Case Series

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Pathology Section

Histopathological Spectrum of Appendiceal Epithelial Neoplasms: A Series of Seven Cases

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ABSTRACT

Appendiceal epithelial neoplasms are uncommon lesions, often detected incidentally on histopathological examination of appendicectomy or resection specimens. They comprise a heterogeneous group of tumours ranging from mucinous neoplasms to invasive adenocarcinomas, with varied morphology, biological behaviour, and clinical outcome. Their relative rarity and overlapping clinical presentation make histopathological evaluation essential for accurate diagnosis and classification. The present case series describes the clinical and histomorphological features of seven cases of epithelial appendiceal neoplasms diagnosed at a tertiary care centre. The cases included four adenocarcinomas- one goblet cell adenocarcinoma, two mucinous adenocarcinomas, and one non-mucinous adenocarcinoma- along with two Low-grade Appendiceal Mucinous Neoplasms (LAMN) and one High-grade Appendiceal Mucinous Neoplasm (HAMN). The median age at presentation was 64 years. There was a female predominance, with six females and one male. Histologically, the lesions showed varied architectural patterns, cytological atypia, mucin production, and differing extent of appendiceal wall involvement. One case was associated with pseudomyxoma peritonei, while another showed synchronous adenocarcinoma of the ascending colon. Serum Carcinoembryonic Antigen (CEA) was elevated in most evaluated cases, whereas Cancer Antigen 125 (CA-125), was elevated in one case. Classification was based on the World Health Organisation (WHO) 5th edition classification, and staging was assessed using the American Joint Committee on Cancer (AJCC) staging system. Follow-up ranged from six months to two years. During the follow-up period, four patients remained disease-free, while one patient demonstrated stable disease while receiving chemotherapy. One patient died due to disease progression, and follow-up information was unavailable for one patient. This series is important as it highlights the rarity and clinicopathological diversity of appendiceal epithelial neoplasms encountered in routine surgical pathology practice. The lesions ranged from low-grade mucinous neoplasms to invasive adenocarcinomas with distinct biological behaviour and differing prognostic implications, including variation in risk of recurrence, progression, and development of Pseudomyxoma Peritonei (PMP). Recognition of these morphological differences is essential for accurate pathological subtyping, as it directly influences staging, prognostic assessment, therapeutic planning, extent of surgical management, postoperative surveillance, and long-term follow-up.

Keywords: Adenocarcinoma, Comedo necrosis, Mucinous, Pseudomyxoma peritonei

INTRODUCTION

Epithelial appendiceal neoplasms are uncommon lesions, with appendicectomy-based studies reporting an incidence of approximately 1.9%-2.1% among appendicectomy specimens [1]. Although many appendiceal neoplasms are identified incidentally following appendicectomy, their clinical presentation can be variable and nonspecific. They may mimic acute appendicitis, intestinal obstruction, or, particularly in women, adnexal or ovarian masses, thereby posing diagnostic challenges [2].

According to the World Health Organisation (WHO) Classification of Tumours: Digestive System Tumours, 5th edition, appendiceal epithelial neoplasms encompass several entities, including serrated lesions/polyps, appendiceal mucinous neoplasms, appendiceal adenocarcinomas, and goblet cell adenocarcinoma [3]. Appendiceal neuroendocrine tumours represent an important additional category of primary appendiceal neoplasms. Among mucinous neoplasms, Low-grade Appendiceal Mucinous Neoplasm (LAMN) and High-grade Appendiceal Mucinous Neoplasm (HAMN) are characterised by distinctive histopathological features and have important implications for clinical management and prognosis. The entity previously referred to as goblet cell carcinoid is now classified as goblet cell adenocarcinoma, reflecting its epithelial nature and malignant potential [3].

Given their relative rarity and diverse clinical and histopathological presentations, recognition of these neoplasms may be challenging in routine practice. The present case series describes seven cases of epithelial appendiceal neoplasms, highlighting their varied clinical presentations and histopathological features and emphasising the importance of accurate pathological diagnosis and classification.

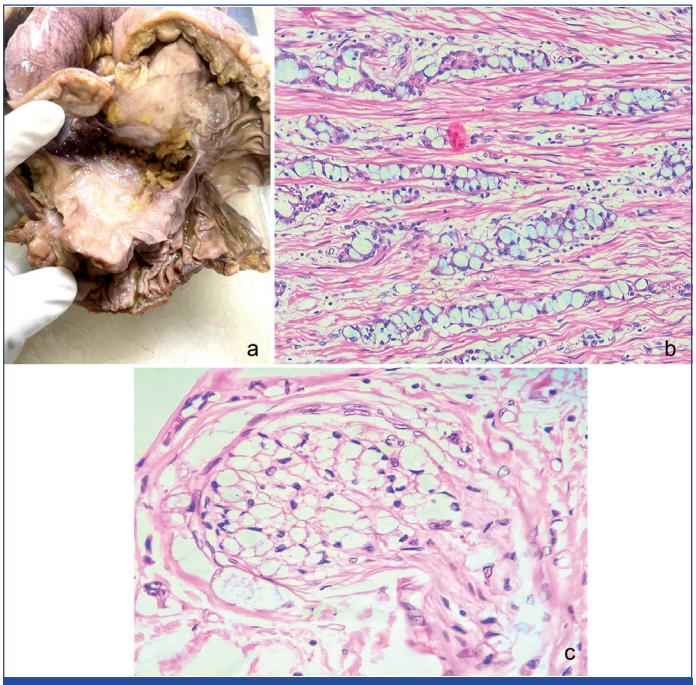
CASE SERIES

Case 1

A 69-year-old female presented with history of abdominal pain, loss of appetite, and weight loss since one month. There was no history of systemic illness reported. On examination, a vague mass was palpable in the right iliac fossa. Biochemical evaluation was within normal limits. Colonoscopy and Contrast-Enhanced Computed Tomography (CECT) abdomen showed distal ileal wall thickening suspicious of inflammatory pathology, with no obvious mass lesion. Serum tumour marker evaluation showed mild elevation of CEA, with a value of 7.2 ng/mL (reference range <5 ng/mL). A clinical diagnosis of carcinoma caecum was made and proceeded with laparoscopic right hemicolectomy.

