Original article

# Clinical presentation of the pseudomyxoma peritonei syndrome

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**Background:** Pseudomyxoma peritonei syndrome is characterized by a gradual expansion of mucoid tumour and fluid at specific sites within abdominopelvic regions as a result of a perforated appendiceal adenoma. The aim was to analyse the presenting symptoms and signs of patients with this condition.
**Methods:** Of 410 patients with appendiceal tumours 217 had the diagnosis of pseudomyxoma peritonei syndrome with histological confirmation. A retrospective review of the clinical characteristics that determine presentation was performed.
**Results:** Overall, suspected acute appendicitis was the most common presentation (27 per cent). For women the diagnosis was most commonly made while being evaluated for an ovarian mass (39 per cent). Increasing abdominal girth was the second most common presentation overall (23 per cent). Thirty patients (14 per cent) presented with new-onset hernia, of which the majority (26) were inguinal hernias.
**Conclusion:** Consideration of appendicitis, increased abdominal girth, ovarian mass and new-onset hernia as caused by this syndrome may facilitate diagnosis and definitive treatment.

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## Introduction

Pseudomyxoma peritonei represents a slowly progressive disease process characterized by copious amounts of mucoid fluid and tumour that, over time, fills the peritoneal cavity. Literally defined, it means 'false mucinous tumour of the peritoneum'[1]. Early descriptions of this condition identified an appendiceal mucinous tumour as the primary site of disease[2]. However, a lack of knowledge concerning the pathogenesis of this rare condition caused numerous diseases that result in extensive mucus accumulation within the abdomen and pelvis to be called pseudomyxoma peritonei. This occurred when the tumour originated from a mucinous adenoma of the appendix, a mucus-producing gastrointestinal adenocarcinoma, a primary ovarian mucinous tumour, or mucinous peritoneal carcinomatosis of an unknown primary tumour.

Sugarbaker and colleagues[3] attempted to redefine a clinical entity which they called the pseudomyxoma peritonei syndrome. They proposed that the term pseudomyxoma peritonei syndrome should be strictly limited to identify a pathologically and prognostically homogeneous group of patients characterized by histologically benign peritoneal tumours associated with a primary appendiceal mucinous adenoma. This tumour has an indolent clinical course and is not considered biologically aggressive because it does not invade or metastasize. Pathologically the peritoneal mucinous lesions are termed 'disseminated peritoneal adenomucinosis' or simply 'adenomucinosis'[4]. According to this definition, cases of mucinous peritoneal carcinomatosis from primary sites other than the appendix, regardless of the presence of abundant extracellular mucin, should not be included as pseudomyxoma peritonei syndrome.

In the past treatment consisted of repeated operative procedures focused at evacuating as much mucinous tumour and free mucus as possible. Eventually there were no further surgical options and the patients succumbed to intestinal obstruction and terminal starvation. This approach resulted in a median survival of 2·5 years, with few patients being alive after 5 years[5–7]. Currently, peritonectomy procedures that allow the surgeon to remove completely all involved parietal and visceral peritoneum, combined with techniques to deliver perioperative intraperitoneal chemotherapy, have changed the approach to the patient with pseudomyxoma peritonei syndrome[8,9]. No longer is the therapy focused on palliation with surgical procedures that temporarily relieve symptoms, but has

 

**Table 1** Clinical presentation of 217 patients with pseudomyxoma peritonei syndrome

| | No. of patients | Men | Women |
|---|---|---|---|
| Appendicitis | 58 (27) | 36 (34) | 22 (20) |
| Increased abdominal girth | 49 (23) | 28 (27) | 21 (19) |
| Ovarian mass | 44 (20) | — | 44 (39) |
| Hernia | 30 (14) | 26 (25) | 4 (4) |
| Ascites | 9 (4) | 5 (5) | 4 (4) |
| Abdominal pain | 8 (4) | 5 (5) | 3 (3) |
| Other | 19 (9) | 5 (5) | 14 (12) |
| Total | 217 (100) | 105 (48) | 112 (52) |

Values in parentheses are percentages

curative intent. The outcome of these patients is now an 87 per cent 5-year disease-free survival rate[6].

