An Overview of Jelly Belly Syndrome (Pseudomyxoma Peritonei)

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Abstract

Often referred to as 'jelly belly syndrome' and treated with a procedure known as 'the Sugarbaker,' Pseudomyxoma peritonei (PMP) is anything but sweet. Pseudomyxoma peritonei is a rare pathological syndrome with an annual occurrence of only 1-2 cases per 1,000,000. PMP most commonly occurs as a result of an appendiceal mucinous neoplasm (AMN) that either extends through the wall of the appendix or causes appendiceal rupture, resulting in dissemination of neoplastic cells within the peritoneal cavity. The most common sites of metastases include the greater omentum, under-surface of the right hemidiaphragm, right subhepatic space, and paracolic gutter. These mucin-producing metastases result in the formation of mucinous ascites, a clinical finding pathognomonic of pseudomyxoma peritonei and how PMP came to be known as 'jelly belly syndrome.' Currently, the only treatment for pseudomyxoma peritonei is cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC), a procedure colloquially referred to as 'the Sugarbaker.' Despite the aggressiveness of this approach, the 5-year overall survival rate is just over 50%.

Although uncommon to receive an AMN with a clinical history of PMP, it is essential for pathologists' assistants (PAs) to be comfortable accessioning and grossing these specimens. Familiarity with both the gross and histological features of pseudomyxoma peritonei ensures that PAs will save the appropriate tissue for cytological, molecular, and genetic testing as well as submit pertinent sections for microscopic review; however, PMP can be intimidating. Literature regarding pseudomyxoma peritonei is often contradictory and the classification of PMP only recently became standardized. The goal of this poster is to present a clear, concise overview of pseudomyxoma peritonei in order to improve pathologists' assistants' understanding of this rare pathological syndrome.

Clinical & Gross Appearance of PMP and AMNs

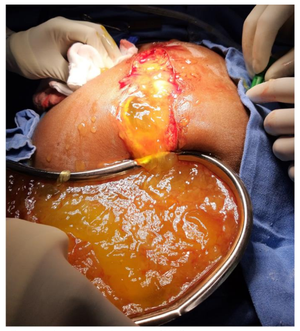


Figure 1. *Pathognomonic mucinous ascites of PMP*[24]

Pseudomyxoma peritonei is most common after the fourth decade of life and has a female predominance[11]. Clinically, PMP frequently presents in late stages as mucinous ascites or 'jelly belly.' Patients who have already accumulated a significant amount of mucin within the peritoneal cavity may also exhibit signs of intestinal obstruction, cachexia, and malnutrition[21]. Rarely, pseudomyxoma peritonei is an incidental finding of routine laparoscopy or laparotomy. Typical intraperitoneal findings include omental caking, scalloping of the liver, and peritoneal tumors. PMP almost never involves the freely moveable surfaces of the intestines[3]. Peritoneal tumors are often described as smooth, shiny, grape-like clusters of nodules[10]. Additionally, the appendix is often diffusely enlarged, dilated, or perforated with evidence of intra or extraluminal mucin[20].

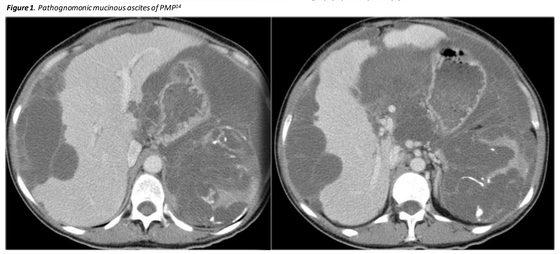


Figure 2. *Radiology of the abdomen demonstrating the effects of peritoneal deposits; note the scalloping of the liver and near-destruction of the spleen*[9]

