Case Series

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Low-grade Appendiceal Mucinous Neoplasm: A Series of Four Cases

Pathology Section

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ABSTRACT

Low-grade Appendiceal Mucinous Neoplasm (LAMN) is a rare malignant neoplasm seen in less than 0.3% of appendectomy specimens. Patients with LAMN can present with abdominal pain, mimicking appendicitis clinically. In later stages, it can rupture, leading to Pseudomyxoma peritonei (PMP). Therefore, a high clinical suspicion is needed for correct diagnosis and management. The prognosis of LAMN depends on the presence or absence of mucin/neoplastic epithelium outside the appendix. For LAMN confined to the appendix, appendectomy alone is sufficient for management, with conservative follow-up. For LAMN with extruded acellular mucin localised to the appendiceal serosa, management involves appendectomy and PMP surveillance. For all mucinous lesions of the appendix, it is essential to submit the entire appendix for histopathologic examination, thoroughly evaluating the presence of mucin/neoplastic epithelium involving the serosa/extra appendiceal tissue for accurate staging and to predict the risk of recurrence and determine further management. Here four cases of LAMN due to their rarity and clinical importance is presented. This study of four cases emphasises that the clinical diagnosis of this rare malignancy is difficult, and radiological investigations were not available as these patients presented with clinical features mimicking appendicitis. Emergency appendectomy was performed in all cases. LAMN should be considered as a differential diagnosis because if not diagnosed and treated in the early stages, it can lead to dreaded complications like PMP. The histopathological examination of all four cases of LAMN showed dissecting acellular mucin in various stages of progression in the appendicular wall, but none involving the serosa. This highlights the importance of timely surgical intervention and histopathological examination for an exact diagnosis and staging of LAMN for further follow-up or treatment.

Keywords: Appendicectomy, Mucin, Pseudomyxoma peritonei

INTRODUCTION

LAMN is a rare malignant neoplasm, accounting for 1% of gastrointestinal neoplasms and is found in <0.3% of appendectomy specimens [1]. This rare malignancy is most commonly discovered incidentally during operative exploration and is often diagnosed late. It can also present with symptoms such as abdominal pain, vomiting, abdominal distention, mass lesion, or intestinal obstruction. In rare cases, urological findings such as haematuria, ureteral obstruction, hydronephrosis, and urinary tract infection may occur [1-3]. LAMN often presents similarly to acute appendicitis due to appendix distension, and a definitive diagnosis can only be made through histopathological examination of the appendix [4]. Ultrasound of the abdomen is considered the primary diagnostic modality for appendiceal lesions, which can potentially differentiate between benign and malignant lesions [5]. LAMNs typically appear as cystic, thin-walled, fluid-filled structures with or without calcifications in the appendix wall [6]. Tumour marker tests, including Carcinoembryonic Antigen (CEA) and Carbohydrate Antigen 19-9 (CA-19.9), should be included in the lab work-up [7]. Research has shown that these tumour markers are more useful as predictive indicators of recurrence rather than diagnostic biomarkers [8]. This appendix tumour presents serious complications, including the risk of appendix rupture and the spread of mucin and neoplastic cells into the peritoneum, leading to PMP [2,3]. Peritoneal seeding typically occurs in the advanced stages of the disease.

In present case series, patients presented with vague appendicitis symptoms, and appendectomies were performed with a clinical diagnosis of acute appendicitis. Histopathological examination of all four cases revealed LAMN with varying degrees of dissecting acellular mucin progression through the appendiceal wall but without involvement of the serosa. Histopathological diagnosis is crucial for staging the neoplasm and guiding further follow-up and treatment. Therefore, timely intervention is necessary to prevent LAMN dissemination and further progression to PMP.

CASE SERIES

The study was conducted at the Department of Pathology of a tertiary care hospital. Out of 166 appendectomy specimens received in the Department of Pathology, Andaman & Nicobar Islands Institute of Medical Sciences, Portblair, Andaman & Nicobar, India from January 2021 to December 2022, four cases were diagnosed as LAMN, based on the World Health Organisation (WHO) diagnostic criteria [9].

