Int J Gynecol Cancer 2003, **13,** 413–418

REVIEW ARTICLE

Pseudomyxoma peritonei: the 'controversial' disease

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Abstract. Galani E, Marx GM, Steer CB, Culora G, Harper PG. Pseudomysoma peritonei: the 'controversial' disease. *Int J Gynecol Cancer* 2003; **13:**413–418.

Pseudomyxoma peritonei (PMP) is a rare disease that is characterized by a large amount of mucinous ascites with peritoneal and omental implants. The etiology of the disease remains unclear. Histologically, two main categories have been described: disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA). It is commonly diagnosed incidentally at laparotomy. Most investigators agree that radical surgical debulking and appendectomy are the cornerstone of treatment, but the optimal management of the disease remains controversial. The role of intraoperative and intraperitoneal chemotherapy has been evaluated by a number of authors. The clinical outcomes vary widely between the benign and the malignant forms and between the different treatment modalities. We discuss the pathology, origin, clinical presentation, diagnosis, treatment, and prognosis of PMP.

KEY WORDS: intraperitoneal chemotherapy, mucinous ascites, pseudomyxoma peritonei.

Pseudomyxoma peritonei (PMP) is a poorly understood disease. Literately translated PMP means false mucinus tumor. The unifying diagnostic feature of PMP is the presence of extracellular mucin in the peritoneal cavity.

The term pseudomyxoma peritonei describes a syndrome which presents with massive amounts of mucinous ascites and peritoneal and omental implants, that over time fill the peritoneal cavity. There is considerable debate regarding the appropriate classification and type of tumor to be included in this syndrome. The main controversy relates to the inclusion or exclusion of the more "malignant" forms of the disease and to the site of origin of the tumor[1]. With advances in immunocytochemistry and genetic analysis, progress has been made to more clearly categorize this entity.

Incidence

PMP is a rare disease that is more common in women than men. Seventy-five percent of patients with PMP are female. The median age is 53 years. The estimated incidence is 2 out of every 10,000 laparotomies performed[2].

Histology

Histologically two main diagnostic categories have been described: the benign form, disseminated peritoneal adenomucinosis (DPAM), and a malignant form, peritoneal mucinous carcinomatosis (PMCA)[1]. A third category has also been described. This is an intermediate form that is called peritoneal mucinous

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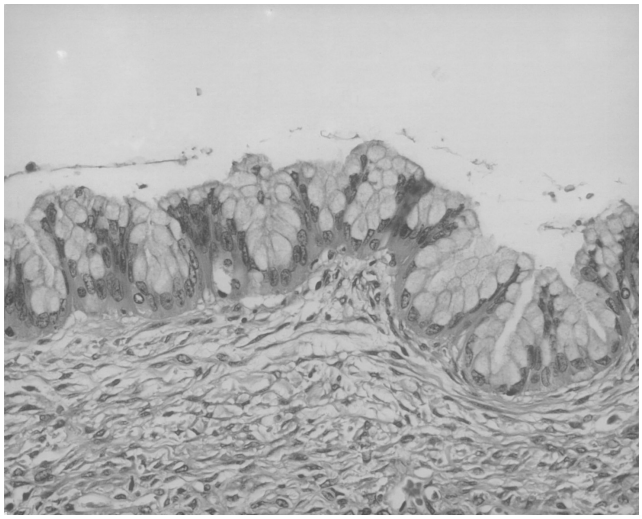

Fig. 1. Simple mucinous epithelium with no atypical features present on surface deposit, classified as DPAM (20x).

carcinomatosis with intermediate or discordant features (PMCA-I/D). It has cytologic features of both DPAM and PMCA. This classification was first proposed by Ronnett *et al*. and is important as it has prognostic significance[1,3,4]. As expected patients with the peritoneal adenomucinosis form have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. Histologic features of DPAM include peritoneal lesions composed of abundant extracellular mucin containing scant simple to focally proliferative mucinous epithelium with little cytologic atypia or mitotic activity (Fig. 1, 2). It may or may not be associated with an appendiceal mucinous adenoma[1]. Cases classified as PMCA are characterized by

