Low-Grade Pseudomyxoma Peritonei Behaving as a High-Grade Disease: A Case Series and Literature Review

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Posted Date: 7 September 2023

doi: 10.20944/preprints202309.0493.v1

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Article

Low-Grade Pseudomyxoma Peritonei Behaving as a High-Grade Disease: A Case Series and Literature Review

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Abstract: Patients with low-grade appendiceal mucinous carcinomas (LAMN) treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have a favorable prognosis. A subgroup presents a clinically aggressive course with disease progress despite any treatment. The purpose of the study is to report the experience with clinically aggressive LAMN patients treated by the same team and review the literature. Four patients with clinically aggressive LAMN were reviewed. Clinical and histopathological characteristics were re-examined. Recurrences and the time of recurrence, as well as the survival time, were recorded. There were 4 men with clinically aggressive LAMN treated with CRS plus HIPEC. One of them underwent CC-0 surgery, two underwent CC-1, and one CC-3 surgery. All received systemic chemotherapy after surgery. Recurrence was recorded in 3 patients in 4-23 months after initial treatment. Two of them underwent secondary CRS. Three patients died of disease recurrence in 13-23 months, and one is alive with disease relapse 49 months after initial surgery. LAMN was identified in both initial specimens and in specimens of reoperation. The prognosis of LAMN patients treated with CRS plus HIPEC is favorable. A small number of them presents clinically aggressive course unresponsive to any treatment. Molecular and genetic studies are required to identify this group of LAMN patients who have an unfavorable prognosis.

Keywords: LAMN; cytoreductive surgery; HIPEC; pseudomyxoma peritonei

1. Introduction

Peritoneum is the largest membrane of the human body. In men, it is a closed space; in women, there is a connection between the peritoneal space and external genitalia. The peritoneum is divided into parietal and visceral. For peritoneal tumors, a distinction is made between primary and secondary tumors [1–4].

Pseudomyxoma peritonei (PMP) is a very rare secondary tumor. Limited cases of primary PMP without distal metastases have also occurred. Diagnosis is not pathological but clinical, defined by mucinous appearance, usually leading to abdominal distension and bowel obstruction. In the vast majority, the mucinous tumor originates from the appendix and, in a few cases, from the ovaries, the pancreas, the gallbladder, the bowel, or finally, from an unknown site. The mucinous tumor is not frequently obvious because of the large volume of the disease. Pseudomyxoma peritonei syndrome is a clinical entity originating from an appendiceal mucinous tumor [1]. This is characterized by the redistribution phenomenon in which there is the accumulation of large-volume mucinous tumors at the greater omentum, the undersurface of the hemidiaphragm, the pelvis, and the left paracolic gutter, and the absence of tumors from sites with intense motility, such as the small bowel [2].

Most patients are asymptomatic, while a small proportion present with symptoms of appendicitis. Although Werth was the first to use the term pseudomyxoma in 1884 in a case of ovarian neoplasm. Robert Michaelis Von Olshausen in 1937, proposed the possible hypothesis of pathophysiology and fully described the disease. Nowadays, the classic theory about the distribution

 doi:10.20944/preprints202309.0493.v1

of PMP is a redistribution phenomenon. This results from free-floating epithelial cells' movements into peritoneal fluid gravity, progressively leading to the "Jelly-Belly" condition. According to the redistribution phenomenon theory, organs and surfaces of the peritoneal cavity could be involved with tumor cells [1–3].

Pathology was reported by Ronnet et, al in 1995 and defined PMP into three entities. Disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and an intermediated hybrid morphological type (PMCA-I/D) [4–7].

