

## PSEUDOMYXOMA PERITONEI

- Pseudomyxoma peritonei syndrome is characterized by mucinous ascites and mucinous tumor disseminated on peritoneal surfaces
  - the disease almost always originates from a perforated appendiceal epithelial tumor.
  - Appendix tumors are unusual, accounting for 0.4% of all of the gastrointestinal tract malignancies.
  - Although rare, the spectrum of malignant disease is complex and has led to confusion in accurate description of the natural history of these tumors.
    - Consequently, many errors in diagnosis and treatment have occurred.
    - Perhaps the most glaring error in management occurs in women who have ovarian tumors as a result of a perforated primary mucinous tumor of the appendix.
  - Appendiceal tumors present with peritoneal seeding in a majority of patients.
  - Dissemination to lymph nodes or to liver is extremely unusual.
  - Advanced treatments of peritoneal carcinomatosis or peritoneal adenomucinosis have changed these survival rates from zero to approximately 80% for all patients.
- The term “mucocele” of the appendix refers to an accumulation of mucus within an abnormally distended appendiceal lumen, regardless of its cause.
  - Mucoceles of the appendix are rare, appearing in 0.2-0.3 % of surgical specimens.
  - A mucocele of the appendix can be caused by:
    - obstruction of the appendiceal lumen
    - mucosal hyperplasia
    - mucinous cystadenoma
    - mucinous cystadenocarcinoma (4).
  - Whatever the cause, obstruction of the lumen and accumulation of yellow mucous within the appendiceal lumen results.
  - Majority of patients with mucocele are asymptomatic.
    - Most mucocele present with acute or chronic right lower quadrant pain (64%)
    - but patients have presented with intussusception gastrointestinal bleeding, intermittent colicky pain, abdominal masses, secondary infection and urologic symptoms.
    - Our patient presented with chronic abdominal pain and an abdominal mass .
  - At barium enema, a smooth globular mass indenting the cecum may be seen, associated with non-filling of the appendix.
    - The combination of appendiceal non-filling and deformity of the inferomedial aspect of the cecum should always suggest the possibility of appendiceal disease, whether this be due to appendicitis (as is usually the case), appendiceal neoplasm or a mucocele.
  - Rupture of an appendiceal mucocele may give rise to pseudomyxoma peritonei in which the peritoneal cavity becomes filled with the gelatinous material either in the form of circumscribed collections or lying free.
    - If this condition is discovered incidentally at laparotomy, a careful search should be made for an underlying tumor, which is most commonly ovarian or appendiceal in origin.
    - CT sometimes shows a characteristic appearance in pseudomyxoma peritonei, with septated fluid-density material in the peritoneal cavity and/or marked deformity and

- scalloping of the liver by the mucinous material.
  - This condition is pathologically divided into 4 categories [5].
    - A very rare type is secondary to occlusion of the lumen from post inflammatory scarring, progeric atrophy, congenital obstruction of Gerlach's valve or extramural compression.
      - This type leads to atrophic mucosa.
    - The other types are classified into a spectrum from mucous hyperplasia to mucinous cystadenoma to mucinous cystadenocarcinoma depending on the pathology of the mucosa.
  - About 25% of mucocoeles are from mucosal hyperplasia [5].
    - These typically have minimal distension.
    - Mucinous cystadenoma, which account for about 60% of mucocoeles, are more markedly distended, however, they are typically asymptomatic.
    - Mucocoeles up to 40x24x20 cm have been reported.
    - Mucinous cystadenocarcinomas (10-15% of cases) are more likely to be symptomatic and are believed to arise in cystadenomas.
    - Thorough investigation of the colorectal tract is recommended after diagnosing an appendiceal mucocoele [5].
    - Mucinous cystadenomas and cystadenocarcinomas may be indistinguishable grossly but histologically can be differentiated by two features:
      - invasion of the appendiceal wall by atypical glands
      - identification of epithelial cells in any intraperitoneal mucinous collection.
  - The distinction between mucinous cystadenomas and mucinous cystadenocarcinomas is important.
    - Cystadenoma is cured by simple appendectomy, even in the presence of periappendiceal fluid collections
    - right hemicolectomy is the best treatment for a malignant mucinous cystadenocarcinoma in a good risk patient.
    - Rupture of appendiceal mucinous cystadenomas and mucinous cystadenocarcinomas may occur and accounts for about 33 per cent of pseudomyxoma peritonei cases [4].
  - The clinical presentation of a mucocoele is usually non-specific and up to fifty percent are discovered incidentally at surgery (2).
    - CT can play an important role in pre-operative diagnosis. The classical CT findings are:
      - A cystic, well-encapsulated round or ovoid mass centered in the right iliac fossa.
      - Mural calcification.
      - Absence of periappendiceal inflammation or abscess (2,3)
        - ◆ Adequate opacification of the terminal ileum and cecum is essential for optimal examination.
- Pseudomyxoma peritonei is characterized on CT by the presence of low attenuation ascites with scalloping of liver contour due to peritoneal implants.
  - Implants can also be seen on the visceral surfaces and as nodules within cavities.
  - These nodules may show calcification usually in a rim like fashion.
  - The absence of scalloping does not rule out pseudomyxoma peritonei.
  - Loculation of ascitic fluid with associated mass effect should also lead to a consideration of pseudomyxoma peritonei.

