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Research Article

Beyond Appendicitis: A Case series highlighting the Clinicopathological, Biochemical, and Radiological Spectrum of Appendiceal Mucinous Neoplasms

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Abstract: ***Introduction:*** Appendiceal mucinous neoplasms (AMNs) are rare epithelial lesions encompassing a wide histopathological spectrum, from low-grade appendiceal mucinous neoplasms (LAMNs) to invasive mucinous adenocarcinomas. Their varied clinical presentations frequently mimic acute appendicitis, creating diagnostic challenges. This study characterises the clinicopathological diversity of AMNs encountered at a tertiary care centre.**Methods:** A retrospective review of all appendicectomy specimens received between January 2019 and December 2024 was conducted. Cases with mucinous lesions were identified, and clinical, radiological, biochemical, and histopathological data were collated from hospital records and archival material. Lesions were classified as per current World Health Organization (WHO) criteria.**Results:** Six cases were identified (four females, two males; age range 38–67 years). The series comprised three LAMNs, one high-grade appendiceal mucinous neoplasm (HAMN), and two mucinous adenocarcinomas. Right iliac fossa pain was the predominant symptom. Imaging findings ranged from an inflamed appendix on ultrasonography to heterogeneous complex masses with peripheral calcification on computed tomography. Carcinoembryonic antigen (CEA) was elevated in two of three cases in whom it was measured; CA-125 was raised in one case. Tumour stages ranged from Tis to T4N1a. Pseudomyxoma peritonei (PMP) was present in two cases.**Conclusion:** AMNs exhibit considerable clinical and morphological heterogeneity. Histopathological examination remains indispensable for definitive diagnosis and staging. The presence of PMP and depth of invasion are critical prognostic determinants. Systematic tumour marker evaluation and appropriate cross-sectional imaging are recommended in suspected cases.

Keywords: Appendiceal mucinous neoplasm; low-grade appendiceal mucinous neoplasm; pseudomyxoma peritonei; mucinous adenocarcinoma.

INTRODUCTION

The appendix is an uncommon site for primary epithelial neoplasms, with an estimated incidence of 0.9–1.4% of all appendicectomy specimens [1]. Appendiceal mucinous neoplasms (AMNs) constitute a distinctive subset characterised by mucin-producing epithelium and a broad clinicopathological spectrum ranging from indolent cystic lesions to aggressive invasive malignancies. Their importance lies not only in their intrinsic behaviour but also in their capacity to cause pseudomyxoma peritonei (PMP), a potentially life-threatening condition characterised by progressive peritoneal mucin accumulation [2].

The current World Health Organization (WHO) classification stratifies AMNs into low-grade appendiceal mucinous neoplasms (LAMNs), high-grade appendiceal mucinous neoplasms (HAMNs), and mucinous adenocarcinomas, based on architectural complexity, cytological atypia, and the presence of destructive invasion [3]. Despite this well-defined classification, these lesions continue to pose diagnostic challenges owing to their non-specific clinical presentations, variable imaging appearances, and potential to mimic acute appendicitis at initial assessment [4].

Literature on the combined clinicopathological characterisation of AMNs from South Asian tertiary care settings remains limited. This study describes six patients with AMNs encountered at our institution over a six-year period, with the objective of delineating the clinicopathological spectrum, correlating histopathological diagnosis with clinical, radiological, and biochemical findings, and identifying key diagnostic pitfalls to inform surgical and pathological practice.

MATERIALS AND METHODS

This was a retrospective, observational study conducted in the Department of Pathology at a tertiary care academic medical centre. All appendicectomy specimens received between January 2019 and December 2024 that exhibited mucinous epithelial lesions on histological examination were included. Specimens submitted for reasons other than mucinous pathology and those with inadequate tissue sampling were excluded.

Clinical data — including age, sex, presenting symptoms, operative details, and preoperative tumour marker levels — were retrieved from the Hospital Information System (HIS) and contemporaneous medical records. Imaging reports were reviewed for all patients who had undergone abdominal ultrasonography (USG) or computed tomography (CT) prior to surgery.

Archival haematoxylin and eosin (H&E)-stained slides were retrieved and reviewed independently by two qualified pathologists. Lesions were classified in accordance with the 2019 WHO Classification of Tumours of the Digestive System [3]. Tumour staging was assigned per the American Joint Committee on Cancer (AJCC) 8th edition staging manual [5]. Disagreements between reviewers were resolved by consensus review on a multi-headed microscope.

Data were tabulated and analysed descriptively. Institutional ethics committee approval was obtained and patient identifiers were anonymised throughout.

