Case Series

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Varied Histomorphological Presentations of Appendiceal Neoplasms: A Case Series of Eight Cases

Pathology Section

DHIVYA BALAIYA[1], ANITHACHELLAM ANNADURAI[2], JAYAKARTHIGA SUBBIAH RAJENDRAN[3]

ABSTRACT

During routine histopathological study of appendicular specimens, we identified eight cases of appendiceal tumours, including five cases of Low-grade Appendiceal Mucinous Neoplasms (LAMN) and three cases of adenocarcinoma. Among the adenocarcinoma cases, one was a rare colorectal type adenocarcinoma in an older male and two were mucinous adenocarcinoma which includes a case of signet ring cell rich type. These tumours were classified and staged according to the recent WHO classification (5th edition) and the eighth edition of the American Joint Committee of Cancer (AJCC) staging manual. The median age in our series was 60 years. Serum markers were evaluated in two cases of Pseudomyxoma Peritonei (PMP), which showed elevated levels of CA-125 and CA 19.9 in each case. In this case series, three patients were initially diagnosed with acute appendicitis, one case as mucocele, two cases underwent surgery for ovarian malignancy, one patient was operated for an incisional hernia, and one patient was diagnosed with acute intestinal obstruction after clinical and radiological investigations. Histopathological examination confirmed the diagnosis of appendicular neoplasms in these eight cases. Meticulous histopathological examination of all appendectomy specimens is important for the proper diagnosis of appendicular neoplasms and to predict their severity. This will help surgeons plan further treatment to increase the patient's survival rate.

Keywords: Columnar epithelium, Low-grade appendiceal neoplasms, Pseudomyxoma peritonei

INTRODUCTION

The appendix is a vestigial organ located 2 cm below the ileocecal junction and lies in the right iliac fossa of the abdomen. Inflammation of the appendix results in appendicitis. Neoplasms of the appendix are very rare and seen in less than 2% of all appendectomy specimens [1,2]. Most often, they are found incidentally in cases operated for acute appendicitis. Studies on appendicular neoplasms show an increase in their incidence [1]. The current WHO classification of digestive tumours (5th edition) categorises epithelial appendiceal tumours as serrated lesions/polyps, mucinous neoplasms, appendiceal adenocarcinoma, and neuroendocrine neoplasms [3]. Among appendicular tumours, neuroendocrine tumours are common, and colorectal type adenocarcinoma is relatively rare. One fascinating entity among appendicular tumours is appendiceal mucinous neoplasms, which encompass a heterogeneous group of lesions and were previously categorised by various classification systems. In this case series, we present eight cases of appendiceal neoplasms reported in our institute. Among these, only four cases were operated on for appendicular pathology. In the other cases, appendicular pathology was identified intraoperatively and confirmed after histopathological examination. These cases presented with complaints of ovarian neoplasms, intestinal obstruction, and incisional hernia. We present this case series for its rarity and different clinical and histomorphological presentations.

CASE SERIES

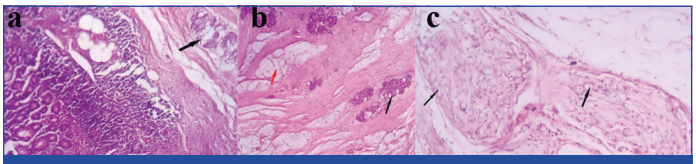
Case 1

A 60-year-old female presented with complaints of excruciating pain on and off for one month, with increased intensity for one day, in the previous scar site from a hysterectomy. Upon examination, a swelling was noticed in the scar area. A clinical diagnosis of an incisional hernia was made, and surgery was planned. Baseline lab investigations were within normal limits. During the operation, the intestines were reduced, and an appendicectomy was performed as the appendix was found to be inflamed. The length of the appendix was 4 cm, and the appendicular lumen was found to be obliterated. Histopathological examination showed clusters and scattered signet ring cells invading into the subserosal adipose tissue, along with pools of extracellular mucin. The resected margin was free of tumour. A final diagnosis of Mucinous adenocarcinoma-Signet ring cell rich was given, with a TNM stage of T3Nx. The resected margin showed no tumour invasion. The patient underwent a right hemicolectomy and was started on chemotherapy [Table/Fig-1,2].

