

Pleural Extension of Mucinous Tumor in Patients With Pseudomyxoma Peritonei Syndrome

Sophie R. Pestieau, MD, Jesus Esquivel, MD, and Paul H. Sugarbaker, MD, FACS

Background: Pseudomyxoma peritonei syndrome is a rare disease arising from perforation of an adenoma of the appendix. The syndrome is characterized by progressive accumulation of mucinous fluid and tumor within the abdomen and pelvis. Although this tumor is only superficially invasive and does not metastasize, it is a fatal disease. Extra-abdominal spread of pseudomyxoma peritonei is a rare occurrence, with few reports in the medical literature. This review focuses on pleural extension of mucinous tumor in patients with pseudomyxoma peritonei syndrome.

Methods: From December 1983 to April 1999, all patients who underwent cytoreductive surgery for pseudomyxoma peritonei syndrome were assessed for pleural involvement at the time of the presentation or follow-up. Clinical information on these patients, including chest computed tomographic scan, was retrospectively reviewed. The mechanisms of extension of mucinous tumor from peritoneal cavity to pleural surface and the results of treatment were of special interest.

Results: Twenty-three of 426 patients (5.4%) showed pleural extension of pseudomyxoma peritonei syndrome. In four patients (17%), extension into the chest occurred before cytoreductive surgery. In 18 patients, the pleural space was entered during a subdiaphragmatic peritonectomy; and, in 12 patients, extension of disease from peritoneal to pleural space occurred. In six patients (26%), surgical interventions were required to excise tumor that had invaded the hemidiaphragm; and, in the six other patients (26%), there was a minor penetration during subphrenic peritonectomy, which was closed immediately. Finally, in seven patients (30%), the mechanism of spread was unknown. Twelve patients were treated for pleural thoracotomy. Eight patients had an attempt to completely eradicate pleural mucinous tumor, and five patients are currently disease free in the chest (22%); four of these five had intrapleural cytoreduction plus intrapleural chemotherapy. The median survival for all 23 patients is 55 months.

Conclusion: Pleural spread of pseudomyxoma peritonei syndrome may be a direct result of cytoreductive surgery and the subphrenic peritonectomy procedure. In some patients, dissecting mucinous tumor may infiltrate through the diaphragm and result in pleural extension. Pleural extension of pseudomyxoma peritonei syndrome carries a poor prognosis. Intrapleural chemotherapy combined with cytoreductive surgery may be of considerable value in treatment and prevention of disease dissemination; it should be considered when pleural extension of mucinous tumor is feared or confirmed at the time of cytoreductive surgery.

Key Words: Intraperitoneal chemotherapy—Intrapleural chemotherapy—Mucinous adenocarcinoma—Pseudomyxoma peritonei syndrome.

Pseudomyxoma peritonei syndrome is a rare disease characterized by progressive accumulation of mucinous tumor and ascites throughout the abdomen and pelvis.^{1,2} The primary tumor is an adenoma of the appendix that

perforates and spreads mucus-producing cells throughout the abdomen, which, over time, fills the peritoneal cavity.³ Although this tumor is only superficially invasive and does not metastasize, it is a fatal disease. The space within the abdomen and pelvis required for function of the gastrointestinal tract becomes replaced by massive amounts of mucinous tumor, which leads to bowel obstruction and, subsequently, death from starvation.

The traditional surgical approach to pseudomyxoma peritonei syndrome involved repeated operative proce-

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From the Washington Cancer Institute, Washington Hospital Center, Washington, DC.

Address correspondence and reprint requests to: Paul H. Sugarbaker, MD, FACS, Washington Cancer Institute, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010; Fax: 202-877-8602.

dures in which the goal was to resect and evacuate as much mucinous tumor as possible. Debulking surgery in the absence of intraperitoneal chemotherapy resulted in a median survival of 2 years and a 5-year survival of about 5%.⁴ Treatment of an increasing number of patients has led to a better understanding of the disease. The pathophysiology of pseudomyxoma peritonei syndrome is characterized by tumor distribution that follows the flow and resorption of peritoneal fluid, which results in massive accumulation in the greater omentum and undersurfaces of the diaphragms. In addition, large tumor deposits will accumulate, by gravity, in the pelvis.^{5,6}