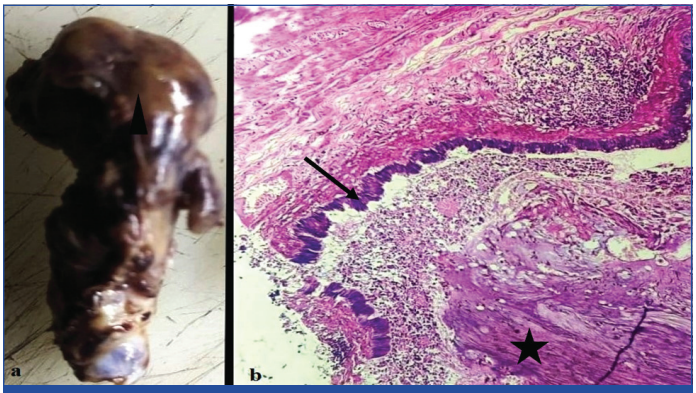
Case 1

A 51-year-old female presented with a sudden onset of colicky pain in the right iliac fossa lasting for one day, accompanied by nausea, vomiting, and fever. She had a history of constant dull aching pain for one month, initially around the umbilicus and later shifting to the right iliac fossa. There was no history of dysphagia, constipation, or urinary symptoms. Physical examination revealed tenderness at the right lower quadrant and McBurney's point. Complete blood count was within normal limits. Radiological investigations were not performed as emergency laparoscopic appendectomy was carried out.

Gross examination revealed an appendix measuring 4.5 cm in length with a grey-brown and congested external surface. On cut-section, a dilated lumen at the tip measuring 2.2 cm in diameter was observed, filled with mucinous material, and mild wall thickening measuring 0.4 to 0.6 cm. Gross examination did not reveal any evidence of perforation or extrusion of mucin [Table/Fig-1a].

Histomorphology showed a mildly dilated lumen with extensive denudation of the lining epithelium, which was replaced by acellular pools of mucin with pushing invasive margins. This mucin

was confined to the lamina propria. The subepithelium exhibited loss of lymphoid follicles and areas of congestion. There was no evidence of invasion into the muscularis propria [Table/Fig-1b]. No definite evidence of dysplasia in glandular epithelium or invasive malignancy was observed. The resected margin was free of mucin or tumour. The final diagnosis of LAMN (pTis-pathological tumor stage carcinoma in situ) was made, and the postoperative period was uneventful. The patient was discharged, and during regular follow-up after three months, the patient remained asymptomatic. Abdominal ultrasound showed no significant findings, and no further intervention was required.

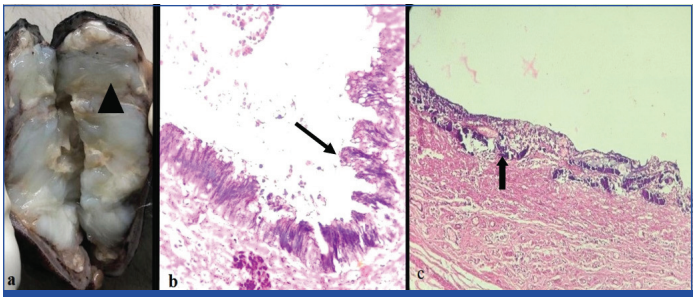


[Table/Fig-1]: Case 1: a) Gross appearance showing dilated tip of appendix (arrowhead) and filled with mucinous material with mild wall thickening; b) Flat lining columnar cells (arrow) and the lumen showing abundant mucin (star) (H&E stain, 10X).

Case 2

A 35-year-old female presented with right lower abdominal pain persisting for three weeks. Upon examination, a mass was palpated in the right lower quadrant. Laboratory investigations revealed elevated CEA levels. During the surgery, a large dilated appendix containing inspissated mucoid material was observed, leading to an open appendectomy.

Gross examination showed an 8 cm long appendix with a diameter of 2.5 cm. The external surface appeared congested. Upon sectioning, the entire lumen was found to be dilated and filled with mucoid material [Table/Fig-2a]. The wall thickness measured between 0.2 to 0.5 cm. No gross evidence of mucin perforation or extrusion was observed.



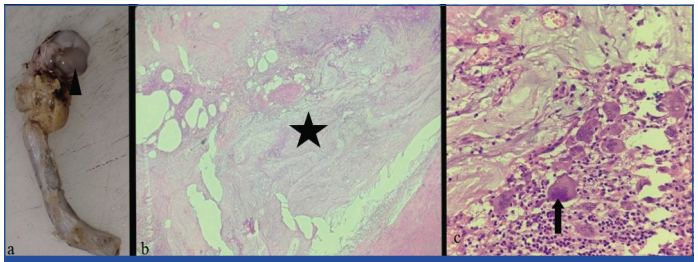
[Table/Fig-2]: Case 2: a) Gross appearance showing entire dilated appendix that was filled with mucoid material (arrowhead); b) Villiform lining columnar cells (arrow) (H&E stain, 40X); c) Foci of dystrophic calcification in the wall (arrow) (H&E stain, 10X).

