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Low grade appendiceal mucinous neoplasm – A case series of 12 cases with review of literature

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Appendiceal neoplasm, Low-grade appendiceal mucinous neoplasm (LAMN), Mucinous Neoplasm, Pseudo-myxoma peritonei (PMP).

ABSTRACT

Background: Low-grade appendiceal mucinous neoplasm is a rare epithelial tumour of the appendix, accounting for 1% of gastrointestinal neoplasms and found in less than 0.3% of appendectomy specimens. It is histologically characterized by a villous or flat proliferative mucinous epithelium with low-grade cytological features. Prognosis depends on the presence of neoplastic epithelium and mucin outside the appendix, which increases the risk of peritoneal dissemination.

Materials and Methods: Present case series reviews 12 cases diagnosed between 2020 and 2024, analyzing clinical, radiological, and histopathological findings. Cases were staged using AJCC 8th edition, emphasizing the importance of standardized examination for accurate diagnosis and prognosis.

Results: The median patient age was 55 years, with a slight female predominance. Abdominal pain was the most common symptom. All cases exhibited intraluminal mucin with low-grade mucinous epithelium. Two cases had extra-appendiceal mucin (pT3 and pT4a), while the remaining were confined to the appendix (pTis). No recurrence was observed.

Conclusions: Low grade appendiceal mucinous neoplasm remains a diagnostic and prognostic challenge, requiring thorough histopathological evaluation. Standardized staging and long-term follow-up are crucial for optimal management.

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INTRODUCTION

Appendiceal epithelial tumours are scarce. Most appendiceal neoplasms are found during surgery or postoperatively in appendectomy specimens. A subgroup of epithelial tumours, including those with uncertain malignant potential and adenocarcinomas, are known for their extensive mucus production and therefore, belong to the group of mucinous appendiceal neoplasms. A subgroup of mucinous appendiceal lesions can be classified as Low-grade appendiceal mucinous neoplasm (LAMN).

Patients with LAMN show different characteristics, clinical course, and survival than patients with a mucinous adenocarcinoma. Patients are generally young, with a median age of approximately 53 years, and with a slightly female predominance (60%). Among all mucinous appendiceal neoplasms without peritoneal spread, it has the most favorable prognosis.[1-3]

MATERIALS AND METHODS

Appendiceal mucinous neoplasms (n = 12) diagnosed between 2020 and 2024 were retrieved from the institutional pathology database after institutional review board approval. Inclusion criteria for this study consisted of meeting the World Health Organization (5th Edition) histologic criteria for LAMN.

Three pathologists reviewed slides for each study case, noting the following gross and microscopic features: dimensions of the appendix, cystic dilation, perforation, acute appendicitis, loss of muscularis mucosae (patchy vs complete), maximum depth of involvement (by acellular mucin or neoplastic epithelium), and peritoneal involvement (in the form of acellular mucin or neoplastic epithelium). An effort was made to distinguish true serosal mucin deposits from artifactual displacement of mucin from the appendiceal lumen occurring during specimen dissection, and the presence of tissue reaction accompanying serosal mucin was noted. Each LAMN was pathologically staged according to the current AJCC staging criteria (8th Edition).

All procedures performed in the study were approved by IRB and/or the national research ethics committee (NHLIRB/2024/FEBRUARY/26th/No.-8) per the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

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CASE REPORTS (Table 1)

Table 1: Summary of twelve cases of Low-grade appendiceal mucinous neoplasm.