Gross examination of the right hemicolectomy specimen comprising terminal ileum, caecum, appendix and ascending colon showed thickened appendix and an infiltrating tumour involving the appendix and caecum, measuring 4.5×3×4.5 cm, obstructing approximately 70% of the lumen, along with multiple pericolic tumour deposits, the largest measuring 1×1 cm [Table/Fig-1a].

Histopathological examination showed clusters of goblet-like mucinous cells and signet ring cells [Table/Fig-1b] with lymphovascular and perineural invasion [Table/Fig-1c]. The tumour extended up to but did not penetrate the serosal surface. Resection margins were free. One of sixteen lymph nodes showed metastatic tumour deposit with extranodal extension.



[Table/Fig-1]: a) Gross showing an infiltrating growth involving the appendix and caecum measuring 4.5×3×4.5 cm; b) Histopathological showing an infiltrating neoplasm composed of goblet cell-like mucinous cells arranged in clusters (H&E, 20X); c) Goblet cell adenocarcinoma showing perineural invasion (H&E, 40X).

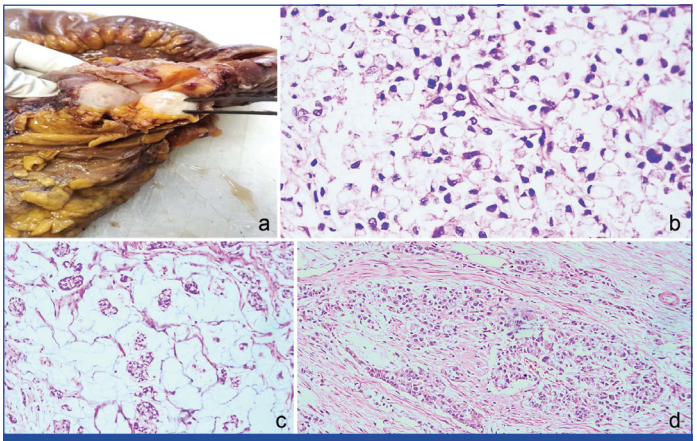
The final diagnosis was goblet cell adenocarcinoma involving the appendix and caecum, with TNM stage pT3N1a (Stage IIIB) [4]. The patient completed eight cycles of adjuvant chemotherapy (Injection Oxaliplatin and Tab Capecitabine) and remains on follow-up with routine assessment with Computed Tomography (CT) scan and CEA levels with no evidence of recurrence at 10 months.

Case 2

A 63-year-old female presented with diffuse abdominal pain and constipation for three days. She was a known case of diabetes mellitus and hypertension. On examination, there was mild abdominal distension with a hard mass palpable in the right iliac fossa. Baseline investigations revealed anaemia with a haemoglobin level of 9.7 g/dL (reference range 12.0-15.5 g/dL). CECT abdomen showed acute small bowel obstruction involving the distal ileum, with probable adherence or infiltration of distal ileal loops by pelvic peritoneal deposits suspicious for metastatic disease. Serum tumour marker evaluation showed markedly elevated CEA {225.3 ng/mL (reference range <5 ng/mL)} and mildly elevated CA-125 {52.45 U/mL (reference range <35 U/mL)}, while carbohydrate antigen 19-9 (CA 19-9) was within normal limits. Clinically, a diagnosis of acute intestinal obstruction with multiple peritoneal deposits suggestive of metastasis from an unknown primary was made. Right hemicolectomy with omentectomy was performed.

Intraoperatively, omental adhesions to the anterior abdominal wall with minimal ascites were noted. Multiple peritoneal, omental, mesenteric, intestinal, and retroperitoneal deposits were seen with omental caking. The ileocolic junction was hard with a 4×3 cm growth showing retroperitoneal infiltration. Gross examination of the right hemicolectomy specimen measuring 41 cm in length, revealed thickened appendix which was adherent to the colon, with an infiltrating grey-white lesion measuring 6×2.5×2 cm [Table/Fig-2a]. Cut-section of pericolic fat showed 22 tumour deposits, the largest measuring 3.5×2×0.5 cm.

Histopathological examination showed tumour cells arranged in glandular and signet ring cell-like architecture [Table/Fig-2b] replacing the appendiceal mucosa, with tumour cells floating in mucin pools [Table/Fig-2c]. Lymphovascular and perineural invasion were noted [Table/Fig-2d]. The tumour involved the appendiceal base and caecal mucosa. Multiple peritoneal deposits infiltrated the muscularis propria and periappendiceal fat. Resection margins were free. Ten lymph nodes showed metastatic deposits. Final diagnosis was mucinous adenocarcinoma (Grade 2) of the appendix, TNM stage pT3N2M1b (Stage IVA). The patient is currently on palliative chemotherapy with CAPOX (Injection Oxaliplatin and Tab Capecitabine) and injection Bevacizumab and is on regular follow-up with stable disease at 11 months with serial monitoring of CEA levels.



