Pseudomyxoma peritonei: What Do We Have?

S Yalcin, E Ergül, B Korukluoglu, B Yalcin

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Abstract

Background: Pseudomyxoma peritonei is a clinical condition that is characterized as a localized or generalized accumulation of abundant gelatinous material within the abdominal and/or pelvic peritoneal cavity which usually shows a protracted clinical course, long-term prognosis is poor and death ultimately occurs as a consequence of intra-abdominal disease progression. We wanted to emphasize the pathological and clinical features of PMP, ideal treatment of the condition, and the outcome.

Data Sources: An extensive Medline search, textbooks, scientific reports and scientific journals are the data sources. We also reviewed reference lists in all articles retrieved in the search as well as those of major texts regarding postsurgical intraperitoneal adhesion formation.

Conclusion: The first step to improve the prognosis is to recognize PMP preferably in an early stage. CT imaging should be the choice of radiological assistance in the diagnosis and follow-up. Cytoreductive surgery with intraoperative HIPEC is a treatment strategy with encouraging survival results for selected PMP patients. The pathologic subtype remains the dominant factor for survival. Improvement of survival can be achieved by combination of surgical experience and adequate patient selection. Multi-instutional studies should be recommended. On the other hand, intraperitoneal PDT is potentially an ideal therapy but it needs improvement.

INTRODUCTION

Pseudomyxoma peritonei (PMP) is a clinical condition that is characterized as a localized or generalized accumulation of abundant gelatinous material within the abdominal and/or pelvic peritoneal cavity associated with a mucinous tumor of the gastrointestinal tract or ovaries [1]. Although the condition usually shows a protracted clinical course, long-term prognosis is poor and death ultimately occurs as a consequence of intra-abdominal disease progression.

We wanted to summarize the pathological and clinical features of PMP, ideal treatment of the condition, and the outcome.

HISTORY AND INCIDENCE

A clinical case consistent with this diagnosis was firstly described by Rokitansky in 1842 [2]. Werth introduced the term of PMP in 1884 when he described its occurrence in association with a mucinous carcinoma of the ovary [3]. In 1901, Frankel reported the relation of PMP with an appendiceal mucocele [4].

It is two to three times more common in females than males. PMP is an unexpected finding which presents in two of every ten thousand laparotomies [2].

DEFINITION AND HISTOPATHOLOGICAL ORIGIN

There is no single definition of PMP. The term is literally interpreted as “false mucinous tumor of the peritoneum”. It is most commonly used for a slowly progressive disease process characterized by extensive mucus accumulation within the abdomen and pelvis. Such a broad definition allows both mucinous adenomas of the appendix and mucus-producing gastrointestinal adenocarcinomas to be included under this entity. Clinically, the term PMP describes a syndrome that produces its symptoms by copious mucus tumor production which results in a “jelly belly” [2].

Although, in clinicopathological, molecular genetic and immunohistochemical studies the origin of PMP has been studied intensively [5,6,7], there is still confusion about the true origin. Many gynecological publications have emphasized the association with ovarian mucinous tumor of low malignant potential, also termed mucinous borderline tumor. Standard textbooks have often simply accepted that any

mucinous ovarian tumor present in a female represents the origin of the disease [8,9] . However, when the appendix is examined histologically, mucoceles, adenomas or carcinomas are found in nearly all cases. This simultaneous disease in most female patients might be explained either on the basis of spread from the appendix to the ovary or on the basis of two independent primary disease processes. If there is a single primary neoplasm other deposits should show features consistent with a clonal origin. If there is more than one primary neoplastic lesion a predisposing field change is implied. It has been suggested that this might arise because of mucinous metaplasia due to chronic irritation from ascitic fluid [7] . Despite this controversy, the appendix is still the alleged dominant origin associated with PMP [10] . Origins other than appendix or ovary are rare and include pancreas, colon or urachus [11,12] .