The purpose of this study was to analyse the presenting symptoms of all the patients with the pseudomyxoma peritonei syndrome treated by a single surgeon (P.H.S.) over a 13-year period. An analysis of their clinical presentation will further characterize the syndrome and assist the clinician in the identification of patients for curative treatments without unnecessary delay.

## Patients and methods

The research records of all the patients with primary appendiceal tumours treated by a single surgeon from February 1985 to October 1998 were reviewed. There were 410 patients with appendiceal malignancy. Of these, 217 patients had the diagnosis of pseudomyxoma peritonei syndrome with a histological confirmation of 'disseminated peritoneal adenomucinosis' resulting from an appendiceal adenoma. Patients who had hybrid appendiceal malignancy were not included; the hybrid tumours were composed largely of adenomucinosis but had components of mucinous adenocarcinoma identified by histological examination[4]. Patients with mucinous adenocarcinomas of the appendix were not included[4]. An analysis of these 217 patients constitutes the basis of the study.

The patients were classified into one of seven groups based on their clinical presentation. Group 1 included patients in whom the diagnosis of pseudomyxoma peritonei syndrome was made at the time they underwent surgery for suspected appendicitis. Group 2 included patients whose initial medical evaluation was performed because of increasing abdominal girth. In this group the patients or family member initially called attention to the expanding abdomen. Group 3 included women whose original presentation was for an ovarian mass. Group 4 included those in whom mucoid material was found during hernia repair. These patients did not have symptoms other than a new-onset hernia. Group 5 included those who presented with non-specific complaints and an outside physician gave a diagnosis of ascites. Investigation for this condition led to the diagnosis of pseudomyxoma peritonei syndrome. Patients with an increasing abdominal girth (a symptom) were sufficiently different from those presenting with ascites (a sign) to constitute separate groups. In one group the patient complained of an expanding abdomen. In the group with ascites a physician's examination or radiological test was necessary to identify fluid within the peritoneal cavity. Group 6 included patients who presented with a chief complaint of abdominal pain. Group 7 represented all the patients who were not included in any of the above groups. None of these patients had additional symptoms that were obviously related to pseudomyxoma peritonei syndrome.

The treatment strategy uniformly involved two principles of management in these patients. First, peritonectomy procedures were used in an attempt to achieve a disease-free status. These procedures involved greater and lesser omentectomy, stripping of the right and left hemidiaphragm, stripping of the pelvis and visceral resections that were required in order to eliminate macroscopic disease surgically. Normal peritoneal surfaces were not stripped away[9]. After operation the peritoneal space was treated with mitomycin C at 12·5 mg/m$^2$ for men and 10 mg/m$^2$ in women. The chemotherapy was instilled in a large volume of 1·5 per cent dextrose peritoneal dialysis solution in order to promote uniform distribution of the drug to all peritoneal surfaces. Mitomycin C treatment was followed by 5 days of intraperitoneal 5-fluorouracil chemotherapy instilled directly into the abdomen in 1 litre of 1·5 per cent dextrose peritoneal dialysis solution. Other treatments such as additional cycles of combined intraperitoneal and systemic chemotherapy, intravenous continuous infusion of 5-fluorouracil and intravenous irinotecan were used after referral back to the local physician on a sporadic basis.

## Results

There were 217 patients with the diagnosis of pseudomyxoma peritonei syndrome of appendiceal origin (*Table 1*). Analysis of the distribution by sex showed no sex preference, with 112 (52 per cent) of the patients being women and 105 (48 per cent) men. The age range was 29–76 (median 49) years.

Suspected acute appendicitis was the most common form of presentation overall, with 58 (27 per cent) of the 217 patients presenting in this manner. When analysed by sex, it constituted the most common presentation for men, with 36

**Table 2** Anatomical distribution of 30 hernias in 217 patients with pseudomyxoma peritonei syndrome

| | No. of patients | Inguinal | | | Umbilical |
|---|---|---|---|---|---|
| | | Right | Left | Total | |
| Men | 26 | 10 | 9 | 19 | 7 |
| Women | 4 | 1 | – | 1 | 3 |
| Total | 30 | 11 | 9 | 20 | 10 |

men (34 per cent) being diagnosed with pseudomyxoma peritonei syndrome at the time of exploration for acute appendicitis. It constituted the second most common presentation in women, with 22 patients (20 per cent).