[Table/Fig-2]: a) Gross examination showing thickened, enlarged and fibrosed appendix with an infiltrating grey-white lesion measuring 6×2.5×2 cm; b) Histopathological image showing high-power view of signet ring cells with intracytoplasmic mucin and peripherally placed nuclei (H&E, 40X); c) Histopathological image showing tumour cells floating in mucinous pools (H&E, 20X); d) High-power view showing perineural invasion by tumour cells (H&E, 40X).

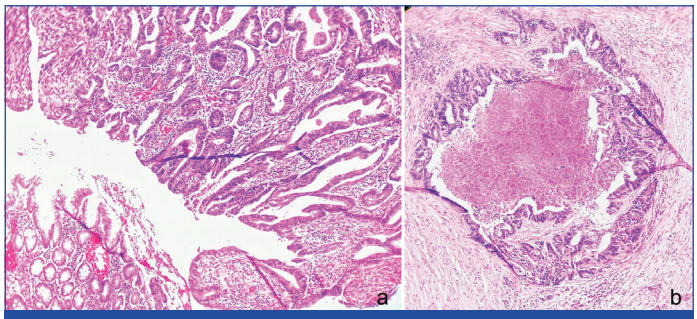
Case 3

A 56-year-old female presented with pain and discharge from the right-side of the abdomen and was initially diagnosed with appendicular abscess. Incision and drainage with pigtail catheter insertion was performed. The patient developed chills on the third postoperative day with right-sided fluid collection, for which laparoscopic drainage of appendicular abscess was done. Two weeks later, she again developed continuous abdominal pain not relieved by medication, associated with fever. Repeat incision and drainage was performed. On examination, sinus tract discharge was noted over the right iliac fossa. Colonoscopy revealed an ulceroproliferative lesion at the appendiceal orifice. Serum tumour markers were not evaluated. Laboratory evaluation revealed anaemia {haemoglobin 9.4 g/dL (reference range 12.0-15.5 g/dL)} and an elevated Erythrocyte sedimentation rate (ESR) of 59 mm/hour (reference range 0-20 mm/hour for adult females). CECT abdomen showed post-appendicectomy status with a well-defined thick-walled irregular partially enhancing collection in the right pelvis abutting the urinary bladder, extending into the intramuscular and subcutaneous plane and opening into the skin of the right inguinal region, suggestive of infective collection. Colonoscopic biopsy was consistent with adenocarcinoma of the appendix. A clinical diagnosis of enterocutaneous fistula with ulceroproliferative lesion at the appendiceal orifice was made, following which right hemicolectomy was performed.

Intraoperatively, caecal wall thickening with an appendiceal orifice lesion extending to the parietal wall was seen. A thick-walled collection connected to the right iliac fossa forming a fistulous tract was identified and drained. Grossly, the right hemicolectomy specimen measured 45 cm in length. The serosa of the caecum showed a shaggy irregular hard area measuring 3.5×2 cm. Cut section showed a dilated and thickened appendix measuring 2.5

cm with a polypoidal growth in the lumen measuring 1×1×0.8 cm. A fistulous tract from the right iliac fossa was also received separately. Cut-section of pericolic fat identified 10 lymph nodes.

Histopathological examination of the appendix showed infiltrating neoplasm composed of glands arranged within desmoplastic stroma, invading from muscularis propria into subserosa [Table/Fig-3a]. Comedo necrosis was noted [Table/Fig-3b]. Extracellular mucin comprised <50% of the tumour. No signet-ring cells, lymphovascular invasion, or perineural invasion were identified. The appendiceal base was involved, while all resection margins were free of tumour. All 10 regional lymph nodes were negative for metastasis. Sections from the fistulous tract showed dense inflammation and granulation tissue with no evidence of malignancy.



[Table/Fig-3]: a) Histopathological section showing an infiltrating adenocarcinoma composed of tumour cells arranged in complex villoglandular, cribriform and glandular patterns within a desmoplastic stroma (H&E, 10X); b) Histopathological image showing focal comedo necrosis within tumour glands (H&E, 20X).

The final diagnosis was non-mucinous, colorectal-type adenocarcinoma of the appendix, staged as pT3N0M0 (Stage IIA) according to the AJCC 8th edition staging system [4]. Follow-up information was unavailable.