First, multiplying adenomucinous tumor cells produce a large amount of intraluminal mucus, and eventually cause obstruction of the appendiceal lumen. Then, rising intraluminal pressure results in the blow-out of the appendiceal mucocele with slow leak of mucus into the peritoneal cavity. The perforation of the appendix may reseal and become even invisible, while over the course of months or, in case of indolent behavior, years, free epithelial cells in the peritoneal cavity continue to proliferate and produce mucinous ascites. Finally, gravity for its part draws tumor cells through the paracolic gutters towards the pelvis. Accumulation and reproduction of the free and implanted tumor cells leads to progressive peritoneal mucinous tumor and ascites, but invasion of the peritoneal surface usually remains absent. The mean interval between the existence of a primary (appendiceal) tumor and established PMP is described to be approximately 21 months, but extremely long intervals have been reported.

On histologic examination, the mucinous implants consist of amorphous mucinous material, fibrous tissue and strips of cytologically bland and non-invasive mucin-secreting epithelium. In general, most cases are CK20-positive and CK7-negative, although expression of CK7 is observed in up to 30% of cases and use of the panel may not be useful in determining the site of origin in the cases with diagnostic problems. The mucinous ovarian neoplasm and the associated appendiceal neoplasm demonstrate an identical pattern of immunoreactivity. These neoplasms also express CDX2 and the accumulation of extracellular mucin has been linked to increased numbers of MUC2-secreting goblet cells [15] .

Generally, PMP has been considered to be a benign condition, but its behavior over time suggests that it should be considered, at best, a “borderline malignant” condition with inevitable disease persistence and progression. Ronnett et al. described PMP as benign and they pathologically classified it into three subtypes with different prognosis [16] , as disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and an intermediate subtype (PMCA-I). Histopathologically, DPAM is characterized by an abundance of mucus with focally adenomucinous epithelium with hardly any atypia or mitotic activity. DPAM has non-invasive properties, an indolent behavior and a good prognosis. PMCA, in contrast, has malignant features. It is characterized by peritoneal tumor composed of more abundant mucinous tumor cells with the architecture and cytological features of carcinoma. It occasionally shows invasive properties, comparable with peritoneal carcinomatosis due to a colorectal tumor, and has a grim prognosis. PMCA-I is characterized by an abundance of DPAM lesions but focal areas with PMCA lesions. The behavior and prognosis of PMCA-I subtype lies somewhere in between DPAM and PMCA [17,18,19] . Bradley at al. reviewed the pathology in 101 PMP patients and concluded that low-grade histology of PMP included those cases referred to as DPAM in the same category as PMCA-I. PMCA cases are classified as PMP-high grade [18] .

DIAGNOSIS

The presenting symptoms of the condition can be classified as symptoms due to the primary tumor, symptoms mimicking acute appendicitis (25%), and co-incidence (20%), presenting like an inguinal herniated sac or an ovarian mass. In 30% of female patients, the first symptom is an ovarian mass. As PMP progresses, the excessive mucous accumulation causes compression of the intestines. Gastrointestinal function is compromised and eventually obstruction is imminent. This is the most important symptom which characterizes the progressive stage of disease (50%) [7] .

Most of the patients have had a vague right lower abdominal pain with no further treatment or a perforated appendix with initially an unidentified tumor and/or unnoticed peritoneal tumor deposits. When they present several months later with abdominal distension, thorough analysis and/or revision of the original specimen from previous surgery reveals the correct diagnosis.

Ultrasonography (US) is the imaging technique by which

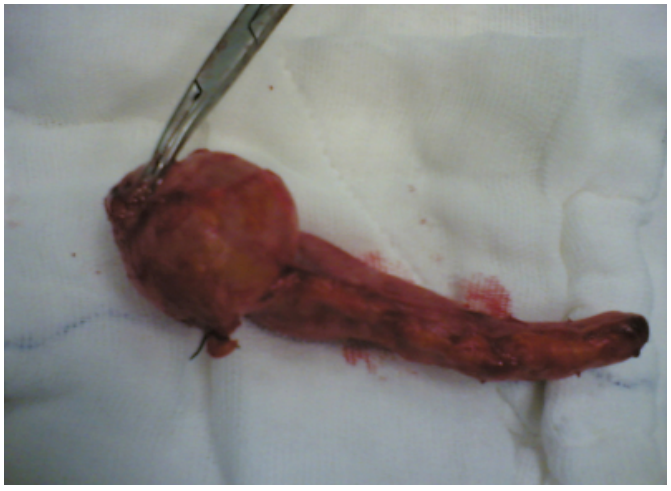
free fluid can be seen and an aspiration for cytology can also be taken. The second choice can be computed tomography (CT), which is pathognomic for PMP. By analyzing density properties (Hounsfield Units [HU]) of the free fluid, the radiologist can diagnose PMP. While normal ascites is characterized by a low density, nearly 0 HU, mucinous ascites has a significantly higher density, 5-20 HU. In addition, CT demonstrates the involvement of the abdominal cavity and the stage of the disease. In early stage, omentum, subhepatic region, ileoceacal region, sigmoid and ovaries may be involved, with visceral sparing. However, in late stage, generally all regions are affected. Other imaging modalities like magnetic resonance (MR), positron emission tomography (PET), radioimmunochemistry and radioimmunoscintigraphy do not seem to have any additional value [19,20,21,22] . When PMP is confirmed by CT, there is a role for serum tumor markers CEA and CA 19.9 in the completion of the diagnostic workup as these tumor markers are raised in most PMP patients and can be used as preoperative benchmark [23] .