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age	60	62	45	85	62	65	58	35
Gender	Female	Male	Female	Male	Male	Male	Female	Female
Chief complaints	Abdominal pain at previous incision site (hysterectomy done for fibroid) with Swelling at previous incision site	Abdominal pain in right iliac fossa. Mc burneys point tenderness present	sharp pain in periumblical region on and off-1 month with increased pain intensity-3 days	Colicky Abdominal pain, abdominal distension O/E-Abdominal distension present	Sharp and intermittent pain in Right iliac fossa	Vomiting, Abdominal pain in right iliac fossa and Tenderness in right iliac fossa	Vague abdominal pain, abdominal distension O/E-Abdominal mass made out	Loss of weight and appetite,amenorrhaoe, Abdominal distsension O/E-Abdominal mass of varying consistency corresponding to 32 weeks.
Radiological feature	Not done	Not done	USG-Acute appendicitis	x-ray Abdomen-multiple air fluid levels with dilated bowel seen	USG-Mucocele with lumen diameter-1.7 cm	Not done	MRI abdomen -Mucinous neoplasm ovary with Pseudo Myxoma Peritonei	MRI abdomen-Ovarian malignancy with Pseudo Myxoma Peritonei

Serum markers	Not done	Not done	Not done	Not done	Not done	Not done	CA 125-27.3 CA 19.9-50.5	CA 125-52.2
Clinical diagnosis/ Differential diagnosis	Incisional hernia	Acute appendicitis/ Appendicular abscess	Acute appendicitis	Acute intestinal obstruction	Mucocele	Acute appendicitis	Ovarian malignancy with pseudomyxoma peritonei	Ovarian malignancy with pseudomyxoma peritonei
Type of surgery	Appendicectomy followed by right hemicolectomy	Appendicectomy	Appendicectomy	Right hemicolectomy	Appendicectomy	Appendicectomy	Total Abdominal Hysterectomy with Bilateral Salphingo Oophrectmy, Appendicectomy, Omental biopsy	Total Abdominal Hysterectomy with Bilateral Salphingo Oophrectmy, Appendicectomy, Omental biopsy
Histopathological diagnosis with AJCC staging	Mucinous adenocarcinoma-signet ring cell rich T3Nx	LAMN Tis (LAMN) Nx	LAMN Tis (LAMN) Nx	Moderately differentiated adenocarcinoma-colorectal type T3N1a	LAMN Tis (LAMN) Nx	LAMN T3 Nx	Mucinous adenocarcinoma with omental and peritoneal infiltration T3 N1a M1b	LAMN with omental and peritoneal involvement. T4a Nx M1a
Follow-up details	Patient on chemotherapy and under follow-up	Under follow-up with no recurrence	Under follow-up with no recurrence	Patient on chemotherapy and under follow-up	Under follow-up with no recurrence	Under follow-up with no recurrence	Patient on chemotherapy	Patient on chemotherapy

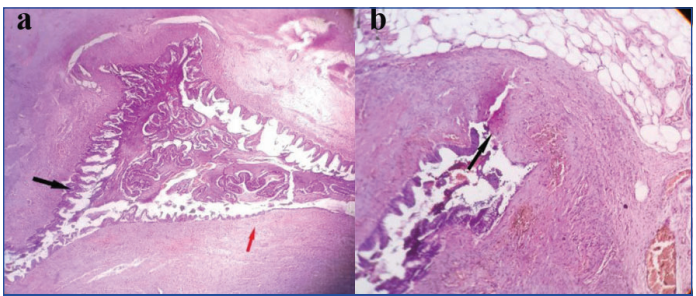
[Table/Fig-1]: Clinical and histopathological findings of eight cases.



[Table/Fig-2]: (a) Histopathology showing appendicular mucosa with underlying nests of signet ring cells (arrow) (H&E 40X); (b) Signet ring cell carcinoma showing nests of signet ring cells (black arrow) along with pools of extracellular mucin (red arrow) (H&E 40X); (c) Signet ring cell carcinoma (black arrows) showing perineural invasion (H&E 100X).

