

Incidental pathologies in appendectomy specimens - An interesting series of cases in a tertiary care center in Eastern India



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ABSTRACT

Acute appendicitis is the most common surgical emergency worldwide, with appendix being the most frequently encountered specimen by a reporting histopathologist. They may sometimes show rare and uncommon histomorphologic pictures that may create diagnostic dilemmas, few of such cases being discussed here. There are two cases of appendicular neuroendocrine tumors (NETs) that initially presented as acute appendicitis clinically, with microscopic tumor foci measuring < 1 cm each. Immunohistochemistry for synaptophysin substantiated the histopathological diagnosis in one case. Neurogenic appendicopathy is another non-neoplastic entity discussed that may be overdiagnosed as appendicular neoplasms such as NET, neuromas, or neurofibromas. Granulomatous appendicitis may be another cause of recurrent appendicitis due to a variety of cases, tuberculosis being one of them and antitubercular therapy being the mainstay of treatment for these cases. Xanthogranulomatous appendicitis may simulate colonic malignancy, Crohn's disease, malakoplakia, etc. Histopathological features are the main diagnostic modalities for these instances. Pinworm is a common helminthic infection of the gastrointestinal tract. Currently, its incidence is on the declining side due to better sanitation practices. However, it must be reported in appendectomy sections, if present, to initiate a course of anthelmintic drugs. Pseudomyxoma peritonei is an uncommon entity classically characterized by mucinous ascites resulting from ruptured appendiceal mucinous tumors, one such rare case being reported here. Low-grade appendiceal mucinous neoplasm is a distinctive entity rarely seen in appendectomy cases, belonging to groups of appendiceal mucinous neoplasms. One such instance has been depicted here.

Key words: Carcinoid; Granuloma; Neurogenic appendicopathy; Pinworm; Pseudomyxoma peritonei; Synaptophysin; Xanthogranulomatous inflammation

INTRODUCTION

Appendectomy is one of the most commonly encountered specimens by histopathologists in their day-to-day practice. The reason for this being acute appendicitis is the most common surgical pathology worldwide, with overlapping clinical presentation with other appendicular pathologies.¹ Pre-operative diagnosis of such cases is not possible without histomorphology.

Appendicular neuroendocrine tumors (NETs) (also known as carcinoid tumor) are very rare neoplasms in the appendix and may be rarely encountered in appendectomy specimens that present clinically as acute appendicitis.² Here, two cases of appendicular carcinoids have been presented.

Neurogenic appendicopathy is a poorly understood disease with dubious and controversial clinical outcomes.³ Although the clinical presentation is similar to acute

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appendicitis, gross appearance is unremarkable.⁴ Hence, histopathology remains the gold standard in the diagnosis of these cases. Here, one such unique case is presented.

Granulomatous appendicitis is an unusual entity encountered, the reason for which may be a variety of systemic disorders such as Crohn's disease, sarcoidosis, and tuberculous etiology.⁵ Clinical presentation as well as gross examination of specimen may be non-specific. One such case is described here.

Xanthogranulomatous inflammation rarely affects the vermiform appendix with no unique features in pre-operative diagnostic studies.⁶ The diagnosis is entirely based on histopathology examination of biopsy sections. One case has been depicted in this study series.

Inflammation of the appendix may be secondary to a various number of causes such as lymphoid hyperplasia, fecoliths, foreign bodies, and tumors. Occasionally, it may be due to parasites where *Enterobius vermicularis* is the most common cause mostly affecting children. However, no age is particularly immune to this infection.⁷ It may be infrequently encountered in appendicular specimens, as has been narrated below.

Pseudomyxoma peritonei (PMP) may originate from ruptured appendiceal mucinous neoplasms, which include low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm, and signet ring cell adenocarcinoma. Rarely, PMP may originate from primary ovarian mucinous tumors.⁸ Histopathological study is essential to determine the grade of the tumor for further therapeutic management. One such distinctive entity has been discussed in this case series. In addition, another case of LAMN is included in the study, highlighting its deceptively low-grade morphology and low-grade cytologic atypia. The LAMNs have a reporting frequency of 0.7–1.7%,⁹ which may be incidental or present with right lower quadrant symptoms.