RESULTS

Six patients (four females, two males; age range 38–67 years) presented with varied abdominal symptoms, most commonly right iliac fossa pain (67%), often mimicking acute appendicitis, while others had diffuse pain, distension, or a palpable mass suggestive of advanced disease (Table:1). Preoperative imaging (available in five cases) ranged from ultrasonographic features of acute appendicitis to contrast-enhanced CT findings of complex heterogeneous masses with wall calcification, septations, and non-visualisation of the appendix. Serum tumour markers demonstrated inconsistent utility: elevated carcinoembryonic antigen (CEA) was observed in one malignant case, while both CA-125 and CEA were elevated in a patient with peritoneal involvement. However, another malignancy showed normal CEA levels, and tumour markers were not evaluated in half of the cases. Histopathologically, the spectrum included three low-grade appendiceal mucinous neoplasms (LAMNs), one high-grade appendiceal mucinous neoplasm (HAMN), and two mucinous adenocarcinomas, demonstrating features ranging from confined mucosal disease (Tis) to invasive and metastatic disease (T4N1a). LAMNs showed typical villiform or flattened epithelium with varying degrees of mucin extension, while HAMN exhibited high-grade cytological atypia with subserosal mucin. Mucinous adenocarcinomas displayed infiltrative glandular architecture, a desmoplastic stroma, and deeper invasion. Pseudomyxoma peritonei was identified in two cases, with acellular extraluminal mucin and evidence of appendiceal perforation in one case, underscoring the heterogeneity in presentation, imaging, biomarker profile, and pathological behaviour of appendiceal mucinous neoplasms (Table:2).

Case 1: A 38-year-old female presented with right iliac fossa pain clinically suggestive of acute appendicitis and underwent appendicectomy. Preoperative ultrasonography revealed features of an inflamed appendix. Tumour markers were not assessed. Intraoperatively, the appendix was distended and adhered to the surrounding structures. Grossly, the appendix was cystically dilated with luminal diameter of 2.5cm. Histopathological examination demonstrated a low-grade appendiceal mucinous neoplasm (LAMN) characterised by a predominantly flattened mucinous epithelium without cytological atypia or invasion. (Figure 1) There was no evidence of acellular or extracellular mucin outside the appendix, and pseudomyxoma peritonei (PMP) was absent. The lesion was confined to the mucosa and staged as Tis.

Case 2: A 56-year-old female presented with diffuse abdominal pain and underwent appendicectomy with omentectomy. Plain CT imaging showed dilated small bowel loops with adjacent mesenteric fat stranding, raising suspicion of bowel obstruction. Biochemically, both carcinoembryonic antigen (CEA) and CA-125 levels were elevated. Intraoperatively, mucinous deposits were found studded over the appendix omentum and bowel. Appendicectomy with omentectomy was done. Grossly, the appendix was swollen with attached tissue. The lumen was dilated by about 1cm, and the appendiceal wall appeared thickened, likely edematous. Histopathological examination demonstrated a low-grade appendiceal mucinous neoplasm (LAMN) characterised by villiform and papillary epithelial architecture, with extension up to the muscularis propria. Acellular mucin was noted within the mesoappendix without serosal involvement.Evidence of perforation was present,(Figure: 2) and features of pseudomyxoma peritonei (PMP) with low grade peritoneal mucinous neoplasia were identified.

Case 3: A 67-year-old female presented with diffuse abdominal pain and distension, suggestive of peritoneal pathology, and underwent appendicectomy with omentectomy. Radiological and tumour marker data were not available. Histopathological evaluation revealed mucinous adenocarcinoma characterised by infiltrative glands within a desmoplastic stroma and abundant extracellular mucin. The tumour invaded up to the serosa and was associated with PMP, indicating peritoneal dissemination. (Figure 3) The lesion was staged as T4, representing advanced malignant disease.

Case 4: A 48-year-old female presented with right iliac fossa pain, fever, and vomiting, closely mimicking acute appendicitis. Ultrasonography demonstrated diffuse inflammatory changes of the appendix and free fluid moted in the right iliac fossa . Tumour markers were not performed. Emergency laparotomy and appendicectomy were done. Intraoperative findings showed an appendix with early mass formation and adhesions. Histologically, the lesion was diagnosed as LAMN with villiform and papillary epithelial proliferation and low-grade cytological features. (Figure 4) The tumour extended into the muscularis propria without evidence of extra-appendiceal mucin or PMP. The pathological stage was T3.