Case 2

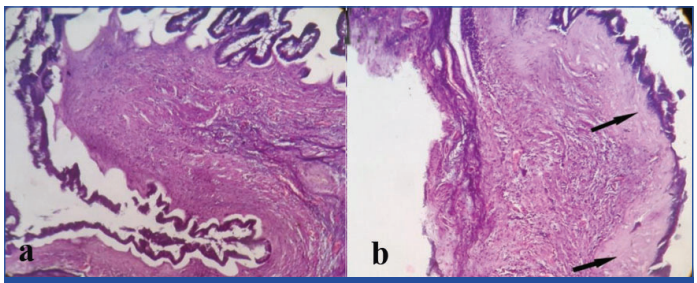
A 62-year-old male presented with right iliac fossa pain for two days and McBurney's tenderness on local examination. Baseline lab investigations were within normal limits, except for an increased neutrophil count. Preoperatively, acute appendicitis was diagnosed, and an appendicectomy was performed. Intraoperatively, the tip of the appendix was found to be cystically dilated. We received a specimen of the appendix measuring 7 cm in length. The cut surface showed a dilated appendicular tip filled with mucin and a thinned-out appendicular wall. Histopathological sections from the appendix showed appendicular mucosa lined by tall columnar epithelium with intracytoplasmic mucin and basally located nuclei, with the lumen filled with mucin. Sections from the resected margin showed no tumour invasion. A final diagnosis of LAMN-Tis Nx was given. The patient was followed-up for two years with no recurrence [Table/Fig-1,3].



[Table/Fig-3]: (a) LAMN showing mucin secreting columnar epithelium with filiform architecture (black arrow) and underlying fibrotic wall (red arrow) (H&E 40X); (b) LAMN showing pushing pattern of invasion into the appendicular wall (black arrow) (H&E 100X).

Case 3

A 45-year-old female complains of sharp pain in the periumbilical region for one month, with increased pain intensity for the past three days. An ultrasound of the abdomen revealed features of acute appendicitis. Baseline lab investigations are normal, except for mild neutrophilic leukocytosis. An emergency appendectomy was performed. On gross examination, we received an appendix specimen with a periappendicular pad of fat measuring 6 cm in length. The cut surface of the appendix showed a lumen filled with mucoid material. Histopathological examination of the appendix showed a dilated lumen filled with mucin, lined by columnar epithelium with nuclear stratification. No evidence of desmoplasia or invasion was seen. The final diagnosis was LAMN-Tis Nx (low-grade appendiceal mucinous neoplasm, confined to the appendix with no lymph node involvement). The resected margin was free of tumour invasion. The patient was followed-up for 18 months with no recurrence [Table/Fig-1,4].



[Table/Fig-4]: (a) LAMN showing undulating layer of mucinous epithelium with mild nuclear stratification and atypia (H&E 40X); (b) LAMN showing fibrotic and hyalinised stroma (black arrows) (H&E 40X).

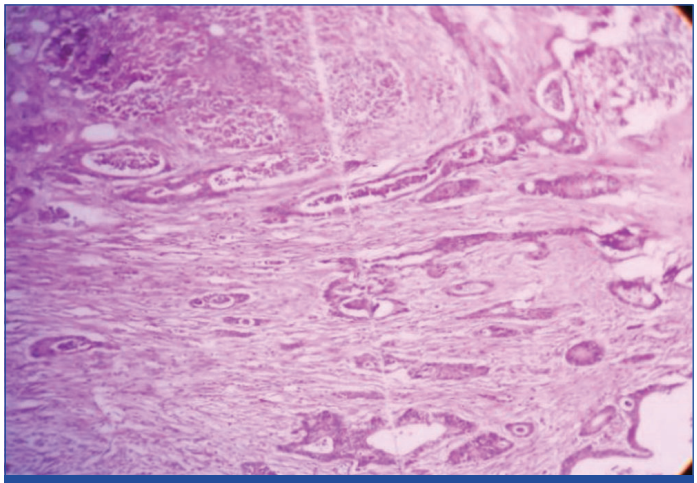
Case 4

An 85-year-old male presented with complaints of abdominal pain, abdominal distension, and vomiting for two days. On examination, abdominal distension was observed, and an X-ray of the abdomen revealed dilated bowels with multiple air-fluid levels. The clinical diagnosis was acute intestinal obstruction, and surgery was planned. Intraoperatively, a diverticulum and stricture were identified, along with a hardened postileal appendix. A right hemicolectomy was performed, and the specimen was sent for histopathological examination.