Aims and objectives

The aims of this study were as follows:

1. To describe some rare histopathologic entities in appendectomy specimens and their gross features along with ancillary investigations
2. To assess the clinical implications of these cases during post-operative follow-up.

MATERIALS AND METHODS

Case series

Case 1

A 21-year-old female patient attended surgical emergency with acute right iliac fossa (RIF) pain along with low-grade

fever and vomiting. She was clinically diagnosed with acute appendicitis and was planned for appendectomy procedure.

The specimen received was of 7 cm length with congested serosa and unremarkable cut-section. The section was submitted from tip and base. On light microscopic examination, there was a 2-mm focus of tumor cells in the tip of the appendix in nesting, organoid, and tubular aggregates with granular chromatin and moderate amphophilic cytoplasm (Figure 1). Mitosis was <2/10 HPF, without any necrosis, lymphovascular space invasion (LVSI), or perineural invasion (PNI). It was reported as a well-differentiated (G1) neuroendocrine tumor, pT1NxMx.

No further adjuvant therapy was prescribed and the patient was doing well during 6 months of follow-up period.

Case 2

An 18-year-old female presented with all features of acute appendicitis and was posted for appendectomy procedure and the specimen was sent for histopathological examination.

Gross examination was unremarkable with congested serosa and unremarkable cross-section. There was a 5-mm focus of tumor cells at the base of the appendix in nesting/organoid pattern, granular chromatin, and moderate eosinophilic cytoplasm. The mitosis count was 10–12/10 HPF without significant necrosis or foci of LVSI/PNI. It was diagnosed as well-differentiated (G2) NETs, pT1NxMx (Figure 2). The diagnosis was further substantiated by positive immunohistochemical (IHC) staining for synaptophysin in the tumor cells and a KI-67 index of 15% in hotspot areas of the tumor (Figure 3 and inset).

The patient was doing well in follow-up period of 7 months.

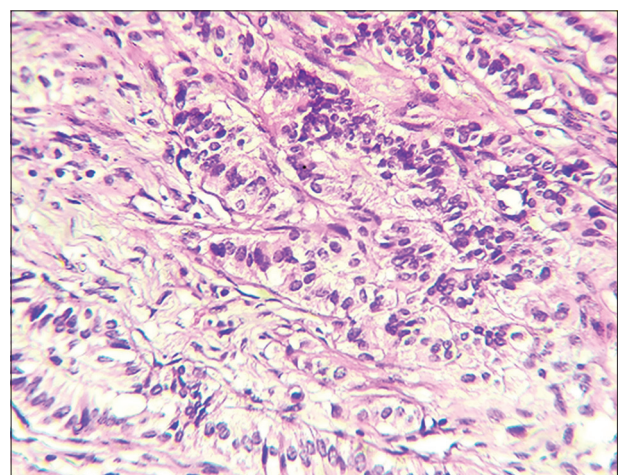


Figure 1: Well-differentiated neuroendocrine tumor (G1), showing organoid and trabecular arrangement of tumor cells (H and E, ×400 magnification)

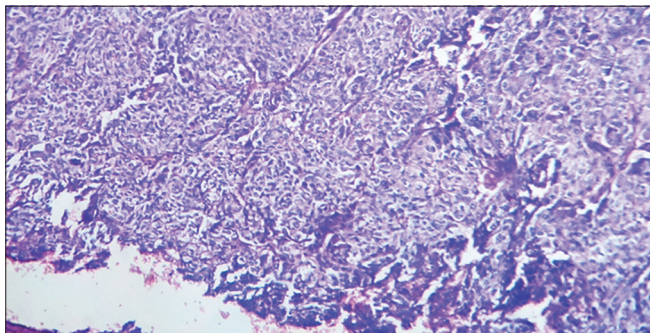


Figure 2: Well-differentiated neuroendocrine tumor (G2) (H and E, ×100 magnification)