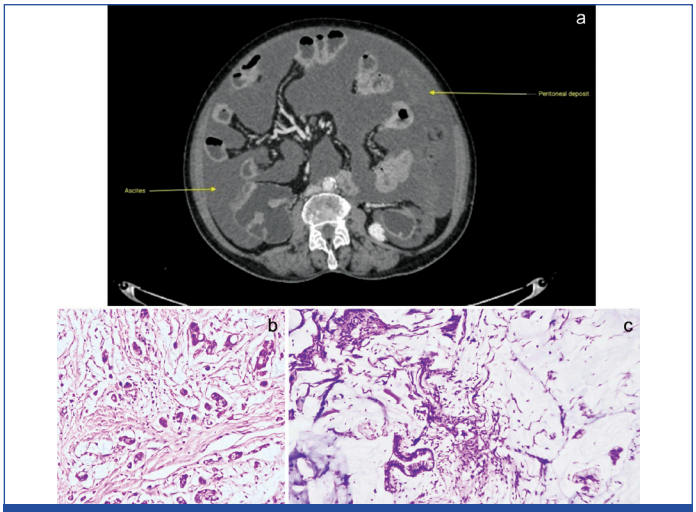
Case 4

A 66-year-old woman with a history of hypothyroidism and hypercholesterolaemia presented with abdominal distension for 2 months. Baseline laboratory evaluation showed haemoglobin of 10.1 g/dL (reference range 12.0-15.5 g/dL) and a markedly elevated ESR of 120 mm/hour (reference range 0-20 mm/hour for adult females). On examination, mild abdominal distension was noted with no palpable mass. MRI was suggestive of peritoneal carcinomatosis/peritonitis encasing the ovaries. CT abdomen showed multiple peritoneal deposits with ascites [Table/Fig-4a]. Intraoperatively, sheet-like mucinous deposits were seen over the pelvic peritoneum, pouch of Douglas, and liver surface. The entire omentum was thickened, nodular, and studded with tumour deposits. The appendiceal tip was enlarged with perforation. Multiple miliary deposits were noted over terminal ileal loops and ascending colon.

Frozen section was submitted from the omentum which showed abundant extracellular mucin with few strips of mucinous epithelium with little atypia.

As the frozen section was performed on a limited omental sample, definitive classification was deferred until evaluation of the appendiceal specimen and permanent sections. Laparoscopic appendicectomy was performed. Gross examination showed appendicectomy specimen measuring 5 cm in length, with perforation at the tip and adherent mucinous material over an area measuring 2.5 x 2.5 cm. Mucin was also noted within the dilated lumen and over the serosal surface.

Histopathological examination showed mucinous adenocarcinoma of the appendix. The lumen was filled with mucin, with extravasated mucin involving the wall and serosa. Clusters of neoplastic cells were seen floating within mucin pools [Table/Fig-4b]. The base was uninvolved. No lymphovascular or perineural invasion was identified. Sections from the omentum showed fatty tissue with extracellular mucin pools and strips of minimally atypical columnar epithelium [Table/Fig-4c].



[Table/Fig-4]: a) CT abdomen showing multiple peritoneal deposits with ascites; b) Histopathological section from appendix showing a mucinous neoplasm with neoplastic epithelial cells floating in extracellular mucin (H&E, 20X); c) Histopathological section from omentum showing abundant pools of extracellular mucin and strips of columnar epithelium with minimal atypia (H&E, 20X).

Final diagnosis was mucinous adenocarcinoma of appendix with low-grade mucinous carcinoma peritonei, TNM stage pT4aNxM1b (Stage IVA) [4].

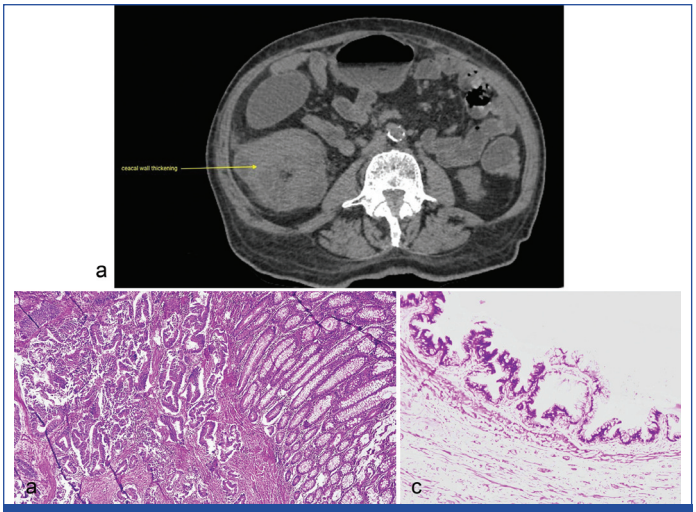
The patient was started on FOLFOX (folinic acid (leucovorin) + 5-fluorouracil + oxaliplatin) chemotherapy and underwent serial monitoring of CEA levels. Despite treatment, the disease progressed, and the patient succumbed to disease approximately two years after diagnosis.

Case 5

An 85-year-old male presented with generalised weakness, anaemia, right-sided abdominal pain, loss of appetite, altered bowel habits and weight loss for four to six months. He was a known case of chronic kidney disease, diabetes mellitus, and hypertension. Laboratory investigations revealed anaemia {haemoglobin 10.1 g/dL (reference range 13.5-17.5 g/dL for males)}, a markedly elevated ESR {120 mm/hour (reference range 0-15 mm/hour for adult males)}, and deranged renal function tests with blood urea of 61 mg/dL (reference range 20-40 mg/dL) and serum creatinine of 1.73 mg/dL (reference range 0.6-1.3 mg/dL). On examination, a mass was palpable in the right iliac fossa. CT abdomen showed carcinoma involving the ascending colon, with circumferential bowel wall thickening of the caecum extending to the proximal ascending colon associated with ileocolic intussusception [Table/Fig-5a]. No features of proximal bowel obstruction were seen. Serum tumour marker evaluation revealed CEA within normal limits. Colonoscopic biopsy showed tubulovillous adenoma with intramucosal carcinoma, following which right hemicolectomy was performed. Intraoperatively, a 6×5 cm tumour involving the caecum with ileocolic intussusception and mild ascites was noted.

Grossly, the right hemicolectomy specimen measured 18 cm in length. A polypoidal growth was identified in the caecum measuring 4.5×5.5×1.1 cm, obstructing 70% of the lumen. The appendix measured 4.5 cm in length and showed thickened wall. Sixteen lymph nodes were identified in the pericolic fat, the largest measuring 1×0.5 cm.