The gross specimen consisted of portion of small intestine, ileocaecal junction with appendix and portion of large intestine. On the external surface, a 2 cm diverticulum was observed 1 cm away from the resected margin of the small intestine, and a stricture was found 8 cm from the ileocecal junction in the small intestine. The external surface of the appendix appeared normal, while the cut surface revealed a firm grey-white mass measuring 1.5×1 cm at the tip. The serosa appeared to be free of tumour, and four lymph nodes were made out in the surrounding fat pad.

Microscopic examination revealed intestinal type malignant glands with desmoplastic stroma infiltrating the subserosal fat pad in sections from the appendix. The sections from the diverticulum and stricture

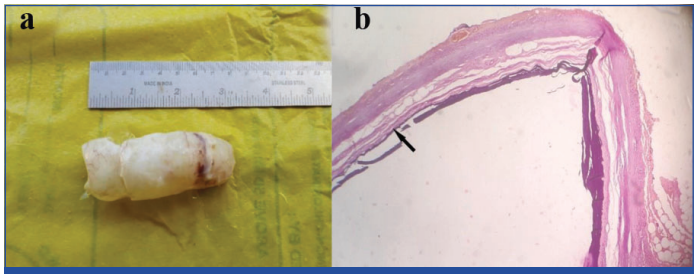
showed mixed inflammatory infiltrate in the wall. One out of the four lymph nodes examined showed metastatic adenocarcinomatous deposits. The resected margins were free of tumour. The final diagnosis was moderately differentiated adenocarcinoma of the appendix, staged as pT3N1a. The patient was placed under follow-up and started on chemotherapy [Table/Fig-1,5].



[Table/Fig-5]: Appendiceal carcinoma-colorectal type showing neoplastic glands with surrounding desmoplastic stroma (H&E 40X).

Case 5

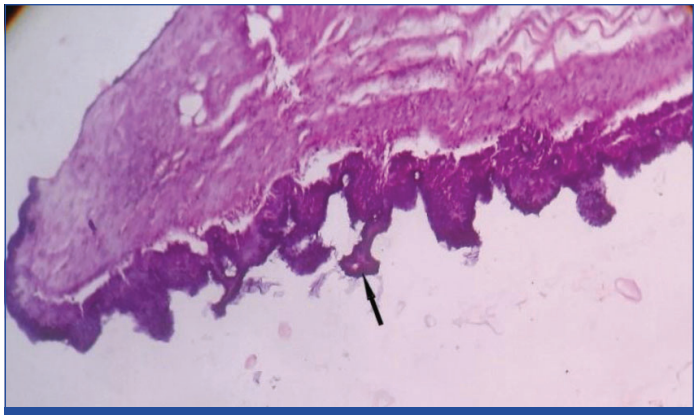
A 62-year-old male presented with complaints of sharp, intermittent abdominal pain in the right iliac fossa for three days. Ultrasonogram revealed a distended appendix. A provisional diagnosis of mucocele was made, and an appendicectomy was performed. Baseline lab investigations were within normal limits. We received a gross specimen of a dilated appendix measuring 8 cm in length. The cut surface showed a luminal diameter of 2 cm filled with mucus material. Sections studied from the appendix showed attenuated mucosa lined by mucin-secreting columnar epithelium with mild nuclear atypia, and the lumen was filled with mucin. A final diagnosis of LAMN with a stage of Tis Nx was given. Resected margins also showed tumour invasion. Revision surgery was performed. The patient was disease-free and followed-up for 12 months [Table/Fig-1,6].



[Table/Fig-6]: (a) Gross photograph showing specimen of dilated appendix filled with mucin; (b) LAMN showing dilated lumen with mucin and attenuated mucosal lining (black arrow) (H&E 10X).