Histology of PMP

Prior to the release of standardized grading criteria for pseudomyxoma peritonei by The Peritoneal Surface Oncology Group International (PSOGI) in 2016, diagnosis of PMP varied significantly. To address these discrepancies, PSOGI divided PMP into five distinct categories based on histomorphology: acellular mucin, low grade mucinous carcinoma peritonei, high grade mucinous carcinoma peritonei, high grade carcinoma peritonei with signet ring cells, and peritoneal carcinomatosis. A diagnosis of acellular mucin represents mucinous ascites without neoplastic epithelium either at the site of origin or distant from it. Low grade mucinous carcinoma peritonei is characterized by low-grade cytology, few mitoses, and mucinous epithelium comprising less than 20% of the tumor volume. High grade mucinous carcinoma peritonei is defined by one or more of the following: high grade cytology, infiltrative invasion into adjacent tissue, angiolymphatic or perineural invasion, cribriform growth, or abundant neoplastic mucinous epithelium comprising more than 20% of the tumor volume. Additionally, high grade mucinous carcinoma peritonei is further broken according to the degree of differentiation. High grade mucinous carcinoma peritonei with signet ring cells is histologically similar to high grade mucinous carcinoma peritonei but also includes signet ring cells comprising more than 10% of the tumor volume. A diagnosis of peritoneal carcinomatosis represents peritoneal dissemination from a non-mucinous appendiceal neoplasm[6]. It is also worth noting that low grade appendiceal mucinous neoplasms and high grade mucinous appendiceal neoplasms commonly correlate with low and high grade carcinoma peritonei, respectively. The PSOGI grading criteria is represented in table 1[6].

Figure 3. *Mucinous neoplasm of the appendix*[4]

Figure 4. *Peritoneal neoplasm; note the grape-like clusters of nodules*[5]

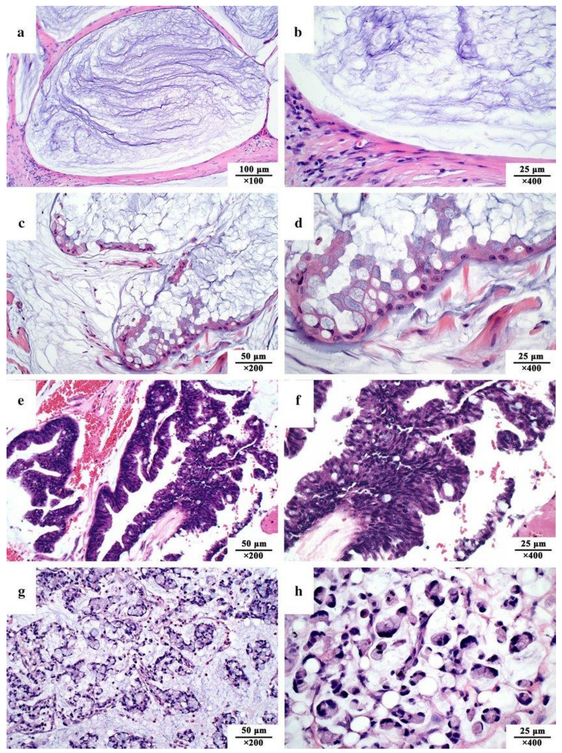


Figure 5. *PSOGI histological classification (H&E) of pseudomyxoma peritonei peritoneal masses a, b: acellular mucin without identifiable tumor cells; c, d: low grade mucinous carcinoma peritonei with arrangement of tumor cells in band, island, and wave clusters; cells in a single layer or pseudostratified with slight nuclear atypia; e, f: high grade mucinous carcinoma peritonei with complex cellular structure including band, island, gland, andcribriform arrangement and severe nuclear atypia; g, h: high grade mucinous carcinoma peritonei with signet ring cells and signet ring cells in mucous*[10]

PSOGI Classification of Pseudomyxoma Peritonei	
Acellular Mucin	Mucin without neoplastic epithelium; can be confined to the vicinity of the organ of origin or distant from it
Low grade mucinous carcinoma peritonei	• Cytologically low grade • Few mitoses • Mucinous epithelium is scant (<20% of tumor volume)

High grade mucinous carcinoma peritonei	Presence of one or more of the following, at least focally:
	• High grade cytology
	• Infiltrative invasion into adjacent tissue
	• Angiolymphatic or perineural invasion
	• Cribriform growth
	• Abundant neoplastic mucinous epithelium (>20% tumor volume)
	Subclassification according to differentiation:
	• Well
	  ○ Composed of predominantly single tubular glands
	  ○ Tumor cells well polarized
	  ○ Remarkable atypia of tumor cells
	  ○ Invasive component
	• Moderately
	  ○ Solid sheets of glandular cells admixed with glandular formations
	  ○ Minimal or absent polarity
	• Poorly
	  ○ Highly irregular to no glandular differentiation
	  ○ Cell polarity has disappeared

High grade mucinous carcinoma peritonei with signet ring cells	Neoplasm with signet ring cell component (recommended minimum of 10% signet ring cells for this classification)
Peritoneal carcinomatosis*	Peritoneal dissemination from non-mucinous appendiceal adenocarcinoma