Histomorphology revealed that the appendix was partially lined by a villiform layer of pseudostratified columnar cells with elongated pencil-shaped nuclei displaying mild atypia [Table/Fig-2b]. Extensive denudation of the surface epithelium was observed, with acellular pools of mucin dissecting through the lamina propria into the fibrotic submucosal layer. The subepithelial tissue showed marked congestion, oedema, and chronic inflammatory infiltrate with loss of lymphoid follicles. Foci of dystrophic calcification were also present [Table/Fig-2c]. There was no evidence of high-grade nuclear features, intramural glandular epithelium, dissection of mucin into the muscularis propria, periappendiceal tissue, or serosa. The resected margin was free of mucin or tumour. The final diagnosis of LAMN (pTis) was made, and the postoperative period was uneventful. The patient was discharged, and during regular follow-up after three months, she remained asymptomatic. Abdominal ultrasound showed no significant findings, and no further intervention was required.

Case 3

A 50-year-old female presented with acute and sharp pain in the right lower abdomen. The patient had been experiencing dull constant pain in the periumbilical region for one month. Imaging studies were not performed due to the long waiting period in the busy emergency ultrasound setup of the limited resource facility. The patient underwent emergency laparoscopic appendectomy.

Gross examination revealed an appendix measuring 6.2 cm in length. The tip of the appendix was dilated, measuring 0.6 cm in diameter, and filled with mucoid material [Table/Fig-3a]. Histomorphology showed villous proliferation of mucinous epithelial cells in the tip of the appendix, displaying abundant apical mucin, elongated nuclei, low N:C ratio, and fine chromatin. The underlying subepithelium exhibited inflammatory cells and abundant extracellular mucin reaching the subserosa [Table/Fig-3b]. Multinucleated giant cells and foamy macrophages were also observed in the subserosal adipose tissue [Table/Fig-3c]. The resected margin was free of mucin or tumour. There was no evidence of high-grade nuclear features, glands, or mucinous epithelial cells in the serosa. The final diagnosis of LAMN (pT3) was made, and the postoperative period was uneventful. The patient was discharged, and during regular follow-up after three and six months, the patient remained asymptomatic. Abdominal ultrasound showed no significant findings, and no further intervention was required. The patient is currently on regular follow-up.



[Table/Fig-3]: Case 3: a) Gross appearance showing dilated tip of appendix and filled with mucoid material (arrowhead); b) Abundant extracellular mucin dissecting muscularis propria reaching to the subserosa (star) (H&E stain, 4X); c) Extracellular mucin, multinucleated giant cells (arrow) and foamy macrophages (H&E stain, 40X).

Case 4

A 37-year-old male presented with dull right lower abdominal pain persisting for two months, with recent worsening of symptoms and the pain becoming sharp. The patient underwent emergency open appendectomy. Imaging studies were not performed.

Gross examination revealed an appendix measuring 3 cm in length and 1.0 cm in diameter. The appendix appeared thickened and fibrosed [Table/Fig-4a]. Histomorphology showed a mildly dilated lumen with denudation of the lining epithelium. The lining was partially composed of a flat layer of columnar cells and replaced by acellular pools of mucin reaching until the muscularis propria [Table/Fig-4b]. The subepithelium exhibited loss of lymphoid follicles and areas of congestion. There was no definite evidence of dysplasia in the glandular epithelium or invasive malignancy. The resected margin was free of mucin or tumour. The final diagnosis of LAMN (pTis) was made, and the postoperative period was uneventful. The patient was discharged, and during regular follow-up after three months, the patient remained asymptomatic. Abdominal ultrasound showed no significant findings, and no further intervention was required.

A summary comparing the four cases is shown in [Table/Fig-5].

DISCUSSION

LAMNs are rare gastrointestinal tract neoplasms that are often misdiagnosed as acute appendicitis. LAMNs commonly present

[Table/Fig-4]: Case 4: a) Gross appearance showing thickened and dilated appendix (arrowhead); b) Flat lining columnar cells surrounded by mucin (arrow) (H&E stain, 40X).

fibrosis [11], whereas serrated lesions have intact mucosal muscle and no fibrosis. All patients in present case series exhibited different degrees of appendiceal fibrosis.

