



Case report

Progression of perforated cystadenoma of the appendix to pseudomyxoma peritonei over 18 years. A case report

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ABSTRACT

Introduction and importance: In the past, mucinous appendiceal neoplasms (MAN) greater than 2 cm in diameter were treated by a right colon resection. New data shows that treatment options are to be determined by the histopathologic grade of the appendiceal tumor and the condition of the wall of the appendix (intact vs. breached).

Case presentation: A 39-year-old woman had an incidental diagnosis of a low-grade appendiceal mucinous neoplasm (LAMN) at the time of a hysterectomy. The appendiceal tumor had small quantities of mucus surrounding an enlarged appendix. No tumor cells were seen in the mucus by histologic study. The patient was placed in follow-up. Eighteen years later she required treatment for advanced pseudomyxoma peritonei.

Clinical discussion: When 5 different histopathologic types of MAN are considered with an intact vs. perforated wall of the appendix, four different treatment options develop. With LAMN and well or moderately differentiated mucinous appendiceal adenocarcinoma (MACA), the patient does not require operative intervention if the wall of the appendix is intact. If mucus or mucus plus tumor cells are identified outside the appendix an intervention is indicated. In patients, as the one presented, in whom only small amounts of mucus are outside the appendix, surveillance may be recommended.

Conclusions: In patients with a diagnosed low-grade MAN, dissemination to regional lymph nodes is rare. Dissemination to the peritoneal space places the patient at risk to develop pseudomyxoma peritonei. As this case report illustrates, if surveillance is recommended, long-term follow-up is required.

1. Introduction

The management of mucinous appendiceal neoplasms (MAN) has changed on several occasions over the past 3 decades. Prior to 2004, the standard of surgical management for a tumor 2 cm or greater was a right colon resection with an ileocolic lymph node dissection. Rationale for the right colectomy with lymph node dissection was the possibility of occult positive lymph nodes. As data was gathered on large numbers of patients with MAN with or without right colon resection, no difference in survival was apparent [1]. Subsequently, several other manuscripts produced the same data [2–5]. The need for right colon resection as treatment for MAN is now determined by two factors. The histopathologic grade of the appendiceal tumor and the condition of the wall of the appendix (intact vs. breached). Regarding histopathology, the appendiceal tumors have by Peritoneal Surface Oncology Group International (PSOGI) and American Joint Commission on Cancer (AJCC) eighth edition, five different grades: Low-grade appendiceal mucinous neoplasm

(LAMN), mucinous appendiceal carcinoma (MACA), well, moderately or poorly differentiated or mucinous appendiceal carcinoma with signet ring cells (MACA-S) [6]. If the resected appendix shows MACA poorly differentiated or MACA-S, a right colectomy with complete ileocolic lymph node dissection is indicated in order to remove possible occult regional lymph node involvement [6]. With LAMN or with MACA well or moderately differentiated, the risk of occult ileocolic lymph node metastases is less than 5% [7]. With these 3 histologic grades the second factor, intact vs. breached wall of the appendix, becomes a determinant for treatment [8]. Even though LAMN and well or moderately differentiated MAN have a low incidence of lymph node metastases, peritoneal metastases occur regularly if tumor cells from the lumen of the appendix are able to enter the peritoneal space. The surgeon at the time of appendectomy and the pathologist at the time of pathologic assessment of the resected appendiceal specimen must carefully assess the condition of the wall of the appendix. Also, mucus within the peritoneal space is assessed for volume, distribution and presence vs. absence of

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epithelial cells. Any suspicious nodules on the periappendiceal tissues must be sampled.

If no evidence for perforation of the wall of the appendix exists, this group of patients do not need an operative intervention to treat peritoneal metastases. However, if the wall of the appendix has been breached, patients require a reoperative procedure to provide prophylaxis against peritoneal metastases. The optimal intervention is radical appendectomy with appendiceal and ileocolic lymph node sampling, greater omentectomy and hyperthermic intraperitoneal chemotherapy (HIPEC) [9,10]. In this case report a patient with LAMN and a small quantity of extra-appendiceal acellular mucus was followed for 18 years. After this prolonged surveillance, treatment of advanced pseudomyxoma peritonei was required [11].