Sr No.	Age (years/ gender	Clinical Presentation	Radiological Presentation	Pertinent gross findings	Presence of Extraappendiceal Mucin	Involvement of Proximal Surgical Margin	Histopathology	Grade/ Stage
1.	56 / F	Abdominal Pain	Dilated Appendix	Size: 4x1x1cm, with presence of mucoid material.	No	Uninvolved	flat and villous neoplastic mucinous epithelium with atrophy of lymphoid tissue and lamina propria. (fig.2)	Grade I / pTis
2.	65 / M	Swelling and pain in right lower abdomen	Solid cystic lesion	Size: 6cm, with solid-cystic cut surface, dilated lumen filled with mucinous material.	Yes	Uninvolved	Mucinous material filling the lumen with loss of lamina propria and muscularis mucosa with fibrosis of submucosa, acellular mucin in the wall.	Grade I / pT4a
3.	75 / M	Mucous discharge per rectum	Mucocele Appendix	Size: 6cm, with presence of jelly like material on cut surface.	No	Uninvolved	Villous and flat proliferation of mucinous epithelial cells with abundant apical mucin and elongated nuclei. Focal loss of underlying lymphoid tissue	Grade I/ pTis
4.	55 / F	Abdominal Pain	Dilated Appendix	Size: 5cm, with jelly like material on cut surface.	No	Uninvolved	Dilated lumina with tenacious mucinous secretion and flat mucinous epithelial cells. Atrophy of underlying lymphoid tissue with crypt loss.	Grade I/ pTis
5.	70 / F	Right flank pain	Dilated Appendix	Size: 3cm, with mucin like material on cut section.	No	Uninvolved	Flat and villous neoplastic mucinous epithelium with atrophy of lymphoid tissue.	Grade I/ pTis
6.	36 / F	Swelling and pain in right lower abdomen	Mucocele Appendix	Size: 7cm, with lumen filled with mucin.	No	Involved	Mucinous epithelium with mild nuclear atypia and pseudo stratification without architectural complexity. Acellular mucin pools in walls focally. Chronic inflammation with foreign body giant cell reaction is seen.	Grade I/ pTis
7.	26 / M	Right flank pain	Inflamed appendix	Size: 7cm, with glistening areas on cut surface.	No	Uninvolved	Low grade nuclear atypia without architectural complexity, atrophy of underlying lymphoid tissue and effacement of muscularis mucosa. Acellular dissecting mucin pools with desmoplastic stromal response involving the subserosa of the appendix are seen. (fig.2)	Grade I/ pT3
8.	32 / F	Right flank pain	Inflamed appendix	Size: 6cm, with dilated lumen at tip containing mucinous material	No	Uninvolved	Mild nuclear atypia and pseudo stratification without architectural complexity. Focally wall shows acellular mucin pools.	Grade I/ pTis
9.	55 / M	Right flank pain	Inflamed appendix	Size: 3.5cm, with obliterated lumen.	No	Uninvolved	Extravasation of mucin upto the muscularuis propria and hemorrhagic infarct.	Grade I/ pTis
10.	35 / F	Right flank pain	Dilated Appendix	Size: 6cm, with jelly like material on cut surface.	No	Uninvolved	Flat proliferation of mucinous epithelium with occasional villi, low-grade nuclear atypia.	Grade I/ Size:pTis
11.	56 / M	Swelling and pain in right lower abdomen	Mucocele Appendix	Size: 14cm, with mucinous material on cut surface. (fig.1)	No	Uninvolved	Thinned out epithelium, focal mucosal denudation, infiltration of muscularis propria by acellular mucin. Flat proliferation of mucinous epithelium, low-grade atypia is seen. Presence of inflammation and foci of fibrosis is evident. (fig.2)	Grade I/ pTis
12.	68 / F	Pain in right lower abdomen	Mucocele Appendix	Size: 11.5cm, with mucinous material on cut surface.(fig.1)	No	Uninvolved	Thinned out epithelium, infiltration of muscularis propria by acellular mucin. Flat proliferation of mucinous epithelium with low-grade atypia. (fig.2)	Grade I/ pTis