- Pseudomyxoma peritonei is also known to develop from ovarian cystadenocarcinoma.
  - In these patients a mucinous neoplasm of the appendix is also nearly always present.
  - Whether the ovarian and appendiceal tumors represent independent primary tumors or whether the ovarian tumors are secondary to appendiceal tumors remains a controversy.
  - Both tumors are actually synchronous, but one may appear many years after the removal of the other.
  - Mucinous cystadenocarcinomas arising from the urachus, uterus, or omphalomesenteric duct are also known to cause pseudomyxoma peritonei.
- The differential diagnosis of mucocele of the appendix includes mesenteric cyst, duplication cyst, right ovarian cyst and hydrosalpinx.

#### PATHOGENESIS: MUC GENES

**Pseudomyxoma peritonei is a disease of MUC2-expressing goblet cells.** O'Connell JT, Tomlinson JS, Roberts AA, McGonigle KF, Barsky SH. Department of Pathology, University of California at Los Angeles School of Medicine, Los Angeles, California 90024. *Am J Pathol* 2002 Aug; 161(2):551-64.

- Pseudomyxoma peritonei, a syndrome first described by Karl F. Rokitansky in 1842, is an enigmatic, often fatal intra-abdominal disease characterized by dissecting gelatinous ascites and multifocal peritoneal epithelial implants secreting copious globules of extracellular mucin.
- Our studies revealed that pseudomyxoma peritonei is a disease of MUC2-expressing goblet cells. MUC2 expression accounts for the voluminous deposits of extracellular mucin (mucin:cell ratios exceeding 10:1) and distinguishes pseudomyxoma peritonei secondarily involving the ovary from primary ovarian mucinous tumors with peritoneal implants. Because mucinous tumors of the appendix similarly express MUC2, the MUC2 expression profile also supports an appendiceal rather than ovarian origin for pseudomyxoma peritonei. Increased steady-state mRNA is observed in pooled cases of pseudomyxoma peritonei.
- Extracellular mucin accumulates dramatically in pseudomyxoma peritonei because the number of MUC2-secreting cells dramatically increase and because this MUC2 has no place to drain. These studies suggest that pseudomyxoma peritonei should be regarded as a disease of MUC2-expressing goblet cells whose MUC2 expression might be susceptible to pharmacological targeting.

#### LABORATORY AND RADIOLOGY

**Prognostic value of baseline and serial carcinoembryonic antigen and carbohydrate antigen 19.9 measurements in patients with pseudomyxoma peritonei treated with cytoreduction and hyperthermic intraperitoneal chemotherapy.** Van Ruth S, Hart AA, Bonfer JM, Verwaal VJ, Zoetmulder FA. Department of Surgical Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands. *Ann Surg Oncol*, 2002 Dec; 9(10):961-7.

- **BACKGROUND:** Tumor markers are useful for diagnosis and follow-up. We studied the prognostic value of baseline and serial carcinoembryonic antigen (CEA) and carbohydrate antigen 19.9 (CA19.9) measurements in patients with pseudomyxoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).
- **METHODS:** Sixty-three patients with pseudomyxoma peritonei were treated with cytoreductive surgery and HIPEC. The tumor markers CEA and CA 19.9 were collected

before therapy and at 3-month intervals during follow-up.