Case 5: A 38-year-old male presented with right iliac fossa pain and a palpable localised mass, raising suspicion for neoplasia. Contrast-enhanced CT (CECT) revealed a heterogeneous lesion with enhancing walls, internal septations, and peripheral calcification, with the appendix not separately visualised. Serum CEA levels were within normal limits. The patient underwent right hemicolectomy. Grossly showed a glistened lesion measuring 4.3cm in greatest diameter with mucoid material and appendix could not be visualized. Histopathological examination showed mucinous adenocarcinoma with infiltrative glandular architecture, a desmoplastic stromal response, and abundant extracellular mucin. (Figure 5) The tumour involved the serosa and demonstrated regional lymph node metastasis, corresponding to stage T4N1a. PMP was absent.

Case 6: A 58-year-old male presented with right iliac fossa pain and a palpable mass. CECT imaging demonstrated a large loculated, peripherally enhancing lesion with internal septations and peripheral calcification, measuring approximately 8.4 × 7 × 7.5 cm, with the appendix not separately identifiable. (Figure 6) Serum CEA was elevated. The patient underwent right hemicolectomy. Intraoperatively, a mass was found at the ileocaecal junction, appendix could not be visualised separately . The grossly cystic appendicular mass had a few small, bulging mucoid nodules on its outer surface. (Figure 7) The lumen was seen filled with lumps of thick mucoid material, admixed with haemorrhages. Histopathology revealed a high-grade appendiceal mucinous neoplasm (HAMN) with villiform and papillary architecture, marked cytological atypia, and subserosal extension (Figure 8). However, acellular mucin was present at the serosal surface. (Figure 9). There was no infiltrative invasion or PMP. The tumour was staged as T4a.

Tables:

Table 1. Summary of clinical, radiological, and biochemical findings

Case	Age/Sex	Clinical Symptoms	Surgical Procedure	Radiological Findings	Tumour Markers
1	38/F	Right iliac fossa pain	Appendicectomy	Inflamed appendix (USG)	Not done
2	56/F	Diffuse abdominal pain	Appendicectomy with omentectomy	Dilated small bowel loops (plain CT abdomen)	CEA - 46.15 ng/ml (Normal range: Smokers - 5.5 - 6.5 ng/ml; Non - Smokers - 3.8 - 5 ng/ml); CA-125 - 62.41 U/ml (Normal: Less than 35 U/ml),
3	67/F	Diffuse abdominal pain and distension	Appendicectomy, omentectomy	Not available	Not available
4	48/F	Right iliac fossa pain, fever, vomiting	Appendicectomy	Inflamed appendix (USG)	Not done
5	38/M	Right iliac fossa pain, localised mass effect	Right hemicolectomy	Appendix not visualised; heterogeneous dense lesion with enhancing walls, septations, and calcification (CECT abdomen)	CEA - 4.17 ng/ml (Normal range: Smokers - 5.5 - 6.5 ng/ml; Non -Smokers - 3.8 - 5 ng/ml
6	58/M	Right iliac fossa pain, localised mass effect	Right hemicolectomy	Appendix not separately visualised; large loculated peripherally enhancing lesion	CEA - 16.47 ng/ml (Normal range: Smokers - 5.5 - 6.5

Case	Age/Sex	Clinical Symptoms	Surgical Procedure	Radiological Findings	Tumour Markers
				(8.4×7×7.5 cm) with peripheral calcification and multiple septations (CECT abdomen)	ng/ml; Non - Smokers - 3.8 - 5 ng/ml)

CECT, contrast-enhanced computed tomography; CEA, carcinoembryonic antigen; CA-125, cancer antigen 125; RIF, right iliac fossa; USG, ultrasonography.

Table 2. Summary of histopathological findings

Case	Diagnosis	PMP	Acellular/Extracellular Mucin	Epithelial Proliferation Pattern	Invasion Depth	Stage
1	LAMN	Absent	Absent	Flattened epithelium	Only at mucosa	Tis
2	LAMN	Present	Absent	Villiform and papillary architecture	Muscularis propria into mesoappendix	T4a
3	Mucinous adenocarcinoma	Present	Extracellular mucin	Villiform and papillary architecture with glands in desmoplastic stroma	Serosa	T4
4	LAMN	Absent	Absent	Villiform and papillary architecture	Muscularis propria	Tis
5	Mucinous adenocarcinoma	Absent	Extracellular mucin	Villiform/papillary architecture with glands in desmoplastic stroma	Serosa with nodal metastasis	T4N1a
6	HAMN	Absent	Acellular mucin	Villiform and papillary architecture	Subserosa	T4a

LAMN, low-grade appendiceal mucinous neoplasm; HAMN, high-grade appendiceal mucinous neoplasm; PMP, pseudomyxoma peritonei.