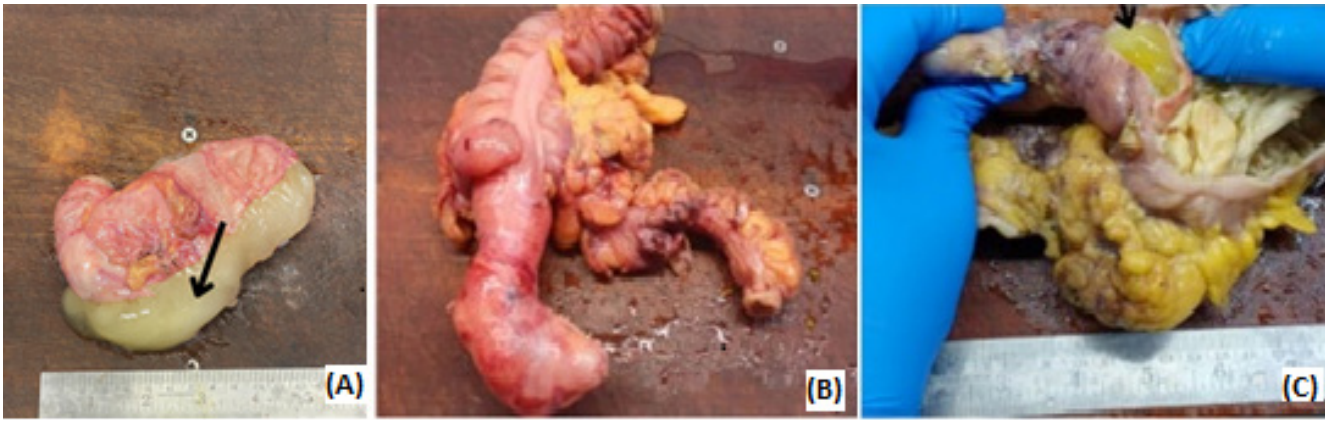

Figure 1:*Gross findings. (A) Cut section of dilated appendix showing extravasation of mucin (Case 11); (B,C) Cut section of tumour showing extravasation of mucin in a dilated appendix (Case 12).*