- **RESULTS:** Preoperative CEA and CA19.9 levels were increased in, respectively, 75% and 58% of the patients. Baseline tumor marker values were related to the extent of tumor. Immediately after HIPEC, both tumor markers decreased markedly ( $P < .0001$ ). CA19.9 was shown to be a more useful tumor marker than CEA for follow-up. Patients who never attained a normal CA 19.9 level showed a higher recurrence rate at 1 year (53%), in comparison to patients who did so (6%). The median lead time of increased CA19.9 to recurrence was 9 months.
- **CONCLUSIONS:** The measurement of the tumor marker CA19.9 is useful in evaluating therapy in patients with pseudomyxoma peritonei treated with cytoreductive surgery and HIPEC. CA19.9 is a prognostic factor for predicting recurrent disease.

#### PROGNOSIS AND TREATMENT

##### **Histopathologic Analysis in 46 Patients with Pseudomyxoma Peritonei Syndrome: Failure versus Success with a Second-Look Operation.** Hui Yan, et al. *Mod Pathol* 2001; 14:164-171.

- Histopathologic assessment of aggressive versus noninvasive character of the mucinous tumor has been shown to have an impact on survival in patients treated with cytoreductive surgery and intraperitoneal chemotherapy.
- Unsuccessful second-look surgery for patients with a clinical diagnosis of pseudomyxoma peritonei tumor was often related to an inaccurate initial histologic classification of appendiceal mucinous tumor. Also, a transition from less to more aggressive histology was frequently seen in patients dying of this disease. Assessment of tumor histology can predict the outcome if a uniform surgical treatment is used in patients with peritoneal dissemination of mucinous epithelial tumors of the appendix.

##### **Patients with pseudomyxoma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis.** Ronnett BM, Yan H, Kurman RJ, Shmookler BM, Wu L, Sugarbaker PH. Department of Pathology, The Johns Hopkins Hospital, Baltimore, Maryland. *Cancer* 2001 Jul 1;92(1):85-91.

- **BACKGROUND:** Pseudomyxoma peritonei (PMP) is a poorly understood condition characterized by disseminated intraperitoneal mucinous tumors, often with mucinous ascites. The term PMP has been applied historically as a pathologic diagnostic term to both benign and malignant mucinous neoplasms that produce abundant extracellular mucin, resulting in a variable and poorly predictable prognosis. A recent study reported a pathologic classification that separated patients into prognostically distinct groups, but the follow-up was relatively short.
- **METHODS:** Long-term follow-up data were analyzed for a previously reported series of 109 patients with PMP to examine the prognostic utility of a pathologic classification system that divided patients into three groups: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA).
- **RESULTS:** Patients with DPAM had 5-year and 10-year survival rates of 75% and 68%, respectively (mean follow-up, 96 months; median follow-up, 104 months). Patients with PMCA had a significantly worse prognosis, with 5-year and 10-year survival rates, respectively, of 14% and 3% (mean follow-up, 27 months; median follow-up, 16 months;  $P = 0.0001$ ).

- **CONCLUSIONS:** The study showed that the term PMP should be used only as a clinical descriptor for patients who have the syndrome of mucinous ascites accompanied by a characteristic distribution of peritoneal mucinous tumors with the pathologic features of DPAM. DPAM should be used as a pathologic diagnostic term for patients with the bland peritoneal mucinous tumors associated with ruptured appendiceal mucinous adenomas and PMP. These patients should not be diagnosed with carcinoma, because they have disease that is distinct pathologically and prognostically from PMCA.

## TREATMENT

**Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei.** Witkamp AJ, de Bree E, Kaag MM, van Slooten GW, van Coevorden F, Zoetmulder FA. Department of Surgical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands. *Br J Surg* 2001 Mar; 88(3):458-63.