Figures

Appendiceal Mucinous Neoplasms

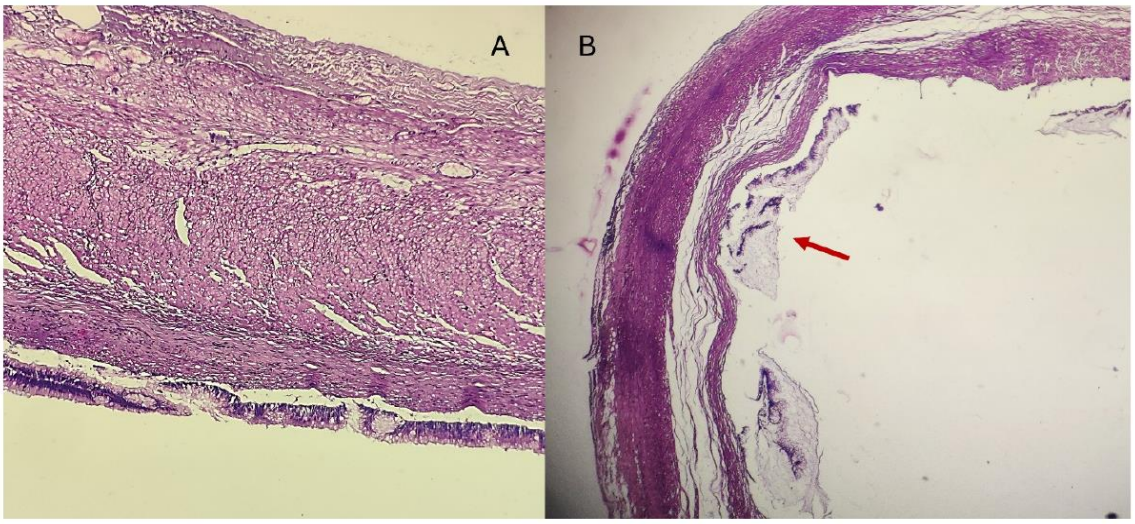

Figure 1. Low-grade appendiceal mucinous neoplasm (LAMN). (A) Appendix showing stripped, flattened mucinous epithelium with obliteration of lymphoid follicles and submucosa, favouring LAMN. (B) Luminal stripped mucin and detached epithelial cells (red arrow) (H&E, 100x).

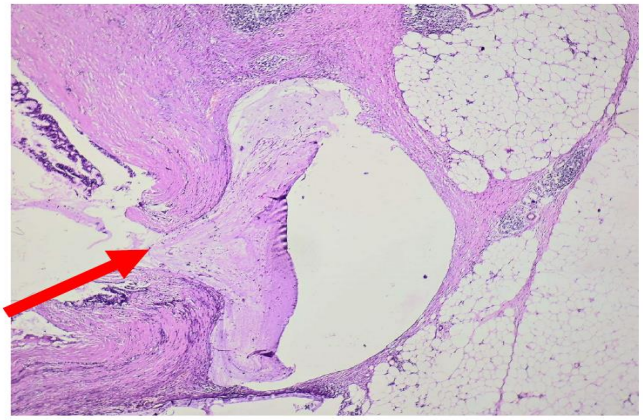

Figure 2. Appendiceal perforation showing full-thickness disruption of the appendiceal wall with extravasation of mucin into the periappendiceal adipose tissue (red arrow) (H&E, 40x).

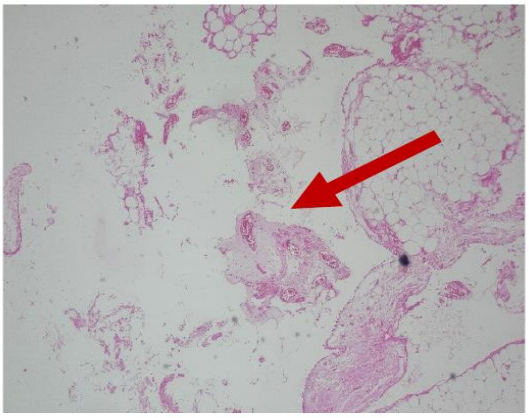

Figure 3. Acellular mucin extending beyond the appendiceal wall into the omentum (red arrow), without identifiable epithelial cells, consistent with acellular pseudomyxoma peritonei; associated neovascularisation is noted (H&E, 100x).