TREATMENT

In patients with appendiceal mucocele a wait and see policy after appendectomy can be justified, but close follow-up with tumor markers and US is essential to detect PMP in an early stage. An appendiceal mucocele at resected material of one of our patients can be seen in Figure 1.

Figure 1

Figure 1: An appendiceal mucocele can be seen at the radix of the appendix



Nerveless data has been presented on alternative non-surgical treatment, like periodic symptomatic drainage of mucinous ascites, mucolytic treatment, peritoneal washing with 5% dextrose and systematic chemotherapy [24,25,26,27] .

The major pitfall of these strategies is the limited number of only case reports with limited follow-up.

Traditional surgical treatment is a widely accepted and applied strategy. The aim of the surgery in PMP is complete cytoreduction as described firstly by Sugarbaker [28] . This procedure involves up to six different peritonectomy procedures in combination with visceral resections as required, to remove all visible tumor, or if it is not possible, to leave tumor deposits less than 2.5mm. Tissue thickness of 2.5 mm is the maximum direct penetration of locally applied chemotherapy. This fundamental technique requires the removal and stripping of all tumour tissues involving the parietal and visceral peritoneum. Small cancer deposits on the visceral peritoneum, especially on the surface of tubular structures, are individually electroevaporated. Large tumor nodules in the small bowel must be resected and all visible tumors must be removed to maximize the benefits of peri-operative intraperitoneal chemotherapy.

Surgery is followed by local drug administration aimed at eliminating microscopic and/or minimal residual disease left in the abdominal cavity following surgical manipulations [29] . The additional effects of hyperthermia, through the use of a special pump, increase local tissue drug concentration and consequently antiblastic drug activity [30] . This technique has been defined as hyperthermic intraperitoneal chemotherapy (HIPEC). These methods can achieve satisfactory results in patients with PMP [31,32,33,34,35] . Intraperitoneal chemotherapy is only required to eradicate microscopic residual disease for its complete success. The pharmacokinetic advantage of the intraperitoneal route of drug administration is not compromised when used as a planned part of a surgical procedure. The high molecular weight of chemotherapy agents and their water solubility (hydrophilic) cause a prolonged retention in the peritoneal space. Also, use of selected drugs under hyperthermic conditions can increase cytotoxicity on the peritoneal surface but not systemic (bone marrow) toxicity. Hyperthermia can improve drug penetration into tumor tissue and optimize the dose intensity of chemotherapy on the abdominal and pelvic surfaces. The combined use of hyperthermia and intraperitoneal chemotherapy enhances the cytotoxicity of chemotherapeutic agents and increases tissue penetration by chemotherapy in cancerous tissue as compared to normal tissue.

The combination of surgery and other modalities than intraperitoneal chemotherapy is uncommon and has shown

various degrees of success. Fernandez and Daly [36] also suggested that radiotherapy may be a useful adjunct and noted an improvement in the 5-year survival rate from 44% for patients receiving chemotherapy to 75% for patients receiving radiation. Their patient numbers and follow-up, however, were too small and too short, respectively, to be statistically conclusive. Photodynamic therapy (PDT) combined with surgery has been applied widely in peritoneal surface disease other than PMP [37] . Intraperitoneal PDT is potentially an ideal therapy for peritoneal carcinomatosis because of its relatively superficial treatment effect. A Phase II trial of intraperitoneal PDT with the first generation photosensitizer, Photofrin, demonstrates that this treatment approach is tolerable clinically but is associated with substantial toxicity suggesting a narrow therapeutic index. It seems technically feasible, but the adjuvant effect for PMP has still to be evaluated. Correlative studies of photosensitizer uptake in human tumor and normal tissues show little tumor selectivity. This lack of photosensitizer selectivity for tumor in combination with tumor hypoxia is likely a major reason for the narrow therapeutic index of intraperitoneal PDT [38] . Other approaches, including the use of nanotechnology, may allow the administration of fractionated PDT which may also improve the therapeutic index of this treatment.