- **BACKGROUND:** Pseudomyxoma peritonei remains a fatal disease. However, extensive surgical cytoreduction combined with intraoperative heated intraperitoneal chemotherapy (HIPEC) has recently emerged as a new treatment modality, which might improve survival.
- **METHODS:** Patients underwent treatment if the tumor appeared to be technically resectable on preoperative abdominal computed tomography and there were no distant metastases. After aggressive surgical cytoreduction, HIPEC with the administration of mitomycin C was performed for 90 min. Depending on the histological grading, patients received adjuvant 5-fluorouracil and leucovorin therapy.
- **RESULTS:** Forty-six patients were treated. Optimal surgical cytoreduction was obtained in 40 patients. Postoperative surgical complications occurred in 18 patients. Four patients died as a direct result of the treatment. Bone marrow suppression due to mitomycin C toxicity occurred in 22 patients. There was no other major toxicity related to the HIPEC procedure. After a median follow-up of 12 months, 40 patients are alive, eight of whom have proven recurrence. The actuarial survival rate (Kaplan-Meier) at 3 years was 81%.
- **CONCLUSION:** These results confirm that extensive surgery combined with HIPEC is feasible in patients with pseudomyxoma peritonei and that improved long-term survival might be achieved.

**Cytoreductive surgery and post-operative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome.** Sugarbaker PH. Washington Cancer Institute, Washington, D.C. *Eur J Surg Oncol* 2001 Apr;27(3):239-43.

- Peritoneal carcinomatosis, regardless of primary tumor type, has always been a lethal condition. Recently special treatments using cytoreductive surgery with peritonectomy procedures combined with peri-operative intraperitoneal chemotherapy have resulted in long-term survival. Pseudomyxoma peritonei may be especially appropriate for these aggressive local regional treatments.
- All patients treated prior to 1999 are presented; patients left with gross residual disease after surgery were not given intraperitoneal chemotherapy, but were later treated with intravenous chemotherapy after cytoreduction. The intraperitoneal chemotherapy was given in the peri-operative period, starting with mitomycin C. For patients whose pathology showed adenomucinosis, intraperitoneal chemotherapy was limited to treatment in the operating theatre with heated mitomycin C. Patients with mucinous adenocarcinoma or

pseudomyxoma/adenocarcinoma hybrid had, in addition to mitomycin C, 5 consecutive days of intraperitoneal 5-fluorouracil. A complete cytoreduction was defined as tumor nodules < 2.5 mm in diameter remaining after surgery. The histopathology categorized the patients as adenomucinosis, intermediate type, or mucinous carcinomatosis. A prior surgical score was used to estimate the extent of previous surgical procedures. The morbidity of treated patients was 27% and the mortality was 2.7%.

- In a multivariate analysis, prognostic factors for survival included the completeness of cytoreduction ( $P < 0.0001$ ), the histopathological character of the appendix malignancy ( $P < 0.001$ ) and the extent of previous surgical interventions ( $P = 0.001$ ). Patients with a complete cytoreduction and adenomucinosis by pathology had a 5-year survival of 86%; while hybrid pathology survival at 5 years was 50%. Incomplete cytoreduction had a 5-year survival of 20% and 0% at 10 years. Cytoreductive surgery and peri-operative intraperitoneal chemotherapy is the current standard treatment for selected patients with peritoneal surface spread of appendiceal primary tumors. Similar strategies for other patients with peritoneal surface malignancy such as peritoneal carcinomatosis from colon or gastric cancer, peritoneal sarcomatosis, or peritoneal mesothelioma should be pursued.

#### INTRAPERITONEAL HYPERTHERMIC PERFUSION (IPHP)

**Peritonectomy and intraperitoneal hyperthermic perfusion (IPHP): a strategy that has confirmed its efficacy in patients with pseudomyxoma peritonei.** Deraco M, Baratti D, Inglese MG, Allaria B, Andreola S, Gavazzi C, Kusamura S. Department of Surgery, Melanoma and Sarcoma Unit, National Cancer Institute of Milan, Italy. *Ann Surg Oncol.* 2004 Apr;11(4):393-8

- **BACKGROUND:** Pseudomyxoma peritonei (PMP) is a rare disease with a poor prognosis characterized by a complete redistribution of mucin within the peritoneal cavity. The aim of this multicentric study was to evaluate the survival, morbidity, toxicity, and mortality of patients with PMP treated by cytoreductive surgery (CRS) with intraperitoneal hyperthermic perfusion (IPHP).
- **METHODS:** Thirty-three patients with PMP (21 males and 12 females) were enrolled in a phase II clinical trial. One patient underwent surgery twice because of disease recurrence. CRS was performed with peritonectomy procedures. The closed abdomen technique was employed for IPHP with the use of cisplatin (25 mg/m<sup>2</sup>/L) plus mitomycin-C (3.3 mg/m<sup>2</sup>/L) for 60 minutes under hyperthermic conditions (42.5 degrees C).
- **RESULTS:** Thirty-one patients (92%) were optimally cytoreduced. Five-year overall survival, progression-free survival, and locoregional progression-free survival rates were 97%, 43%, and 59% respectively. Grade II and grade III morbidity was observed in 5 patient (15%) and 6 patients (18%) respectively. There was one treatment-related death (3%), 21 days after treatment.
- **CONCLUSIONS:** CRS associated with IPHP permitted complete tumor removal with an acceptable morbidity and mortality for patients with PMP. This study confirms the efficacy of the combined treatment in terms of long term survival and local disease control.

