The Pathology of PMP and Appendix Tumours: A Primer for Non-Pathologists

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The pathology and classification of pseudomyxoma peritonei (PMP) and its appendiceal precursors can be confusing. This brief set of slides aims to provide an overview suitable for clinicians who want to understand the principles.

This presentation is based on the WHO classification

- The WHO classifications can be found in the “blue books”.[1,2]
- The terminology is based on the Delphi consensus of the Peritoneal Surface Oncology Group International (PSOGI).[3]

1. Chapters by J Misdraji, NJ Carr and RK Pai in: WHO Classification of Tumours Editorial Board. Digestive System Tumours. Lyon, France: IARC; 2019.

2. Pseudomyxoma peritonei. In: WHO Classification of Tumours Editorial Board. Female Genital System Tumours. Lyon, France: IARC; 2020.

3. Carr NJ, Cecil TD, Mohamed F et al. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia. Am. J. Surg. Pathol. 2016; 40; 14-26.

Classifying PMP

PMP is graded histologically into four categories:

	Category	WHO grade	Typical histological features
1	Acellular mucin*	Not graded	Acellular mucin in the peritoneal cavity without identifiable mucinous epithelial cells
2	Low-grade mucinous carcinoma peritonei	G1	Strips of mucinous epithelium showing little atypia lying in abundant extracellular mucin
3	High-grade mucinous carcinoma peritonei	G2	High-grade cytological atypia, arbitrarily involving >10% of the tumour
4	High-grade mucinous carcinoma peritonei with signet ring cells	G3	Signet ring cells present

* Acellular mucin may be part of the PMP syndrome, but other conditions can also produce it. In particular, ruptured mucinous cystadenomas of the ovary can release large amounts of acellular mucin into the peritoneal cavity, but removal of the ovarian primary is curative.

Terminology

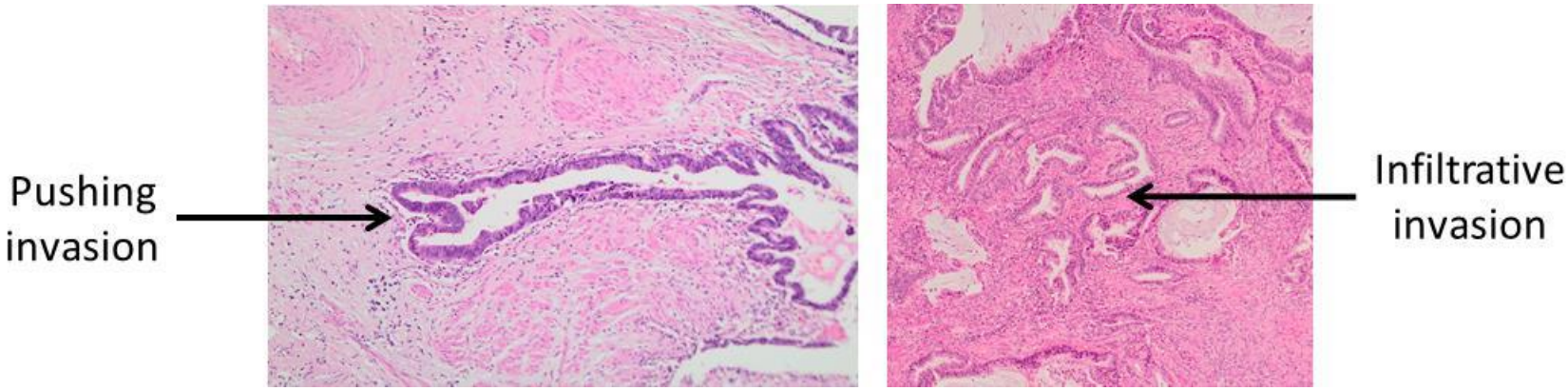
Disseminated peritoneal adenomucinosis (DPAM) is an alternative name for low grade mucinous carcinoma peritonei, but is no longer recommended.

“Pseudomyxoma peritonei” itself has been a contentious term, but its use is still appropriate and is the preferred terminology of the WHO.

Mucinous appendiceal neoplasms

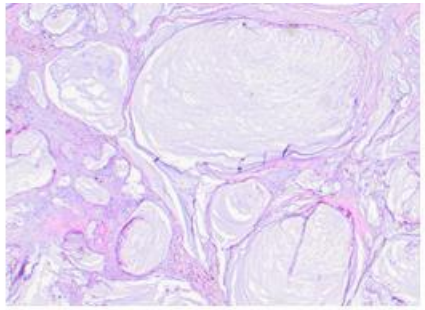
There are four main types of mucinous appendiceal neoplasm:

	Type of appendiceal neoplasm	Cytology	Type of invasion	Grade
1	Low-grade appendiceal mucinous neoplasm (LAMN)	Low grade	Pushing	G1
2	High-grade appendiceal mucinous neoplasm (HAMN)	High grade	Pushing	G2
3	Mucinous adenocarcinoma	Any grade	Infiltrative	G2
4	Mucinous adenocarcinoma with signet ring cells	Signet ring cells present	Infiltrative	G3