2. Materials and methods

Data on this patient was prospectively recorded and then retrospectively reviewed at an academic institution. This research work has been reported in line with the SCARE 2020 criteria [12]. This study was registered as a case report on the www.researchregistry.com website with UIN 7412.

The peritoneal cancer index (PCI) was determined prospectively at the time of abdominal exploration [13]. The PCI was an assessment of the distribution and extent of peritoneal dissemination in 13 abdominopelvic regions recorded by the surgeon at the time of abdominal exploration with the assessment continued throughout CRS. The PCI was determined by visual inspection of the abdominal and pelvic parietal and visceral peritoneal surfaces. All biopsies must be sent as separate specimens for histologic study. If the specimen plus adherent mucus is totally acellular mucus, the tumor nodule is reported in the PCI.

A completeness of cytoreduction (CC) score was determined on the patient [13]. This score was determined by the surgeon at the completion of the CRS. A CC score of 0 indicated no visible evidence of disease. A CC score of 1 indicated tumor nodules less than 2.5 mm in diameter without a confluence of disease at any site. A CC score of 2 indicated tumor nodules between 2.5 mm and 2.5 cm in the absence of a contiguous layer of disease at any anatomic site. A CC score of 3 indicated tumor nodules greater than 2.5 cm or a confluence of disease layered out at any site within the abdomen or pelvis.

3. Case presentation

August 1983: With a diagnosis of severe menorrhagia associated with a uterine leiomyoma, this 39-year-old patient was taken to surgery for hysterectomy by a gynecologist. Through a Pfannenstiel incision an abdominal exploration was performed. An enlarged uterus with leiomyomas was visualized. The remainder of the exploration was normal except for the appendix. It was elongated and dilated to 1.5 cm in diameter. The mesentery of the appendix was coated by mucoid material. The appendix was removed and subjected to cryostat section. No abnormal tissue was detected histologically. Following hysterectomy and appendectomy the abdomen was closed.

Pathologic examination of the appendix revealed an appendix 7 cm in length and 5 mm in diameter. There was a swelling of the mid-portion of the appendix to 9 mm. The mucus accumulation associated with the appendix noted in the operating theater remained attached to the specimen was approximately 3 cm in diameter. A second mucoid aggregate closely associated with the appendix also 3 cm in diameter was removed at surgery. No gross perforation of the appendix was evident. Histologic sections of the appendix revealed a cavity filled by a clear mucoid fluid. The wall of the appendix showed replacement of the lamina propria by columnar mucus-secreting epithelium. The mucoid mass showed foci of calcification with new bone formation. No atypical cells were present. At the tip of the appendix was a separate 3 mm nodule identified as a carcinoid tumor.

The final pathologic diagnosis was cystadenoma of the appendix

with involvement of the serosal surface of the appendix by mucoid exudate. Although gross perforation was not described, perforation could not be ruled out because of the acellular mucus documented outside of the appendix. A small carcinoid tumor was separate from the cystadenoma.

After much discussion the patient was placed into follow-up which included CT and carcinoembryonic antigen (CEA) tests. In January of 1997 (14 years after appendectomy), CT showed a 2.5 cm cyst on the right adnexa.

January 1997: A laparoscopic examination was performed by a gynecologic oncologist. This showed a 2.5 cm cyst on the right Fallopian tube. Mucoid excrescences were diffusely present on right and left ovary and Fallopian tube, on the peritoneal surface of the bladder, on the undersurface of the right hemidiaphragm and on the omentum. An estimated 100 cc of mucoid fluid was present in the cul-de-sac. A laparoscopic resection of Fallopian tubes and ovaries, removal of mucoid fluid and biopsy of multiple peritoneal implants was performed. Because the Fallopian tubes and ovaries were adherent to the posterior peritoneal surfaces and the prior hysterectomy site, a retroperitoneal dissection was necessary. Histologic examination showed multiple sites of LAMN consistent with pseudomyxoma peritonei.