Histopathology of the caecal growth showed infiltrating moderately differentiated adenocarcinoma arising from tubulovillous adenoma with villoglandular architecture, invading into muscularis propria and pericolic fat [Table/Fig-5b]. No lymphovascular or perineural invasion was seen. Resection margins were free. Sections from appendix showed filiform villous mucinous epithelial proliferation replacing the mucosa, lined by tall columnar cells with low-grade atypia, with absent lymphoid tissue in the lamina propria [Table/Fig-5c]. All sixteen lymph nodes showed reactive changes.



[Table/Fig-5]: a) CT abdomen showing carcinoma involving the ascending colon with circumferential bowel wall thickening of the caecum extending into the proximal ascending colon; b) Histopathological section from caecum showing an infiltrating adenocarcinoma composed of tumour cells arranged predominantly in a villoglandular pattern (H&E, 10X); c) Section from appendix showing replacement of normal appendiceal mucosa by filiform villous mucinous epithelial proliferation (H&E, 20X).

The final diagnosis was moderately differentiated adenocarcinoma of the caecum arising in a tubulovillous adenoma (pT3N0M0; Stage IIA)[4], with an incidental low-grade appendiceal mucinous neoplasm (LAMN; pTisN0; Stage 0).

Adjuvant chemotherapy was administered for the synchronous caecal adenocarcinoma. The patient remains on follow-up with no evidence of recurrence at one year with serial monitoring of CEA levels.

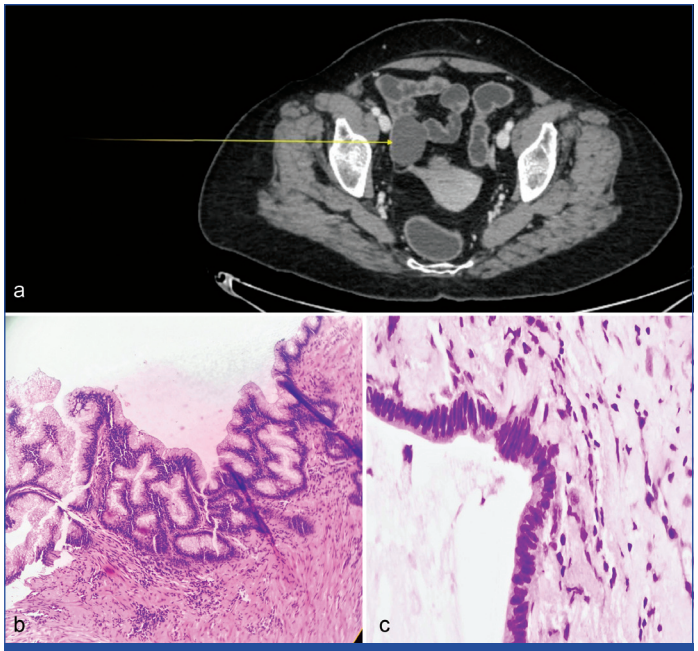
Case 6

A 67-year-old female, known case of hypertension, presented with abdominal pain for one month. There was no history of abdominal distension or weight loss. Routine biochemical parameters were within normal limits. Ultrasound showed a cystically dilated appendix. Both adnexa showed cystic lesions. Serum CEA was mildly elevated {12.76 ng/mL (reference range<5 ng/mL)}. CT abdomen showed a hypodense cystic lesion in the right adnexa closely abutting the right ovarian ligament [Table/Fig-6a]. Clinical and radiological diagnosis was appendiceal malignancy with ovarian metastasis/ovarian tumour. She underwent radical appendicectomy with bilateral salpingo-oophorectomy. Intraoperatively, there was no ascites. A 4×4 cm cystic mass arising from the tip of the appendix was identified. The appendix was ruptured with focal mucin spillage into the peritoneal cavity. Frozen section was suggestive of HAMN.

Gross examination showed a dilated distal appendix measuring 8.5×3×3 cm. On cut-section, the wall was thinned out and the lumen was filled with solidified mucin. Cut-section of left ovary revealed brownish mucoid fluid and showed a uniloculated cyst measuring 1.5×1.5 cm without solid areas. Right ovary showed multiple tiny cysts.

Histopathology showed cystically dilated appendix lined by filiform villous mucinous epithelium [Table/Fig-6b] with hyperchromatic pleomorphic nuclei. Lamina propria showed fibrosis with absent lymphoid tissue [Table/Fig-6c]. Tumour showed pushing growth pattern with mural involvement and acellular mucin extending into subserosa. Omental biopsy was free of neoplasm. Peritoneal fluid cytology showed acellular mucin without identifiable neoplastic epithelium. Given the intraoperative evidence of appendiceal rupture with mucin spillage and the presence of extra-appendiceal acellular mucin, the lesion fulfilled the AJCC TNM criteria for M1a and was staged as pT3NxM1a (Stage IVA) [4]. Left ovary showed benign mucinous cystadenoma. Right ovary showed multiple inclusion cysts.

Final diagnosis was HAMN, TNM stage pT3NxM1a (Stage IVA) [4]. The patient has been on follow-up for 6 months with no recurrence, reassessed with serial monitoring of CEA levels and CECT abdomen.