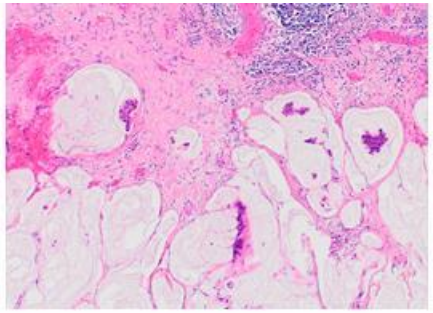


Mucinous appendiceal neoplasms

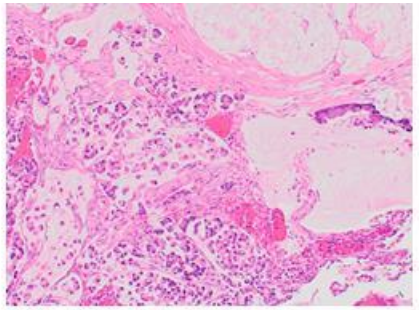
LAMN is the commonest mucinous appendiceal neoplasm and the commonest cause of the PMP syndrome. HAMN can also lead to PMP. Mucinous adenocarcinomas can either produce PMP or behave as conventional adenocarcinoma.



Low grade mucinous carcinoma peritonei



High grade mucinous carcinoma peritonei



High grade mucinous carcinoma peritonei with signet ring cells

Discordant histology

The grade of the peritoneal disease usually matches that of the appendiceal primary, but occasionally the grade differs (e.g. LAMN with high grade mucinous carcinoma peritonei). This is termed “discordant histology”.

Therefore, the appendiceal primary and peritoneal disease should be graded separately and independently. It appears that prognosis is more related to the histology of the peritoneal disease.

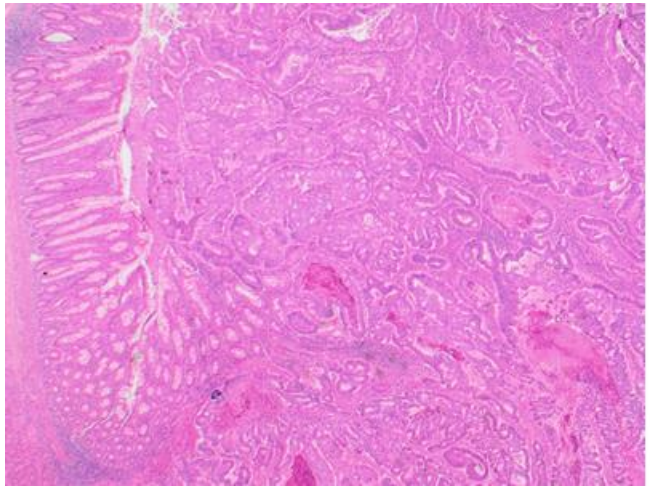
Another example of discordance is seen when low grade PMP is found at the first operation but high grade PMP is found at a subsequent operation. Presumably this represents progression of the disease with increasing genetic abnormalities over time.

Non-mucinous appendiceal adenocarcinoma

As elsewhere in the GI tract, adenocarcinomas are not called “mucinous” if less than 50% of the tumour consists of extracellular mucin.

Adenocarcinomas that are not mucinous are unusual in the appendix. They are less well understood than their mucinous counterparts.

Grading uses the same terminology as colorectal adenocarcinomas.



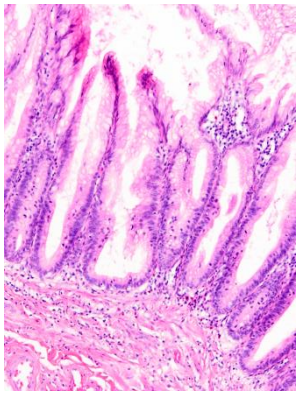
Appendiceal adenocarcinoma. This lesion resembles a typical colorectal adenocarcinoma morphologically.

Precursors

A likely precursor lesion of mucinous neoplasms is the appendiceal serrated polyp. They are common and morphologically resemble sessile serrated lesions of the colorectum very closely, but they have different genetic abnormalities – hence the appendiceal lesions are given a different name, “serrated polyp”.

Dysplastic serrated polyps are seen occasionally and are often associated with LAMN, HAMN or mucinous adenocarcinoma. Sometimes, a continuum from dysplastic serrated polyp through LAMN and HAMN to adenocarcinoma can be identified in an appendix.

Colorectal-type tubular, tubulovillous and villous adenomas are rare in the appendix. Non-mucinous adenocarcinomas may be associated with them.