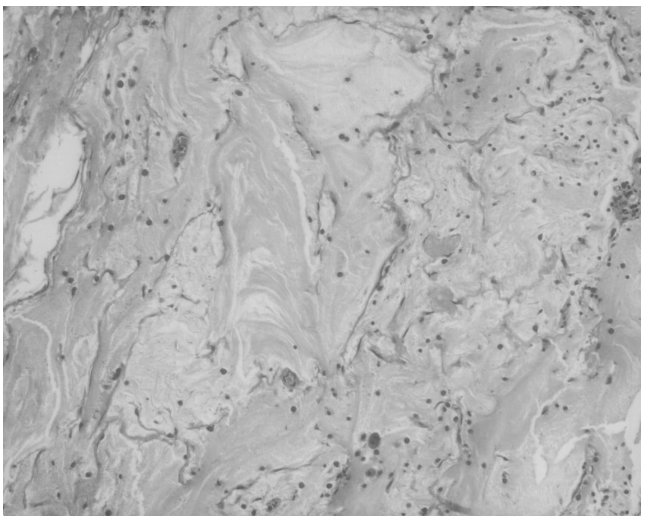

Fig. 2. Peritoneal mucinous carcinomatosis (PMCA) showing infiltrating malignant glands and cells within a desmoplastic stroma (10x).

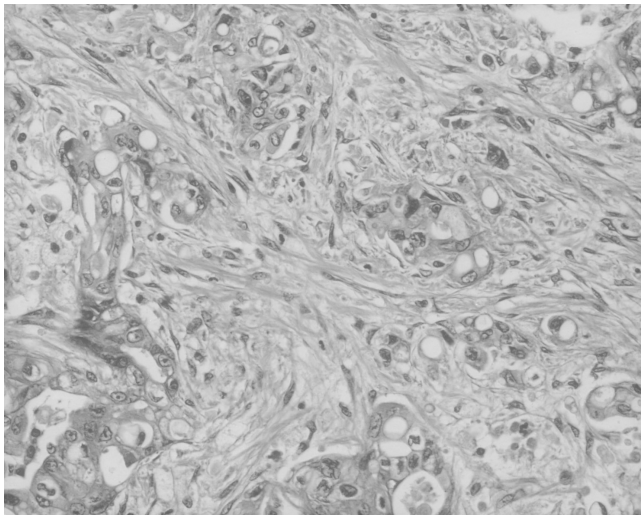

Fig. 3. DPAM composed of surface deposits of abundant extracellular mucin containing scattered inflammatory cells. Scant simple mucinous epithelium was visible in other areas (10x).

peritoneal lesions composed of more abundant mucinous epithelium with the architectural and cytologic features of carcinoma (Fig. 3). In some cases an associated mucinous adenocarcinoma may be found[1]. In a clinicopathologic analysis of 109 cases, about 60 percent were classified as DPAM-consistent with an origin from an appendiceal mucinous adenoma. About 28 percent were classified as PMCA-consistent with origin from an appendiceal or intestinal mucinous adenocarcinoma. Approximately 13 percent of the cases with intermediate features were derived from well-differentiated appendiceal or intestinal mucinous adenocarcinomas[1].

Origin

There is continued debate regarding the site of origin of PMP. It is most commonly associated with mucinous tumors of the appendix or the ovary. Women with PMP may have both, appendiceal and ovarian mucinous tumors. The ovarian tumors in most of these cases are secondary to appendiceal tumors[5-7], but it may be difficult to determine the histogenetic origin of these tumors. PMP has been reported rarely in association with mucinous carcinomas of other organs, including the bile ducts, stomach, pancreas, colon, fallopian tube, uterine corpus, urachus, urinary bladder, breast, and lung[2]. Despite increasing research regarding the origin of PMP using flow cytometry, genetic analysis, and immunopathologic analysis, conflicting results are still reported.

Overall it seems the vast majority of cases of PMP have been shown to result from primary mucinous adenomas of the appendix[5,6].

Clinical presentation

PMP is commonly diagnosed incidentally at laparotomy, which is usually performed for other indications such as suspected appendicitis or ovarian carcinoma. The most commonly described symptoms and signs are abdominal distention and abdominal pain. Abdominal masses or palpable ovarian masses and hernias are other clinical manifestations commonly seen. Nausea, vomiting, fatigue, and urinary tract symptoms have also been reported[8]. The range of presenting symptoms is wide and is dependant on the anatomic site of the disease. Rare presenting problems include cholecystitis, infertility investigation, postmenopausal bleeding, abnormal Papanicolaou smears, pelvic pain, pelvic masses, surgery for fibrosis, laparoscopy for tubal ligation, abdominal aortic aneurysm repair, deep vein thrombosis, rectal bleeding, nephrectomy, and anemia[9]. A case of intestinal obstruction has also been reported[10]. A rare presentation of an inguinal hernia with splenic metastasis was reported[11]. PMP syndrome may be associated with splenic mucinous epithelial cysts[12]. Extra-peritoneal spread of PMP is infrequent. There are few reports in the medical literature of pleural extension of mucinous tumor in patients with PMP syndrome. These are associated with a poor prognosis[13]. Pulmonary parenchymal metastasis, treated with metastasectomy, have also been described[14].

