also been reports of increased morbidity from these treatment methods. Incomplete chemotherapy course, abdominal pain, seizure, neutropenia and thrombocytopenia have been reported in association with intraperitoneal chemotherapy.\(^40\) Besides hematologic toxicity, hyperthermic intraoperative intraperitoneal chemotherapy also has nonhematologic-associated morbidity as well. Intestinal perforations, anastomotic and bile leaks, fistula, bleeding, dehiscence, pancreatitis, and pulmonary embolism have all been documented.\(^19,41\)

Photodynamic therapy had been reported in use with pseudomyxoma peritonei. Although a complicated technique was described, selective destruction of malignant cells with the prevention of normal tissue is the goal of this treatment.\(^42\) Photodynamic therapy destroys malignant tumors through the uptake of photosensitizing compounds, which are then activated by exposure to light of a particular intensity and wavelength.\(^43\) The patients may develop cutaneous photosensitivity, transient abnormalities of liver function test, postoperative hemorrhage, necrotizing pancreatitis, ureteral leakage, and intestinal fistulas.\(^42\)

### Prognosis

Reports in the literature estimate the overall 5-year survival rate for patients with pseudomyxoma peritonei to be approximately 50% (range 11-75%).\(^7,9,44\) Patients with ovarian tumors of low malignant potential have a significantly better prognosis than patients with adenocarcinoma.\(^45,46,47\) The overall 5- and 10-year survival rates for patients with borderline tumors are 85-90% and 75-80%, respectively. In the study by Kaern et al., they noted that pseudomyxoma peritonei was among the prognostic factors that negatively affected survival.\(^45\) The series reported by Wertheim et al. also noted that 40% of the patients with borderline tumors had died or developed a recurrence after a median follow-up interval of 3 years.\(^21\) and therefore they agreed with Kaern et al. that when pseudomyxoma peritonei is found in association with these tumors, the prognosis may be worse than when pseudomyxoma peritonei is not present.

The significance of epithelial cells in peritoneal specimens of pseudomyxoma peritonei is another controversial subject of interest.\(^48,49\) Although epithelial cells have been found in a few cases of pseudomyxoma peritonei in the literature,\(^50,51,52\) Shin et al. reported the presence of epithelial cells in the majority of their patients.\(^53\) The specimen collection
method (ascitic fluid by paracentesis vs. intraoperative collection or washing), and the extent of sampling (i.e. cell block preparation) may have contributed to the high frequency of epithelial cells detected in these cases. Prior reports have suggested the association of epithelial cells existent and disease recurrence or poor prognosis. Shin et al. did not show the relation between epithelial cells being found and patient outcomes in their report, but one of the patients had no epithelial cells in either the cytology specimen or in multiple peritoneal and omental biopsy specimens, and was alive with no evidence of disease at 24 months of follow-up.

In conclusion, pseudomyxoma peritonei is a rare condition. It most commonly arises from mucinous tumors of the ovary and appendix. Aggressive cytoreductive surgery, including appendectomy, bilateral oophorectomy followed by removal of mucinous nodules from the omentum and peritoneal surfaces, is the current standard treatment. To achieve satisfactory cytoreduction could be difficult to obtained even in the hand of skilled surgeons, however proper preoperative investigation and evaluation then refer to more equipped center and better care team would be the best benefit for the patients. Prevention of recurrent by mucolytic agent is recommended. Adjuvant therapy or new modalities of treatment maybe useful for highly selected patients in each situation and should be further studies for the best survival.

References
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