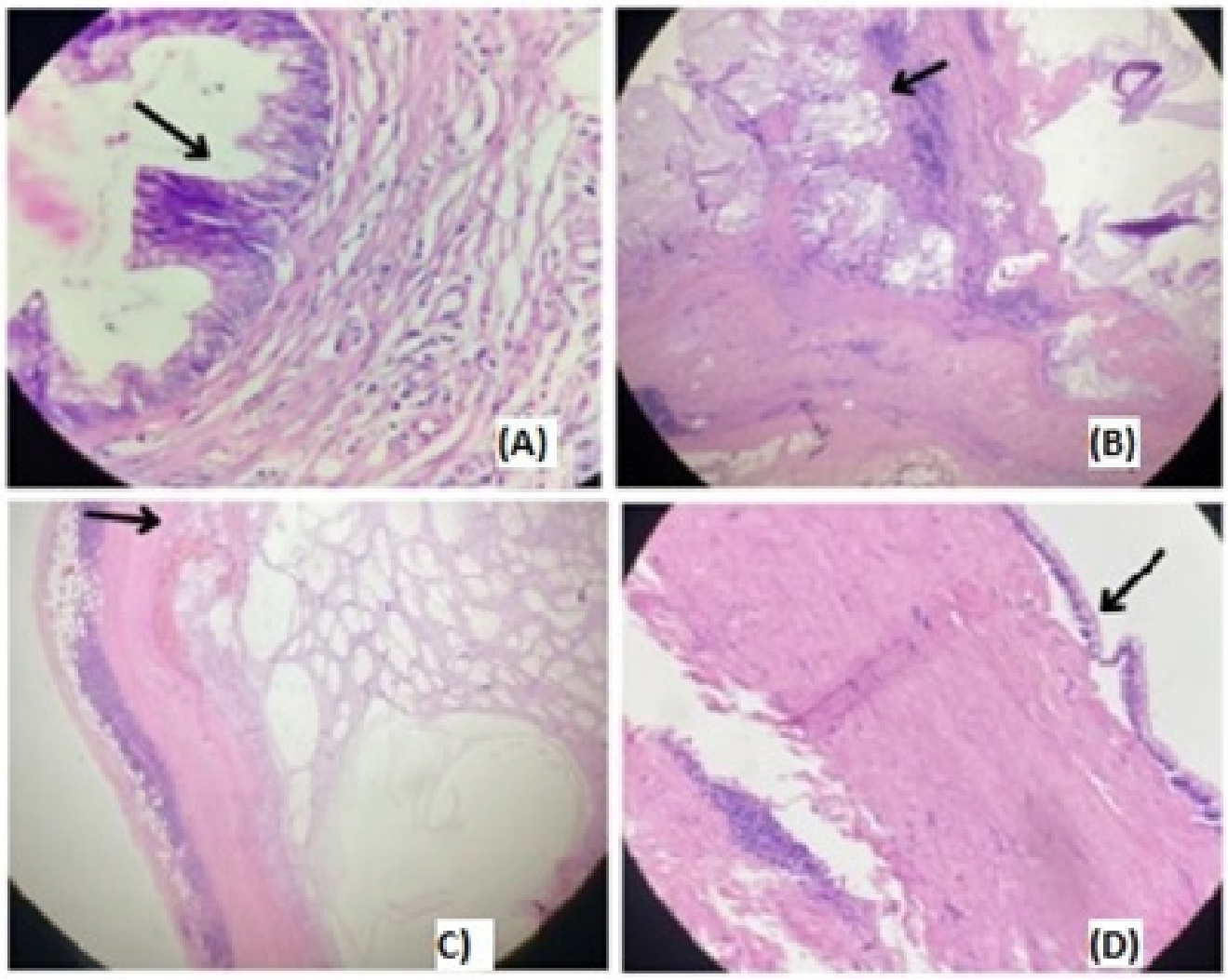

Figure 2: *(A)High power view showing laters of dissection mucin. (Case1) [H&E, 40x]; (B) Mucinous deposits. (Case 7) [H&E, 10x]; (C) Low power view showing layers of dissecting mucin. (Case 12) [H&E, 10x]; (D) Mucinous epithelium with atrophic lymphoid follicles. (Case 12) [H&E, 10x].*

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DISCUSSION

LAMN is a rare malignancy accounting for 1% of gastrointestinal neoplasms and is found in less than 0.3 % of appendectomy specimens.[4-6] The classification, nomenclature, and histological criteria of mucinous epithelial tumours in the appendix have been the source of considerable controversy. In particular, mucinous epithelial tumours that penetrate deeply into or through the appendiceal wall and disseminate to the peritoneal cavity, resulting in pseudomyxoma peritonei (PMP), were the source of much of this controversy.[7] For example, the exact nature of their biological potential (benign vs malignant, invasive vs non-invasive) has been the source of debate and confusion. Historically, they were classified as either ruptured adenomas with the dissemination of adenomatous epithelium or as adenocarcinomas.[8,9]

LAMNs are mucinous neoplasms with low grade-cytological features that are either confined to the mucosa or show "pushing" invasion into or through the wall of the appendix and when the appendix ruptures, they may spread into the peritoneal cavity as pseudomyxoma peritonei. Earlier, low-grade appendiceal mucinous tumours were classified as "malignant mucoceles" or "grade I, non-invasive, papillary adenocarcinoma of the appendix".[10-12] Later, these lesions were reclassified as benign neoplasms and the term cystadenoma was applied to denote their resemblance to colonic adenomas and to reflect their low-grade cytologic features, lack of destructive invasion, and benign clinical course.[13,14] However when these tumours spread beyond the appendiceal wall, terms such as "ruptured mucinous cystadenoma" or "mucinous adenocarcinoma" have been used, which has created confusion. Due to poorly defined criteria for tissue invasion in these tumours, terms such as "mucinous tumours of uncertain malignant potential" or "borderline tumour" were used.

