

Mucinous tumours of appendix and ovary: an overview and evaluation of current practice

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ABSTRACT

Mucinous lesions of the appendix and ovary are commonly encountered in routine practice. There are several published classification schemes for appendiceal mucinous neoplasms with resultant inconsistent use of terms and clinical doubt. While nomenclature is more settled with regards to ovarian mucinous neoplasms, the difficulty here lies with distinguishing primary from secondary mucinous tumours. This review highlights the terminology and nomenclature for appendiceal mucinous tumours, the relationship with ovarian mucinous neoplasms and pseudomyxoma peritonei, and the features that assist in separating primary from secondary ovarian mucinous tumours.

INTRODUCTION

There is still considerable controversy and debate regarding the classification and nomenclature especially of appendiceal mucinous neoplasms. Additionally, the exact relationship between such lesions in the appendix and ovary are still unclear. Currently, as per WHO classification of tumours, appendiceal mucinous neoplasms are classified as adenoma and invasive adenocarcinoma.¹

While invasive adenocarcinoma with clear-cut malignant features is at one end of the spectrum, there are other mucinous neoplastic lesions that do not demonstrate any invasive features or marked histological atypia, but still have the potential to spread, recur and metastasise, and others result in the clinical entity known as 'pseudomyxoma peritonei'. Thus, the WHO classification and approach to mucinous appendiceal neoplasms does not quite provide clinically useful information in different clinical scenarios. The challenge is to identify the non-invasive mucinous neoplasms that are prone to behave aggressively. Lack of uniform histological terminology for the types of neoplastic proliferations encountered in the appendix complicates matters, and as a result, there is no standard clinical approach, and resultant appropriate clinical management is often unclear.

Some authors make a diagnosis of adenocarcinoma if there are any tumour cells outside of the appendix, while others believe that histologically and cytologically, bland epithelial proliferations should not be considered as mucinous adenocarcinoma especially when these proliferations do not invade or metastasise to other organs as do usual invasive mucinous adenocarcinomas.²⁻⁴

Pseudomyxoma peritonei is defined as a clinical entity typified by gross and diffuse intra-abdominal mucinous ascites accompanied by cytologically bland or low-grade mucinous epithelium on the peritoneal surface. Currently, there is consensus

that pseudomyxoma peritonei occurs almost always in association with a mucinous neoplasm arising in the appendix.⁵ Pseudomyxoma peritonei has a protracted clinical course, multiple recurrences, results in progressive fibrous adhesions and oftentimes, fatal obstructive disease. Aggressive surgical cytoreductive therapy and intraperitoneal chemotherapy have been reported to improve clinical outcomes and new modalities, such as targeted therapy against growth factors such as epidermal growth factor, have been considered more recently.^{4, 6}

Similarly, mucinous neoplasms of ovary can be very challenging when it comes to distinguishing primary from metastatic tumours. Metastatic mucinous carcinomas appear to be more common than primary ovarian mucinous carcinomas.⁷ In a study by a Johns Hopkins group, the authors reported a ratio of 2.73:1 for metastatic versus primary ovarian tumours (including atypical proliferative (borderline) tumours and carcinomas in the primary ovarian mucinous tumour group).⁸

A very common scenario is that of an ovarian mucinous tumour associated with pseudomyxoma peritonei. The majority of these tumours are now considered to be of appendiceal origin with the very rare exception of origin in the ovary in a background of an ovarian teratoma.

The purpose of this overview is to trace the evolution of terminology for mucinous tumours in the appendix, describe the relationship with ovarian mucinous tumours and highlight the issues in separating primary from metastatic mucinous neoplasms in the ovary.

APPENDICEAL MUCINOUS NEOPLASMS

Woodruff and McDonald originally classified mucinous appendiceal neoplasms as 'benign mucocoele' and 'cystadenocarcinoma'. They defined the histological criteria for a diagnosis of cystadenocarcinoma as having a 'papillary arrangement of the mucous membrane and hyperchromatic, elongate nuclei'.

