Pathology of Mucinous Appendiceal Tumors and Pseudomyxoma Peritonei

Veena Ramaswamy¹

Received: 7 January 2016 / Accepted: 2 March 2016 / Published online: 19 March 2016
© Indian Association of Surgical Oncology 2016

Abstract Neoplasms of the appendix are rare, but because of their unusual presentation and unpredictable biologic behavior, it is important to diagnose them correctly. Mucinous tumors account for 58 % of malignant tumors of appendix in SEER database and the remaining are carcinoids. The mucinous appendiceal tumors have a potential to spread to the peritoneum and viscera in the form of gelatinous material with or without neoplastic cells resulting in Pseudomyxoma peritonei. (PMP) PMP is a clinical entity that has a unique biological behavior and can arise from seemingly benign tumors to frankly malignant ones. Several classifications exist for PMP of which Ronnet's classification has been the most popular. In 2010, the WHO proposed a 2 tier classification that classified PMP as either low grade or high grade based on the presence of mucin, cytological and architectural features. According to this classification when the underlying cause for PMP is an appendiceal tumor it is always a mucinous adenocarcinoma rather than a mucocoele or adenoma and these terms should no longer be used. This system of classification helps in predicting the behavior of the tumor and proper treatment strategies. The understanding of the pathogenesis of the disease has also improved with identification of newer biomarkers and molecular genetic alterations. IHC markers CK 20, CDX2 and MUC2 are found to be positive in these tumors in addition to KRAS mutation and loss of heterozygosity in some gene loci. Proper histopathologic classification and predicting the tumor behavior requires a close interaction between the pathologist and the surgeon. The use of the combined modality treatment of cytoreductive surgery (CRS) and hyperthermic intraperitoneal

chemotherapy (HIPEC) has led to a 5-year survival ranging from 62.5 % to 100 % for low grade, and 0 %-65 % for high grade disease. This article focuses on the etiopathogenesis, clinical behavior, diagnosis and classification of mucinous tumors of the appendix and pseudomyxoma peritonei.

Keywords Pseudomyxoma peritonei · Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · Immunohistochemistry · Cytokeratin

Introduction

Neoplasms of the appendix are rare, found in less than 2 % of surgically removed appendices [1]. They account for only 1 % of intestinal neoplasms. Broadly, they can be classified as epithelial and non-epithelial tumors (comprising of endocrine tumors, sarcomas and lymphomas) [2]. Carcinoid tumors are the most common, comprising over 40–50 % of appendiceal neoplasm in most series followed by adenocarcinomas. Most primary appendiceal adenocarcinomas are of the mucinous type, arise from an adenomatous polyp or serrated adenoma and frequently present with the Pseudomyxoma peritonei syndrome [3–5] [6].

Appendiceal neoplasms are distinct from colorectal carcinoma and tend to have a less aggressive natural history [7, 8]. Peritoneal spread is seen in a majority of these patients whereas lymphatic spread is only seen in 2 % of the patients [9, 10] Mucinous appendiceal tumors have wide spectrum of clinical behavior ranging from almost benign looking tumors that progress very slowly to high grade adenocarcinomas that recur rapidly and have a poor 5 year survival. Some indolent appearing tumors can also be aggressive.

Several classification systems with inconsistent histologic criteria have added to the controversy around these tumors. Tumors confined to the appendix have an excellent prognosis.

✉ Veena Ramaswamy
rveenatra@gmail.com

¹ SRL LAB, Fortis Hospital, No 154/9, Opposite IIM-B, Bannerghatta Road, Bangalore 560076, India

The mucinous tumors can penetrate deeply into and through the appendicular wall, spreading through the peritoneal cavity in the form of gelatinous deposits, resulting in a condition called pseudomyxoma peritonei (PMP), with a malignant potential [9]. PMP is diagnosed by the presence of free or organized mucin with or without neoplastic cells in the peritoneal cavity and the typical pattern of redistribution. [11].

Gelatinous material in the peritoneal cavity was first described by Werth in 1884 and was termed PMP because the material was not composed of true mucin [12]. Its origin was believed to be rupture of a pseudo mucinous cyst of the ovary. Frankel in 1901 reported the first case of PMP secondary to a ruptured cyst of appendix [13].

94 % of cases of PMP develop from a mucinous tumor of the appendix [14–17]. About 20 % of patients with a mucinous neoplasm of appendix develop PMP [18]. PMP has also been reported from primary mucinous carcinoma of ovary, adenocarcinoma of gall bladder, stomach, colorectum, pancreas, fallopian tubes, urachus, lung and breast [19].

PMP occurs in 7th decade of life and more common in females with a M: F ratio of 1:4. It is an unexpected finding in about 2 of every 10,000 laparotomies. In comparison, adenocarcinoma of the appendix has an annual incidence of 0.2/1,00,000 and in 0.1 % of appendectomies. The age at presentation is between 6th and 7th decade with median age at presentation of 65 years. It appears to be more common in males than females [20].

Etiology and Pathogenesis

The adenoma-carcinoma sequence is found to occur in appendix as in rest of colon [21]. Some adenocarcinomas arise from goblet cell carcinoids [22].

Adenocarcinoma of appendix is found more often in association with Chronic Ulcerative colitis or associated colonic neoplasia. Dysplastic epithelium seen in ulcerative colitis and in colonic malignancy or polyps are thought to be the source of the disease [20].