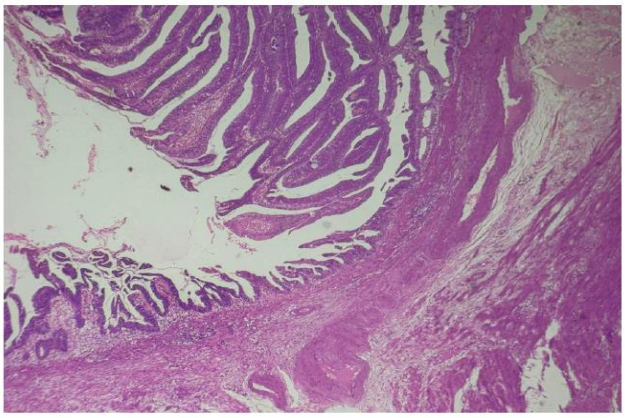

Figure 4. Low-grade appendiceal mucinous neoplasm (LAMN) showing villiform and papillary mucinous epithelial architecture with low-grade cytological atypia and a pushing pattern of invasion into the appendiceal wall, resembling a diverticulum (H&E, 100x).

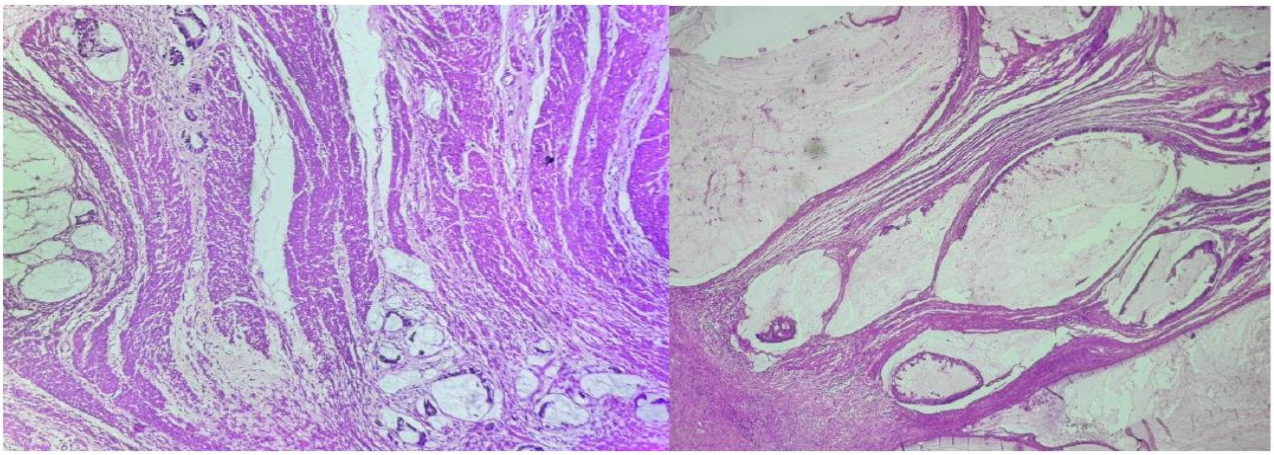

Figure 5. Mucinous adenocarcinoma. (A, B) Irregular glandular structures infiltrating desmoplastic stroma with high-grade nuclear atypia, consistent with invasive mucinous adenocarcinoma (H&E, 200x).