Case 6

A 65-year-old male presented with complaints of vomiting and abdominal pain in the right iliac fossa for two days. On examination, there was tenderness in the right iliac fossa. Baseline lab investigations were within normal limits. A laparoscopic appendicectomy was performed, revealing an appendix measuring approximately 6 cm in length. The lumen was found to be dilated, measuring 1.6 cm in diameter, and filled with mucoid material. The section studied from the appendix showed attenuated mucosa lined by mucin-secreting columnar epithelium with focal papillary projections. Extracellular mucin was observed dissecting the muscularis propria. The section studied from the resected margin showed no tumour infiltration. A final diagnosis of LAMN (Low-grade Appendiceal Mucinous Neoplasm) was given, with a stage of T3Nx. The patient has been on follow-up for nine months with no recurrence [Table/Fig-1,7].



[Table/Fig-7]: LAMN showing mucin secreting columnar epithelium with focal filiform architecture (black arrow) and fibrotic stroma (H&E 40X).

Case 7

A 58-year-old female presented with complaints of vague abdominal pain and abdominal distension for the past six months. On examination, an abdominal mass corresponding to 32 weeks of gestation was observed. MRI revealed bilateral mucinous neoplasms of the ovaries with omental metastasis. Serum markers were evaluated, showing normal levels of CA 125 (27.3 U/mL) and elevated levels of CA 19-9 (50.5 U/mL). The patient underwent hysterectomy with bilateral salphingo-oophrectomy and appendicectomy, with a clinical diagnosis of ovarian neoplasm with Pseudomyxoma Peritonei (PMP).

On gross examination, we received bilateral ovaries, one measuring 17×15×8 cm and the other measuring 18×12×6 cm. The capsules were found to be intact. The cut surface revealed multiloculated cysts filled with mucoid material. The cyst wall thickness ranged from 0.2 to 0.7 cm. The specimen of the uterus with cervix measured 10×6×4 cm. The cut surface showed an endometrial thickness of 0.2 cm, and the myometrium showed no remarkable changes.

The specimen of the appendix measured 4 cm in length. The cut surface revealed a gelatinous mass measuring 1.5×1 cm at the tip of the appendix.

Microscopic examination showed a malignant neoplasm composed of cords and poorly formed glands with intracellular mucin invading the subserosa, along with areas of abundant extracellular mucin in the appendix sections. The resected margin was free of tumour invasion.

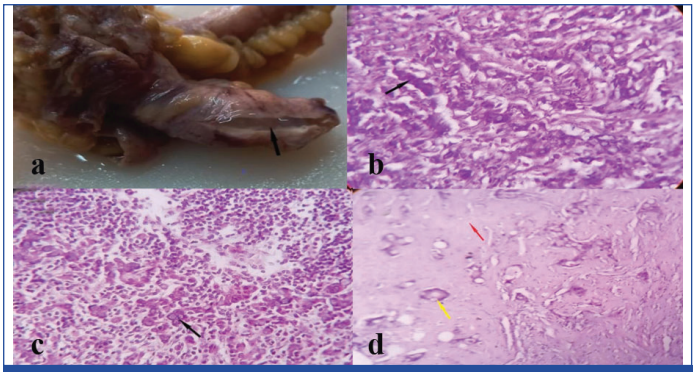
Sections studied from both ovaries showed features of benign mucinous cystadenoma, with the cyst wall lined by mucin-secreting tall columnar epithelium. Sections studied from the uterus showed features of proliferative endometrium and chronic cervicitis.

Sections from one lymph node also shows metastatic adenocarcinomatous deposits and the omentum revealed lobules of mature adipocytes with large pools of acellular mucin, while the peritoneum showed a mesothelial lining with underlying stroma showing tumour infiltration and surrounding desmoplasia.

A final diagnosis of mucinous adenocarcinoma of the appendix with PMP-T3 N1a M1b was given. The patient is undergoing chemotherapy and being followed-up [Table/Fig-1,8].

Case 8

A 35-year-old female presented with complaints of loss of appetite, weight loss, lower abdominal pain, and two months of amenorrhea. On examination, an abdominal mass corresponding to 32 weeks of gestation was detected, with varying consistency. MRI of the pelvis suggested the possibility of a cystadenomatous ovarian neoplasm. The serum marker CA 125 was evaluated and found to be elevated (52.2 U/mL). Total abdominal hysterectomy with bilateral salpingo-oophorectomy was planned with a clinical diagnosis of ovarian malignancy with PMP.