The neoplastic process starts in the appendix with neoplastic transformation of the appendiceal goblet cells and subsequent formation of a mucinous tumor. The tumor cells maintain their level of mucin expression while proliferating. Hence the overall level of mucin rises. This is followed by intraluminal accumulation of mucin and eventual development of a mucocele. A small perforation or rupture will result in escape of mucin and cells into the peritoneal cavity [23]. These tumor cells lack cell surface adhesion molecules, exfoliate easily and passively circulate with the peritoneal fluid and redistribute throughout the peritoneal cavity. As a result the tumor implants and mucin collections form at the peritoneal fluid reabsorption sites and at dependent portions within the abdomen and pelvis, to create characteristic pattern of

PMP (Fig. 1). Bulky deposits are often found within the greater omentum, lesser omentum, and beneath right hemi diaphragm. In addition, due to gravity, the cells also deposit in cul-de-sac pouch of Douglas, right retro hepatic space, left abdominal gutter, and the fossa created by the ligament of Treitz become filled with mucoid tumor mass [25, 26].

Consistently there is absence of tumor deposits on the peritoneal surfaces of intestine and mesentery due to continuous peristaltic activity, with the exception of antrum of stomach and pylorus, ileo-caecal valve region and recto sigmoid colon. These three regions are retroperitoneal and hence fixed.

Accumulating mucin increases intra-abdominal pressure and compresses visceral organs. Furthermore, extensive involvement of the peritoneal surface promotes viable inflammation and fibrotic response with the development of bowel obstruction as a fatal complication [25, 26].

Mucinous deposits comprise of acellular mucin or cells with varying degrees of atypia with or without invasion. Fibrosis and/or a desmoplastic reaction is often present.

A mucinous appendiceal tumor that shows mucin with or without epithelial cells on the serosal surface or free in the peritoneal cavity puts the patient at an increased risk of developing pseudomyxoma peritonei, which usually happens at an interval of 2–5 years and these patients need to be on an intense follow up [27, 28]. Dissection of the appendiceal wall by acellular mucin and rupture with spillage of mucin into the peritoneal cavity may occur in benign lesions [1, 3, 12, 29–31]. Thus, acellular mucin in the wall or in the immediate vicinity of the appendix may raise the suspicion of an invasive tumor, but it is not diagnostic [32–34].

Role of mucin

Mucins are a group of high molecular weight heavily glycosylated proteins also called MUC proteins. They are differentially expressed in the specialized epithelial cells of mucosal surfaces in a relatively organ and cell type specific manner. There are two types of mucins – Membrane associated mucins and secreted mucins. The membrane associated mucins communicate information about extracellular conditions, mediate intracellular signal transduction and contribute to morphology and behavior of cells. The secreted mucins act as physical barrier for epithelial surfaces, and are a part of defensive system at the mucosal surfaces. There are two types of secreted mucins – gel forming and non-gel forming. Colonic mucus is a gel forming mucin that has two layers – an outer layer with gut flora and an inner dense layer firmly attached to the epithelium and bacteria free. MUC2 is specifically secreted in the small intestine and colon. The inner layer of MUC2 is uncleaved while the outer layer is cleaved proteolytically [35].

In PMP, mucin is ectopically secreted and increasingly deposited in peritoneal cavity where it is unable to degrade or

Fig. 1 Schematic representation of the events resulting in the development of PMP. The pathologic process starts with a neoplastic transformation of the appendiceal goblet cells and development of a primary mucinous tumor (1). Overproduction of mucin and obstruction of the appendiceal lumen lead to the development, and subsequent rupture, of a mucocoele (2). shedded tumor cells gain access to the peritoneal cavity and circulate with the peritoneal fluid (3). Accordingly, tumor cells redistribute and accumulate within the dependent portions of the peritoneal cavity (3*, downward arrows) as well as at the peritoneal fluid reabsorption sites (3**, upward arrows). Reproduced with permission from Ref 24.

drain away forming voluminous gels over months and years. Most of the tumor cells are surrounded by the mucin coat that allows them to move freely, disseminate and redistribute within the peritoneal cavity. This coating also acts as a protective shield against immune recognition and chemotherapy. MUC2, MUC5AC and MUC5B are gel forming mucins that are found in PMP. MUC2 is known as PMP specific mucin [29, 36]. MUC2 is more extensively glycosylated, more voluminous and hence there is abundant mucin collection with an average mucin:cell ratio of >10:1. It is concluded that PMP is a disease of MUC2 secreting goblet cells and hence MUC2 could serve as a marker for PMP [29, 36]. O Connell showed that primary ovarian mucinous tumors express MUC5AC while solitary appendiceal mucinous tumors express MUC2 and MUC5AC [36].

Genetic susceptibility

Patients with Familial Adenomatous Polyposis coli (FAP) are at an increased risk of developing mucinous Adenocarcinoma of appendix. The risk is not known for patients with HNPCC, Peutz-Jegher's polyps and Juvenile polyposis syndrome. KRAS mutation has been observed in 70 % of appendiceal adenomas, mostly in codon 12 and 13. In addition, loss of heterozygosity for 5q22, 6q, 17p13 and 18q21 with allelic imbalance of tumor suppressor gene are implicated. In cases of Pseudomyxoma Peritonei, LOH at one or two polymorphic microsatellite loci is seen in approximately 50 % of cases [37]. This is considered an indication of monoclonality.

Clinical Presentation

Most cases of adenocarcinoma of appendix usually present with symptoms of acute appendicitis. Remaining patients present with abdominal mass.