With the major extent of tumor removed laparoscopically, the patient was again placed into follow-up with CT and CEA assays. The patient maintained herself in excellent physical and mental condition.

November 2000: CT of chest, abdomen and pelvis with oral and intravenous contrast was interpreted as increasingly abnormal. The liver and spleen were normal but fluid was present within the porta hepatis and in the right subhepatic space. Anterior to the right psoas muscle was a 4 × 2 cm fluid-filled mass. The pelvis was filled by an abnormal high attenuation fluid.

At age 51, the patient was asymptomatic but requested definitive treatment of the pseudomyxoma peritonei syndrome.

November 2000: The patient underwent an 8-h cytoreductive surgical procedure with HIPEC mitomycin C and EPIC 5-fluorouracil by a surgical oncologist specially trained in peritoneal surface malignancy. This procedure required a peritonectomy of the right and left hemidiaphragms, splenectomy, greater and lesser omentectomy, cholecystectomy, pelvic peritonectomy, and rectosigmoid colon resection with low stapled anastomosis. Bilateral ureterolysis was required because ureters were fixed in retroperitoneal fibrosis. The umbilicus and laparoscopic port required resection because they contained mucinous tumor. The peritoneal cancer index was 25. The completeness of cytoreduction score was 1.

Histopathologic examination showed metastatic low-grade mucin-producing tumor compatible with pseudomyxoma peritonei. Lymph nodes resected from the mesoappendix and right inguinal region were negative for tumor.

The patient had no postoperative adverse events. There was a 21-day hospitalization required in order for bowel function to return to near normal. No further treatments were recommended.

December 2021: The patient now at age 78 has no evidence of disease and normal bowel and bladder function.

4. Discussion

4.1. Update of the histopathologic terminology

In 2001, Ronnett and colleagues defined three groups of mucinous appendiceal neoplasms (MAN). They were diffuse peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinoma (PMCA) and a smaller group of patients with intermediate features (PMCA-I) [14]. Ronnett's descriptions of the tumor histology and associated survival resulted from study of multiple peritoneal metastases specimens of tumor gathered at the time of CRS. Misdraji et al. in 2003 focused on the primary appendiceal tumor. Also, 3 histologic groups were defined. The low-grade appendiceal mucinous neoplasm (LAMN), the mucinous

appendiceal adenocarcinoma (MACA), and a discordant group. In 2018, Valasek and Pai updated the pathologic description of MAN. They described LAMN, a high-grade appendiceal mucinous neoplasm (HAMN) lacking an infiltrative pattern, and MACA. The mucinous adenocarcinoma group showed 4 grades: well differentiated, moderately differentiated, poorly differentiated and poorly differentiated with signet ring cells [11]. Throughout the remainder of this case report, the updated American Joint Committee on Cancer (AJCC) classification will be utilized.

4.2. Duration of follow-up not yet well defined

This patient had 14 years from identification of a “cystadenoma of the appendix” with acellular mucus globules outside of the appendix until laparoscopic identification of pseudomyxoma peritonei syndrome. It was 18 years from appendectomy until definitive cytoreductive surgery with HIPEC and EPIC. The implications of this case report are obvious for follow-up patients who have a MAN diagnosed by appendectomy and then, without further treatment, are placed into follow-up. This minimally aggressive mucinous neoplasm may progress very slowly over decades. If an early diagnosis of progression of pseudomyxoma peritonei is to occur meticulous radiologic and tumor marker follow-up is mandatory.

4.3. Optimal radiologic follow-up

The patient in this case report was followed for 18 years with serial CT plus CA19–9 and CEA tumor markers. As the radiologic expertise to reliably image MAN has improved, MRI with diffusion-weighted imaging has emerged as the radiologic procedure of choice for long-term follow-up of pseudomyxoma peritonei [15]. The MRI depicts more tumor deposits and smaller tumor deposits than CT [16]. Also, the radiation exposure that builds up with repeated CT examinations does not exist with MRI. The expense of MRI and the time required for the examination is greater. Currently, if both options are available MRI is the favored radiologic study for early detection of disease progression of MAN in a patient under long-term surveillance.