Present case series revealed that LAMNs were more likely to occur in adult females, which was consistent with previous reports [2,11-13]. The symptoms of LAMNs were mainly similar to appendicitis, presenting with lower abdominal pain. In a study by Bell PD et al., it was found that more than half of the patients were symptomatic, with abdominal pain being the most common presentation [13]. The tip or the entire appendix was dilated to varying degrees. Calcification, as noted in one of the cases, is a good indication for the preoperative diagnosis of LAMNs by radiologists [10]. However, no imaging was available in any of these cases.

Features	Case 1	Case 2	Case 3	Case 4
Age (years)	51	35	50	37
Sex	Female	Female	Female	Male
Right lower abdominal pain	One month	Three weeks	One month	Three months
Surgery	Laparoscopic appendectomy	Open appendectomy	Laparoscopic appendectomy	Open appendectomy
Length of appendix	4.5 cm	8 cm	6.2 cm	3 cm
Lumen diameter	2.2 cm	2.5 cm	0.6 cm	1.0 cm
Lumen of appendix	Tip was dilated and filled with mucoid material	Entire lumen was dilated and filled with mucoid material	Tip was dilated and filled with mucoid material	Appendix was thickened and fibrosed
Perforation	Not identified	Not identified	Not identified	Not identified
Histologic type	LAMN	LAMN	LAMN	LAMN
Tumour extent	Acellular mucin confined to lamina propria	Acellular mucin in lamina propria focally dissecting upto submucosal layer	Abundant acellular mucin reaching to the subserosa	Acellular mucin invades muscularis propria
Lymphovascular and perineural invasion	Not identified	Not identified	Not identified	Not identified
Margins	Negative for non invasive tumour/ mucin	Negative for non invasive tumour/mucin	Negative for non invasive tumour/mucin	Negative for non invasive tumour/mucin
Regional lymphnodes	No regional lymph nodes submitted or found	No regional lymph nodes submitted or found	No regional lymph nodes submitted or found	No regional lymph nodes submitted or found
Additional findings	None identified	Calcification	Giant cell reaction	None identified
Distant metastasis	Not applicable	Not applicable	Not applicable	Not applicable
Pathologic staging	pTisNxMx (LAMN)	pTisNxMx (LAMN)	pT3NxMx (LAMN)	pTisNxMx (LAMN)

[Table/Fig-5]: Summary of comparison of present case series.

with pain in the right iliac fossa, resembling acute or recurrent appendicitis. According to the 5th edition of the WHO classification of digestive system tumours [9], the histological criteria for LAMN in the appendix are a mucinous tumour with low-grade cytology and a pushing margin/invasion. High-Grade Appendiceal Mucinous Neoplasm (HAMN) in the appendix refers to a mucinous tumour with high-grade cytology and a pushing margin/invasion. Invasive mucinous adenocarcinoma refers to high-grade appendiceal tumours with features of tissue invasion and irregular gland proliferation, often associated with stromal desmoplasia and signet ring cells.

LAMNs are a relatively homogeneous group of mucinous tumours with low-grade cytologic atypia, similar to low-grade dysplasia in other parts of the gastrointestinal tract [2]. In later stages, LAMNs can rupture and disseminate as intraperitoneal mucinous tumours, which is associated with a poor prognosis [3].

Pai RK et al., first used the term "low-grade mucinous neoplasm with low risk of recurrence" if the mucin located outside the appendix was acellular, or "low-grade mucinous neoplasm with high risk of recurrence" if it contained neoplastic epithelium [10].

LAMNs should be differentiated from serrated lesions. LAMNs exhibit pushing infiltration with varying degrees of appendiceal wall

The microscopic findings in all cases showed the appendix partially lined by a villiform layer of pseudostratified columnar cells or a flat layer of columnar cells with apical mucin. There were also instances of extensive denudation, covered by acellular pools of mucin, which dissected through the lamina propria into the fibrotic submucosal layer. In one case, extracellular mucin invaded the muscularis propria and reached the subserosa, resulting in pT3 staging. In a series of five cases by Wang AS et al., all cases were limited to the appendix, and one out of five cases (20%) had pT3 staging [14]. A similar percentage was also found in the study by Misdraji J et al., (20%) [12]. The underlying subepithelial tissue exhibited marked congestion, oedema, scattered chronic inflammatory infiltrate, and the loss of lymphoid follicles in all cases, which was consistent with the study by Misdraji J et al., [12]. One case showed foci of dystrophic calcification. Calcification was found in 42% of cases in the study by Misdraji J et al., [12] and 50% of cases in the study by Bell PD et al., [13]. Many multinucleated giant cells and foamy macrophages were also noted in one case of the present study. Pai RK and Longcare TA mentioned in a study of appendiceal mucinous tumours that extravasated mucin initiates a chronic inflammatory reaction associated with fibrosis, granulation tissue, and dystrophic calcification [15].