The presentation of PMP depends on progression of the disease. 30–50 % of the patients present in advanced stage with abdominal distention, ascites and intestinal obstruction [38]. Localized disease often presents with abdominal pain of acute appendicitis, presumed cholecystitis, and pelvic mass due to mucinous tumors of ovary in 50–80 % of patients. [27]. Inguinal hernia is one of the presenting symptoms in men. Hence when a mucoid fluid is encountered at the time of hernia repair, the fluid should be recovered and hernia sac should be examined microscopically. [39, 40].

It has been proved in several studies through molecular genetic analysis and immunohistochemistry that the synchronous ovarian mass in patients with adenocarcinoma of appendix is often a secondary involvement rather than a second primary in the ovary. PMP arising from a primary ovarian tumor is usually a borderline mucinous tumor or invasive mucinous carcinoma. It is also supported by the fact that these tumors are more often seen on the right side or are bilateral. Mucinous cysts of the spleen are rarely seen [30, 31, 41–45].

Diagnosis

Pre-operative diagnosis of mucinous adenocarcinoma of appendix and that of PMP can be done by careful evaluation of

the following findings; these are useful in cases presenting with mass or PMP and not as acute appendicitis.

- Ultrasonography and Fine Needle aspiration – USG is not conclusive as the mucinous ascites resembles free fluid in the peritoneal cavity. FNA may give a false negative result when there are no cells seen and a scanty mucinous material is obtained [46].
- CT scan – Is most widely used. High density of mucin, characteristic pattern of accumulation and extent of disease for proper pre-operative planning and prognostic purpose is used [47].
- MRI – For localizing the tumor, T1 and T2 weighted MRI is more sensitive in distinguishing between ascitic fluid and mucin [48].
- PET CT – Most useful for predicting peritoneal dissemination and pre-operative evaluation of pathologic grade and potential for complete cytoreduction. The role is still controversial.
- Circulating tumor markers – CEA and CA 19.9 tumor markers are found to have high level in adenocarcinoma of appendix with PMP. CA 125 is also found to be high but with ovarian involvement. Its diagnostic utility is still debated. These markers are important prognostically and also useful for follow up of patients undergoing CRS and HIPEC [47, 48, 49].
- Histopathology, with immunohistochemistry is the final diagnostic modality.

Macroscopic Appearance

In primary adenocarcinoma, the appendix is enlarged, deformed or may be completely destroyed. Well differentiated tumors are often cystic. The tumor may appear as a grossly swollen appendix due to accumulation of mucin in the lumen due to obstruction proximally. This is termed a mucocoele and is only a descriptive term and not a pathologic diagnosis. The tumor may present on gross as polypoid, ulcerative or infiltrative growth. Proximal 1/3rd is often involved. Tumors in the base should be distinguished from caecal tumors invading the appendix. An appendix of >2.0 cm in diameter is often neoplastic [49, 50].

Pseudomyxoma Peritonei presents with multiple gelatinous nodules in the peritoneum, omentum, ligament of Teitz and various other sites. These nodules vary in size from a few mm to a few centimeters. Presence of tumor implant of >5.0 cm on jejunum, proximal ileum or adjacent mesentery is more consistent with mucinous adenocarcinoma with secondary carcinomatous involvement [50].

Microscopic Appearance

Histologically, malignant glandular epithelium arranged as strips, clusters or complex glands are seen in pools of mucin. The tumor is seen infiltrating beyond the lamina propria through the muscularis mucosae, in contrast to an adenoma which is limited to the lamina propria with an intact muscularis mucosae. Extracellular mucin is seen on the external surface. Extracellular mucin beyond the right iliac fossa is suggestive but not diagnostic of metastasis [50].

Majority of the appendiceal tumors are well differentiated and mucinous. Some tumors may show signet ring cells. Again there is controversy regarding what is to be termed as a signet ring tumor. Some authors have proposed that if signet ring cells are more than 50 %, then the tumor should be designated as signet ring cell carcinoma, while others believe that any number of signet ring cells should be termed as a signet ring cell carcinoma [51]. The presence of signet ring cells makes the tumor a high grade one with a poorer prognosis compared to non-signet ring tumors.

Pseudomyxoma peritonei is characterized by presence of mucinous material on peritoneal surface. It may be free acellular mucin [Fig. 2a] or organizing mucin with proliferating capillaries and fibroblasts [Fig. 2b] or mucin with malignant cells floating in it. The pleomorphic cells are usually scanty and if present are tall columnar mucinous cells of intestinal type. The mucinous deposits are often seen in greater omentum, beneath right hemidiaphragm, right retro hepatic space, ligament of Teitz, left abdominal gutter and pelvis. These deposits may be seen on the surface without invasion or may be seen infiltrating the substance of the tissue. Tumors lacking epithelium are also considered as malignant. The growth is confined to the abdomen for many years [25, 52, 53].

Appendiceal tumors express CK20, CEA, CDX2, MUC2 and MUC 5AC and are usually negative for CK7 and CA 125. These immunohistochemistry markers can be used to determine the primary tumor site in a patient with PMP [6, 46, 54, 55].

Increased N-Cadherin expression and reduced E-Cadherin expression has been observed in these tumors. This shift in cadherin phenotype and vimentin expression may reflect epithelial – mesenchymal transition state in which epithelial cells switch to mesenchymal phenotype, a process that promotes metastasis [56]. Other markers that are frequently altered in mucinous adenocarcinoma are β -Catenin, Cyclin D1, Ki-67, NF-kB, VEGF, E-Cadherin and p53 [57].