4.4. Avoid extensive debulking surgery prior to definitive treatment

In the patient presented, after 18 years of slow progression of disease, cytoreductive surgery, HIPEC and EPIC were able to provide an additional 21 years of disease-free survival. Although pseudomyxoma can recur after 18 years, our database does not show any recurrences at 21 years. This patient is likely to be cured of pseudomyxoma peritonei. Her long-term survival has occurred despite a PCI of 25 [13]. There are several reasons for the favorable surgical result in the patient presented with cytoreductive surgery and perioperative chemotherapy. First, even though this disease progressed over 18 years, a transition from low-grade to higher-grade disease did not occur [17]. Second, an extensive debulking causing deep entrapment of mucinous tumor within scar tissue did not occur. The peritoneum is the first line of defense against infection but also against invasion of tumor. As shown by our data on prior surgical score, the interventions that occur prior to definitive cytoreductive surgery plus perioperative chemotherapy have a profound effect on outcome [13]. Sugarbaker and Chang showed that the most detrimental clinical feature for survival of a MAN patient requiring an extensive cytoreduction was a prior diagnosis of ovarian cancer [18]. These women had an error in diagnosis of ovarian cancer but, in reality had MAN. The diagnosis of ovarian cancer led to an extensive cytoreductive surgery with pelvic and para-aortic lymph node dissection. This resulted in high prior surgical score. Guaglio et al. published that women who had a misdiagnosis of ovarian cancer had reduced survival and increased adverse events associated with the urinary tract at the time of definitive CRS [19]. A special problem was ureteral injury after prior cytoreduction for ovarian cancer.

4.5. Four different recommendations for management of patients with mucinous appendiceal neoplasms

In Table 1, the clinical and histopathologic features to be considered in the decision to observe or to proceed with definitive treatment of an appendiceal neoplasm are enumerated. In group 1, the clinical situations that are of such low risk for progression of pseudomyxoma that further follow-up and intervention is not indicated. If the LAMN is not perforated progression is extremely unlikely [8]. If the tumor is not ruptured with the appendectomy procedure and the margin on the caecum is negative, the process can be regarded as a benign mucocele.

In Table 1 group 2, the LAMN has perforated but the mucus in the immediate vicinity of the appendix is of small volume and does not contain epithelial cells. The condition is usually considered of such low risk that follow-up is indicated.

However, there are some clinical situations in which follow-up in the absence of further intervention may not be the optimal plan. If reliable follow-up with radiologic studies plus tumor markers CEA and CA19-9 will not be available over several years, a different recommendation may be prudent. Most likely, if continued reliable contact with the patient is not possible, a definitive intervention is indicated.

In Table 1 treatment group 3, a definitive intervention in the absence of bowel resection is recommended. If the perforated LAMN has mucus outside the appendix that contains epithelial cells, an intervention should be recommended. Also, if the mucus that has leaked from the LAMN mucocele is of moderate to large volume intervention is indicated. This recommendation persists even if no epithelial cells are identified within extensive mucus harvested at the time of appendectomy.

The current treatment recommendation for maximal protection from a perforated low-grade MAN from progression to pseudomyxoma peritonei in the future is as follows. The minor cytoreduction procedure requires greater omentectomy and definitive resection of all visible mucinous deposits. Also, a careful inspection of the prior appendectomy site, resection of residual mesoappendix and the peritoneum in the immediate vicinity of the appendix is indicated. This has been referred to as a radical appendectomy [20]. If there are suspicious appendiceal or ileocolic lymph nodes apparent they should be subjected to cryostat

Table 1
Clinical and histopathologic features to be considered in optimal management of an appendiceal mucinous neoplasm at risk for pseudomyxoma peritonei. (LAMN = low-grade mucinous appendiceal neoplasm, MACA = mucinous appendiceal cancer, HIPEC = hyperthermic intraperitoneal chemotherapy).