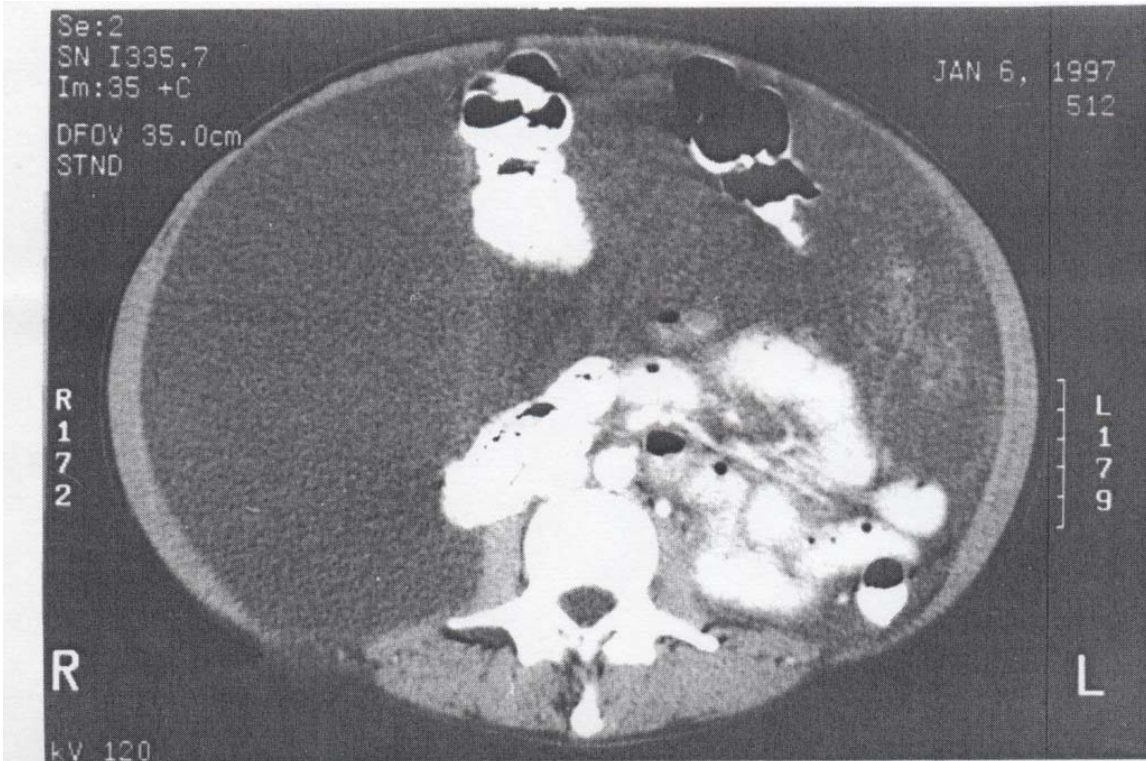
The Sugarbaker technique combines complete surgical tumor removal (complete cytoreduction) with intraoperative heated chemotherapy, and is followed by postoperative intraperitoneal chemotherapy. The operation takes about 10 hours and includes:

- removal of the right hemicolon, spleen, gallbladder, greater omentum and lesser omentum
- stripping of peritoneum from the pelvis and diaphragm
- removal of the uterus and ovaries
- removal of the rectum in some cases

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PMP1 CT image through the mid-abdomen in a patient with pseudomyxoma peritonei. The small bowel is compartmentalized by the large volume of mucinous ascites. The patient had a prior greater omentectomy, so that the "omental cake" was not present. Both small and large bowel show continued function. There are no air-fluid levels, and there is no dilation of the small bowel suggesting an absence of obstruction.