Serrated polyp

Staging appendiceal neoplasms

The TNM classification of appendiceal neoplasms can be found in the UICC and AJCC manuals. It is different from the staging of colorectal carcinoma in several respects. Important differences include:

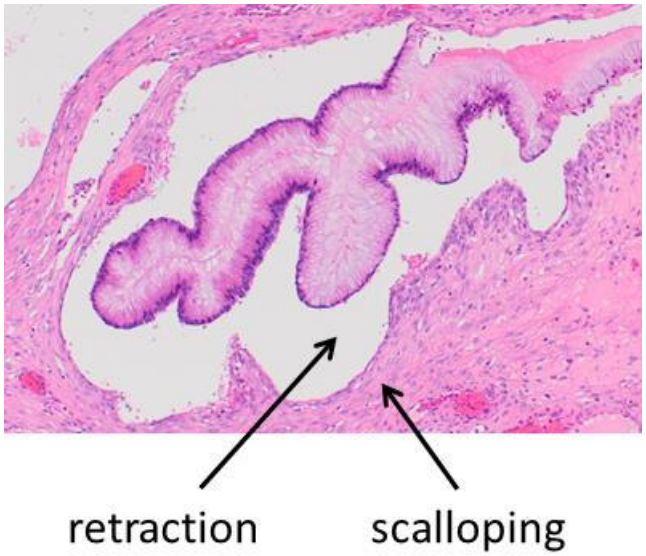
- For LAMNs, there is no pT1 or pT2; instead lesions confined to the submucosa or muscularis propria are designated pTis(LAMN), reflecting the very low risk of recurrence in such lesions.
- Acellular peritoneal mucin is pM1a, reflecting the better prognosis compared to mucin with cells.
- Peritoneal mucin with neoplastic cells is pM1b. This includes metastasis to the ovaries and omentum.
- Non-peritoneal metastasis is pM1c. This designation implies haematogenous spread (e.g. lung or bone) or distant lymphatic spread.

Ovarian mucinous tumours

Mucinous adenocarcinomas of the ovary tend to behave as conventional adenocarcinomas rather than producing PMP.

On rare occasions, an ovarian teratoma can develop a mucinous tumour that looks and behaves exactly like an appendiceal mucinous tumour, and even shares key genetic mutations. Such lesions can lead to true PMP.

Distinguishing a primary ovarian cystadenoma from a metastasis can be very difficult. Metastatic low grade appendiceal mucinous neoplasms in particular can closely mimic an ovarian primary. Although there are morphological clues that may suggest metastasis (e.g. epithelial retraction and scalloping) and immunohistochemistry may be helpful (e.g SATB2), no feature is pathognomonic. The appendix needs to be examined histologically to definitively exclude an appendiceal primary.

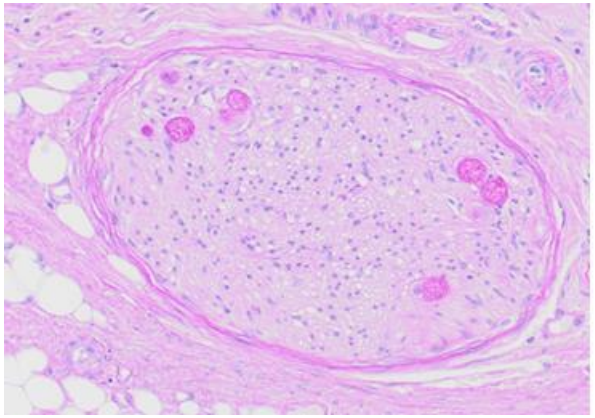


Goblet cell adenocarcinoma

Goblet cell adenocarcinoma (GCA) was called “goblet cell carcinoid” for many years. This name was confusing because GCAs are a type of adenocarcinoma and are not part of the neuroendocrine tumour family. Thankfully, the WHO has now authorised a change in terminology to the more appropriate “GCA”.

GCAs are rare. They can spread to the peritoneum and can cause large Krukenberg tumours. They are sometimes treated with cytoreductive surgery and heated intraperitoneal chemotherapy.

Because they are rare, indications for right hemicolectomy following the finding of a GCA in the appendix are controversial. However, in principle all GCAs are potentially malignant.



Individual cells of a GCA (purple) infiltrating a nerve

Grading goblet cell adenocarcinoma

Many grading classifications have been proposed. The Tang system was pre-eminent for many years, but the WHO has recently introduced a different system. The two classifications are contrasted in the table. Note that Tang grades do not necessarily correspond to any particular WHO grade.

Tang		WHO	
A	Clustered or cohesive growth, minimal atypia, little or no desmoplasia	G1	>75% tubular/clustered growth
B	Atypical architectural or cytological features	G2	50-75% tubular/clustered growth
C	Confluent sheets of signet ring cells or areas of poorly differentiated adenocarcinoma	G2	<50% tubular/clustered growth

Neuroendocrine neoplasms

Neuroendocrine tumours (NETs), previously known as “carcinoids”, are not uncommon in the appendix. Most are cured by appendicectomy.

Almost all appendiceal NETs are G1 or G2. The most reliable indicator of metastatic potential is tumour size. Other features of the primary tumour have little if any association with prognosis.

Neuroendocrine carcinomas and mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) have been described in the appendix but are exceptionally rare.

Please note:

- NETs have nothing to do with goblet cell adenocarcinomas
- The term “MiNEN” must not be used for goblet cell adenocarcinoma