The broad spectrum of clinical presentations reflects the diffuse nature of the disease within the peritoneal cavity as well as the wide range of tumor histopathologic features.

Diagnosis

The diagnosis of PMP is often difficult. It usually has an insidious presentation. Ultrasonography is frequently performed as the initial diagnostic procedure. Typical findings are nonmobile echogenic ascites with multiple semisolid masses and scalloping of the hepatic and splenic margins[15]. Furthermore ultrasound may be helpful in diagnostic and therapeutic paracentesis, as mucin is difficult to aspirate.

Computer tomography (CT) of the abdomen and pelvis is the most widely applied technology and has been used with great success in the diagnosis of the PMP syndrome. CT findings are often highly suggestive of PMP and sometimes these are pathognomonic[16]. The most common finding is a large volume of mucinous ascites, which has the density of fat, and displaces the small bowel and the normal mesenteric fat. Other characteristic findings are omental thickenings, multiseptated lesions, scalloping of organs, and curvilinear calcifications[15,17]. Sugarbaker *et al*. have used CT as a tool for differentiating between peritoneal adenomatosis and peritoneal carcinomatosis[16].

The role of magnetic resonance imaging (MRI) in the diagnosis of PMP is not clear. There are no data to suggest that MRI is better than CT. It has been reported that MRI may be particularly sensitive in detecting visceral invasion, but this is based on a single study of three patients[18]. At this stage this mode remains investigational.

Plain radiography and contrast studies are not particularly useful in the diagnosis of PMP. Sometimes large mucinous abdominal masses may present with displacement of the bowel centrally or with obliteration of the border of the psoas muscle[19]. Rarely, punctuate or curvilinear calcifications may be noted. Double contrast techniques may demonstrate the lack of bowel lumen involvement that is characteristic of the noninvasive deposits of PMP[2].

Histologic diagnosis is required and remains the "gold standard." This can be achieved by paracentesis, laparoscopy, or laparotomy.

Treatment

There is currently no accepted standard treatment for PMP. Options vary considerably and often reflect the extent of disease, histologic subtype, and general condition of the patient and surgical preference of the treating doctor. Options include: observation, surgery, laparoscopic intervention, chemotherapy, radiotherapy, immunotherapy, and mucolytic agents. All of these have been utilized in the management of the disease.

Surgery

Surgical debulking and appendectomy is widely regarded as the mainstay of treatment of PMP syndrome. Sugarbaker from the Washington Cancer Institute has published extensively regarding therapeutic options, particularly regarding surgery. The surgical approach varies widely, however, he describes an aggressive surgical intervention as essential to improve prognosis. Certain features of PMP syndrome make it amenable to curative surgery. These include: low biologic aggressiveness of appendiceal cancer with rare metastasis to lymph nodes and viscera, early peritoneal dissemination, accumulation in anatomically resectable sites by peritonectomy, and location of the disease to a local body cavity amenable to high dose regional chemotherapy[20]. A recent

publication by Sugarbaker has suggested that an aggressive approach impacted on outcome. He combined "maximal" surgical debulking with "maximal" regional chemotherapy. Surgery involved between one and six peritonectomy procedures with electro-evaporative surgery and intraperitoneal intraoperative heated chemotherapy and postoperative intraperitoneal chemotherapy[20]. With this extensive cytoreductive approach combined with early intraperitoneal chemotherapy, the morality rate was 2.7%. The main morbidity included pancreatitis (7.1%), fistula formation (4.7%), and anastomotic leaks were similar to general surgical techniques at 2.4%. Twenty-seven percent of the patients had grade III/IV morbidity. Although these data are impressive, there was no control group. It is unlikely that randomized trials in this setting will be performed.

Witkamp *et al*. have also recently described a more extensive cytoreductive surgical procedure with intraoperative heated intraperitoneal chemotherapy being a feasible approach with a potential improvement in long-term survival[22]. The complication rate and mortality are high and as a result has not been adopted widely. Despite this, long-term survival seems to be improved.

Older data and reports have defined a more palliative surgical intervention as being appropriate for this patient group, however, with increasing data suggesting a benefit with maximal debulking procedure, it is likely that a more aggressive approach will be adopted into clinical practice.

Patient selection, particularly relating to comorbidity and performance status as well as disease extent, will impact on the optimal management of these patients. Being such a rare tumor with marked variation in histopathology, it is unlikely that the most effective approach will be defined by randomized clinical trials.