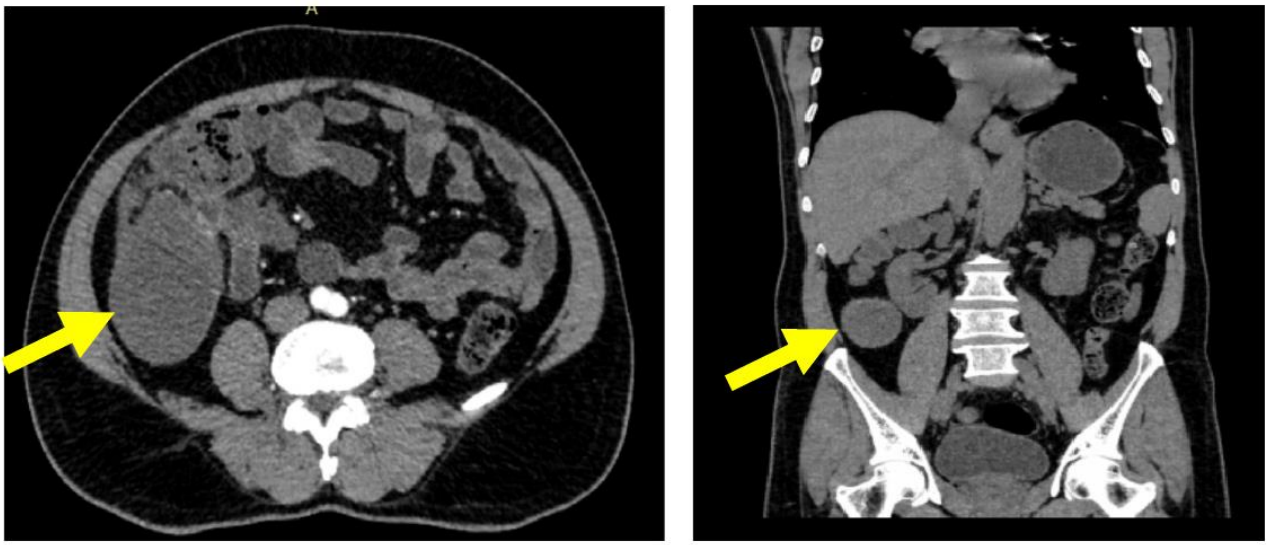

Figure 6. Contrast-enhanced CT abdomen. (A) Axial and (B) coronal images showing a large loculated heterogeneous right iliac fossa mass with peripheral wall calcification, thick enhancing walls, and internal septations (yellow arrows), corresponding to advanced appendiceal mucinous neoplasm. The appendix is not separately identifiable.

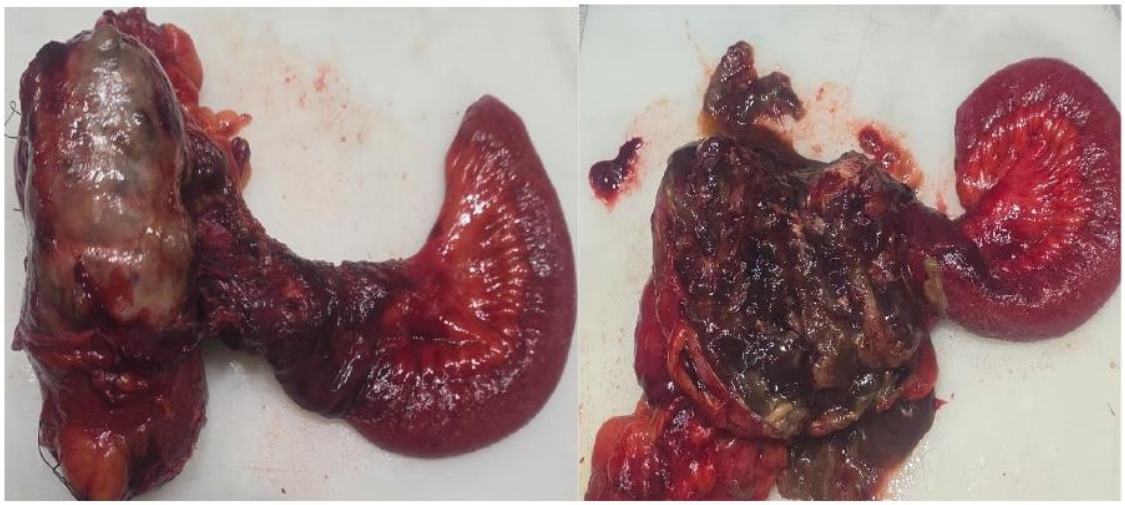

Figure 7. Gross morphology of appendicectomy specimens. (A) Markedly distended cystic appendix with gelatinous mucinous content. (B) Large heterogeneous mass with variable mucinous content.