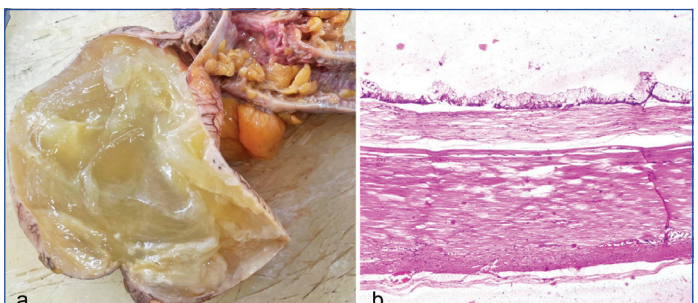
[Table/Fig-6]: a) CT abdomen showing a hypodense cystic lesion in the right adnexal region closely abutting the right ovarian ligament; b) Histopathological section showing a cystically dilated appendix lined by filiform villous mucinous epithelium with enlarged hyperchromatic pleomorphic nuclei (H&E, 20X); c) Histopathological showing columnar epithelial cells with hyperchromatic mildly pleomorphic nuclei. The lamina propria shows fibrosis with absence of lymphoid infiltrates (H&E, 40X).

Case 7

A 40-year-old female, a known case of bronchial asthma, presented with abdominal pain around the umbilical region for three weeks and abnormal uterine bleeding for four months. Laboratory investigations revealed anaemia with a haemoglobin level of 10.2 g/dL (reference range 12.0-15.5 g/dL). On examination, a cord-like mass was palpable in the right iliac fossa. CECT abdomen showed an elongated cystic structure arising from the right iliac fossa with homogeneous low-density content, thin walls, and tiny polypoidal calcification in close relation to the medial wall of caecum, suggestive of appendiceal mucocele. Bulky uterus with fibroids was also noted. Serum tumour marker evaluation showed elevated CEA levels {12.2 ng/mL (reference range<5 ng/mL)}. Clinical diagnosis of appendiceal mucocele with uterine fibroid was made. She underwent right hemicolectomy with total abdominal hysterectomy and bilateral salpingectomy.

Grossly, the appendix was dilated and thin-walled, measuring 12 cm in length and 3 cm in greatest diameter. Outer surface was smooth and intact with congested blood vessels. Cut section showed the lumen filled with thick gelatinous mucoid material [Table/Fig-7a]. Wall thickness ranged from 0.2 to 0.3 cm.

Histopathological examination showed replacement of normal appendiceal mucosa by villous mucinous epithelium with focal epithelial proliferation [Table/Fig-7b]. Acellular mucin was seen dissecting through the fibrotic appendiceal wall. Base and resection margins were free of tumour. Sections from uterus showed submucosal and intramural leiomyoma.



[Table/Fig-7]: a) Grossly dilated thin-walled appendix measuring 12×3 cm and filled with thick gelatinous mucoid material; b) Histopathological section showing replacement of normal appendiceal mucosa by villous mucinous epithelium resting on a fibrotic appendiceal wall (H&E, 20X).

Final diagnosis was LAMN, TNM stage pTisN0 (Stage 0) [4]. The patient has been on follow-up for 9 months with no recurrence. The clinicopathological features of all seven cases are summarised in [Table/Fig-8].

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age/Sex	**69/F**	**63/F**	**56/F**	**66/F**	**85/M**	**67/F**	**40/F**
Clinical presentation	Abdominal pain, loss of appetite and weight loss for 1 month	Diffuse abdominal pain for 3 days	Previous appendicular abscess drainage 9 months earlier with persistent right iliac fossa discharge	Abdomina l distension for 2 months	Generalised weakness, anaemia, anorexia and weight loss for 4-6 months	Abdominal pain for one month	Abdominal pain for 3 weeks with abnormal uterine bleeding for 4 months
Radiological feature	Colonoscopy and CECT showed distal ileal wall thickening suspicious of inflammatory pathology; no definite mass lesion	CECT showed acute small bowel obstruction involving distal ileum	Colonoscopy showed ulceroprolif erative lesion at appendicular orifice	MRI showed diffuse peritoneal nodular thickening, omental caking and deposits near appendix	CT showed circumfer ential caecal wall thickening suggestive of carcinoma ascending colon	Ultrasound showed cystically dilated appendix with bilateral adnexal cystic lesions	CECT showed appendiceal mucocele; bulky fibroid uterus
	Carcinoma cecum	Acute intestinal obstruction	Enterocuta neous fistula with appendicular lesion	Peritoneal carcinoma tosis/ peritonitis	Carcinoma cecum	Appendicular malignancy with ovarian metastasis/ ovarian tumour	Mucocele appendix
Type of surgery	Laparoscopic right hemicolectomy	Right hemicolectomy	Right hemicolectomy	Appendicectomy and omental biopsy	Right hemicolectomy	Radical appendicectomy with bilateral salpingo-oophorectomy	Right hemicolectomy with TAH and bilateral salpingectomy
Histopatholog-ical diagnosis	Goblet cell Adenocarci noma-Grade 2, diffusely involving appendix and caecum	Mucinous adenocarci noma, Grade 2	Adenocarci noma (non-mucinous), colorectal type	Mucinous adenocarc inoma with low grade mucinous carcinoma peritonei	Moderatel y differentia ted caecal adenocarc inoma arising in tubulovillo us adenoma with associated LAMN	HAMN	LAMN
TNM Staging	pT3N1a Stage IIIB	pT3N2M1b Stage IVA	pT3N0M0 Stage IIA	pT4aNxM 1b Stage IV A	T3 N0 M0 Stage IIA	PT3NxM1a Stage IV A	pTisN0 Stage 0

[Table/Fig-8]: Clinicopathological profile and TNM staging of all seven cases.
LAMN: Low-grade appendiceal mucinous neoplasm; HAMN: High-grade appendiceal mucinous neoplasm

DISCUSSION

Epithelial appendiceal neoplasms are uncommon tumours with appendicectomy based studies reporting an incidence of approximately 1.9-2.1% of appendicectomy specimens [1].