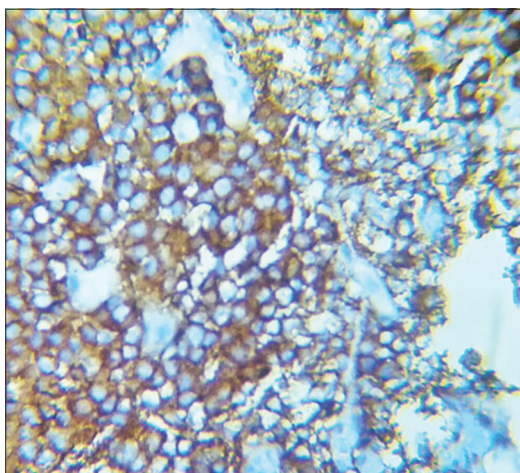


Figure 3: Positive synaptophysin stain in carcinoid tumor (IHC, ×400 magnification); Inset showing low Ki-67 index (IHC, ×100 magnification)

Case 3

A 35-year-old male patient presented with recurrent RIF pain for 8 months with clinical suspicion of recurrent appendicitis. Following appendectomy, the specimen was sent for histopathological study.

Gross examination of the appendix was unremarkable with no serosal congestion and obliterated lumen at the tip (Figure 4). On biopsy sections, the lumen was obliterated with spindle cell proliferation, adipocytes, fibrocollagenous tissue, focal chronic inflammation, and few aggregates of neuroendocrine cells (Figure 5). The diagnosis of neurogenic appendicopathy was opined.

In 4 months of follow-up period, the patient was doing well with complete remission of pre-operative symptoms.

Case 4

A 28-year-old male patient presented with clinical symptomatology of recurrent appendicitis with frequent episodes of diarrhea. Following the surgical removal of the appendix, the specimen was received in the pathology department for histopathological study.

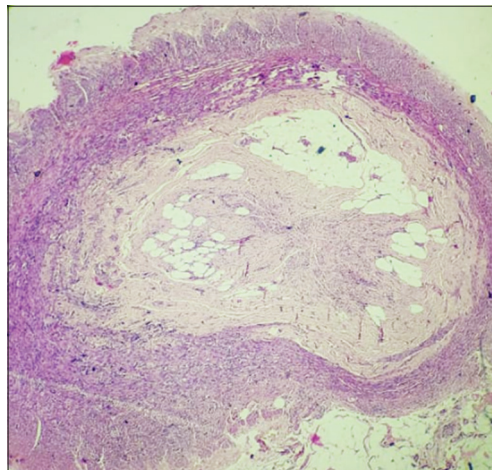


Figure 4: Obliterated tip of the appendix (H and E, ×40 magnification)

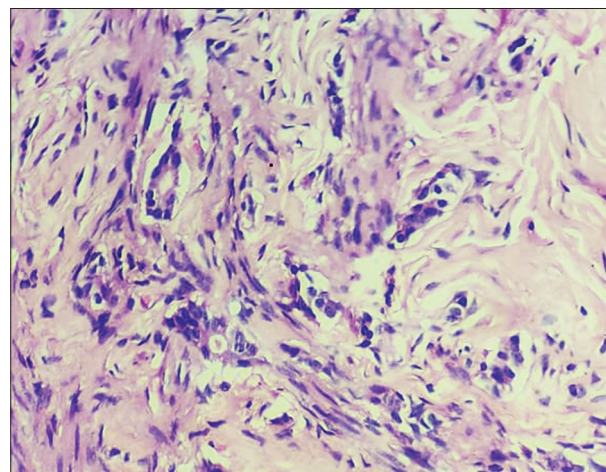


Figure 5: Proliferation of neuroendocrine cells (H and E, ×400 magnification)

The appendix measuring 5.5 cm in length showed serosal congestion with identifiable lumen. Sections submitted from the tip and body of the appendix showed multiple epithelioid granulomas with Langhans giant cells within the wall and peri-appendiceal fat (Figures 6 and 7). Ziehl–Neelsen stain from biopsy section was negative. However, the tissue sent for culture showed the presence of *Mycobacterium tuberculosis*. Thus, it was a case of granulomatous. Thus, it was a case of Granulomatous Appendicitis of tubercular etiology. The patient was then put on antitubercular therapy for extrapulmonary tuberculosis and was doing well in the 10-month follow-up period.

Case 5

A 50-year-old female patient presented with typical features of acute appendicitis in surgical emergency, followed by emergency appendectomy. As a part of routine protocol, the tissue was sent to the histopathology department for examination.