Later in the 1960s and 1970s, non-invasive tumours were classified as mucinous cystadenomas, or villous adenomas of the appendix, similar to the terminology used for colorectal adenomatous polyps with a similar morphology.^{3, 9} With introduction of the term 'adenoma' and the fact that these non-invasive tumours have the potential to spread within the peritoneal cavity, recur and even cause mortality in a percentage of patients, further complicated the issue. This confusion and controversy still continues today to a large degree.

An attempt has been made to resolve this confusion by introducing terminology in the appendix, such as borderline tumour,¹⁰ mucinous tumours of

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low malignant potential¹¹, and low-grade appendiceal mucinous neoplasm (LAMN)¹² by different authors. These terms try to convey the potential aggressiveness and possible fatal behaviour of these tumours despite bland histologic appearances of the appendiceal tumour and even the mucinous epithelium in peritoneal tissue.

In a review of 184 appendiceal mucinous tumours by the Armed Forces Institute of Pathology in 1995, the authors classified appendiceal mucinous lesions as adenoma, mucinous tumour of uncertain malignant potential and adenocarcinoma.² They defined adenoma as dysplastic tumours with intact muscularis mucosae with or without mucin dissecting through the appendiceal wall. Mucinous tumour of uncertain malignant potential was defined as dysplastic lesions with well-differentiated mucinous epithelium pushing deeply into the underlying tissue without obvious invasion or mucin present in the wall. Adenocarcinoma was defined as the presence of any neoplastic cells beyond the muscularis mucosae. This group considered any evidence of growth of tumour cells outside the appendix as a feature diagnostic of malignancy, therefore, any appendiceal mucinous tumour associated with pseudomyxoma peritonei is classified as adenocarcinoma, even if histologically typical of a non-invasive appendiceal cystadenoma. One problem with this classification was lack of clear definition for 'pushing invasion' that was used to categorise the new term 'appendiceal mucinous tumour of uncertain malignant potential'.² On the other hand, the definition of adenocarcinoma is the presence of neoplastic epithelium outside the appendix, and this depends on tissue sampling by the surgeon and the pathologist rather than on pure histological criteria alone.

In 2003, Misdraji,¹³ in a review of 107 low-grade appendiceal mucinous tumours, introduced the term, low-grade appendiceal mucinous neoplasm, for all low-grade mucinous tumours of the appendix that lack destructive invasion of the appendiceal wall, whether confined to the appendix or whether there is spread to the peritoneum. They used the term, adenocarcinoma, only for tumours with either high-grade cytology and/or destructive invasion.

In 2005, Pai and Longacre proposed the following classification for appendiceal mucinous neoplasms: adenoma, mucinous tumour of uncertain malignant potential, mucinous tumour of low malignant potential and adenocarcinoma.¹⁴

This classification introduced the new category of 'appendiceal mucinous tumour of low malignant potential' to define tumours that have spread to the peritoneum but are not clearly 'invasive'. This classification however, still contains subjective categories, such as uncertain malignant potential and low malignant potential which lack definitive, clear-cut morphological/histological criteria.¹⁴

Later in 2009, the same group (Pai and Longacre) based on reviews of 116 cases, proposed another classification. They suggested that in order to guide clinical management more accurately, it is required to incorporate cytoarchitectural features and extent of disease at presentation to define the categories of appendiceal tumours.¹¹

This classification divides mucinous lesions of appendix into four categories as follows:

1. Mucinous adenoma: defined cytologically as a low-grade mucinous columnar epithelial proliferation with flattened or villous architecture, absence of extra-appendiceal epithelium, extra-appendiceal mucin and invasion. The recommended clinical management is complete excision with a negative surgical margin.
2. Low-grade mucinous neoplasm with low risk of recurrence: Defined as a cytologically low-grade mucinous columnar

epithelial proliferation with flattened or villous architecture, with extra-appendiceal acellular mucin present, and absence of extra-appendiceal neoplastic epithelium and invasion.