Table 1. *Classification of PMP adapted from PSOGI*[6]

Histology of AMNs

By definition, appendiceal mucinous neoplasms have extended through the mucosa of the appendix, differentiating them from appendiceal adenomas. AMNs are classified as either low grade appendiceal mucinous neoplasms or high grade appendiceal mucinous neoplasms according to their epithelial features. LAMNs tend to have cells with abundant mucin, elongated nuclei, and low-grade atypia whereas the nuclei of HAMNs often appear more compressed and may have high grade nuclear atypia. Histologically, both low and high grade appendiceal mucinous neoplasms may demonstrate villous or flat architecture; however HAMNs may also exhibit convoluted, micropapillary, or even cribriform morphology. Additionally, it is not uncommon to observe associated lymphoid atrophy, crypt loss, and effacement of the muscularis mucosae. If there is dissection of mucin extending to the extra-appendiceal surface, serosal reaction and neovascularization may be distinguishable on H&E and can be used to differentiate genuine mucinous deposits from the deposition of mucin during gross examination[5].

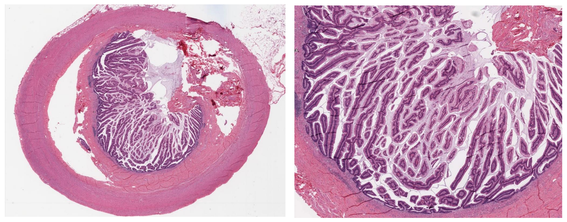


Figure 6. *H&E of LAMN on cross-section (left) and close-up of cross-section demonstrating villous architecture (right)*[3]

Genetic Profile & Pathophysiology of PMP

Genetic analysis of Pseudomyxoma peritonei is limited due to its infrequent occurrence; however, multiple recent studies have independently identified mutations in three key genes which are consistently seen in cases of PMP: *KRAS*, *GNAS*, and *Tp53*[11]. Other genetic aberrations, such as those in *APC* and *PIK3CA*, have been identified in relation to PMP, though these are less frequent. PMP is genetically similar to colonic adenocarcinoma and colorectal cancer (CRC); however, it has been found to have higher mutation rates in *KRAS* and *GNAS* and lower rates of *Tp53* mutations[10]. In fact, AMNs exhibit one of the highest rates of *KRAS* mutations amongst all human cancers[15]. Another unique feature of pseudomyxoma peritonei is a correlation between *GNAS* and *KRAS* mutations: *GNAS*-mutated PMP is more likely to have concurrent *KRAS* mutations compared to *GNAS*-wild-type PMP[10]

Kirsten rat sarcoma virus, also known as *KRAS*, is a protein-encoding proto-oncogene of the mammalian ras gene family located at 12p12.1. *KRAS* encodes a protein that is a member of the small GTPase superfamily[8]. This protein, K-ras, functions to relay signals from outside of the cell into the nucleus, via participation in the RAS/MAPK pathway. These cellular signals then function to promote normal cell proliferation and differentiation[18]; however, a mutation causing a single amino acid substitution results in a transformed version of the K-ras protein[8]. Mutated versions of K-ras are associated with a plethora of both neoplastic and non-neoplastic conditions, including cancers of the gastrointestinal system. In neoplastic conditions, K-ras most commonly sustains a mutation in which the protein is perpetually 'turned on,' resulting in constant cell signaling and uncontrolled cellular proliferation[18].

Guanine nucleotide-binding protein alpha subunit, or *GNAS*, is a complex, protein-encoding gene composed of 22 exons, located at 20q13.32[17]. This gene, which is regulated by imprinting and four alternative promoters[16], controls maternally, paternally, and biallelically expressed transcripts and gives rise to multiple different proteins. Alternative splicing of downstream exons results in the formation of different variants of the stimulatory G-protein alpha subunit (Gαs)[17]. Gαs plays an essential role in the signal transduction pathway. In response to receptor-ligand interactions, Gαs stimulates adenylyl cyclase to catalyze the conversion of adenosine triphosphate (ATP) to the second messenger cyclic adenosine monophosphate (cAMP), which subsequently activates protein kinase A (PKA). Once activated, PKA can then travel to the nucleus to modulate gene expression[16]. In pseudomyxoma peritonei, a mutation in *GNAS* stimulates increased mucin production via the cAMP-PKA signaling pathway. This mutation produces an altered form of Gαs with reduced endogenous GTPase activity. As a consequence of this decreased GTPase activity, GTP cannot be hydrolyzed and Gαs can continuously stimulate mucin production[10].