The differential diagnosis for PMP are a variety of benign and malignant lesions. Ruptured mucinous cystadenoma of appendix or ovary, endometriosis with myxoid change, melioidosis, soft tissue neoplasm with myxoid change and ruptured viscus with mucin extravasation are some of the benign lesions that can be confused [58–60]. PMP needs to be distinguished from a peritoneal mucinous carcinomatosis from a primary mucinous carcinoma. Thorough sampling

Fig. 2 **a** Acellular mucin **b** organizing mucin **c** neoplastic cells with low grade features **d** neoplastic cells with high grade features

with search for neoplastic epithelium and mucin is essential with the use of IHC where necessary [24].

Pathologic Classification

Classification of Appendiceal tumors

Woodruff and McDonald classified cystic mucinous tumors of appendix in 1940 as Benign Mucocele and Cystadenocarcinoma [61]. A classification of appendiceal tumors was proposed by Carr and colleagues from AFIP in 1995 based on their study of 184 tumors at the Armed Forces Institute of Pathology which classified these tumors into 3 categories:

- Adenoma: Dysplastic epithelium with mucin dissecting into wall with intact muscularis mucosae.
- Mucinous tumors of uncertain malignant potential: Well-differentiated mucinous epithelium without invasion or with mucin in the wall or outside the appendix with loss of muscularis mucosae.
- Adenocarcinoma: Invasive neoplastic cells beyond muscularis mucosae [50].

In 2003 Misraji and colleagues classified them as low-grade mucinous neoplasms and mucinous adenocarcinoma [62].

Pai and Longacre [11] in 2005 proposed the following classification:

- Adenoma: Mild-to-moderate atypia, mitosis, no stromal invasion, perforation with

Mucin

- Mucinous tumor of uncertain potential (MTUMP): Adenoma with positive margin, mucin present within the wall.
- Mucinous tumor–low malignant potential (MTLMP): Adenoma with neoplastic cells in peritoneum.
- Adenocarcinoma: Invasive mucinous tumor [63].

The WHO classification in 2010 removes these confusions, proposes a simple classification of appendiceal tumors into Adenoma, Adenocarcinoma – NOS, Mucinous Adenocarcinoma, Signet ring adenocarcinoma and an undifferentiated carcinoma. WHO regards any neoplastic epithelial proliferation confined to the appendiceal mucosa with an intact muscularis mucosae, as adenoma. These are often incidental findings in appendectomy specimens. Appendiceal mucinous tumors with extra appendiceal neoplastic epithelium are classified as mucinous adenocarcinomas and subcategorized as low grade and high grade. Diagnosis of adenocarcinoma is made when the tumor invades beyond muscularis mucosae, sometimes with broad fronts [64].

Classification of Pseudomyxoma Peritonei

The most popular classification of Pseudomyxoma peritonei was proposed by Ronnette et al. in 1995, who correlated the histology with the prognosis and proposed a three tiered classification – Diffuse Peritoneal Adenomucinosi (DPAM), Peritoneal Mucinous Adenocarcinoma (PMCA) and Peritoneal Mucinous Adenocarcinoma with intermediate features (hybrid tumors). According to this classification, DPAM represents the classic Pseudomyxoma peritonei with paucicellular mucinous ascites on the surface of the peritoneum without invasion, and an indolent clinical course, whereas PMCA has a higher percentage of overtly malignant cells/cell groups invading the tissue and a poorer prognosis. Intermediate tumors (hybrid tumors) have both features with PMCA representing at least 5 % of the tumor [45].

Bradley et al. concluded that DPMA and intermediate grade tumors behave in a same manner. They considered DPMA as a very well differentiated mucinous adenocarcinoma and proposed the classification of PMP as – Mucinous carcinoma peritonei low grade and Mucinous carcinoma peritonei high grade. [65].

In 2010, the American Joint Committee on Cancer (AJCC) and WHO proposed the histological classification of PMP based on the understanding of the histogenesis, molecular genetic findings and clinical behavior of the lesions [64]. This classification divides PMP in to two groups –.

Low grade PMP Mucin pools with low cellularity (<10 %), bland cytology and non- stratified cuboidal epithelium [Fig. 2c].

High grade PMP Mucin pools with high cellularity, moderate/severe cytologic atypia [Fig. 2d] and cribriform/signet ring morphology with desmoplastic stroma.

Some authors believe that the peritoneal mucin deposits are the consequence of rupture and spillage of mucin and adenomatous epithelium into the peritoneal cavity, rather than carcinoma. WHO regards any neoplastic epithelial proliferation confined to the appendix mucosa as an adenoma. Appendiceal mucinous tumors with extra-appendiceal neoplastic epithelium are classified as mucinous adenocarcinomas and subcategorized as low- or high-grade because increasingly severe cyto-architectural atypia is associated with poorer outcome. They have also stated reasons why PMP should be considered a carcinoma and not an adenoma -

- Some carcinomas are extremely well differentiated with minimal cytological atypia. Hence low grade cytology does not exclude the diagnosis of malignancy. Concept of adenoma is also not reconciled with low grade malignant behavior of PMP.