Contributions to the improved outcome of patients with pseudomyxoma peritonei syndrome have occurred as a result of a complete clearance of all tumor and mucus from the peritoneal cavity in a single operation; this complete cytoreduction, by using peritonectomy procedures, is used in combination with heated intraoperative intraperitoneal chemotherapy and early intraperitoneal chemotherapy directed at microscopic residual disease. Five-year survival with the combined treatment approaches 85%.¹

The success of these new treatment strategies within the peritoneal cavity and a prolonged survival has led to the identification of a previously unrecognized site of mucinous tumor progression within the pleural cavity. The focus of this study is 23 patients who had a pleural extension of mucinous tumor. The mechanism of disease penetration through the diaphragm and treatments used within the thoracic cavity are reviewed.

MATERIALS AND METHODS

From December 1983 to April 1999, 426 patients with the diagnosis of pseudomyxoma peritonei syndrome underwent cytoreductive surgery. All patients who had an entrance into the pleural space or chest computed tomographic (CT) documentation of pleural involvement are included in this study. The mean follow-up was 36 months (range, 2–101 months), and the median follow-up was 39 months. No patients were lost to follow-up. The clinical course of these patients was examined during four time periods. The precytoreduction events occurred before a definitive operation when the diagnosis of pseudomyxoma peritonei syndrome was made. Before, or at, this time no surgical procedure had been performed on the undersurface of either hemidiaphragms. The operative events occurred during the definitive cytoreduction. During this time period, patients were classified into two groups according to the operative procedure performed on the undersurface of the diaphragm. The first group had a stripping of the hemidiaphragm, which led to a small perforation. This pene-

tration site was immediately sutured in a watertight fashion. The second group had tumor invasion of the diaphragm, so that a major resection of its central tendon was necessary. The third time interval represents the time when pleural involvement was diagnosed in the patients who had no known diaphragm penetration. The fourth time interval includes the treatment of pleural extension.

RESULTS

There were 23 (5.4%) of 426 patients with pseudomyxoma peritonei syndrome who developed pleural extension of mucinous tumor. In all 23 patients, extension to the thoracic cavity was documented by chest CT scan; in 13, it was confirmed by biopsy. Pleural extension was unilateral in 21 patients (91%) and involved the right side in 12 patients and the left side in 9 patients. The extension was bilateral in two patients (9%). Of 426 patients treated for pseudomyxoma peritonei syndrome, penetration of the diaphragm occurred at the time of cytoreduction in 18 patients (4.2%) and pleural extension was documented at a later time in 12.

The mean age was 49 years, with a range of 34 to 79 years. There were 13 females and 10 males. The median interval between abdominal cytoreduction and the diagnosis of pleural extension was 19 months (range, 0–76 months). Extension to the pleural cavity was always on the same side as diaphragm violation, except for one patient who presented with bilateral pleural extension. By CT scan, the disease involved the pleura and the pleural space only. There was no evidence of mediastinal adenopathy or parenchymal metastases. Patients presented with either pleural thickening ($n = 5$), up to 10 intrapleural tumor nodules ($n = 15$), more than 10 nodules ($n = 2$), or bilateral involvement ($n = 1$).

Mechanisms of Pleural Extension of Mucinous Tumor

Four of the 23 patients had pleural involvement at the time of diagnosis of their disease (Fig. 1). They showed CT evidence of pleural pseudomyxoma before the definitive cytoreduction. In one patient, congenital pleuroperitoneal

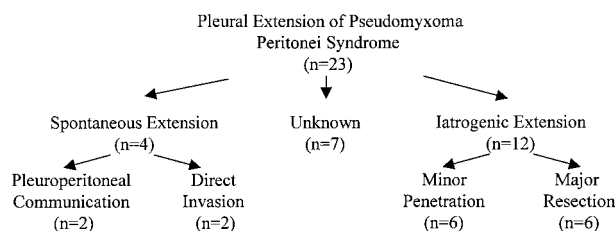


FIG. 1. Mechanisms of pleural extension of mucinous tumor.

communication of the right hemidiaphragm allowed tumor to pass from the peritoneal to the pleural cavity. In a second patient, a nonaggressive histological type of tumor had passed through the diaphragm at the time of diagnosis. Diaphragm fenestration on the left side is highly suspected in this patient. In two patients, the diagnosis was an intermediate grade and a more aggressive type of mucinous tumor. These patients had copious amounts of fluid in the right pleural space at the time of diagnosis. A resection of the entire central tendon of the hemidiaphragm was required at the time of cytoreduction.

