

# A practical approach for diagnosis of appendiceal mucinous neoplasms

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## Abstract

Classification of appendiceal mucinous neoplasms remains controversial, and while multiple classification systems have been proposed, no single system is universally utilized. A recent consensus by the Peritoneal Surface Oncology Group International (PSOGI) provides clear diagnostic criteria for appendiceal mucinous neoplasms and their corresponding risk for pseudomyxoma peritonei. Here, we briefly review appendiceal mucinous neoplasms and associated risk for pseudomyxoma peritonei, and discuss the diagnostic difficulties, our approach, and the reporting guidelines proposed.

**Keywords** appendiceal mucinous adenoma; appendiceal mucinous neoplasm; HAMN; high grade appendiceal mucinous neoplasm; LAMN; low grade appendiceal mucinous neoplasm; mucinous adenocarcinoma; pseudomyxoma peritonei

## Introduction

Pseudomyxoma peritonei (PMP) is a rare clinical syndrome characterized by accumulation of mucin and tumour implants in the peritoneum.<sup>1–3</sup> Prognosis is poor, with reports of improved survival following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).<sup>2</sup> Most examples of PMP develop from mucinous appendiceal neoplasms. Given the high cost and debilitating side effects of HIPEC, appropriate pathologic grading of appendiceal mucinous neoplasms is imperative. Unfortunately, classification of appendiceal mucinous neoplasms remains controversial, and while multiple classification systems have been proposed, no single system is universally utilized. We present a brief review of the classification of appendiceal mucinous neoplasms centred on diagnostic difficulties and our approach to such neoplasms.

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## Appendiceal mucinous adenoma

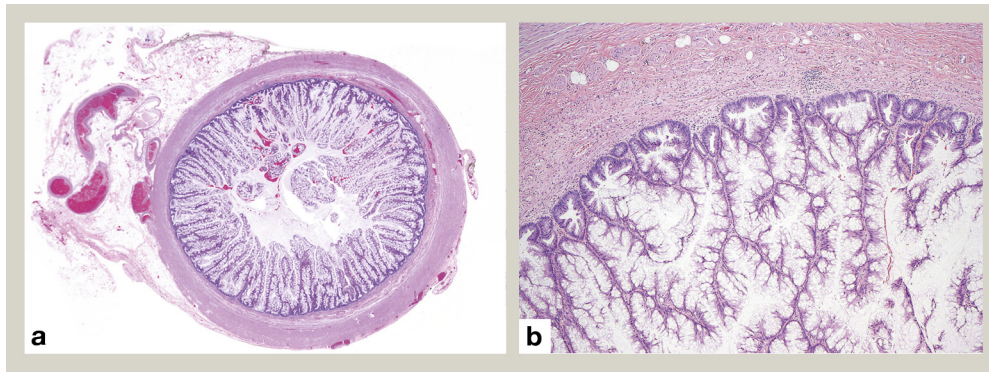
Although once debated, appendiceal mucinous adenomas are currently recognized by the World Health Organization as benign neoplasms.<sup>4,5</sup> They frequently occur in patients over 50 years, with a female predominance, and may be diagnosed incidentally in asymptomatic patients presenting with symptoms that mimic those of appendicitis.<sup>5,6</sup> Less frequently, they present as a mass or intussusception.

Macroscopically, the appendix appears normal or may be distended with intraluminal mucin only barring iatrogenic perforation. Microscopically the adenoma is a proliferation of simple or focally stratified mucinous epithelium, without cytologic atypia (Figure 1a).<sup>6</sup> The neoplasm is often circumferential and solely involves the mucosa without hyalinization of the muscularis mucosae (Figure 1a and b). As such, dissection of mucin through the appendiceal wall is absent (Table 1). Localized appendiceal tubular adenomas may be encountered in patients with familial adenomatous polyposis and rarely are sporadic.<sup>5,7</sup> Grading of appendiceal mucinous adenomas (low- or high-grade) is similar to that for tubular adenomas of the colon.<sup>5</sup>

The differential diagnosis includes retention cysts and low-grade appendiceal mucinous neoplasm (LAMN). Retention cysts lack neoplastic epithelium although evaluation of the entire appendix may be necessary to exclude an adenoma.<sup>5</sup> Identification of any residual papillary architecture as well as tall mucinous columnar cells is helpful in making a diagnosis of adenoma. Features such as nuclear pseudostratification in an otherwise flattened epithelium are suggestive but not diagnostic of neoplasia since reactive epithelial changes include focal nuclear pseudostratification. Examination of the muscularis mucosae is key in identifying a LAMN. The muscularis mucosae is intact throughout a mucinous adenoma. However involvement of a true appendiceal diverticulum by adenoma presents a potential diagnostic pitfall. A diagnosis of appendiceal mucinous adenoma requires a diligent review of the entire appendix to exclude extra-mucosal involvement, and appendectomy is curative.<sup>5</sup> However, many pathologists are reluctant to diagnose mucinous adenoma and essentially regard all such lesions as LAMN, as noted below since the interpretation of mucinous adenoma implies negligible risk for progression to pseudomyxoma peritonei whereas an interpretation of LAMN leaves the possibility open. However, this approach can sometimes lead to overtreatment of extremely low-risk lesions.