3. Low-grade mucinous neoplasm with high risk of recurrence: this is a cytologically low-grade mucinous columnar epithelial proliferation with flattened or villous architecture, with the presence of any extra-appendiceal neoplastic epithelium, but an absence of invasion.
4. Mucinous adenocarcinoma: which is characterised by the presence of invasion that is defined as irregular, jagged, neoplastic glands beyond the muscularis mucosa, usually high-grade cytological features, with a simple or complex architecture.¹¹

Although there are occasional studies suggesting that if the appendix is grossly unremarkable, the chance of finding any pathology in appendix is low,¹⁵ this is not the consensus opinion and, currently, most centres require an appendectomy in any case of pseudomyxoma peritonei and/or mucinous ovarian lesion.⁶

There are also occasional reports in the literature using the term, primary mucinous borderline tumour of the appendix. This is not well-known nor a widely accepted/used terminology and, furthermore, there is no clear definition or diagnostic criteria for this term.¹⁶

It would appear that many gastrointestinal and gynaecologic pathologists use the terminology introduced by Misdraji¹³: LAMN for all low-grade mucinous tumours of the appendix lacking destructive invasion of the appendiceal wall, that are either confined to the appendix or that have spread to the peritoneum, and adenocarcinoma for tumours with either high-grade cytology and/or destructive invasion. The obvious attraction is that this classification employs just two categories of mucinous neoplasm, and if the lesion does not have the cytomorphological features of adenocarcinoma, it is by default a LAMN.

As can be seen from the above discussion, there have been numerous studies that have demonstrated the pathobiology of mucinous neoplasms of the appendix and suggested terminology for the various types of mucinous neoplasms encountered in the appendix. While these may be fundamentally sound and outcomes based, uptake and use is not uniform. There is an urgent need for standardisation of terminology and adoption of an optimal, clinically relevant classification system by organisations, such as the American Joint Committee on Cancer (AJCC), or WHO. Until such time that there is consensus and universal organisational ratification of terminology, we suggest that reporting pathologists should qualify their classification of appendiceal mucinous lesions by stating which particular system they have used. This will allow for oncologists to have a clearer idea of the nature of the lesion and will also allow for a valid comparison by other pathologists.

OVARIAN MUCINOUS LESIONS

Unlike the plethora of terms for mucinous lesions in the appendix, the terminology and nomenclature for primary ovarian mucinous tumours is settled and includes: mucinous cystadenoma, mucinous tumour of low malignant potential/mucinous borderline tumour (with or without intraepithelial carcinoma) and invasive mucinous carcinoma. Although the histological criteria and nomenclature for primary mucinous ovarian tumours appears to be well defined and standardised, the main diagnostic challenge of excluding a metastatic lesion from a primary ovarian mucinous neoplasm still remains. Several studies aiding this distinction have been published recently, and there has been

a significant change in the pathological approach to ovarian mucinous neoplasms. As a result of these investigations, it is now known that primary ovarian mucinous carcinomas are now much less common than previously thought. A considerable proportion of tumours previously treated as ovarian primaries have been shown to represent metastatic mucinous tumours from other organs.^{7 17 18} Two major categories of tumour have almost completely disappeared from the diagnostic spectrum. The first group is the ovarian 'borderline' mucinous tumour associated with pseudomyxoma peritonei. Most of the available data in the literature support the concept that these lesions originate from a primary appendiceal mucinous lesion.

The second group of lesions that are not routinely diagnosed is the widely disseminated primary ovarian mucinous carcinomas. Primary ovarian carcinoma of pure mucinous morphology has been shown to be low-grade and low-stage at presentation in the vast majority of cases, and very unlikely to demonstrate an aggressive clinical behaviour.¹⁹

Several criteria have been advanced to help distinguish primary ovarian mucinous tumours from metastatic mucinous tumours. Very large size, unilaterality, the presence of benign and borderline areas, expansile pattern of invasion, smooth surface and absence of extraovarian disease, all favour a primary ovarian neoplasm. By contrast, bilateral ovarian involvement, smaller size, ovarian surface involvement, multiple nodules and an infiltrative pattern of stromal invasion favour an extraovarian origin. However, not infrequently, there are cases that do not follow the aforementioned broad prescriptive patterns and thus pose significant diagnostic difficulty.