Misdraji, in 2003, proposed the term "low-grade appendiceal mucinous neoplasm (LAMN)" to describe confined appendiceal neoplasms with or without pushing invasion, which explains their indolent but progressive malignant behavior yet an absence of infiltrative invasion or high-grade cytology. The tumours associated with extra appendiceal mucin were classified by Pai and colleagues, as "low-grade mucinous neoplasm with low risk of recurrence" if the mucin located outside the appendix was acellular or "low-grade mucinous neoplasm with a high risk of recurrence" if it contained neoplastic epithelium.[15] In the 2010 WHO classification of appendiceal tumours, the term LAMN was incorporated into the spectrum of appendiceal adenocarcinomas describing them as low-grade mucinous adenocarcinoma with pushing rather than infiltrative invasion.

LAMNs usually present in 6th decade of life, although the age range of presentation is quite broad. There is a predilection for females. Patients may present with abdominal pain, a palpable abdominal mass, or even ovarian metastasis. Other presentations include intussusception of the appendix or the finding of mucin within a hernia sac. Approximately 15-20% of LAMNs are discovered incidentally in patients who have undergone surgery for an unrelated condition.[16]

Activating mutations in the Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide (GNAS) gene are seen in 50% of LAMNs and the cell lines, this was associated with increased expression of the mucins MUC2 (Mucin 2) and MUC5AC (Mucin 5AC). GNAS mutations play an important role in the prominent mucin production that is a hallmark of LAMNs and PP.[17]

On USG, mucinous neoplasms appear as an encapsulated, elongated, or ovoid cystic lesion in the appendix with an internal onion-skin appearance, which represents lamellated mucin and is considered pathognomonic.[17] On CT, an appendix with a diameter of more than 15mm, soft tissue mass, wall thickening, or irregularity should raise the suspicion of mucinous neoplasm.[18]

Clinically, the majority of our cases presented with abdominal pain or discomfort, which are broadly non-specific. Histopathological evaluation is essential for the diagnosis. While LAMNs have an indolent course, they must be managed properly so that they do not progress into a much more challenging and life-threatening condition known as PMP.

Histologically, LAMN is characterized by a villous or flat proliferative intestinal-type mucinous epithelium with low-grade cytological features. In typical LAMNs, there is a loss of the normal mucosal architecture, at least focally, such as obliteration of the lamina propria and muscularis mucosa, fibrosis of the submucosa, and atrophy of the lymphoid follicles. (fig.2) Historically, tumours that were confined to the mucosa were previously classified as "adenomas". But they may also infiltrate deeply into, or through the appendiceal wall and disseminate to the peritoneal cavity, resulting in a clinical syndrome known as PMP. Although LAMNs confined to the appendiceal lumen do not show definitive malignant features, they can proliferate outside the appendix in a malignant manner and can result in the development of PMP, a life-threatening complication with 45% 10-year survival.[19,20]

Before diagnosing LAMN, it is essential to consider and rule out other conditions with similar clinical and radiological features. These mimics include:

1. Appendiceal diverticulitis - A common mimic of LAMN. Both conditions can show cytological atypia, crypt disarray, hyperplastic/serrated features, lymphoid atrophy, and extrusion of mucin into the wall of the appendix or beyond the serosa. Features favoring LAMN are a villous architecture, mucinous epithelial cells, effacement of lamina propria, crowded

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crypts and cytological dysplasia. Features favoring diverticular disease include preservation of essential mucosal architecture, hyperplastic and hypermucinous changes confined to the luminal portion of the mucosa, and reactive atypia rather than dysplasia.

2. Uncomplicated or perforated acute appendicitis - Appendectomy specimens obtained after an episode of perforated appendicitis frequently display exuberant mucosal hyperplasia, diverticula, and organizing mucin pools in and around the appendix, all of which can closely mimic low-grade appendiceal mucinous neoplasms.[21]

   Our case series showed no evidence of perforation (macroscopically) and lack of histological signs of acute inflammation favored the diagnosis of LAMN.