This classification was based on the histology of the peritoneal disease than the primary tumor, which was unusual in oncology [4]. Later, various medical societies attempted to classify PMP according to current oncologic requirements. The current classification defined that the peritoneal disease and the appendiceal tumor should be reported separately [4,6]. The peritoneal disease is classified into the following categories; 1) acellular mucin, 2) low-grade mucinous carcinoma peritonei (LAMN), 3) high-grade mucinous carcinoma peritonei (HMAC) or peritoneal mucinous carcinomatosis (PMCA), and 4) high-grade mucinous carcinoma peritonei with signet-ring cells (PMCA-S). The term PMP should be avoided with the acellular mucin unless the syndrome is clinically obvious [5]. All the above histolopathological categories have a profound impact on survival, provided CRS and HIPEC are utilized [7]. For patients with LAMN and PMP, a large PSOGI multi-centric study showed that 5- and 10-year survival rate was 81% and 70% respectively [8]. This means that LAMN is a disease of low aggressiveness and the patients with LAMN treated properly with CRS plus HIPEC are expected to survive for long.

Due to the rarity of PMP, consensus had a significant impact in the management of the disease. Currently, there are 5 up to dated consensus teams around the world coming from PSOGI, CCWG, CACA, LARPD, and BSSO. Since the first consensus published by PSOGI, a combination of cytoreductive surgery procedures (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has provided a treatment option and is regarded as a standard of care. However, the role of HIPEC remains controversial.

In 2004, Mohamed et al. studied 11 cases of disseminated peritoneal adenomucosinosis (DPAM) that succumbed to a rapidly progressive disease [9]. The purpose of the study is to report 4 patients with LAMN treated with extensive cytoreduction and HIPEC that were found to have clinically aggressive PMP.

2. Materials and methods

2.1. Clinical features

Our study group consisted of 4 patients with a pathological diagnosis of DPAM.

Despite the initial cytoreduction combined with HIPEC and intravenous chemotherapy, all these patients recurred with invasive disease. Patients were matched for age, gender, and co-morbid factors (smoking history, alcohol consumption, diabetes, cardiovascular disease). Co-morbid factors (smoking history, alcohol consumption, diabetes, cardiovascular disease) were recorded in detail, and then the patients were assessed according to ASA classification. Prior surgical score (PSS), peritoneal cancer index (PCI), and completeness of cytoreduction score (CC) have been validated.

Many cytoreductions were recorded. In patients with PSS-0, diagnosis of carcinomatosis is obtained with biopsies, while in patients with PSS-1, previous laparotomy without resections. PSS-2 indicated laparotomy with limited resections, and PSS-3 consisted of patients with full cytoreduction procedures (more than 5 regions) [10].

2.2. Cytoreduction protocol

All patients were treated according to the standardized protocol of cytoreductive surgery and HIPEC. Complete CRS may require six steps of peritonectomy, while the target is to eliminate all tumor deposits in the peritoneal cavity. Peritonectomy procedures may involve greater omentectomy with splenectomy, left and/or right upper quadrant peritonectomy, lesser omentectomy with

 doi:10.20944/preprints202309.0493.v1

cholecystectomy, pelvic peritonectomy with rectosigmoid or subtotal colectomy, and total or partial resection of the stomach. The procedure was performed by the same surgical team.

Every patient is provided with thromboprophylaxis and perioperative antibiotics. The cytoreductive procedure was performed with the patient in a lithotomy position and through a midline incision extended from the xiphoid to the pubis. After lysis of the adhesions, the extent of the peritoneal disease was recorded according to PCI. The tumor volume was assessed as small and large volume. Implantations with maximal diameter < 0.5 cm were considered as small volume tumors, while implantations with maximal diameter > 0.5 cm or confluent of any diameter were considered as large volume tumors. The resection of the peritoneal disease was possible using the standard peritonectomy procedures [11]. After surgical resection of the tumor, the completeness of cytoreduction was assessed using the CC-score. CC-0 surgery indicated patients without macroscopically visible residual tumors. CC-1 surgery indicated patients with residual tumors that had a maximal diameter < 0.25 cm. CC-2 indicated residual tumor > 0.25 cm and < 2.5 cm, while CC-3 indicated residual tumor > 2.5 cm [10,12]. After tumor resection, HIPEC was performed for 90 min at 42.5–43◦C. HIPEC was administered using the open abdominal (Coliseum) technique. A heater circulator with two roller pumps, one heat exchanger, one reservoir, an extracorporeal system of two inflow and two outflow tubes, and 4 thermal probes was used for HIPEC (Sun Chip, Gamida Tech, France). A prime solution of 2-3 liters of Normal Saline or Ringer's Lactate was instilled prior to the administration of the cytostatic drug and as soon as the mean abdominal temperature reached 40◦C the cytostatic drugs were instilled in the abdomen. Mit-C (15mg/m^2) and doxorubicin (15mg/m^2) were used in HIPEC and 5-FU (400mg/m^2) plus Leucovorin (20mg/m^2) were given intravenously. Bi-cavitary HIPEC was performed in those cases where the diaphragm was opened during the subdiaphragmatic peritonectomy procedure. The reconstruction of the continuity of the gastrointestinal tract was made after the completion of HIPEC. Proximal stoma was always performed if more than two anastomoses should be protected. All patients remained in the ICU for at least 24 h until hemodynamic stabilization. The morbidity and in-hospital mortality were carefully recorded. Patients with CC-2 or CC-3 surgery were treated with systemic chemotherapy after initial treatment.