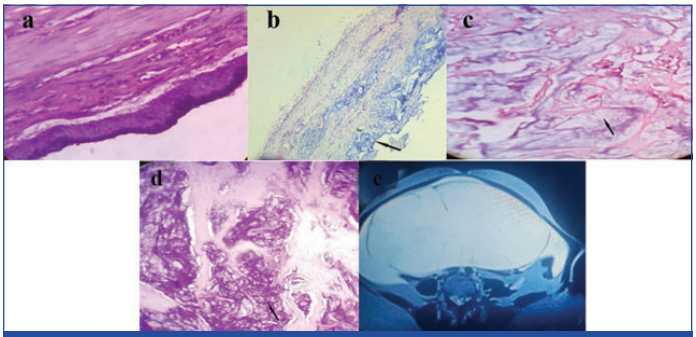
[Table/Fig-8]: (a) Gross specimen of Appendiceal adenocarcinoma which is partially opened and filled with mucin; (b) Appendiceal adenocarcinoma showing neoplastic cells (black arrow) with intracellular mucin arranged as cords (H&E 100X); (c) Lymphnode showing metastatic adenocarcinomatous deposits (black arrow) (H&E 100X); (d) Peritoneal biopsy showing infiltrating neoplastic glands (yellow arrow) with surrounding desmoplasia (red arrow) (H&E, 100X).

We received a single grey-white cystic soft tissue mass measuring 17×15×1 cm, with an attached tube measuring 6 cm in length. The capsule was intact, and the cut surface showed a multiloculated cyst filled with mucoid material. The specimen of the uterus with cervix measured 10×5×3 cm, and the cut surface showed an endometrial thickness of 2 mm. The appendix specimen measured 3 cm in length, with the tip of the appendix appearing normal with a patent lumen.

Microscopic examination revealed that sections from the ovary showed features of a benign mucinous cystadenoma, with the cyst wall lined by tall columnar epithelium, basally located nucleus, intracytoplasmic mucin, and congested vessels in the stroma. Sections studied from the uterus showed features of proliferative endometrium and chronic cervicitis. The bilateral tubes and the other ovary showed normal histology.

Sections studied from the appendix showed mucosa lined by columnar epithelium with nuclear stratification and atypia. Pools of acellular mucin were seen dissecting the serosa. The base of the appendix was free of tumour invasion. Sections studied from the omentum and peritoneum showed pools of acellular mucin. The final report indicated a low-grade appendiceal neoplasm with PMP, with TNM stage T4aNx M1a.

As the capsule of the ovary was intact, mucin was seen over the serosal aspect of the appendix, and MRI of other organs was normal, the appendicular origin of PMP was confirmed. The patient is currently undergoing chemotherapy and is under follow-up [Table/Fig-1,9].



[Table/Fig-9]: (a) LAMN showing single layer of mucinous epithelium with mild nuclear atypia with underlying fibrotic stroma (H&E 100X); (b) Appendicular wall showing dissecting mucin(H&E 40X); (c) Omental biopsy showing pools of acellular mucin (arrow mark) (H&E 40X); (d) Peritoneal biopsy showing pools of acellular mucin (black arrow) (H&E, 40X); (e) MRI showing pseudomyxoma peritonei.

DISCUSSION

Appendiceal mucinous neoplasms are present in 0.2% to 0.3% of appendectomy specimens, constituting a wide spectrum of lesions from Low-Grade Mucinous Neoplasms (LAMN) to mucinous adenocarcinomas [4]. Previously, various classification systems were suggested by Pai RK et al., Misdraji J et al., and Carl NJ et al., which lacked uniformity and were the subject of debate [5-7]. The older classification systems included mucocele, which is now outdated. In a study by Misdraji J et al., appendiceal tumours were classified into two categories: LAMN and adenocarcinoma [6]. According to the recent WHO classification, previously used terms such as Mucinous cystadenoma, borderline tumour of the appendix, and mucinous tumour of uncertain malignant potential are no longer recommended and have been replaced by the new terminology LAMN [3].