Increasing abdominal girth, not associated with any other signs or symptoms, was the second most common presentation overall, with 49 patients (23 per cent) seeking medical evaluation because of an expanding abdomen. When analysed by sex, it was the second most common presentation for men (27 per cent) and the third most common presentation for women (19 per cent).

For women the diagnosis most commonly resulted from the evaluation of an ovarian mass. Forty-four women (39 per cent) presented in this way. These patients had pelvic symptoms. On pelvic examination or ultrasonography as part of the investigation of these patients, an ovarian mass secondary to the perforated appendiceal adenoma was discovered.

Presentation with a new-onset hernia was the fourth most common clinical entity, recorded in 30 (14 per cent). Twenty hernias were inguinal and the other ten umbilical. The majority of the hernias (26 of 30) were present in men (*Table 2*).

Nine patients (4 per cent) had the diagnosis of pseudomyxoma peritonei syndrome established when ascites was diagnosed by a radiological test and subsequently sampled by paracentesis. This represents a small group of both men and women. In almost all patients the intra-abdominal fluid accumulation is usually a thick mucoid material. In these nine patients it was a thin serous fluid.

Eight patients (4 per cent) presented with vague non-specific abdominal pain. Investigation for this pain, usually with computed tomography of the abdomen and pelvis, led to the diagnosis of pseudomyxoma peritonei syndrome.

Nineteen of the 217 patients were grouped in the 'other' category. Five of these were men and 14 women. There was a wide variety of initial signs and symptoms, some of which were incidental findings. In women, the majority were associated with gynaecological complaints or investigation for infertility (*Table 3*).

**Table 3** Less common initial presentation in 19 of 217 patients with pseudomyxoma peritonei syndrome

| | No. of patients |
|---|---|
| Women | |
| Infertility investigation | 3 |
| Presumed cholecystitis | 3 |
| Postmenopausal bleeding | 2 |
| Abnormal Papanicolaou smear | 1 |
| Pelvic pain | 1 |
| Pelvic mass | 1 |
| Surgery for fibroids | 1 |
| Laparoscopy for tubal ligation | 1 |
| Surgery for right colonic cancer | 1 |
| Total | 14 |
| Men | |
| Abdominal aortic aneurysm repair | 1 |
| Deep vein thrombosis | 1 |
| Rectal bleeding | 1 |
| Nephrectomy | 1 |
| Anaemia | 1 |
| Total | 5 |

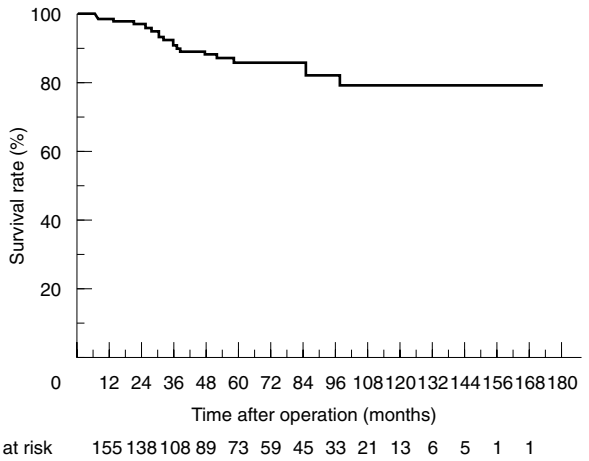


**Fig. 1** Kaplan–Meier survival distribution of patients with the pseudomyxoma peritonei syndrome treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. Some 217 patients were evaluated at the Washington Hospital Center. Follow-up data are available for 168 patients who had treatment at this institution (three patients lost to follow-up)

The median follow-up of the 168 patients treated at this institution is 46·7 months. The median survival has not yet occurred. The 5-year survival predicted by a Kaplan–Meier distribution is 81 per cent. *Fig. 1* shows the survival distribution for these patients.

The mortality rate for these 168 patients was 3 per cent in-hospital or within 3 months of operation. Survival, morbidity and mortality were not significantly related to the presenting symptom or sign.