All patients were followed up every 3-4 months for the first year after initial treatment and every 6 months later. The follow-up included physical examination, thoracic and abdominal CT or MRI or PET-CT scan, hematologic and biochemical examinations, and tumor markers (CEA, CA 19-9, and CA-125). Recurrences and the sites of recurrence were recorded in detail.

All specimens were examined in detail. The subtype of the tumor, the degree of differentiation, the number of resected, and the infiltrated lymph nodes were recorded, as well as the site and the depth of implantations.

All patients signed an informed consent, and the Ethical Committee of the Hospital approved the study.

2.3. Statistical Analysis

Means with standard deviation or medians with interquartile range were reported for continuous variables, while frequencies with percentages were used for categorical variables in the descriptive statistics of patient demographics and disease characteristics. Statistical analysis was performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA).

3. Results

Our study group consisted of 4 male patients (9.8%), among 41 LAMN patients treated by our team from 2005-2018. The mean age of diagnosis is 48.5 years (ranges 40-63).

No patient had a history of smoking or alcohol consumption, but one of them had intermittent atrial fibrillation. Two patients had been treated with neo-adjuvant chemotherapy with oxaliplatin, 5-FU, and Leucovorin, which offered significant benefits by reducing the extent and the tumor volume, as shown by CT scanning. The average PSS score was 0.5, the median PCI score was 30 (SD 5.39), and the mean cytoreduction procedure duration was 8.2 hours. Upon initial diagnosis, all

 doi:10.20944/preprints202309.0493.v1

patients were assessed as PSS-1. However, two patients who underwent reoperation were assessed as PSS-3.

One patient underwent CC-0 surgery, which included bilateral subdiaphragmatic peritonectomy procedure, greater omentectomy with splenectomy, lesser omentectomy, cholecystectomy and resection of the omental bursa, bilateral lateral peritonectomy, right colectomy, pelvic peritonectomy, and total gastrectomy with a loop ileostomy which was reconstructed four weeks later.

Two patients underwent CC-1 surgery because we assumed that a small volume residual tumor would be left behind very close to the mesenteric edge of the small bowel, although no visible tumor was identified after resection. Both patients underwent bilateral subdiaphragmatic peritonectomy procedure, greater omentectomy plus splenectomy, cholecystectomy with omental bursectomy, bilateral lateral peritonectomy procedure, pelvic peritonectomy, and subtotal colectomy. One of them underwent additional total gastrectomy and loop ileostomy that was reconstructed five weeks later. The other patient underwent additional segmental intestinal resection. All the above patients received HIPEC. The last patient underwent CC-3 surgery without HIPEC because he had a large volume tumor in and around the hepatoduodenal ligament and was strictly adherent to the inferior vena cava, which made a potentially curative resection. This patient was offered palliative subtotal colectomy, greater omentectomy with splenectomy, and ileostomy. The mean duration of all surgical operations was 8.2 hours. Histopathologically, all the resected specimens were infiltrated by mucin. In 2 specimens, the infiltration of the peritoneal surfaces of the small and the large bowel and the mesentery was visible. In one of the specimens, four infiltrated lymph nodes were retrieved, while in the other three, the resected lymph nodes were normal. The mean total number of resected lymph nodes was 100 (2-159). Two patients were complicated by urine infection.