The effects of systemic chemotherapy in PMP seem to have limited success. The locoregional spread of well-differentiated tumor with a poor blood supply greatly diminishes the efficacy and possible benefit of systemic therapy. Most studies except Jones et al. [24] question an objective response of PMP to systemic chemotherapy and consider systemic therapy to be reserved for a palliative setting in patients with recurrent or progressive disease [39,40] .

In late stage disease, when the entire abdomen is filled with mucinous tumor and ascites, immediate combined modality treatment looses its benefit [39] . A two step procedure might be worthwhile under these conditions. Firstly, the most feasible resections which include ileocaecum, omentum and ovaries must be performed. In a second stage, when the patient has recovered, the cytoreduction can be completed with intraperitoneal HIPEC.

FOLLOW-UP AND OUTCOME

After treatment, patients should be monitored for recurrent or progressive disease. A CT scan is a very important tool for detecting progressive disease and can be performed 3 months after the treatment. The following scans should be performed every 6 months in the first year and once a year or when progression is suspected in the next years.

Smeenk et al. [39] have found in their large cohort study that cytoreductive surgery in combination with intraoperative HIPEC is a feasible treatment strategy for PMP in terms of survival. The pathologic subtype remains the dominant factor in survival. Patients should be centralized to improve survival by a combination of surgical experience and adequate patient selection. They found that 5-year survival of low grade tumors (so-called DPAM) is more than 75%. But, survival of the patients who suffered from PMCA is worst.

Recently, in 2007, Sugarbaker [41] reviewed current evidence on cytoreductive surgery and perioperative intraperitoneal chemotherapy (PIC) for PMP. The median survival ranged from 51 to 156 months, and the overall morbidity rate varied from 33% to 56%; mortality rates ranging from 0% to18% were found in this study.

In our hospital, between 1997 and 2007, 21 patients underwent peritonectomy procedures as cytoreductive surgery and HIPEC. Out of them, 7 patients had low-grade appendiceal tumor or PMP. Median follow-up was 5 years. All patients had a low-grade tumor. Median survival was not reached. Just one of our patients died due to acute myocardial infarction at 5 years after surgery and HIPEC.

CONCLUSION

PMP is a rare disease, with a grim prognosis when not treated properly. The first step to improve the prognosis is to recognize this syndrome preferably in an early stage. CT imaging should be the choice of radiological assistance in the diagnosis and follow-up. Cytoreductive surgery with intraoperative HIPEC is a treatment strategy with encouraging survival results for selected PMP patients, especially in low-grade disease. The pathologic subtype remains the dominant factor for survival. Improvement of survival can be achieved by combination of surgical experience and adequate patient selection. Multi-institutional studies should be recommended. On the other hand, intraperitoneal PDT is potentially an ideal therapy but it needs improvement. The clinical implementation of new technologies may allow for highly effective and well tolerated treatment of intraperitoneal carcinomatosis with PDT.

CORRESPONDENCE TO

Dr. Emre Ergül Askaabat Cad. Eser Sitesi B Blok 3.Giris

Daire: 11 Bahcelievler 06490 Ankara / Turkey Phone: +905056821500 Fax: +903122123414 E-mail: dreergul@gmail.com

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Author Information

Samet Yalcin, M.D.
General Surgery Department, Ankara Atatürk Teaching and Research Hospital

Emre Ergül, M.D.
General Surgery Department, Ankara Atatürk Teaching and Research Hospital

Birol Korukluoglu, M.D.
General Surgery Department, Ankara Atatürk Teaching and Research Hospital

Bülent Yalcin, M.D.
Department of Medical Oncology, Ankara University School of Medicine