Twelve patients who developed CT evidence of pseudomyxoma extension to pleural surfaces had known penetration of the diaphragm at the time of cytoreduction (Fig. 1). These 12 patients are from a group of 18 who had entrance into the pleural space at the time of subdiaphragmatic peritonectomy. Six patients had a minor penetration during subdiaphragmatic peritonectomy, which was immediately sutured in a watertight fashion; six required resection of the central tendon of the hemidiaphragm because of invasive subdiaphragmatic tumor.

In seven patients, pleural pseudomyxoma developed during the follow-up period (Fig. 1). These patients did not have thoracic extension by chest CT scan at the time of diagnosis of pseudomyxoma peritonei syndrome; neither was there penetration at the time of cytoreductive surgery. Despite a presumably intact diaphragm, pleural extension occurred. The mechanism of disease extension through the hemidiaphragm could not be established with certainty. One suspects that unrecognized minor disruption of the diaphragm related to surgical trauma was responsible.

The mean time interval between cytoreductive surgery and diagnosis of pleural extension of mucinous tumor was shorter for the 12 patients with known penetration of the hemidiaphragm (21 months; range, 3–76 months) than for the 7 patients with no known penetration (28 months; range, 3–67 months).

Treatment

The pleural extension of pseudomyxoma peritonei did not progress as an indolent disease. By chest CT scan, there was disease expansion in all 23 patients. Treatment was initiated in 12 patients (Fig. 2). Four developed symptoms and had a thoracotomy for palliation of dyspnea within 15 months (range, 0–42 months) of the diagnosis of pleural involvement. Eight had asymptomatic disease in the absence of peritoneal recurrence and had a thoracotomy with intrapleural chemotherapy (n = 7), or without intrapleural chemotherapy (n = 1) within 6 months (range, 0–17 months). Five patients, four treated with intrapleural chemotherapy and one with localized disease treated by cytoreduction only, are currently free of disease with a follow-up range of 2 to 42 months.

Treatment of pleural extension of mucinous tumor from pseudomyxoma peritonei syndrome is associated with high morbidity and mortality. In this current review, two patients died after thoracotomy for treatment of their pleural involvement. Two of these deaths were within a month of thoracotomy. One died of *Aspergillus fumigatus* pneumonia and one died of congestive heart failure.

Eleven patients had combined peritoneal recurrence and pleural extension. These patients did not have defin-

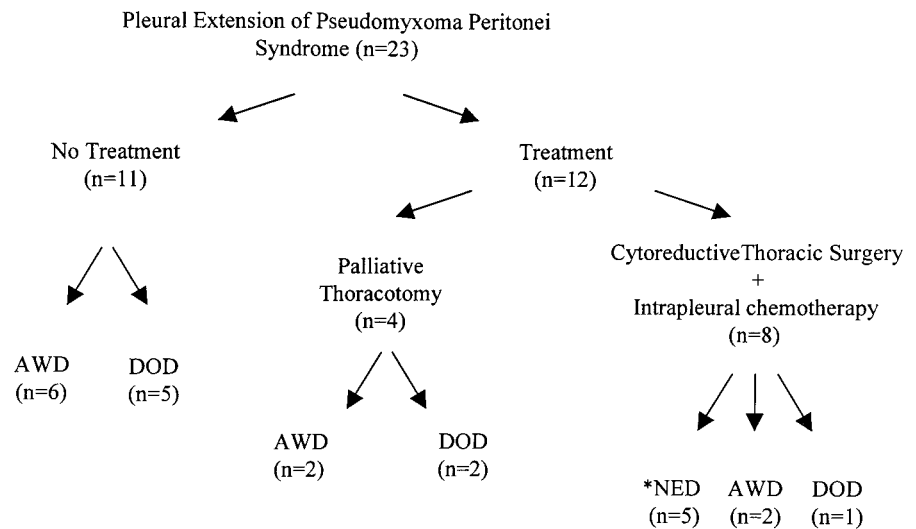


FIG. 2. Treatment and follow-up of patients with pleural extension of mucinous tumor. * No intrapleural chemotherapy in one patient with localized extension on the diaphragmatic surface. NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease.

itive intrathoracic treatment but had systemic palliative chemotherapy.