Two patients were re-operated because of recurrence. In one of them who had undergone CC-0 surgery, recurrence was recorded in 23 months. The patient underwent CC-0 surgery plus HIPEC in which the left rectus abdominal muscle was resected with a tumor originating from its upper part and invading the left part of the muscle entirely. The disease relapsed within six months after the second cytoreduction. The other one who had undergone CC-1 surgery presented with recurrence in 6 months. The patient underwent segmental intestinal resection, which was assessed as CC-3 surgery and died 23 months after initial surgery. All resected specimens were LAMN. Currently, one patient is still alive with disease recurrence 49 months after initial surgery. The other three patients died of disease 13, 19, and 23 months after initial surgery. Both patients that had undergone CC-1 surgery presented multiple segmental intestinal obstructions which were not amenable to surgical management. The follow-up period spanned 50 months with a median survival rate of 21 months (SD 13.75) and a 25% 5-year survival.

4. Discussion

Classification of PMP has been a topic of controversy for many years. Currently, the most widely accepted classification of PMP is presented in Table 1 [13–15].

Lesion	Terminology
Mucin without epithelial cells	Accelular mucin
PMP with low-grade histological features	Low-grade or disseminated peritoneal adenomucinosis (DPAM)
PMP with High-grade histological features	High-grade or Peritoneal mucinous carcinomatosis (PMCA)
PMP with signet ring cells	High-grade or Peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S)

Cytoreductive surgery and perioperative intraperitoneal chemotherapy are considered as the standard of care for PMP. Histological characteristics of the tumor are crucial in the appropriate treatment strategy, while invasive histological types require more aggressive surgical interventions.

In the past, PMP was thought to be a benign disease treated by debulking and evacuation of mucinous ascites [13–15]. The disease rapidly progressed, requiring aggressive debulking surgical operations followed by various adjuvant treatments that achieved prolonged survival in 20-30% [13,14]. The patient with PMP may remain asymptomatic even for many years, but the disease almost always recurs. The patients ultimately die of intestinal obstruction. Repeated debulking operations become ineffective because the disease recurs, usually more aggressively. The lysis of the adhesions is usually impossible, or it results in bowel injury and subsequent fistula formation [16]. Cytoreductive surgery in combination with perioperative intraperitoneal chemotherapy has been established as the standard treatment of PMP. The addition of early postoperative intraperitoneal chemotherapy (EPIC) has been shown to provide additional survival in patients with LAMN [17]. In PMP, survival depends mainly on the tumor grade. The majority of long-term survivors are those with LAMN [3,7]. According to Ronnett classification low-grade tumor-cells do not have adhesion molecules on their surface in contrast to high-grade tumor cells. As a consequence, the low-grade cancer emboli cannot seed peritoneal surfaces with intense motility. On the contrary, the high-grade tumor cells are usually found on the peritoneal surfaces, even on those with intense motility, such as the small bowel [18]. The current PMP classification is different than Ronnett's classification (table 1) for mucinous tumors, although LAMN resembles histopathologically to DPAM [3–5]. DPAM cancer emboli are never found adherent to peritoneal surfaces with intense motility in contrast to LAMN emboli that are usually found strictly adherent on them. Huang et al. have studied the impact of CRS plus HIPEC followed by EPIC in LAMN. The LAMN tumors were classified as those with neoplastic epithelium present (LAMN-NEP) and those with neoplastic epithelium absent (LAMN-NEA). They found that the median survival for LAMN-NEP patients was significantly lower if they were treated with CRS plus HIPEC+EPIC compared to those treated with CRS plus HIPEC while the median survival for LAMN-NEA patients showed a trend to better survival if they were treated with CRS plus HIPEC+EPIC, although not statistically significant [17]. The field of Tumor Biology has been extensively documented, revealing significant differences in survival rates and clinical outcomes. The MUC1 and MUC2 antigens have a significant impact on a patient's prognosis, particularly when it comes to MUC1 expression, which is often associated with poor outcomes [9].