Tumor protein 53, also known as *Tp53*, is a protein-encoding tumor suppressor gene located at 17p13.1[12]. *Tp53* encodes tumor protein p53, which resides in the cell nucleus, where it can directly bind to DNA in order to modulate cellular division and prevent uncontrolled growth. When the cell genome undergoes damage, p53 plays a crucial role in either activating other genes to repair the damage or initiating apoptosis. The function of *Tp53* cannot be understated and has even earned this gene the nickname 'the guardian of the genome.' Because of its crucial role in regulating cellular repair and death, mutations in this gene are implicated in nearly half of all cancers. In neoplastic conditions, p53 most commonly sustains a mutation resulting in a single amino acid substitution and the subsequent production of an altered form of p53. This transformed version of p53 is then unable to induce apoptosis in damaged cells, resulting in the accumulation of DNA damage and continued, unchecked cell proliferation[19].

Prognosis & Treatment of PMP

Pseudomyxoma peritonei has a poor 5-year overall survival rate at just over 50%. Currently, the best prognostic indicators of PMP are tumor grade and lymph node involvement, with higher grade and lymph node involvement favoring a worse prognosis[10]. The standard treatment for PMP is known as 'the Sugarbaker.' This procedure, used to treat diffuse metastatic disease of the abdomen, involves cytoreductive surgery followed by heated intraperitoneal chemotherapy. The goal of CRS is to reduce the amount of neoplastic cells within the peritoneal cavity by removing both mucin and peritoneal tumor deposits. HIPEC is then initiated by introducing catheters into the open peritoneal cavity to directly deliver heated chemotherapy agents to the abdomen, targeting cells that could not be removed during surgery. If this approach is unsuccessful, traditional chemotherapy may also be administered[3].

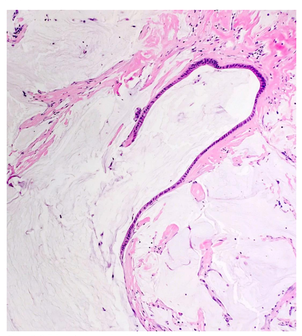


Figure 7. *Cellular extra-appendiceal mucin*

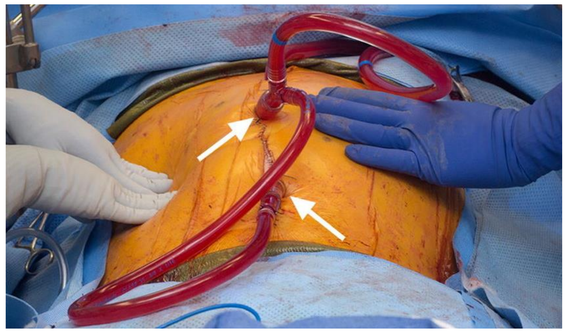
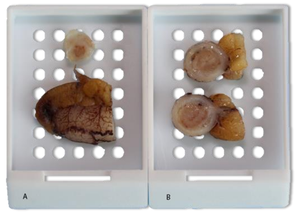


Figure 8. *HIPEC procedure*[2]



Although many pathologists' assistants will never encounter a case of PMP, it is essential to understand how to approach these specimens. Appropriate sections should include the appendix in cross-section as well as representative sections of solid and mucinous peritoneal deposits at one section per centimeter. All lymph nodes should also be submitted. Furthermore, PAs should consider saving tissue for additional testing. More information can be found on the AAPA website.

Key Points

- PMP is a rare clinico-pathological syndrome with only 1-2 cases per 1,000,000
- PMP most commonly occurs as a result of a perforated AMN
- AMNs with mucin extending through the wall of the appendix are most likely to result in PMP
- Mucin-producing metastases within the peritoneum result in the formation of mucinous ascites, a finding pathognomonic of PMP
- Classification of PMP was only recently standardized by PSOGI in 2016, dividing PMP into five distinct categories based on histomorphology
- PMP is genetically similar to colonic adenocarcinoma and CRC
- The most common mutations seen in PMP occur in KRAS, GNAS, and Tp53
- Current treatment for PMP includes CRS followed by HIPEC
- The primary role of the pathologists' assistant is to submit pertinent sections for microscopic review

Resources

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