In the recent years there is an increase in their incidence. These tumours may clinically and radiologically mimic other intra-abdominal conditions such as ovarian tumours, intestinal obstruction, or acute appendicitis [2]. Under the current WHO classification of digestive tumours (5th edition), appendiceal tumours are currently classified as serrated lesions/polyps, mucinous neoplasms, appendiceal adenocarcinoma, and neuroendocrine neoplasms. Neuroendocrine Tumour (NET) is the most common primary tumour of the appendix. Recent updates in the WHO classification have introduced a new entity called HAMN and goblet cell carcinoid has been reclassified as goblet cell adenocarcinoma with aggressive behaviour [3].

This case series highlights the diverse histomorphological spectrum of epithelial appendiceal neoplasms encountered in a tertiary care setting, ranging from LAMNs to invasive adenocarcinomas, including goblet cell adenocarcinoma and HAMN. Owing to their rarity, variable biological behaviour, and frequent overlap in clinical and radiological presentation with other intra-abdominal conditions, these tumours often pose significant diagnostic challenges. Histopathological examination remains the cornerstone for definitive diagnosis, accurate classification, staging, and risk stratification. Early recognition of these lesions is clinically important, as their management, prognosis, and follow-up vary considerably depending on tumour subtype and extent of disease. The present study was undertaken to highlight the clinicopathological features, diagnostic spectrum, and clinical significance of epithelial appendiceal neoplasms in order to improve recognition of these uncommon but clinically relevant lesions.

The age of patients ranged from 40 to 85 years, with a mean age of 64 years, and a female predominance was observed. This is in concordance with previous studies, including that by Alakus H et al., which reported a higher proportion of cases in females [5]. A significant finding in this study is that the majority of cases presented at advanced stages, including peritoneal dissemination which emphasises the importance of early detection and histopathological evaluation. This is likely due to nonspecific clinical and radiology findings. Most patients presented with abdominal pain, intestinal obstruction, or abdominal distension, mimicking more common conditions such as appendicitis or carcinoma caecum. Similar findings have been reported in study by Rizzello F et al., [6].

In our series, adenocarcinomas constituted the majority (4/7 cases, ~57%), which is comparable to previous reports in which adenocarcinoma represents the most common malignant epithelial neoplasm of the appendix [7]. Among these, the predominant type was mucinous adenocarcinoma which is consistent with prior literature demonstrating a higher frequency of mucinous histology in appendiceal malignancies. Mucinous tumours are of particular importance because they have a propensity for peritoneal dissemination and association with pseudomyxoma peritonei. One case in our series was associated with pseudomyxoma peritonei, a finding well documented in studies by Pai RK et al., where LAMN and mucinous adenocarcinoma are key precursors of pseudomyxoma peritonei [8]. Pseudomyxoma peritonei is due to the rupture of the appendiceal wall and dissemination of mucin-producing epithelium into the peritoneal cavity. It increases the morbidity and requires aggressive management, as emphasised in Peritoneal Surface Oncology Group International (PSOGI) guidelines [9].

The CEA levels showed a stage and histology dependent trend, with significant elevation in mucinous adenocarcinomas with peritoneal involvement. Whereas non-mucinous and low-grade neoplasms showed minimal or no elevation. This suggests its utility as a supportive biomarker in advanced disease rather than an early diagnostic tool [Table/Fig-9] which is comparable to Bąk M et al.,

Case	Histologic Type	CEA (ng/mL)	Stage	Clinicopathological correlation
1	Goblet cell adenocarcinoma	7.2	IIIB	Mild elevation of serum CEA above reference range
2	Mucinous adenocarcinoma	225.3	IVA	Markedly elevated CEA associated with advanced-stage disease
4	Mucinous adenocarcinoma with low-grade mucinous carcinoma peritonei	100.7	IVA	Elevated CEA associated with pseudomyxoma peritonei and peritoneal dissemination
5	Adenocarcinoma caecum with LAMN	4.37	II A	Serum CEA within normal limits
6	HAMN	12.76	IV A	Elevated CEA noted in association with peritoneal extension
7	LAMN	12.2	0	Mild elevation of CEA in a localised mucinous neoplasm

[Table/Fig-9]: Clinicopathological Relationship of Serum CEA Levels with Histologic Type and Stage of Appendiceal Neoplasms.
CEA- carcinoembryonic antigen; LAMN- low-grade appendiceal mucinous neoplasm; HAMN- high-grade appendiceal mucinous neoplasm; PMP- pseudomyxoma peritonei; Stage IVA/IIIB/IIA/0, tumour stages according to the applicable AJCC staging system

where CEA was strongly tied to peritoneal dissemination and was supportive for advanced disease detection [10].

One case showed association with ovarian pathology. As there is a difference in management and prognosis it is important to distinguish primary ovarian mucinous tumours from metastatic appendiceal tumours [11]. One case of LAMN was associated with a synchronous caecal adenocarcinoma. This highlights that appendiceal mucinous neoplasms may coexist with other primary colorectal malignancies and warrant thorough colonic evaluation of the patient [12]. The case of goblet cell adenocarcinoma exhibited mixed glandular and neuroendocrine differentiation. It was also diffusely involving the appendix and adjacent caecum and presented at advanced stage of III B. Similar findings have been described by Tang LH et al., who emphasised its poor prognosis and need for aggressive management [13].