In the majority of cases, PMP is usually asymptomatic, especially in the initial stages. When mucus builds up, it can lead to discomfort and pain in the abdomen, which may worsen with time. Regarding preoperative evaluation, numerous articles suggest that serum tumor markers may have a predictive role. Patients with high levels of CA 19-9 are more likely to experience recurrence, whereas there is a clear correlation between CEA serum levels and the PCI index.

Computed tomography (CT), has been the most common imaging in the detection of PMP. Sensitivity depends on the tumor size and location of tumor nodules. Although sensitivity ranges from 59-94%, most experts suggest that CT evaluation is the preferable imaging modality. Magnetic resonance imaging (MRI) can be used as an alternative imaging modality, but it has limitations in cases where there is involvement of the small bowel and hepatic hilar lesions [18–20].

There is limited data available regarding the role of PET-CT. However, PET-CT is primarily beneficial for evaluating the extent of cytoreduction and systemic metastases disease [18].

The Role of laparoscopic surgery in diagnosis remaining controversial. There are authors who suggest that laparoscopic evaluation is feasible and safe but have also limitations [18,19].

In our study, the proportion of clinically aggressive LAMN cases was higher than that reported by Mohamed [9]. Recurrence developed very soon after treatment. The histopathologic characteristics of the disease remained the same although the clinical course was particularly aggressive. Survival of patients with mucinous peritoneal carcinomatosis does not exceed 14% [7]. In our study 3 out of 4 patients died in less than 2 years after initial surgery, despite systemic chemotherapy.

All previous observational reports have shown that overall survival is significantly better in low-grade PMP tumors [8,21–23]. The series of patients in the study of Mohamed et al. included DPAM tumors with a clinical course of an invasive process that very soon relapsed despite CRS plus perioperative chemotherapy [9]. The authors attempted to correlate the tumors' aggressiveness with

 doi:10.20944/preprints202309.0493.v1

the expression of mucin antigens MUC1 and MUC2 but they found no difference compared to a series of control patients and they concluded that there is a subset of patients with low-grade PMP presenting with clinically aggressive course that need further investigation at a molecular and genetic level. A prognostic gene signature for LAMN metastatic to the peritoneum was identified in 2015 by Levine EA et al. This implies that such genetic signatures in the subset of more aggressive LAMN have significantly different clinical outcomes even after aggressive therapy consisted of CRS and HIPEC. The value of pathologic analysis defining the aggressive subset is important and needs to be identified. However the genetic signature improves the ability for prognosis [24].

Today the treatment of PMP patients in specialized centers involved in CRS and perioperative intraperitoneal chemotherapy has shown that the overall survival has been significantly improved [8,21–23,25–27]. Centralization of PMP patients is required and has been suggested since 1994 by PH Sugarbaker [28].

Treatment

The goal of the treatment is to completely remove the visible tumor and use hyperthermic intraperitoneal chemotherapy (HIPEC). Proper patient positioning is crucial in order to access the abdomen. Preferable is a moderated lithotomy position. Long midline incision from Xiphisternum to the pubis is usually performed while the disease extension is assessed via PCI index. This system divides the abdomen into 9 anatomical areas, with 4 further areas in small bowel mesentery. A score of 0-3 is given for each of the 13 areas (0=no tumor, 1=<0.5cm, 2=0,5-5cm, 3=.5cm), and a total score (0-39) is calculated. We start with right parietal peritonectomy with gonadal exposure and right diaphragmatic peritonectomy to mobilize the liver. Similar approaches followed on the left side. Radical great omentectomy was also performed inside gastroepiploic vessels while the spleen is carefully assessed for disease. Lesser omentectomy is usually carried out. Ovaries and gallbladder are routinely removed. In some limited cases, distal gastrectomy may be performed. If achieving complete CRS is not feasible, our strategy should be to perform a maximum tumor debulking (MTD).