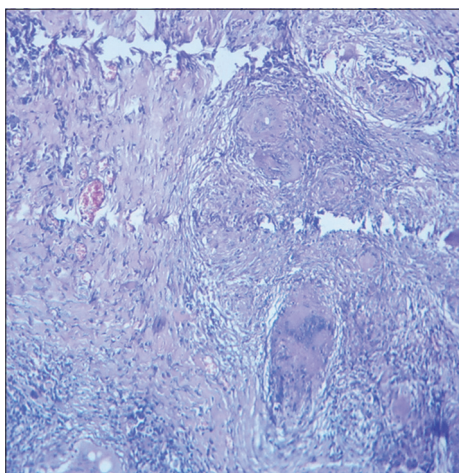


Figure 6: Multiple granulomas in the appendicular wall (H and E, ×100 magnification)

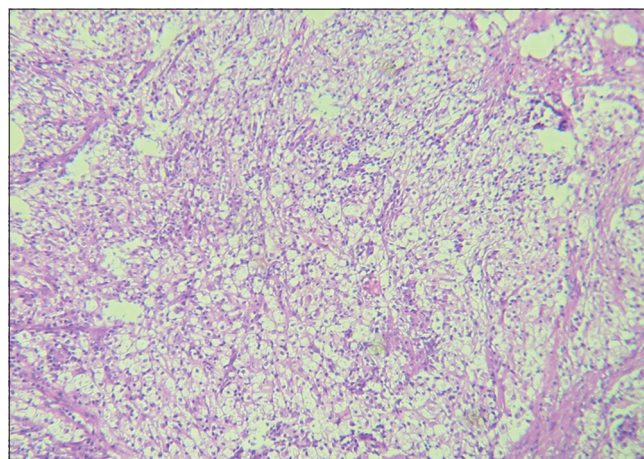


Figure 8: Sheets of foamy macrophages within the wall of the appendix (H and E, ×100 magnification)

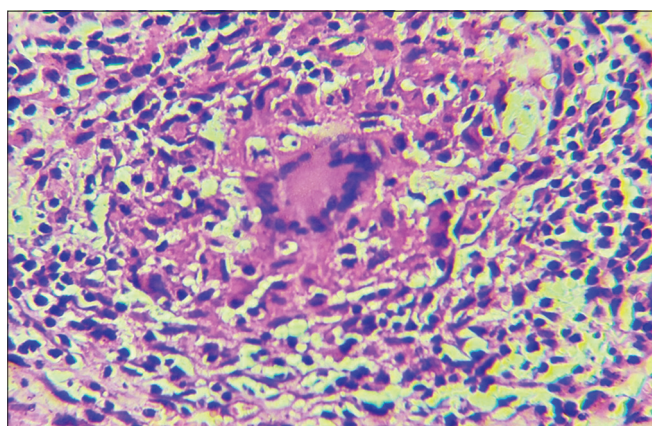


Figure 7: Langhans giant cells within granuloma (H and E, ×400 magnification)

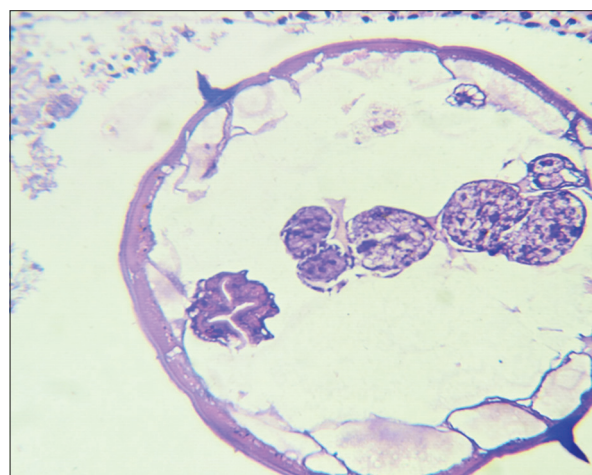


Figure 9: Pinworm within the appendicular lumen (H and E, ×400 magnification)

A 6-cm appendix was received with unremarkable serosa and patent lumen. Sections showed focal mucosal ulceration with infiltration of foamy histiocytes, cholesterol clefts, and few foreign-body giant cells within the wall of the appendix (Figure 8). Areas of congestion were also seen. The picture was typical to that of xanthogranulomatous appendicitis.