	Present study, 2023	Misdraji J et al., 2003 [12]	Pai RK et al., 2009 [10]	Bell PD et al., 2020 [13]	Wong M et al., 2020 [16]	Wang AS et al., 2022 [14]
Institution	Andaman & Nicobar Islands Institute of Medical Sciences, Portblair, Andaman & Nicobar, India	Massachusetts General Hospital, Harward Medical School, Boston, USA and University of Massachusetts Memorial Health Care, Worcester USA	Stanford University Hospital, USA	University of Rochester Medical Center, Rochester, USA	Cedars-Sinai Medical Center, Los Angeles, USA	University of Central Florida College of Medicine, Orlando, USA
Number of cases	04	88	101	117	64	05
Male:Female Ratio	1:3	18:70 20% and 80%	30:71 30% and 70%	41:76 35% and 65%	1:2	3:2
Mean age (years)	43.25 (35-51)	55 (20 y-87)	NA	66 (40-95)	55	62 (45-79)
Symptomatic cases	All cases symptomatic	74%	55%	56%	14%	All cases symptomatic
Gross: Dilation	75%	69%	69%	78%	96%	100%
Gross: Rupture	None	9%	26%	6%	25%	None
Flat vs Villiform mucosa	50% and 50%	50% and 50%	27% and 73%	38% and 62%	NA	20% and 80%
Denudation/Ulceration	50%	50%	NA	79%	NA	None
Calcification	25%	42%	29%	50%	NA	NA
Positive surgical margin	None	NA	9%	6%	NA	NA
Stage pTis	75%	8%	27%	66%	61%	80%
Stage pT3	25%	23%	None	9%	1.5%	20%
Stage pT4	None	69%	73%	26%	37.5%	None

[Table/Fig-6]: Summary of comparison with other case series [10,12-14,16].

The surgical margins of the appendix were free of tumour in all four cases. In the study by Wang AS et al., all five cases of LAMN had tumour-free surgical margins [14], while Pai RK et al., and Bell PD et al., reported 9% and 6% of the cases, respectively, with positive surgical margins [10,13]. Three cases showed acellular mucin confined to the lamina propria and muscularis propria, resulting in a pathological staging of pTis (LAMN), and one case showed acellular mucin dissecting the muscularis propria and invading the subserosa, staged as pT3 (LAMN). In the present study, the majority (75%) of cases were confined to the muscularis (pTis), which was similar to the studies by Bell PD et al., (66%), Wong M et al., (61%), and Wang AS et al., (80%) [13,14,16].

A summary comparing the present case series with other studies is shown in [Table/Fig-6] [10,12-14,16].

In cases of LAMN confined to the appendix, appendectomy alone is the appropriate treatment since these tumours do not spread through lymphatics or haematogenous routes. However, in cases where the appendectomy margins are involved by acellular mucin or neoplastic epithelium, patients are managed through conservative follow-up and surveillance [2,17]. When acellular mucin is found on the surface of the appendix without spreading into the peritoneal cavity, an appendectomy is usually sufficient, along with routine follow-up and imaging to detect PMP [2,18]. Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (CRS-HIPEC) is now recognised as the standard care for cases where appendiceal neoplasms have spread to the peritoneum [19, 20].

All four cases in the present study were limited to the appendix, and appendectomy alone was deemed sufficient as the standard treatment. No further management was required, and all cases had uneventful follow-up.

CONCLUSION(S)

LAMN is a rare appendiceal mucinous tumor and prognosis is dependent on the presence or absence of extra appendiceal mucin and neoplastic epithelium. Evaluation of the appendix should be performed carefully to determine the prognosis and treatment of these tumours. Low-grade appendiceal mucinous neoplasms can rupture and lead to PMP with high-risk of mortality. For LAMN confined to the appendix, appendectomy alone is sufficient for management, with conservative follow-up and imaging if the margins involved by acellular mucin or neoplastic epithelium. For LAMN with extruded acellular mucin localised to the appendiceal serosa, management is done with appendectomy and PMP surveillance. This case series of LAMN suggests the importance of considering the possibility of appendiceal neoplasm in patients presenting with symptoms of acute appendicitis and timely intervention for management of such patients and preventing development of PMP.

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