 

## Discussion

Current thinking regarding the pathophysiology of the pseudomyxoma peritonei syndrome can be summarized as follows. An adenoma arises within the appendiceal lumen and with progressive growth the lumen of the appendix becomes occluded. This occlusion leads to distension of the distal portion of the appendix, not only by mucus produced by the normal appendiceal epithelium but also by the adenoma. The wall of the appendix ruptures and leak of mucus containing epithelial cells from the adenoma occurs[3].

Analysis of the present data indicates that this process is, in a majority of patients, a subclinical event. Even the patients diagnosed with pseudomyxoma peritonei syndrome while undergoing an operation for suspected acute appendicitis already had significant disease present throughout the abdomen and pelvis. The most likely explanation is that the appendix may repeatedly decompress by perforation and resealing. The primary lesion grows little in size over the years but the epithelial cells, widely distributed around the peritoneal space, continue to proliferate and produce large quantities of mucus. Eventually an episode of appendiceal distension and rupture will result in bacterial contamination and the symptoms of appendicitis may occur. In many of the patients who were operated on for acute appendicitis, it was reported that mucus was extruding from the lumen of the appendix into the peritoneal cavity. In the present study, symptoms of appendicitis occurred in 58 (27 per cent) of the 217 patients and was the most common presentation.

The location and quantity of mucinous tumour within the abdomen and pelvis can be characterized by the redistribution phenomenon[3]. Tumour cells are surrounded by a slippery mucoid matrix and move with the normal flow of the peritoneal fluid. Portions of the peritoneum that are in motion, such as the visceral peritoneum on the small bowel surface, are seeded only sparsely. The abdominal surfaces that absorb peritoneal fluid, such as the greater omentum and the undersurface of the diaphragm, are coated by tumour cells as fluid is pulled to these anatomical sites. Massive accumulation of tumour in the greater omentum contributes significantly to the increase in the patients' abdominal girth, which was the second most common clinical presentation, occurring in 23 per cent of patients.

In 39 per cent of women the clinical presentation was that of an ovarian mass. The pathophysiology of an ovarian mass occurring in the presence of a perforated appendiceal adenoma can be understood by studying the ovarian physiology during ovulation. The reproductive system of the female shows regular cyclical changes. At the follicular phase of each ovarian cycle one ovarian follicle starts to grow and distend. At about the day 14 of the menstrual cycle the distended follicle ruptures and the ovum is extruded into the abdomen. The follicle that ruptured promptly fills with blood forming a corpus haemorrhagicum. At the time of the ovarian follicle rupture, epithelial cells floating freely in peritoneal fluid adhere to the ruptured follicle. These tumour cells become trapped in the corpus luteum and proliferate inside the ovary while the surface of the ovary undergoes its natural cicatricial process with no evidence of the mucinous tumour within. Over time a cystic ovarian mass caused by an expansion of mucinous tumour cells will become symptomatic or detectable by pelvic examination. This symptom was not recorded in postmenopausal women.

The free-floating tumour cells that migrate with the peritoneal fluid around the abdomen and pelvis may accumulate in an umbilical hernia sac or a patent processus vaginalis. As these tumour cells proliferate and continued mucus production occurs, they may produce a new-onset umbilical or inguinal hernia. Hernia was the fourth most common presentation in this series.

The treatment strategy used in this series resulted in an 81 per cent 5-year survival rate. There was a 3 per cent mortality rate associated with the treatments[7]. Prompt recognition of the clinical presentation of pseudomyxoma peritonei syndrome combined with aggressive treatments using peritonectomy and perioperative intraperitoneal chemotherapy resulted in a beneficial result. As earlier referrals occur, the survival statistic is likely to improve and the morbidity and mortality rates reduce.

In summary, the pseudomyxoma peritonei syndrome is caused by an appendiceal adenoma that distends the appendix and ruptures, releasing mucus-producing tumour cells into the peritoneal cavity. In most patients the initial appendiceal perforation is a subclinical event. Mucinous tumour progression and mucus production continue, redistributing the process throughout the abdomen and pelvis. The site at which the process causes a presenting sign or symptom is dictated by patient factors such as the progression within a hernia sac or in a ruptured ovarian follicle. Cytoreductive surgery using peritonectomy combined with perioperative intraperitoneal chemotherapy was employed successfully as a potentially curative treatment strategy in these patients.

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