In our case series, we have eight cases of appendicular tumours, including five cases of LAMN and three cases of adenocarcinoma. Based on mucin production, there are seven cases of mucinous neoplasms and one case of non-mucinous colorectal type adenocarcinoma. The affected age group ranges from 35 to 65 years, with a median age of 60 years, which is similar to the results of Gundoger O et al., and, contrary to that, males are more affected by LAMN in our series [8,9].

LAMN is uncommon and accounts for 0.2% to 2% of all appendectomy specimens [7]. LAMN is characterised by several patterns, ranging from the classical filiform/villous form to an attenuated monolayer of mucinous epithelium that may show mild nuclear stratification. The appendicular wall shows varying degrees of fibrosis, hyalinisation, and calcification. Mucin may be seen dissecting the appendicular wall, which may extend to the peritoneal surface. Appendiceal carcinomas are distinguished from LAMN by their infiltrative pattern of invasion rather than broad pushing margins seen in LAMN [3]. In our present case series, all five cases of LAMN showed fibrotic submucosa and absent lymphoid tissue. Two cases showed filiform and attenuated mucosa, while one case showed scalloped architecture [Table/Fig-10]. LAMN is staged according to the AJCC staging manual, and the prognosis of LAMN is stage-dependent [3,10]. HAMN is rare and shows similar histopathological features as LAMN but with a degree of high-grade nuclear atypia.

S. No.	Microscopic feature	No of cases (total cases-5)[1]
1	Filiform/villous architecture	2
2	Undulating/scalloped	1
3	Attenuated/flattened mucosa	2
4	Fibrotic submucosal tissue	5
5	Absent lymphoid tissue	5
6	Pushing pattern of invasion	2
7	Dissecting mucin	2

[Table/Fig-10]: Microscopic features of LAMN.
Only five cases were low-grade mucinous neoplasm rest were Adenocarcinoma

Studies by Collin DC reported an incidence of 0.082% of appendicular carcinoma [11]. In our series, there are two cases of mucinous adenocarcinoma and one case of non-mucinous colorectal-type adenocarcinoma. Similar to the literature, females are affected by mucinous adenocarcinoma in the age group of 50-70 years, while a single case of non-mucinous colorectal-type adenocarcinoma is seen in a male [3].

According to the Peritoneal Surface Oncology Group International (PSOGI) guidelines, they recommend including tumour markers (CEA, CA 19.9, CA 125) in the preoperative workup [2]. In our series, tumour markers were studied in only two cases that presented as ovarian neoplasms. CA 125 (52.2 U/mL) and CA 19.9 (50.5 U/mL) were elevated in each case, respectively, and both were associated with PMP. PMP, also called jelly belly, is characterised by the presence of mucinous ascites. It is a rare condition with an incidence of 1 to 2 per million per year and is more common among females [12]. The most common cause of PMP is mucinous neoplasms of the appendix, followed by neoplasms of the ovary, endocervix, alimentary organs, urachus, urinary bladder, lung, mucinous cyst of

the spleen, and breast [13]. In the case of peritoneal metastasis, the grade of peritoneal tumour predicts the prognosis rather than the appendiceal tumour grade [3].

CONCLUSION(S)

Appendicular neoplasms are very rare, and the current WHO classification of appendicular tumours is simplified for both surgeons and pathologists. This case series of appendicular neoplasms shows different nonspecific clinical presentations, varied histopathological presentations, and an increased incidence of appendicular neoplasms in society. All appendectomy specimens should undergo careful histopathological examination, especially in older individuals. Additionally, the inclusion of tumour markers in the pre-operative workup should be mandatory in cases of PMP. This will help surgeons with early diagnosis, proper management, and prevention of disease progression.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Pathology, Thanjavur Medical College, Thanjavur, Tamil Nadu, India.
2. Assistant Professor, Department of Pathology, Thanjavur Medical College, Thanjavur, Tamil Nadu, India.
3. Assistant Professor, Department of Pathology, Thanjavur Medical College, Thanjavur, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dhivya Balaiya,
Assistant Professor, Department of Pathology, Thanjavur Medical College,
Thanjavur-613004, Tamil Nadu, India.
E-mail: dhivyasmc05@gmail.com

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