3. Serrated polyps of the appendix – Sessile serrated lesions of the colorectum have different genetic abnormalities and do not have the same spectrum of appearances as colorectal lesions. Serrated polyps are characterized by preservation of mucosal architecture with no loss of muscularis mucosae. By contrast, most LAMNs have an undulating or flattened pattern of growth. In borderline cases, a diagnosis of LAMN is suggested by the presence of filiform villi, areas of undulating or flattened architecture, hyaline dense fibrosis of the underlying tissues, loss of muscularis mucosae, or any evidence of pushing invasion, including the presence of mucin (that may or may not also contain neoplastic epithelium) in the wall or outside the appendix. Many appendices with LAMN or adenocarcinoma contain areas of serrated polyp, suggesting that these may be a precursor to more aggressive tumours.

4. On rare occasions, endometriosis with intestinal metaplasia – It can resemble an appendiceal mucinous neoplasm. The epithelial component acquires an intestinal phenotype characterized by columnar mucin-secreting cells, sometimes with goblet cell morphology. Dissecting acellular mucin is common and epithelial atypia may be seen. Recognizing endometrial stroma surrounding the glands will lead to the correct diagnosis and conventional endometriosis is usually visible elsewhere in the appendix.[22]

Staging Challenges in Appendicectomy Specimens: -

1. LAMN Stage pT_{is} vs pT_3 - LAMN confined to the muscularis propria is assigned the T category of Tis (LAMN); pT1 and pT2 designations do not apply. If acellular mucin or mucinous epithelium is identified beyond the muscularis propria in the subserosa or mesoappendix, it should be classified as pT3, as long as the mucin does not involve serosal (visceral peritoneal) surface. Some cases have been reported that show effacement of appendiceal wall by proliferative mucinous epithelium resulting in "mucin resting on subserosa" thereby mimicking pT3.[23] In these cases, the distinction between pTis and pT3 is based on the finding of residual muscularis propria. It has been suggested that the pT3 category could be down-staged as the outcome is similar to pTis (LAMN) group.

2. LAMN T_{is} versus T_{4a} - LAMN can involve the serosal surface (visceral peritoneum) of the appendix without diffuse peritoneal involvement. The involvement in these cases may be by acellular mucin and/or neoplastic mucinous epithelium. It is also important to be aware that mucin can be extruded onto the appendiceal surface due to handling or disruption of the specimen, either intraoperatively or during gross examination. Thus, the mere presence of mucin on the surface of the specimen does not warrant a T4a designation. For the acellular mucin to be considered for staging, associated features such as mesothelial hyperplasia, neovascularization, dissection of tissue planes, and/ or inflammation should be present.

   None of these patients developed recurrence. The one patient with a pT3 LAMN did not recur after months of follow-up. All patients with pT4a LAMN underwent cytoreductive surgery and additionally received intraperitoneal chemotherapy, but the duration is not known as the patient was treated at an outside institution. As our case series is limited and exhibits the majority of pTis cases, follow-up was not maintained in all the cases. The cases that were followed up showed no recurrence and required no further management.

CONCLUSIONS

Here we have presented twelve appendicectomy specimens with all the cases exhibiting morphological findings of LAMN. As stated in various literature, the presence or absence of mucinous epithelial cells in extra-appendiceal mucin is the critical factor in determining the prognosis. As many appendiceal tumors are found incidentally, the gross examination should be meticulously performed, with inking of specimen and margin status (proximal resection margin).

Simultaneously, a synoptic report should be provided with the inclusion of all the essential data elements (histologic grade, margin status, tumor extent, lymphovascular invasion, etc. Mimics of LAMN should be ruled out, to lessen the overdiagnosis of low-grade appendiceal mucinous neoplasm.

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