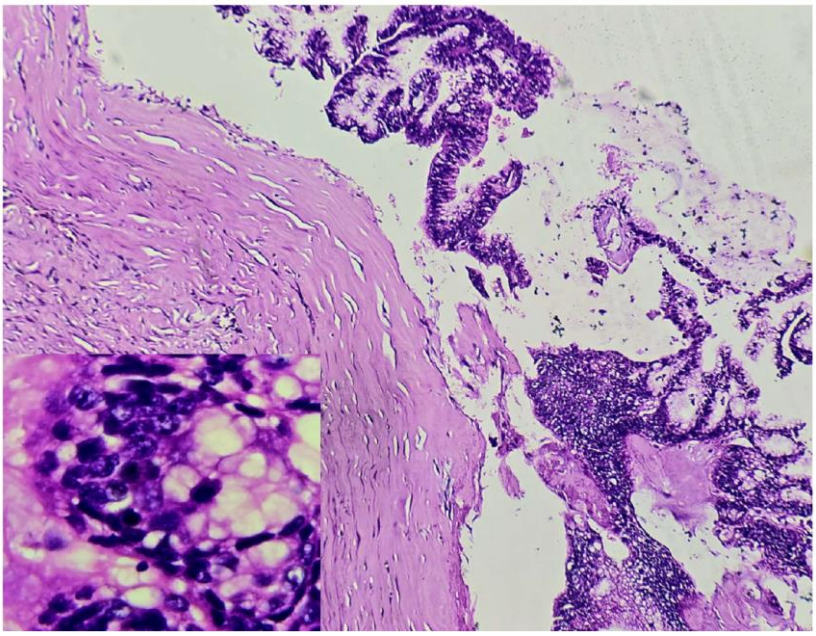

Figure 8. High-grade appendiceal mucinous neoplasm (HAMN) showing villiform architecture with high-grade cytological atypia, including nuclear pleomorphism, prominent nucleoli, and increased mitotic activity (inset) (H&E, 200x).

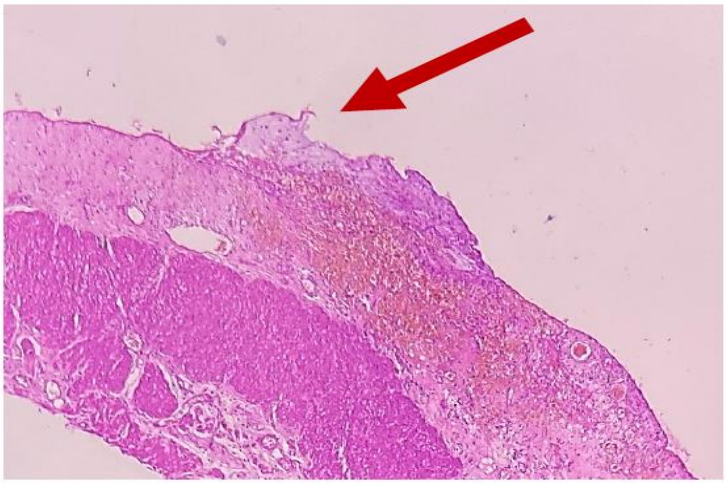

Figure 9. Acellular mucin extending beyond the appendiceal wall and involving the serosal surface (red arrow), without identifiable epithelial cells, consistent with acellular pseudomyxoma peritonei; prominent neovascularisation is noted (H&E, 100x).

DISCUSSION

This study encapsulates the clinicopathological heterogeneity of AMNs encountered in routine surgical pathology practice. Although the series is small by design, the diversity of presentations, imaging patterns, tumour marker profiles, and histopathological diagnoses across just six cases underscores the diagnostic complexity of these lesions.

The non-specific clinical presentation of AMNs is a well-documented diagnostic challenge. In our series, the predominance of RIF pain , the cardinal symptom of acute appendicitis meant that the majority of patients were listed for appendicectomy under an inflammatory or infective provisional diagnosis. This is consistent with observations by Pai and Longacre [4], who emphasised that AMNs frequently masquerade as inflammatory appendiceal conditions, and with the broader literature reporting that up to 50% of AMNs are discovered incidentally or after an appendicectomy performed for suspected appendicitis. The case of HAMN presenting as renal colic, as described by Amir et al., illustrates the even broader differential that clinicians must entertain when considering appendiceal pathology [6].

Radiological imaging is integral to the preoperative evaluation of suspected AMNs, yet its utility varies substantially with tumour stage. In our two patients who underwent CECT, the characteristic features of advanced AMNs non-visualisation of the normal appendix, complex cystic masses with curvilinear peripheral calcification, thick enhancing walls, and internal septations were well-demonstrated, consistent with the imaging descriptions reported by Pickhardt et al. and Dhage-Ivatury et al. [7,8] The 2023 Italian Society of Surgical Oncology consensus further emphasises that contrast-enhanced CT is the modality of choice for characterising AMNs and guiding surgical planning [9].

In contrast, the two patients who underwent USG alone were diagnosed as having acute appendicitis, highlighting the limited sensitivity of ultrasonography for detecting underlying mucinous neoplasia when appendiceal dilatation is minimal or when the gland is obscured by inflammation. In clinically unsuspected cases or when appendiceal dilatation is minimal, contrast-enhanced computed tomography (CECT) of the abdomen plays a pivotal role. CECT is recommended when ultrasonography is equivocal or when subtle findings such as mild luminal dilatation, focal wall thickening, mural calcification, or minimal periappendiceal fat stranding raise concern for an underlying neoplasm CECT characteristically demonstrates the “scalloping effect” along the surfaces of visceral organs, caused by compression from accumulated viscous mucin and associated organizing fibrosis. Despite these characteristic imaging findings, the preoperative diagnosis of PMP remains challenging because of its heterogeneous clinical and radiological presentation [7,10,11].