The post-operative follow-up period of 3 months was typically uneventful.

Case 6

A 15-year-old boy presented with typical symptoms of acute appendicitis, followed by appendectomy procedure.

The specimen was procured for histopathological study in the department of pathology. The appendix measuring 7 cm in length showed serosal congestion with otherwise unremarkable gross appearance. Sections showed dense inflammation with mucosal ulceration and congestion along with luminal *E. vermicularis* (pinworm) (Figure 9). The final diagnosis was acute appendicitis with pinworm infestation.

The patient was given antihelminthic treatment in the follow-up period with uneventful post-operative recovery.

Case 7

This was a challenging case of a 48-year-old woman who presented with huge progressive abdominal distension over the past 4 months. Ultrasound examination showed mucinous ascites with omental caking, left ovarian cystic SOL measuring 20×18×15 cm along with a small appendicular cystic SOL measuring 6×5×3 cm. Serum tumor marker study showed raised CEA levels (22 ng/mL) and normal CA-125 (10 units/mL). A planned laparotomy procedure was done, which resulted in aspiration of 2 L of mucinous ascitic fluid. Ovarian cystectomy and appendectomy along with omental biopsy specimens were sent for histopathological study.

Sections from multiloculated ovarian cyst showed borderline mucinous tumor without any invasive focus (Figure 10). Sections from appendiceal tumor showed LAMN (Figure 11) and omentum showed acellular pools of mucin

only (Figure 12). The overall histomorphological features were of PMP with synchronous LAMN and borderline mucinous tumor of the ovary. Immunohistochemistry done showed a positive CK 20 stain (Figure 13) and negative CK7 staining in the mucinous epithelium of appendix and ovarian tumors, thus confirming primary origin from the appendiceal low-grade mucinous neoplasm.

The patient was then followed up for chemotherapy in the oncology department and was doing well in 6 months' time following cytoreductive surgery.

Case 8

A 60-year-old woman presented with acute right lower quadrant pain in the abdomen with low-grade fever and was operated for appendectomy with strong clinical suspicion for acute appendicitis.

The appendectomy specimen received showed the dilated tip of the appendix filled with mucin. The dilated lining showed attenuated mucosa and lymphoid follicles with adenomatous proliferation of mucinous epithelial cells with low-grade cytologic atypia. There were pools of

acellular mucin up to muscularis propria (Figure 14). The histopathological diagnosis of LAMN, pTis was made.

Considering that this was an early-stage disease with no peritoneal seeding, the patient was kept on follow-up and was doing well for 6 months post-surgery.

The above findings are summarized in Table 1.

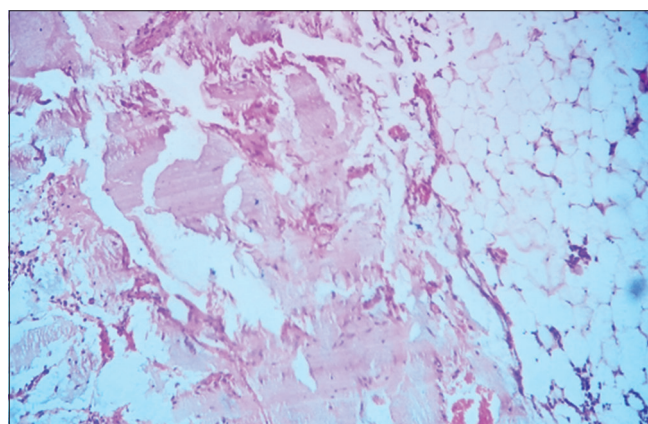


Figure 12: Acellular pool of mucin in the omentum (H and E, ×40 magnification)

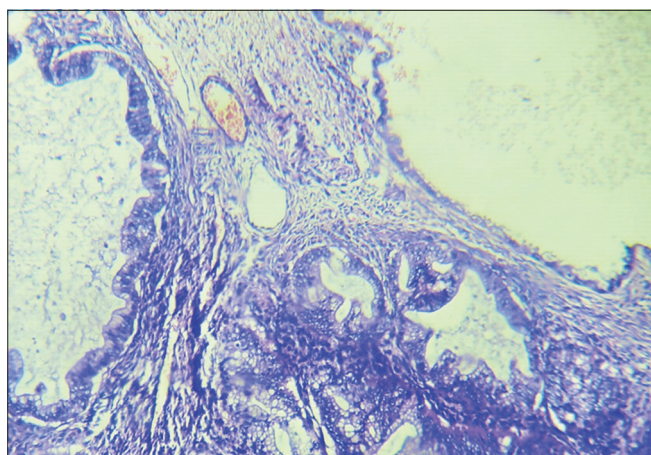


Figure 10: Borderline mucinous tumor of ovary (H and E, ×100 magnification)