This is seen particularly in cases with a primary appendiceal mucinous neoplasm that is not obvious, grossly. The patient usually presents with a large unilateral multicystic ovarian mass without surface involvement, a borderline-like pattern of epithelial proliferation and focal confluent growth that falls short of being diagnostic for invasive adenocarcinoma. There is no evidence of extraovarian disease and the intraoperative comment is that the appendix looked unremarkable, grossly. Sometimes, the degree of nuclear atypia is more than what is expected in primary ovarian mucinous borderline tumours, and then a diagnosis of mucinous borderline tumour with intraepithelial carcinoma enters the differential diagnosis.

To compound matters further, pathologists might be asked to differentiate primary from metastasis on an intraoperative frozen section. Older studies suggest that using tumour size and laterality (bilateral tumours of any size or a unilateral tumour <10 cm favours metastatic, while a unilateral tumour >10 cm suggests a primary) can accurately distinguish primary and metastatic tumours in a majority of cases.^{8 20} However, the pitfall of these studies is that a substantial proportion of tumours previously classified as primary ovarian neoplasms, actually represented metastases from tumours elsewhere. Many investigators have tried to refine these old criteria and propose more accurate criteria to aid an accurate diagnosis in this clinical scenario.

Yemelyanova *et al* published a series of 194 cases of primary and metastatic mucinous ovarian tumours in 2008.⁸ They suggested that using the following criteria: bilateral tumours of any size, or a unilateral tumour <10 cm, favoured a metastatic lesion; while a unilateral tumour >10 cm favoured a primary, approximately 84% of all mucinous tumours were correctly classified, including 100% of all primary tumours and 77% of metastatic tumours.⁸ When they changed the size threshold to 12 cm, they showed that 100% of primary tumours and 80% of metastases (86% of all tumours overall) were correctly classified. Using 13 cm as the size criterion, their data showed correct

classification of 98% of primary tumours and 82% of metastases (87% overall).⁸

Then they tried to apply this algorithm to different subgroups based on the site of origin of the metastatic tumours. They concluded that metastatic colorectal carcinomas were the most common metastatic tumours to the ovary. Additionally, metastatic colorectal carcinomas and metastatic endocervical carcinomas were responsible for the greatest number of exceptions, even when using the optimised size criterion, to their algorithmic approach.⁸

Based on the above data and other studies it is suggested that metastasis from colorectal carcinomas should be considered when there are microscopic features suggestive of that diagnosis, even without known history of primary colorectal carcinoma, and no matter what the algorithm suggests. The morphological features suggestive of metastatic colorectal carcinoma include tumours with mucinous or hybrid mucinous/endometrioid differentiation in which the degree of nuclear atypia is more than what is usually found in primary ovarian mucinous tumours and, those tumours with 'garland pattern' glands containing 'dirty necrosis'.^{21 22}

Ronnett *et al* described the morphologic spectrum of ovarian metastases from appendiceal adenocarcinomas. Their data suggested that metastatic appendiceal adenocarcinoma should be considered in the differential diagnosis of mucinous ovarian tumours with signet-ring cell, goblet cell or intestinal-type differentiation, particularly in cases of bilateral ovarian masses or extraovarian spread of tumour.²³

The presence of numerous mitotic figures and apoptotic bodies in tumours with mucinous or hybrid mucinous/endometrioid differentiation is a feature suggestive, but not characteristic, of the human papillomavirus (HPV)-related tumours and should prompt further investigation to exclude the possibility of a primary cervical adenocarcinoma.⁸ The modified algorithm proposed by Yemelyanova *et al*⁸ is a useful adjunctive tool to distinguish primary versus metastatic ovarian tumours. However, there are still exceptions to the rule that require further investigations and other ancillary techniques, such as immunohistochemistry, to reach a definitive diagnosis.

ROLE OF IMMUNOHISTOCHEMISTRY

The role of immunohistochemistry in determining the origin of ovarian tumour (primary vs metastasis) is not straightforward or simple. Pathologists use immunohistochemistry with variable frequency. When there is no clinical history of an extraovarian primary site, but some morphological features suggestive of metastasis, immunohistochemistry can be helpful. The most commonly used markers to better characterise the origin of ovarian mucinous tumours are CK7, CK20 and CDX-2, bearing in mind that the results of immunohistochemical staining are not definitive or conclusive in many cases.