Serum tumour markers provide valuable supportive information in the diagnostic evaluation. In our series, elevated CEA was confined to cases of mucinous adenocarcinoma. The Chicago Consensus Working group showed that CEA, CA-125 and CA19-9 levels are usually elevated particularly in patients with pseudomyxoma peritonei (PMP) [12]. Critically, CEA was normal in one of our adenocarcinoma cases, corroborating the well-recognised limitation that serum markers lack both sensitivity and specificity as standalone diagnostic tests. CA-125 elevation likely reflected peritoneal involvement and mucinous tumour burden, given its established role as a marker of mesothelial perturbation [13]. The absence of marker assessment in three cases represents a clinical gap; systematic preoperative tumour marker profiling should be incorporated into the workup of any patient with suspected appendiceal pathology, particularly when imaging suggests a cystic or mucinous lesion.

Histopathology remains the definitive modality for diagnosis, classification, prognostication, and guiding postoperative management. The transition from LAMN to HAMN and mucinous adenocarcinoma reflects a stepwise accumulation of architectural and cytological alterations. LAMNs characteristically show villiform or papillary epithelial proliferation with pushing rather than infiltrative invasion; the absence of destructive stromal invasion differentiates them from adenocarcinoma even when extra-appendiceal mucin is present [14]. The presence of acellular extra-appendiceal mucin, as observed in two cases, has important prognostic implications: while acellular mucin deposits alone do not warrant an adenocarcinoma diagnosis, their presence indicates the potential for PMP and warrants careful peritoneal surveillance.

HAMNs represent a recently formalised WHO category and are characterised by high-grade cytological atypia without the infiltrative growth pattern of adenocarcinoma [3]. Their clinical significance lies in their intermediate biological behaviour and higher risk of progression to peritoneal disease [15]. In one of our case, the combination of high-grade features, subserosally invasive acellular mucin, and T4a staging mandated right hemicolectomy to ensure adequate oncological clearance.

PMP occurred in two of our six cases, both associated with higher tumour stages. PMP results from peritoneal seeding of mucin-secreting epithelium following appendiceal perforation or rupture, and its prognosis is strongly influenced by the grade of the originating neoplasm [16]. Mehta et al. reported that peritoneal involvement is more common than lymph node metastasis in AMNs [17], a pattern reflected in our series, where two cases had peritoneal dissemination compared with one case of regional nodal involvement.

AJCC 8th edition staging stratifies AMNs into clinically meaningful prognostic groups based on invasion depth, nodal status, and distant spread [5]. Tumours invading the muscularis propria (T3) or beyond (T4) carry greater risks of peritoneal dissemination, PMP, and disease recurrence following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC). The T4N1a case in our series — with its desmoplastic stromal response, nodal metastasis, and predominantly mucinous high-grade carcinoma — exemplifies the aggressive end of the AMN spectrum and required right hemicolectomy with systemic oncological follow-up.

HAMN and LAMN demonstrate a high frequency of concurrent KRAS and GNAS mutations, supporting a shared histogenetic origin and distinguishing them from mucinous adenocarcinoma. The acquisition of TP53 mutations in HAMN may contribute to progression toward a more advanced phenotype [18]. Comprehensive molecular profiling may in future augment histopathological grading to refine risk stratification and guide targeted therapy, although this remains investigational in routine clinical practice [19].

This series has inherent limitations. The small sample size precludes generalisability and formal statistical analysis. Tumour markers were not uniformly assessed, limiting the completeness of biochemical and radiological data. Molecular profiling and immunohistochemical ancillary studies were not performed. Despite these limitations, the series provides a contemporaneous description of the clinicopathological spectrum of AMNs from a tertiary care South Asian setting, which is underrepresented in the published literature.

CONCLUSION

Appendiceal mucinous neoplasms exhibit considerable clinical, radiological, biochemical, and morphological diversity. Their frequent mimicry of acute appendicitis underscores the imperative for pathologists to examine all appendicectomy specimens comprehensively and for clinicians to maintain a high index of suspicion when imaging reveals cystic or mucinous appendiceal abnormalities. Histopathological classification per WHO criteria and AJCC staging remain the cornerstones of diagnosis and prognostication. Systematic preoperative tumour marker assessment and judicious use of CECT should be standard in the workup of suspected cases. The depth of invasion and the presence of PMP are key prognostic determinants. Prospective multicentre studies incorporating molecular profiling are needed to further delineate the biological heterogeneity and optimal management of this rare but clinically significant group of neoplasms.

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