Table 1 Comparison of Different Classification of Appendiceal Mucinous Neoplasms and Pseudomyxoma Peritonei (Reproduced from Ref 64 with permission)

	Carr and Sobin 2010	Misdragi et al. 2003	Pai and Longacre 2009	Ronnette et al. 1995	Bradley et al. 2006	AJCC & WHO 2010
Tumor confined to appendix						
Limited to mucosa						
Low grade cytology	Adenoma	Low grade appendiceal mucinous neoplasm	Adenoma	NA	NA	Adenoma
High grade cytology	Adenoma	Noninvasive mucinous Cystadenocarcinoma	Adenoma	NA	NA	Adenoma
Positive surgical margin	Adenoma	Low grade appendiceal mucinous neoplasm	Uncertain malignant potential	NA	NA	Adenoma
Neoplastic epithelium in appendix wall	Uncertain malignant potential	Low grade appendiceal mucinous neoplasm	Uncertain malignant potential	NA	NA	Invasive mucinous adenocarcinoma
Tumor beyond appendix						
Low grade epithelium in peritoneal mucin	Invasive mucinous adenocarcinoma	Low grade appendiceal mucinous neoplasm	High risk for recurrence	Disseminated peritoneal adenomucinosi	Low grade mucinous carcinoma peritonei	Low grade mucinous adenocarcinoma
High grade epithelium in peritoneal mucin	Invasive mucinous adenocarcinoma	Invasive mucinous adenocarcinoma	Invasive mucinous adenocarcinoma	Peritoneal mucinous carcinomatosis	High grade mucinous carcinoma peritonei	High grade mucinous adenocarcinoma

- Parenchymal invasion of solid organs (Ovary and spleen) is common in PMP which is generally a feature of malignancy.
- Some tumors with broad growth pattern, as seen in mucinous carcinoma, may invade, with pushing margins. So infiltrating glands or desmoplasia may not be seen.
- Mucinous tumors beyond appendix are associated with progressive mucinous ascites, disease recurrence and death in at least 50 % of patients, indicating a spectrum of malignancy.

Hence WHO recognizes PMP as a carcinoma from a primary mucinous adenocarcinoma elsewhere, most commonly from appendix [64]. A comparison of the various classification is shown in Table 1.

In the recently published consensus for the classification and pathologic reporting of PMP and associated appendiceal neoplasms, published by the members of the Peritoneal Surface Oncology Group International (PSOGI), the same classification was recommended by a panel of experts at the end a modified Delphi process [66]. The recommendations of the panel are shown in Table 2.

Histologic Correlation with Prognosis

Several studies have concluded that the histopathologic pattern correlates well with the outcome of the patient. Yantiss et al. found that 96 % of patients with acellular mucin were disease free at 52 months of follow up while 33 % with malignant cells developed widespread disease [67]. They concluded that patients with acellular peri-appendiceal mucin are unlikely to develop

recurrent disease. It is also shown that tumors limited to appendicular mucosa have no potential for aggressive disease when completely removed. Tumors with acellular mucin limited to appendicular wall and/or mesoappendix are also cured by excision. Any proliferation of the tumor beyond the muscularis mucosae is at risk of peritoneal dissemination [68]. An inaccurate clinical and pathologic assessment of the original malignancy accounted for the poor outcome, with second relook surgery in many patients [42]. Misdrji concluded that presence of any epithelium outside appendix has an increased risk of recurrence and potential death. Hence extra appendiceal mucin must be completely examined to confirm the absence of epithelium [15]. Sugarbaker et al. introduced and popularized the combined modality treatment of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for treating patients with PMP [69, 70]. Chua et al reported the results from a multi institutional registry of two thousand two hundred ninety-eight patients from 16 specialized units underwent CRS and HIPEC for PMP. The median survival rate was 196 months (16.3 years) and the median progression-free survival rate was 98 months (8.2 years), with 10- and 15-year survival rates of 63 % and 59 %, respectively [70]. Patients with low grade tumors (DPAM) had a much better outcome than patients with high grade tumors (PMCA) ($p < .001$), similarly, patients with less extensive disease fared better than those with more extensive disease as determined by the peritoneal cancer index (PCI) ($p = .013$) [70]. Inappropriate diagnosis may lead to several types of non-definitive treatment like debulking surgery or chemotherapy which has a negative impact on survival.

This emphasizes the importance of adequate sampling in determining the prognosis of patients with appendiceal mucinous neoplasms. The entire appendix should be submitted

Table 2 Classification of PMP (Peritoneal disease component) (Reproduced with permission from Ref 66)

Lesion	Terminology
1. Mucin without epithelial cells	Acellular mucin (A descriptive diagnosis followed by a comment is likely to be appropriate, depending on the overall clinical picture. It should be stated whether the mucin is confined to the vicinity of the organ or origin or distant from it, ie, beyond the right lower quadrant in the case of the appendix. The term PMP should be normally avoided unless the clinical picture is characteristic)
2. PMP with low-grade histologic features*	Low-grade mucinous carcinoma peritonei OR Disseminated peritoneal adenomucinosi (DPAM)
3. PMP with high-grade histologic features*	High-grade mucinous carcinoma peritonei OR Peritoneal mucinous carcinomatosis (PMCA)
4. PMP with signet ring cells	High-grade mucinous carcinoma peritonei with signet ring cells OR Peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S)
Omental cake and ovarian involvement can be consistent with a diagnosis of either low-grade or high-grade disease	

for examinations, as lesions with extra appendiceal tumor cells are more likely to progress to disseminated disease and result in death of the patient, even if mucin is pauci-cellular and confined to the peri-appendiceal region. Patients with high risk of disease progression should be put on an intensive follow up for the first 5 years after diagnosis.