In cases with the following immunohistochemical coordinates: CK7 negative; CK20 and CDX-2 diffusely positive, we add a comment in the report that a colorectal origin is favoured, however, correlation with clinical findings is recommended.

An example of less conclusive immunohistochemical results is the immunoprofile: CK7 positive and CK20, CDX-2: focal positive staining. This immunoprofile is shared among primary ovarian mucinous carcinomas and pancreatobiliary, upper gastrointestinal tract and even, lung and breast carcinomas. Therefore, this CK7/20/CDX-2 limited panel is not helpful in some situations. Several attempts, with limited or very little success, have been made to include more specific markers to better determine the origin of an ovarian mucinous tumour.

Even after clinical correlation and immunohistochemistry, there will still be some ovarian mucinous tumours that cannot be definitively classified as primary versus metastatic. In these circumstances, the final classification and decision making for clinical management will depend on clinicopathological correlation and discussion in a multidisciplinary team meeting.

A vexing scenario that frequently confronts the gynaecological pathologist is distinguishing primary versus metastatic ovarian mucinous lesions in context of pseudomyxoma peritonei. Pseudomyxoma peritonei is a clinical condition that might be associated with pelvic/ovarian masses that are often bilateral. It is assumed that this is caused by rupture, leakage and/or metastasis of a mucinous neoplasm within the abdomen.

The appendix may appear unremarkable, grossly, or can be distended or indeed ruptured. Careful intraoperative assessment of the entire gastrointestinal tract, pancreatobiliary system and appendix is necessary and, an appendectomy is performed even if the appendix appears normal, grossly.⁶

The majority of these tumours are now considered from appendiceal origin with the very rare exception of a mucinous tumour arising in the background of primary ovarian teratoma.^{24 25} This has been investigated morphologically, immunohistochemically, and also molecular genetics by several authors.^{25–27} Appendiceal tumours are typically low-grade mucinous neoplasms and oftentimes do not show obvious invasion, as discussed earlier in this review.

The majority of data available support the concept that primary ovarian carcinomas are usually present as stage 1 disease, while widely disseminated mucinous carcinomas are rarely of ovarian origin. Therefore, in the clinical situation of a widely disseminated mucinous carcinoma and the presence of ovarian mass, a thorough work-up to exclude extraovarian origin is warranted. The current consensus is that true primary ovarian mucinous carcinomas are usually low-grade and low-stage at presentation, and do not behave aggressively.^{28 29}

As a result of this approach, there has been a reduction in the incidence of primary ovarian mucinous neoplasms (either borderline or carcinoma) in comparison to serous, clear cell and endometrioid carcinomas.¹⁹

Pinto *et al* in a study on 25 metastatic ovarian tumours, supported the idea that metastatic ovarian mucinous carcinomas are associated with more aggressive behaviour, higher morbidity, and with a higher chance of bilaterality, although they can occur as unilateral large masses as well (larger than 13 cm in diameter).³⁰

PSEUDOMYXOMA PERITONEI

Pseudomyxoma peritonei is a clinical entity in which there is mucinous ascites. It is currently accepted that it occurs most often secondary to an appendiceal mucinous lesion.³¹ The pathologic classification of pseudomyxoma peritonei and associated appendiceal tumours is also shrouded with controversy, not standardised, and contains varying terminology. In 1997, Ronnett *et al* introduced two pathologically and clinically distinct terms associated with pseudomyxoma peritonei.¹⁸ They defined 'disseminated peritoneal adenomucinosis' (DPAM) as voluminous mucinous ascites associated with histologically bland peritoneal mucinous neoplastic epithelium. They suggested that this process is often due to a ruptured appendiceal mucinous adenoma and has an indolent clinical course when surgically treated, but may recur over months to years. The second term, 'peritoneal mucinous carcinomatosis' (PMCA) by definition is characterised by the presence of abundant peritoneal mucinous tumour, (similar clinical presentation to

adenomucinosis) but the neoplastic mucinous epithelium demonstrates the architectural and cytologic features of carcinoma. This condition is associated with gastrointestinal mucinous adenocarcinomas and significantly worse prognosis compared with adenomucinosis. At that time, they also described a third group with intermediate or discordant histological features that were clinically similar to pure peritoneal carcinomatosis (PMCA-I).¹⁸ This group often had concomitant ovarian mucinous tumours that suggested primary ovarian neoplasia, however morphologic, immunohistochemical and molecular studies supported an appendiceal origin.¹⁸