The median survival of patients with pleural extension of mucinous tumor was 55 months. The survival curve of the 23 patients is shown in Fig. 3.

DISCUSSION

After a redistribution phenomenon, mucinous tumor cells accumulate on abdominal surfaces, which absorb peritoneal fluid, such as the greater omentum and the undersurface of the diaphragm.^{5,6} It is, therefore, very common that patients with extensive peritoneal involvement will also present with a thick layer of tumor on the undersurface of the diaphragm. Pleural pseudomyxoma occurred as a direct extension through the diaphragm in all 23 patients. Twelve had iatrogenic extension as a result of diaphragm penetration, four had spontaneous extension, and seven had an unknown mechanism of extension.

With spontaneous pleural involvement the disease was present by CT scanning before surgical interventions beneath the diaphragms. In two patients, intermediate grade mucinous tumor, in large volume, had invaded the central tendon of the diaphragm and extended into the pleural space. Over time, tumor extension by dissecting mucus can result in an infiltrative process that carries tumor from the peritoneal surfaces to other sites. The pleural environment was as supportive of mucinous tumor cells as was the peritoneal cavity, which led these cells to follow the same uninhibited growth pattern.² In one patient, congenital diaphragmatic fenestrations were documented (Pestieau SR, Wolk R, Sugarbaker PH, unpublished data, 1999). In another patient, we assumed that access of mucinous tumor cells to the left pleural cavity occurred by a similar mechanism. In both these patients with adenomucinosis, thoracic

cytoreduction combined with intrapleural chemotherapy achieved a disease-free status in the pleural space.

Improvement in surgical techniques and the development of peritonectomy procedures for the undersurface of the diaphragm have enabled surgeons to achieve a complete cytoreduction of the disease. However, in selected cases, this may change the natural history of the disease. Penetration of the diaphragm barrier, either by stripping of its parietal peritoneum or by excising its tendinous midportion, allows the passage of pseudomyxoma peritonei syndrome cells into the pleural cavity. A 75% frequency of pleural extension of pseudomyxoma peritonei when the pleural space was entered has previously been reported.² This is iatrogenic extension of the disease. Tumor cells present within the peritoneal cavity may be disseminated into the pleural cavity during surgery. It is an important observation that requires adjustment of therapy for future patients. Tumor cells entrapped in the pleural cavity are not exposed to perioperative intraperitoneal chemotherapy, because the defect caused in the diaphragm, either by penetration or excision, was closed before the infusion of chemotherapy. The possibility of pleural spread after entering the diaphragm suggests that it is crucial to keep the diaphragms intact during subphrenic peritonectomy. What to do in cases of dense involvement of the tendinous part of the diaphragm may be a dilemma for surgeons. The choice between resection with entrance into the pleural space or residual disease on the hemidiaphragm may be difficult. At institutions where intraoperative chemotherapy is available, this treatment should, in our opinion, be used to treat the pleural surfaces after partial resection of the hemidiaphragm.

Minor penetrations of the diaphragm, which were immediately sutured in a definitive manner to prevent thoracic extension of this disease, resulted in dissemination in six patients. In our opinion, this approach should no longer be recommended if penetration of the diaphragm occurs during subphrenic peritonectomy. In most patients, this resulted in disease progression within the pleural space. In our current practice, the minute hole into the chest is enlarged to allow the surgeon's hand to enter the chest through the diaphragm. Heated intraoperative chemotherapy, after a complete cytoreduction, is used to treat the pleural as well as the peritoneal surfaces. Alternatively, a chemotherapy perfusion of the chest through a thoracotomy tube or separate thoracotomy could be recommended. Further follow-up is necessary before new treatment strategies can be assessed critically.