An appendectomy should always be performed in all cases of Pseudomyxoma peritonei as appendix is proved to be the primary site in 94 % of the cases. An accurate pathological assessment of malignancy is very essential for better management strategies and outcome. The pathology report should include the site of origin of the tumor with presence or absence of rupture, assessment of peritoneal lesion as acellular mucin [Fig. 2a]/ organizing mucin [Fig. 2b]/mucin dissecting with fibrosis and presence or absence of neoplastic cells and the cytological atypia with architectural complexity [Fig. 2c and d] [65].

Summary and Conclusion

Mucinous tumors of the appendix and PMP are a complex but rare group of disorders that have generated a lot of interest in recent years due to the application of radical surgical procedures for treating these patients which result in a prolonged survival. Considerable controversy exists in the pathologic classification and nomenclature of the disease. Clear understanding of the diverse histopathologic presentation of this tumor helps in proper pathological interpretation and better communication with the surgeon. As most cases of PMP are secondary to a mucinous adenocarcinoma of appendix, entire appendix has to be processed to identify the tumor followed by the application of IHC stains where necessary. These tumors pursue a predictable course based on the stage and grade of the tumor. Tumors confined to the appendiceal mucosa are cured by simple excision of the appendix while those beyond the mucosa with epithelial proliferation are associated with dissemination of the disease. Histological grade of the disease is important as tumors with a low grade are managed with CRS and HIPEC alone while those with high grade disease might require chemotherapy in addition to the above. It is also needed for determining the prognosis prior to selecting patients for this aggressive form of therapy. Hence adoption of a uniform reporting system as per WHO and AJCC criteria is very essential for patient management. When PMP is an incidental finding during an exploratory laparotomy its best to take proper peritoneal biopsies and remove the appendix followed by referral to a specialized center.

References

1. Connor SJ, Hanna GB, Frizelle FA (1998) Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. *Dis Colon Rectum* 41(1):75
2. Shankar S, Ledakis P, El Halabi H, Gushchin V, Sardi A (2012) Neoplasms of the Appendix Current Treatment Guidelines. *Hematol Oncol Clin N Am* 26:1261–1290
3. Kabbani W et al. (2002) Mucinous and nonmucinous appendiceal adenocarcinomas: Different clinicopathological features but similar genetic alterations. *Mod Pathol* 15(6):599–605
4. Muller D (1980) Appendiceal neoplasm resulting from a malignant transformation of a villous adenoma. *Chirurg* 51(9):609–610
5. Pai RK, Longacre TA (2005) Appendiceal mucinous tumors and pseudomyxoma peritonei: Histologic features diagnostic problems, and proposed classification. *Adv Anat Pathol* 12(6):291–311
6. Guo AT, Song X, Wei LX, Zhao P (2011) Histological origin of pseudomyxoma peritonei in Chinese women: clinicopathology and immunohistochemistry. *World J Gastroenterol* 17:3531–3537
7. Sugarbaker PH (2005) Are there curative options to peritoneal carcinomatosis? *Ann Surg* 242(5):748–750(author reply 750-1)
8. Sugarbaker PH (2006) New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? *Lancet Oncol* 7(1):69–76
9. Gonzalez-Moreno S, Brun E, Sugarbaker PH (2005) Lymph node metastasis in epithelial malignancies of the appendix with peritoneal dissemination does not reduce survival in patients treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 12(1):72–80
10. Gonzalez-Moreno S, Sugarbaker PH (2004) Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. *Br J Surg* 91(3):304–311
11. Moran BJ, Cecil TD (2003) The etiology, clinical presentation, and management of pseudomyxoma peritonei. *Surg Oncol Clin N Am* 12:585–603
12. Werth R (1884) Klinische und Anatomische Untersuchungen Zur Lehre von der Bauchgeswulsten und der laparotomy. *Arch Gynecol Obstet* 84:100–118
13. Frankel E (1901) Uher das sogenaute pseudomyxoma peritonei. *Med Wochenschr* 48:965–970
14. Carr NJ et al. (2012) Pathology and Prognosis in Pseudomyxoma Peritonei: A review of 274 cases. *J Clin Pathol* 65(10):919–923
15. Misdraji J (2010) Appendiceal Mucinous Neoplasms: Controversial issues. *Arch Pathol Lab Med* 134(6):864–870
16. Young RH (1994) Pseudomyxoma Peritonei and selected other aspects of the spread of appendiceal neoplasms. *Semin Diagn Pathol* 21(2):134–150
17. Charalampos S et al. (2014) Appendiceal Mucocoele and Pseudomyxoma Peritonei: The clinical boundaries of a subtle disease. *Am J case rep* 15:355–360
18. Misdraji J (2015) Mucinous epithelial neoplasms of the appendix and pseudomyxoma peritonei. *Mod Pathol* 28:S67–S79. doi:10.1038/modpathol.2014.129
19. Agrawal AK, Bobiński P, Grzebieniak Z, Rudnicki J, Marek G, Kobiela P, Haloń A (2014) Pseudomyxoma peritonei originating from urachus—case report and review of the literature. *Curr Oncol* 21(1):e155–e165
20. Baratti D, Kusamura S, et al. (2008) Pseudomyxoma Peritonei: Clinical Pathological and biological prognostic factors in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *Ann Surg Oncol* 15(2):526–534