LAMN and HAMN together accounted for 3/7 cases (~43%) in the study. LAMN shows low grade atypia with pushing growth pattern, whereas HAMN shows high grade atypia without infiltrative invasion. As highlighted in recent WHO updates, the distinction is crucial, due to differences in biological behaviour and risk of recurrence. The findings are in agreement with a study by Shaib WL et al., which emphasise the increasing recognition of these entities due to improved histopathological criteria [14].

Although histopathological examination remains the mainstay for diagnosis of appendiceal epithelial neoplasms, immunohistochemistry may be useful in selected cases with diagnostic difficulty. It is particularly helpful in distinguishing primary appendiceal tumours from metastatic mucinous neoplasms involving the ovary or peritoneum. Markers such as CK20, CDX2 and SATB2 support lower gastrointestinal origin, while neuroendocrine markers including chromogranin and synaptophysin may be useful in goblet cell adenocarcinoma [15]. In the present study, diagnosis was established on routine histomorphology with clinicoradiological correlation. However, immunohistochemistry may serve as a useful adjunct in difficult cases and in confirming the site of origin wherever required.

Appendiceal epithelial neoplasms are often difficult to diagnose preoperatively because the clinical and radiological findings are frequently non-specific and may mimic appendicitis, intestinal obstruction, or ovarian pathology. Misdraji J noted that many mucinous appendiceal neoplasms are diagnosed only after histopathological examination of the resected specimen [16]. Although imaging findings such as appendiceal dilatation, mural calcification, cystic lesions, and periappendiceal mucin have been described, these are not consistently seen. Similar variability was observed in the present study, where the diagnosis was confirmed only after histopathological evaluation. A few patients in our series, particularly elderly individuals, presented with vague abdominal symptoms and were diagnosed at a later stage, which is in keeping with previous studies reporting delayed diagnosis due to subtle and overlapping clinical presentation. Lamps LW have also reported that appendiceal neoplasms are frequently detected incidentally in appendicectomy specimens removed for suspected appendicitis or other abdominal conditions [17]. This highlights the importance of routine microscopic examination and adequate sampling of the appendix. Carr et al., further emphasised that careful pathological examination is essential for assessing epithelial atypia, perforation, extra-appendiceal mucin, and peritoneal spread, as these findings have important prognostic significance [7].

A major challenge in the diagnosis of appendiceal epithelial neoplasms is the lack of specific clinical and radiological features, resulting in many cases being diagnosed only after histopathological examination of the resected specimen. This may contribute to delayed diagnosis and advanced-stage presentation. In the present series, three patients presented with stage IVA disease, reflecting the tendency of these tumours to remain clinically silent until extra-appendiceal spread occurs [2,18]. Accurate histopathological classification has gained greater importance following the WHO 5th edition classification and PSOGI recommendations. LAMN and HAMN may share similar architectural features but differ in cytological atypia and biological behaviour. While LAMN generally follows an indolent course, HAMN and invasive adenocarcinomas are associated with a greater risk of progression and peritoneal dissemination. Careful assessment of invasion, perforation, extra-appendiceal mucin, peritoneal involvement, and lymph node status is therefore essential for prognostic stratification [19].

AJCC staging was useful in assessing disease extent and guiding management. Localised lesions showed favourable outcomes following surgery, whereas cases with nodal metastasis or peritoneal dissemination presented at advanced stages and required systemic chemotherapy. The distinction between M1a disease (acellular peritoneal mucin) and M1b disease (peritoneal deposits containing neoplastic epithelium) is clinically important because the latter is associated with a poorer prognosis [19]. Management was influenced by both tumour subtype and stage. Localised LAMN and HAMN were managed primarily by surgical excision, whereas invasive adenocarcinomas and goblet cell adenocarcinoma with nodal or metastatic disease received adjuvant or palliative chemotherapy. These findings highlight the importance of accurate histopathological classification and staging in determining prognosis, treatment planning, and follow-up [19].

Histopathological examination remains the gold standard for diagnosis of appendiceal epithelial neoplasms, with classification based on architectural features, cytological atypia, evidence of invasion, and peritoneal spread. The WHO 5th edition classification of digestive system tumours has further refined the diagnostic categories of appendiceal neoplasms, helping in better standardisation and reporting [3]. Accurate histopathological diagnosis is important because prognosis and management differ among tumour subtypes. LAMN confined to the appendix usually has a favourable outcome following surgical excision, whereas HAMN and invasive adenocarcinomas are associated with increased risk of recurrence, peritoneal dissemination, and poorer prognosis. Identification of pseudomyxoma peritonei and peritoneal spread is also clinically relevant, as these cases may require more aggressive management including cytoreductive surgery with or without HIPEC, as recommended in PSOGI guidelines [9]. Therefore, correct classification and staging are essential for prognostic assessment, treatment planning, and follow-up.

CONCLUSION(S)

This case series underscores the heterogeneous nature of appendiceal neoplasms and their diagnostic challenges, often presenting at advanced stages. Early identification, accurate histopathological classification, staging and multidisciplinary management are crucial, particularly with associated PMP and synchronous tumours. Tumour markers like CEA can be used as a supportive biomarker especially in advanced mucinous tumours. Thorough grossing and microscopy remain essential for precise diagnosis, staging, and optimal prognostication.

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