Chemotherapy

The role of chemotherapy in PMP is yet to be defined. There are insufficient data regarding the role of adjuvant chemotherapy. PMP is an ideal tumor to be considered for intensive regional chemotherapy. It is an intraperitoneal tumor with no lymphatic or hematogenous spread. The rationale for intraperitoneal therapy is that direct infusion of the drugs into the peritoneal cavity permits delivery of high concentrations of drug to abdominal and pelvic surfaces where the tumor is located without producing toxic systemic levels. The pharmacologic advantage is the result of the peritoneum–plasma barrier. Hydrophilic drugs of large molecular size leave the peritoneal cavity more slowly than when they are metabolized systemically. This advantage persists even if the drugs are instilled into the peritoneal cavity that has had an extensive surgery.

There are no randomized data evaluating the role of adjuvant chemotherapy. Results from phase II trials and retrospective reviews are conflicting. The most widely used chemotherapeutic agents are 5-fluorouracil (5-FU), cyclophosphamide, mitomycin C, and cisplatinum. The Mayo Clinic series[21] retrospective nonrandomized analysis showed that survival rates were significantly better in patients treated with intraperitoneal infusions than in those treated with systemic chemotherapy. There are the obvious concerns regarding patient selection and potential for bias in this nonrandomized trial. No difference in survival was seen between groups treated and not treated with chemotherapy in the series from Memorial Sloan-Kettering Cancer Center[21].

Sugarbaker *et al*. have described a protocol of intraoperative intraperitoneal chemotherapy with mitomycin C, heated to 44°C, that was initiated after complete resection of the tumor, followed by intraperitoneal 5-FU for 5 days. They reported a 5-year survival rate of approximately 90% in the most favorable prognostic group of patients[16]. Heated perioperative intraperitoneal chemotherapy has also recently been described by other authors[22,23]. The rationale of intraoperative chemotherapy is that it allows uniform distribution of the drug into the peritoneal cavity that postoperative intraperitoneal chemotherapy infusion does not achieve due to intestinal adhesions. Furthermore, the use of chemotherapy after complete removal of the malignancy maximizes the efficacy of the treatment that now targets only microscopic foci and no measurable lesions. Additionally, the penetration of the drug into tissue is augmented by heat[16].

Other treatment modalities

Mucolitic agents have been widely used for the treatment of PMP but their efficacy is limited. Green *et al*.[24] first used a dextrose solution to "loosen" the peritoneal mucinous deposits. The potential benefits were to assist with closed catheter palliative drainage of fluid and to facilitate surgical cytoreduction procedures. This has not been confirmed in clinical studies.

Intraperitoneal radioisotopes and external radiotherapy have also been used, but experience with these agents is limited[25]. Fukuma *et al*.[26] have described anecdotal cases of successful treatment of

PMP with immunotherapy, with a streptococcal preparation, OK-432, as adjuvant treatment after surgery.

Prognosis

With such a wide spectrum of disease ranging from benign to malignant form and wide variations in treatment modalities, it is not surprising that prognosis is difficult to accurately define. This is further complicated by the fact that the estimation of recurrence rates is based on different series with small numbers of patients and different inclusion criteria and different therapeutic modalities.

A number of prognostic features have been identified by Sugarbaker[20]. These are histopathologic type, extent of cytoreduction, and extent of previous surgical interventions. Patients with complete cytoreduction and adenomucinosis had a 5-year survival rate of 86%, and patients with intermediate histologic features had 5-year survival rates of 50%. Patients with incomplete cytoreduction had 5-year survival rates of 20% and 0% at 10 years.

PMP is associated with high recurrence rate. According the data from the Mayo Clinic based on their study of 56 cases of PMP, 76% of patients developed recurrence and 50% of recurrences occurred within 2.5 years[25]. Most of the patients had carcinoma of the appendix (52%) or ovary (34%). According to their data, 5 and 10 year survival rates were 53% and 32%, respectively, and the median survival was 5.9 years[23]. Another study by Whitkamp *et al*. report a 5-year survival of 27% for peritoneal carcinomatosis of colorectal origin and of 86% for cases of PMP after complete cytoreduction and intraperitoneal chemohyperthermia[22].

Conclusions

PMP is a rare and complex disease with a broad spectrum of presentation and outcomes. Definitive data regarding the optimal approach to managing this disease are not available due to the paucity of randomized trials. Unfortunately it is unlikely that these trials will be performed due to the rarity of this disease. This highlights the importance of developing groups dealing with these rare tumors to allow formal data collection and to provide some guidance as to optimal therapeutic options in managing these patients.

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Accepted for publication April 28, 2003.