Group	Recommendation	Indicated Features
Group 1	No definitive intervention or intensive follow-up indicated:	
1		<ul style="list-style-type: none"> LAMN of any size with appendiceal walls intact resected without trauma to the specimen and a negative margin of resection.
Group 2	No definitive intervention but intensive follow-up indicated:	
2		<ul style="list-style-type: none"> LAMN that is perforated with small amounts of mucus outside the appendix. There is an absence of epithelial cells in the periappendiceal mucus.
Group 3	Definitive intervention with radical appendectomy, HIPEC and intensive follow-up indicated:	
3		<ul style="list-style-type: none"> LAMN that has perforated the appendix with epithelial cells in the periappendiceal mucus. LAMN with large amount of acellular mucus pooling in the right paracolic sulcus, right retrohepatic space or within the pelvis. MACA with well or moderate differentiation removed by radical appendectomy with negative lymph nodes in the mesoappendix.
Group 4	Definitive intervention with right colon resection and intensive follow-up indicated:	
4		<ul style="list-style-type: none"> MACA with high-grade histopathology MACA with signet ring cells Adenocarcinoma with neuroendocrine features (adenocarcinoid) Involved lymph nodes.

section. This minor cytoreductive surgery is followed by the HIPEC procedure usually with a mitomycin C chemotherapy solution. Following HIPEC, the abdomen is closed. This definitive treatment carries an extremely low morbidity and mortality but should not be recommended unless it is indicated. The intervention can be performed through a laparotomy incision by laparoscopy [21–24].

In none of the possible interventions from LAMN or from well or moderately differentiated MACA is a prophylactic right colon resection indicated because the incidence of occult lymph node metastases is so low that resection of the ascending colon, terminal ileum and adjacent ileocolic lymph nodes should not occur. However, if mucinous peritoneal metastases is layered out on the terminal ileum, right hemicolectomy may be necessary for complete cytoreduction. If the resected neoplasm shows a MACA of low or of moderate differentiation, right hemicolectomy is not routine. Sugarbaker showed that the incidence of occult positive lymph nodes with low or moderate grade appendiceal neoplasm is 5% or less. A radical appendectomy with sampling of the 2–4 lymph nodes in the mesoappendix is adequate to rule out occult disease in ileocolic lymph nodes [7]. The use of HIPEC is mandatory to provide prophylaxis against progression of mucinous peritoneal metastases. If doubt exists regarding an adequate margin on the appendiceal stump, a limited cecal resection is recommended.

In treatment group 4 of Table 1, because there is a high risk of occult lymph node metastases a limited right colon resection and ileocolic lymph node dissection is indicated. The MAN recommended for right colon resection shows a poorly differentiated histopathology, signet ring cells, or adenocarcinoid features. With perforation of the appendix complete cytoreduction including right colectomy and HIPEC are indicated.

Duration of surveillance

Recently, a large multi-institutional study of 217 patients, perforation of a LAMN with mucus or mucus plus epithelial cells outside the appendix were recommended for radiologic surveillance for 3 years [25]. The patient presented in this manuscript had 18 years between diagnosis of LAMN with mucus but not epithelial cells outside the appendix. Long-term (decades) of follow-up may be necessary to optimize the management of these MAN patients with low-grade disease.

5. Conclusion

Treatment groups 1 through 4 can be described for MAN based on the gross and microscopic pathology of the resected appendiceal specimen and an assessment of the dissemination of mucoid tumor into the peritoneal space. The size of the MAN used in the past to select appropriate management strategies is no longer recommended. Misdrjaji and colleagues established that the size of the mucinous tumor has no prognostic implications [8]. As more patients are recommended for follow-up only (Treatment group 2), a proper duration for the intensive follow-up needs to be defined.

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Ethical approval

MedStar Health Institutional Review Board has determined that a case report of less than three [3] patients does not meet the DHHS definition of research (45 CFR 46.102(d)(pre-2018)/45 CFR46.102(l)(1/19/2017)) or the FDA definition of clinical investigation (21 CFR 46.102(c)) and therefore are not subject to IRB review requirements and do not require IRB approval.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

This study was registered as a case report on the www.researchregistry.com website with UIN 7412.

Guarantor

Paul H. Sugarbaker, MD

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Paul H. Sugarbaker is responsible for the case report, discussion and selection of references.

Declaration of competing interest

None.

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