Bradley *et al* reviewed a series of 101 patients with pseudomyxoma peritonei of appendiceal origin.³² All patients were treated with the same standardised protocol. The cases were divided according to previously published criteria into DPAM (58 cases), PMCA²³ and PMCA-I.²⁰ All cases with a signet-ring cell component were considered as PMCA. Based on their data of 1-year, 3-year and 5-year survival outcomes, they did not find a significant difference between DPAM and PMCA-I with regards to outcomes and parenchymal organ invasion. However, survival outcomes were significantly worse for PMCA. Based on these findings, they suggested a classification as follows: mucinous carcinoma peritonei low grade and, mucinous carcinoma peritonei high grade.³² However, this approach has not been widely used.

As discussed earlier, appendiceal origin is now considered the main aetiology for pseudomyxoma peritonei. The associated appendiceal tumour is frequently a low-grade mucinous neoplasm without obvious invasion; occasionally, invasive adenocarcinomas are also encountered. The outcome of the disease seems to be determined by the underlying appendiceal pathology.

LOCALISED EXTRA-APPENDICEAL MUCIN DEPOSITION

Occasionally, appendiceal mucinous neoplasms are associated with localised periappendiceal mucin deposits without diffuse peritoneal involvement. These mucin deposits may be acellular or contain neoplastic epithelium.

The biologic importance of localised, extra-appendiceal mucin, and the presence of neoplastic epithelium within mucin on patient outcome, are not clear.

Yantiss *et al* reviewed 65 patients with appendiceal mucinous neoplasms and localised periappendiceal mucin deposits without diffuse peritoneal involvement.³³ Patients were assessed for the presence of extra-appendiceal epithelium and followed them up for a mean period of 48 months. In 75% of patients, the appendix was submitted in total for histologic evaluation. 77% of cases contained acellular periappendiceal mucin, and in the remaining 23%, the mucin contained scanty neoplastic epithelium (size range: 1–12 cell clusters). Only 2 of 49 (4%) patients with acellular periappendiceal mucin developed diffuse peritoneal disease in the follow-up period. However, in neither of these two cases was the appendix submitted, in total, for histologic examination. By contrast, 5 of 15 (33%) patients with cellular periappendiceal mucin developed mucinous ascites, and one patient died of disease. The authors concluded that patients with appendiceal mucinous neoplasms and localised acellular periappendiceal mucin are unlikely to develop recurrent disease.³³

CONCLUSIONS

Mucinous neoplasms in the appendix and ovary are clearly linked. The state of the appendix is of paramount importance when assessing a mucinous ovarian tumour. In the presence of

pseudomyxoma peritonei, any mucinous tumour in the ovary is presumed to be of appendiceal origin until proven otherwise. There is no consistency with regards to terminology for mucinous neoplasms within the appendix. We recommend that pathologists use one of the suggested classification systems, but state clearly which one is being used and provide a detailed microscopic description so that some clinical relevance and context can be established. Secondary mucinous tumours to the ovary are far commoner than primary tumours, and clinicopathological correlation is very important.

We would also like to highlight the need for a widely accepted classification system for all appendiceal mucinous tumours, preferably one endorsed by the AJCC or WHO.

Take home messages

- ▶ The terminology for appendiceal mucinous is varied and inconsistently applied.
- ▶ While the terminology for ovarian mucinous neoplasms is settled, the diagnostic dilemma is separation of primary from secondary.
- ▶ Metastatic mucinous tumours are more common in the ovary than primary tumours.
- ▶ A mucinous ovarian tumour, in the presence of pseudomyxoma peritonei, is likely to be of appendiceal origin.

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