21. Stocchi L, Wolff BG, Larson DR, Harrington JR (2013) Surgical treatment of appendiceal mucocele. *Arch Surg* 138:585–590. PMID: 12799327
22. Holt N, Grønbaek H (2013) Goblet Cell Carcinoids of the Appendix. *Sci World J* 2013:6. doi:10.1155/2013/543696
23. Hinson FL, Ambrose NS (1998) Pseudomyxoma peritonei. *Br J Surg* 85:1332–1339
24. Amini A, Masoumi-Moghaddam S, Ehteda A, Morris DL (2014) Secreted mucins in pseudomyxoma peritonei: pathophysiological significance and potential therapeutic prospects. *Orphanet J Rare Dis* 9:71. doi:10.1186/1750-1172-9-71
25. Sugarbaker PH (1994) Pseudomyxoma peritonei. A cancer whose biology is characterized by a redistribution phenomenon. *Ann Surg* 219:109–111
26. Carmignani CP, Sugarbaker TA, Bromley CM, Sugarbaker PH (2003) Intraperitoneal cancer dissemination: mechanisms of the patterns of Spread. *Cancer Metastasis Rev* 22:465–472
27. Smeenk RM, Bruin SC, van Velthuisen ML, Verwaal VJ (2008) Pseudomyxoma peritonei. *Curr Probl Surg* 45:527–575
28. Murphy EM, Farquharson SM, Moran BJ (2006) Management of an unexpected appendiceal neoplasm. *Br J Surg* 93:783–792
29. O'Connell JT, Tomlinson JS, Roberts AA, McGonigle KF, Barsky SH (2002) Pseudomyxoma peritonei is a disease of MUC2-expressing goblet cells. *Am J Pathol* 161:551–564
30. Ronnett BM et al. (1997) Pseudomyxoma Peritonei: New concepts in diagnosis, origin, nomenclature, and relationship to mucinous borderline (low malignant potential) tumors of ovary. *Anat Pathol* 2:197–226
31. Ronnett BM et al. (1995) Disseminated Peritoneal adenomucinosis and Peritoneal mucinous adenocarcinoma: A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis and relationship to Pseudomyxoma Peritonei. *Am J Surg Pathol* 19(12):1390–1408
32. Alderdice JM, Hayes D (1983) Mucoceles of the appendix: their underlying epithelia, behaviour and associated tumours. *Ulster Med J* 52:131–135
33. Carr NJ, Montgomery E (1994) Patterns of healing in the appendix: the morphological changes in resolving primary acute appendicitis and a comparison with Crohn's disease. *Int J Surg Pathol* 2
34. Moran CG, Morgan RH (1988) Pseudomyxoma extraperitonei. *R Soc Med* 81:668–669
35. Johansson ME, Larsson JM, Hansson GC (2011) The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host-microbial interactions. *Proc Natl Acad Sci U S A* 108(Suppl 1):4659–4665
36. O'Connell JT, Hacker CM, Barsky SH (2002) MUC2 is a molecular marker for pseudomyxoma peritonei. *Mod Pathol* 15:958–972
37. Shih IM et al. (2001) Molecular genetic analysis of appendiceal mucinous adenomas in identical twins, including one with Pseudomyxoma Peritonei. *Am J Surg Pathol* 25(8):1095–1099
38. Nawaz A, Karakurum A, et al. (2009) Pseudomyxoma Peritonei manifesting as intestinal obstruction. *South Med J* 93(9):1–4
39. Esquivel J, Sugarbaker PH (2000) Clinical presentation of the Pseudomyxoma peritonei syndrome. *Br J Surg* 87:1414–1418
40. Esquivel J, Sugarbaker PH (2001) Pseudomyxoma peritonei in a hernia sac: analysis of 20 patients in whom mucoid fluid was found during a hernia repair. *Eur J Surg Oncol* 27:54–58
41. Yan H, Pestieau SR, et al. (2001) Histopathologic analysis of 46 patients with Pseudomyxoma Peritonei syndrome: Failure versus success with a second look operation. *Mod Pathol* 14(3):164–171
42. Prayson RA et al. (1994) Pseudomyxoma Peritonei: A clinicoathologic study of 19 cases with emphasis on site of origin and nature of associated ovarian tumors. *Am J Surg Pathol* 18(6): 591–603
43. KR L, Scully (2000) Mucinous tumors of ovary: A clinicopathologic study of 196 borderline tumors (of intestinal type) and carcinomas, including an evaluation of 11 cases with Pseudomyxoma Peritonei. *Am J Surg Pathol* 24(11):1447–1464
44. McKenney JK et al. (2008) Ovarian mature Teratoma with mucinous epithelial neoplasms: Morphologic heterogeneity and association with Pseudomyxoma Peritonei. *Am J Surg Pathol* 32(5):645–655
45. Young RH et al. (1991) Mucinous tumors of appendix associated with mucinous tumors of ovary and Pseudomyxoma Peritonei: A Clinicopathologic analysis of 22 cases supporting an origin in appendix. *Am J Surg Pathol* 15(5):415–429
46. Smeenk RM, Verwaal VJ, Zoetmulder FA (2007) Pseudomyxoma peritonei. *Cancer Treat Rev* 33:138–145
47. Kreel L, Bydder GM (1980) Computed tomography of fluid collections within the abdomen. *J Comput Tomogr* 4:105–115
48. Buy JN, Malbec L, Ghossain MA, Guinet C, Ecoiffier J (1989) Magnetic resonance imaging of pseudomyxoma peritonei. *Eur J Radiol* 9:115–118
49. Wolff M, Ahmed N (1976) Epithelial neoplasms of the vermiform appendix (exclusive of carcinoma): adenocarcinoma of the appendix. *Cancer*:379493–379510
50. Carr NJ, McCarthy WF, Sobin LH (1995) Epithelial noncarcinoid tumors and tumor-like lesions of the appendix. A clinicopathologic study of 184 patients with a multivariate analysis of prognostic factors. *Cancer* 75(3):757–768
51. Shetty S, Natarajan B, Thomas P, Govindarajan V, Sharma P, Loggie B (2013) Proposed classification of pseudomyxoma peritonei: influence of signet ring cells on survival. *Am Surg* 79(11):1171–1176
52. Jurgeleit HC (1986) Pseudomyxoma peritonei: a localized, benign variant of appendiceal origin. *Dis Colon Rectum* 29:469–470
53. Fernandez RN, Daly JM (1980) Pseudomyxoma peritonei. *Arch Surg* 115:409–414
54. Semino-Mora C, Liu H, McAvoy T, Nieroda C, Studeman K, Sardi A, Dubois A (2008) Pseudomyxoma peritonei: is disease progression related to microbial agents? A study of bacteria, MUC2 AND MUC5AC expression in disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. *Ann Surg Oncol* 15: 1414–1423
55. Flatmark K, Davidson B, Kristian A, Stavnes HT, Forsund M, Reed W (2010) Exploring the peritoneal surface malignancy phenotype—a pilot immunohistochemical study of human pseudomyxoma peritonei and derived animal models. *Hum Pathol* 41:1109–1119
56. Bibi R, Pranesh N, Saunders MP, Wilson MS, O'Dwyer ST, Stern PL, Renehan AG (2006) A specific cadherin phenotype may characterize the disseminating yet non-metastatic behaviour of pseudomyxoma peritonei. *Br J Cancer* 95:1258–1264
57. Dordevic B et al. (2008) Pseudomyxoma Peritonei and Mucinous ovarian tumors. *Acta Medical Medianae* 4
58. Clement PB, Granai CO, Young RH, RE S (1994) Endometriosis with myxoid change. A case simulating pseudomyxoma peritonei. *Am J Surg Pathol* 18:849–853
59. Sugi Subramaniam RV, Karthikeyan VS, Sistla SC, Ali SM, Sistla S, Ram D, Sudhagar R (2013) Melioidosis presenting as pseudomyxoma peritonei: yet another pretense of the great mimicker: an unreported entity. *Surg Infect* 14(63):415–417
60. Mirich DR, Gray RR, Grosman H (1989) Abdominal plexiform neurofibromatosis simulating pseudomyxoma peritonei on computed tomography. *J Comput Assist Tomogr* 13:709–711