Completeness of cytoreduction was assessed at the end of the operating procedure with CC score. (CC0=complete, CC1=disease<0,25cm, CC2=0,25-2,5cm, CC3=>2,5cm). Cytoreductive surgery should be discontinued when dealing with significant small bowel serosa involvement. There are several conditions that can hinder the possibility of undergoing additional surgery. These include infiltration of the pancreatic surface, ureteric obstruction, liver metastases, and the requirement for gastric resection. Another reason may be the significant involvement of the liver pedicles.

Once the cytoreduction is finished, we proceed with the intra-operative hyperthermic chemotherapy as mentioned in our cytoreduction protocol previously. Possible anastomoses are performed after HIPEC protocol, while low rectal anastomoses protected usually by ileostomy.

HIPEC regimens

Oxaliplatin is a platinum complex agent with proven toxicity in colon and appendiceal neoplasms, used in various HIPEC protocols. It appears with high possibility of bleeding. In clinical practice, it is used in Elias high dose Oxaliplatin Regimen, Glehen medium Dose Oxaliplatin Regimen, and Wake Forest University Oxaliplatin Regimen [18,19].

Mitomycin C is an alkylating agent. It is mainly used in peritoneal malignancy, colorectal cancer, appendiceal tumors, ovarian cancer, gastric cancer and peritoneal mesothelioma. Current applies in Sugarbaker specimen, Dutch High Dose Triple Dosing Mitomycin C Regimen, American Society of Peritoneal Surface Malignancy Low Dose [18,19].

Doxorubicin is an antracyclin agene mainly used in breast cancer, bladder cancer, lymphoma and peritoneal cancer. Current applies in combination with platinum agents.

HIPEC procedure is usually followed by perioperative chemotherapy. There are many studies that suggest combined systemic chemotherapy plus HIPEC increase the 5-year survival of patients in high-grade or signet ring cell histology patients [18,19].

 doi:10.20944/preprints202309.0493.v1

Follow up

A recurring disease was observed in 25% of patients even after the initial CC0 resection. For low-grade cases, CT scans three months after surgery and then annually were conducted for the first six years, while high-grade disease cases received frequent screenings. Serum tumor markers are important for detecting recurrence and as a prognostic tool. At present, there are no guidelines that are universally accepted about the follow-up period [9,17–21].

5. Conclusion

Pseudomyxoma peritonei (PMP) is a rare condition with a poor prognosis. Early recognition is crucial for improving oncological outcomes. The optimum treatment strategy includes cytoreductive surgery followed by HIPEC procedure. These procedures are complex and performed only in experience centers. If these procedures are not able to be performed, debulking surgery may be considered as an alternative option.

A small number of patients present a clinically aggressive course, although the majority may survive for long provided, they undergo CRS and perioperative intraperitoneal chemotherapy. The identification of these patients is challenging but encouraging results have been shown through molecular and genetic studies. Further studies are required for the identification of this subgroup of patients.

It is important to centralize patients in dedicated centers to prevent high rates of morbidity and mortality.

The management of PMP was greatly influenced by consensus guidelines due to its rarity. While global recommendations may assist us in developing effective strategies, there is still a need for additional research to improve oncological outcomes.

Author Contribution: A.T. was responsible for designing and supervising the study, collecting the data, and writing the manuscript. P.B, D.K and A.K, contributed to writing the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were waived for this study due to the study's retrospective design.

Informed Consent Statement: All patients are required to sign a consent form and be provided with complete information regarding their medical condition, including the proposed treatments, potential risks, and benefits.

Data availability statement: Datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest: The authors declare no conflict of interest.

Abbreviations

LAMN	Low Grade appendiceal mucinous carcinomas
CRS	Cytoreductive Surgery
HIPEC	Hyperthermic intraperitoneal chemotherapy
PMP	Pseudomyxoma peritonei
DPAM	Disseminated peritoneal adenomucocinosis
PMCA	Peritoneal mucinous carcinomatosis
PMCA I/D	Hybrid type of mucinous carcinomatosis
HMAC	High Grade mucinous carcinoma peritonei
PSOGI	Peritoneal Surface Oncology Group International
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
PET	Positron emission tomography
EPIC	Early Postoperative intraperitoneal Chemotherapy

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