Intrapleural chemotherapy has been used and reported as an adjuvant treatment to surgery in cases of pulmonary malignancy with pleural dissemination. It appeared safe with minimal morbidity. Matsuzaki et al.⁷ reported the

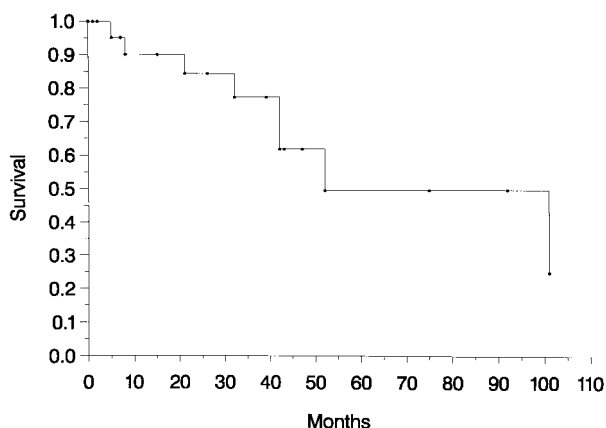


FIG. 3. Kaplan-Meier survival distribution of 23 patients with pseudomyxoma peritonei syndrome from onset of pleural extension.

administration of intrapleural perfusion of heated chemotherapy for the treatment of malignant pleural seeding or effusion from lung cancer. It consisted of an irrigation of the pleural space with heated (43°C) saline solution that contained cisplatin. It was performed in 12 patients who had undergone surgical resection. The median survival of the 12 patients treated with intrapleural heated chemotherapy was 20 months, whereas 7 patients who were treated by surgery alone had a median survival of 6 months. Ichinose et al.⁸ also reported the use of intraoperative intrapleural cisplatin in seven patients with pleural carcinomatosis, which was found at the time of thoracotomy for non-small-cell lung cancer. The intraperitoneal lavage was given after completion of intrathoracic surgical procedures. This treatment was well tolerated, without adverse side effects, with a follow-up range of 6 to 29 months. A larger series of 32 lung cancer patients with carcinomatous pleuritis, reported by Doi et al.,⁹ were treated by pulmonary resection in combination with postoperative intrathoracic chemotherapy. Local relapse was detected in only four cases, and the median survival period was 25 months, which was significantly longer than the 15 months in the resection-alone group.⁹ Higashiyama et al.¹⁰ also reported a case of invasive thymoma with pleural dissemination successfully treated with intrapleural heated chemotherapy after pleuropneumectomy.

Treatment of pleural extension of mucinous tumor from pseudomyxoma peritonei syndrome is associated with high morbidity and mortality. Prevention of direct pleural extension of mucinous tumor at the time of diaphragm penetration is important. At present, heated intraoperative chemotherapy directed toward the eradication of microscopic residual disease is recommended for use in the pleural as well as the peritoneal cavity. Timely use of this treatment may be of great benefit in the control of tumor cells that have contaminated the pleural surfaces. In our opinion, prevention of pleural pseudomyxoma is most reliably accomplished by the timely infusion of intraoperative chemotherapy into the pleural space whenever the diaphragm has been penetrated. Although the number of patients in whom intraoperative intrapleural chemotherapy has been used at the time of diaphragm penetration is small and the follow-up is short, it is thought that this suggested treatment should decrease the recurrence rate or prevent the development of pleural extension of mucinous tumor in such cases.

To use intrapleural chemotherapy, combined intraperitoneal and intrapleural perfusion is recommended. After the abdominal cytoreduction is completed, a Tenckhoff catheter is positioned for infusion and four suction catheters positioned for drainage. The abdomen is manually lavaged along with infusion and drainage of heated intraoperative

chemotherapy by using mitomycin C. By enlarging the defect created in the diaphragm, infusion of chemotherapy in the pleural space can be achieved in the same time period as the intraperitoneal chemotherapy. The entire parietal and visceral pleura can be uniformly treated by chemotherapy and hyperthermia, which, therefore, prevents tumor cell entrapment. In this case, the outflow from the thorax is maintained by a suction catheter within the chest. An alternate potential treatment is the administration of intrapleural chemotherapy through a separate thoracotomy. However, by enlarging the already present defect in the diaphragm, safe access to the pleura is allowed, which enables the chemotherapy wash to be administered throughout the entire pleural cavity, without the need for a thoracotomy incision.

In conclusion, pleural extension of mucinous tumor may occur spontaneously or as a result of cytoreductive surgery. In both cases, the prognosis is poor. Prevention of disease extension is therefore crucial. Intrapleural chemotherapy combined with pleural cytoreductive surgery should be performed whenever pleural dissemination is suspected.

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