61. Higa E, Rosai J, Pizzimbono CA, et al. (1973) Mucosal hyperplasia, mucinous cystadenoma, and mucinous cystadenocarcinoma of the appendix. A re-evaluation of appendiceal “mucocele”. *Cancer* 32(6):1525–1541
62. Misdraji J, Yantiss RK, Graeme-Cook FM, et al. (2003) Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. *Am J Surg Pathol* 27(8):1089–1103
63. Pai RK, Longacre TA (2005) Appendiceal mucinous tumors and pseudomyxoma peritonei: histologic features, diagnostic problems, and proposed classification. *Adv Anat Pathol* 12(6):291–311
64. Panarelli N, Yantiss R (2011) Mucinous Neoplasms of the Appendix and Peritoneum. *Arch Path Lab Med*: Oct 135(10): 1261–1268. doi:[10.5858/arpa.2011-0034-RA](https://doi.org/10.5858/arpa.2011-0034-RA)
65. Bradley RF, Cortina G, Geisinger KR (2007) Pseudomyxoma Peritonei: Review of the controversy. *Curr Diagn Pathol* 13(5): 410–416
66. Carr NJ, Cecil TD, Mohamed F, Sobin LH, Sugarbaker PH, González-Moreno S, Taflampas P, Chapman S, Moran BJ (2016) A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *Am J Surg Pathol* 40(1):14–26. doi:[10.1097/PAS.0000000000000535](https://doi.org/10.1097/PAS.0000000000000535)
67. Appelman HD (1991) Epithelial neoplasia of the appendix. In: Norris HT (ed) *Pathology of the small intestine, colon and anus*, Ed. Churchill Livingstone, New York, pp. 263–303
68. Sugarbaker PH (1989) Surgical treatment of peritoneal carcinomatosis: 1988 Du Pont lecture. *Can J Surg* 32:164–170
69. Sugarbaker PH, Kern K, Lack E (1987) Malignant pseudomyxoma peritonei of colonic origin. Natural history and presentation of a curative approach to treatment. *Dis Colon Rectum* 30:772–779
70. Terence CC, Brendan JM, Paul HS, Edward AL, Olivier G, Francois NG, Dominique E, Dario B, Marcello D, Armando S, David LM, Peritoneal Surface Oncology Group International; University of New South Wales, Sydney, Australia; NCG Pseudomyxoma Peritonei Centre, The North Hampshire Hospital, Basingstoke, United Kingdom; Washington Hospital Center, Washington, DC; Wake Forest School of Medicine, Winston-Salem, NC; Centre Hospitalo-Universitaire Lyon Sud, Lyon, France; Institut Gustave Roussy, Villejuif, France; Istituto Nazionale per la Cura e lo Studio dei Tumori, Milan, Italy; Mercy Medical Center, Baltimore, MD (2012) Early- and Long-Term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol* 30(20):2449–2456