## Low-grade appendiceal mucinous neoplasm (LAMN)

LAMNs often present in females, in the sixth decade. Macroscopically the appendix may be unremarkable or distended with mucin (Figure 2a). Mucin deposits may be present within a thinned wall (Figure 2b), or present on the serosal surface due to rupture. Microscopically, LAMNs display villous mucinous epithelium with flat, columnar or cuboidal epithelial cells (Figure 3a–d). Extensive mucin accumulation within the appendiceal lumen leads to “pressure atrophy,” and flattening of the epithelium (Figure 3c). The LAMN epithelium often appears deceptively bland, with a hyperplastic (cuboidal epithelial cells with abundant intracytoplasmic mucin compressing the nuclei) rather than neoplastic (elongated, pseudostratified nuclei with



**Figure 1** Mucinous adenoma. (a) At low power, note the circumferential involvement with otherwise preserved architecture. (b) At higher power, the adenoma features abundant mucinous epithelium.

apical or scant cytoplasmic mucin) appearance (Figure 3b & d).<sup>4,8</sup> Scant lamina propria with atrophy of lymphoid follicles (Figure 3a & c) and a fibrotic or hyalinized muscularis mucosae (Figure 3c and d) are also characteristic features of LAMN.

Characteristically, LAMNs display a “pushing” pattern into the appendiceal wall (Figure 4a); an attenuated lamina propria and muscularis mucosae are indicative of pushing invasion such that some observers regard LAMNs with this pattern as low-grade adenocarcinomas (Table 1). This pattern is not associated with the infiltrative, single cell invasion characteristic of conventional invasive adenocarcinoma. Desmoplasia and tumour budding are a feature of overt malignancy. Pushing invasion through the appendiceal wall results in extra-appendiceal mucin accumulation that presents a diagnostic dilemma. LAMNs characteristically grow slowly and have an associated risk for pseudomyxoma peritonei (discussed later), but do not usually spread beyond the peritoneum or metastasize to lymph nodes.<sup>4</sup>

The differential diagnosis for LAMN includes reactive epithelial changes in a mucocele, appendiceal mucinous adenoma and invasive mucinous carcinoma. Appendiceal mucinous adenomas are perhaps the most difficult to exclude due to their nonneoplastic cytology. However, a serrated appearance, well preserved lamina propria, and involvement of the mucosa alone are clues to diagnosis. Additionally the adenoma typically is circumferential and should not extend longitudinally down the appendix. Adenomas involving appendiceal diverticula (Figure 5b) are often encountered as difficult cases especially when associated with abundant mucin or in an everted diverticulum with serrated epithelium exposed on the serosal surface. Careful (low power microscopy) examination of the entire appendix often leads to identification of the diverticulum. A preserved lamina propria is also present.

### Risk assessment for pseudomyxoma peritonei in appendiceal mucinous adenoma and low grade appendiceal mucinous neoplasms

Several schemes for risk assessment of mucinous neoplasms of the appendix are available, all of which use different terminology. An early study of histopathologic features of mucinous appendiceal neoplasms showed that extra-appendiceal neoplastic epithelium, high grade cytology, architectural complexity, and

invasion were of prognostic value.<sup>8</sup> Risk categories were identified as mucinous adenoma, low risk LAMN, high risk LAMN, and mucinous adenocarcinoma. All but the adenocarcinoma category demonstrate low grade cytologic atypia (mildly enlarged hyperchromatic nuclei with inconspicuous nucleoli and minimal mitotic activity), simple architecture, and lack of invasion. There is essentially no risk of PMP in a true appendiceal adenomas, as they lack both extra-appendiceal mucin and invasion on histologic examination of the entirely submitted appendix.<sup>8,9</sup> As such, complete appendectomy is essentially curative.

The presence of mucin deposits outside the appendix has historically been associated with an unfavourable prognosis, likely due to the impossibility of histologically assessing the entire peritoneal surface for neoplastic epithelium. Low risk LAMNs are regarded as those either confined to the appendix or exhibiting extra-appendiceal mucin as focal deposits on the serosa, copious peri-appendiceal mucin, or peritoneal mucin deposits outside the right lower quadrant, *devoid of epithelial cells* (Figure 4a and b).<sup>4,6,8</sup> More recent studies have shown a 4%<sup>10</sup> and 8%<sup>8</sup> risk of peritoneal recurrence, with the acknowledgment that the appendix was not entirely submitted for microscopic examination in all cases with recurrence. Of note, the degree of cellularity has not been shown to increase risk; it is solely the presence or absence of epithelial cells that is of prognostic significance.<sup>8,11</sup> Also, although the presence of mucin outside the right lower quadrant was suggested to reduce survival<sup>7</sup> in a very early study, it was not been conclusively proven due to the heterogeneity of neoplasms represented in the study and more recent studies are in consensus with Young et al.<sup>8,10,11</sup>

While reporting the risk of recurrence as low is an imperfect quantification, the use of mucinous appendiceal tumour of uncertain malignant potential is an imprecise, ‘catch-all’ phrase that confers even less information.<sup>8</sup> As such, confusion may ensue about the possibility of a high risk neoplasm. In light of a limited number of reported cases, the optimal management for low-risk LAMNs remains unclear. Follow-up with radiographic imaging of the abdomen and pelvis appears to be adequate surveillance for low risk LAMN in the limited number of cases reported.<sup>8</sup> In practice we report these cases as “*Low-grade appendiceal mucinous neoplasm (LAMN) with extra-appendiceal mucin deposits devoid of epithelium,*” and include a note stating that there is a low risk of subsequent pseudomyxoma peritonei.

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