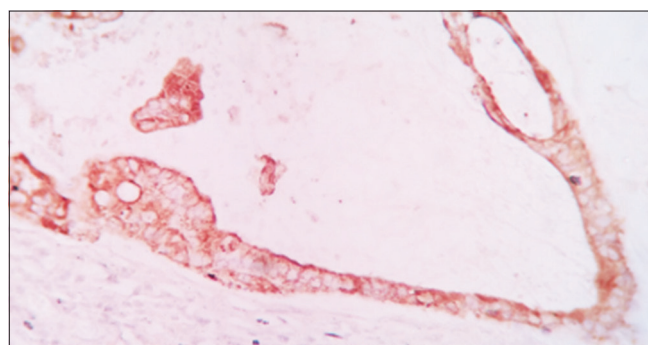


Figure 13: Positive CK20 stain in low-grade appendiceal mucinous neoplasm (IHC, ×100 magnification)

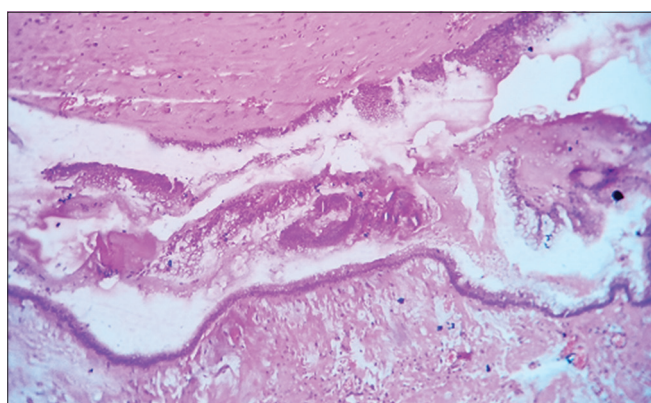


Figure 11: Low-grade appendiceal mucinous neoplasm (H and E, ×100 magnification)

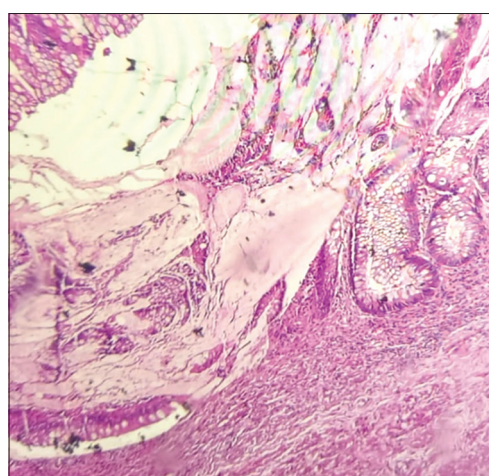


Figure 14: Pools of dissecting mucin in low-grade appendiceal mucinous neoplasm (H and E, ×100 magnification)

Table 1: Summary of all the cases with respect to demography, clinical presentation, histopathological findings, ancillary tests, and long-term follow-up outcome

S. No.	Age (years)/Sex	Clinical presentation	Histopathological diagnosis	Ancillary studies	Follow-up period
1.	21/Female	Acute RIF pain, fever, vomiting	Well-differentiated (G2) neuroendocrine tumor, pT1NxMx	--	For 6-month period - uneventful
2.	18/Female	Acute RIF pain, low-grade fever	Well-differentiated (G2) neuroendocrine tumor, pT1NxMx	IHC for synaptophysin - Positive IHC for KI-67-15%	For 7-month period - uneventful
3.	35/Male	Recurrent episodes of RIF pain	Neurogenic appendicopathy	--	For 4-month period - complete remission of symptoms
4.	28/Male	Recurrent episodes of RIF pain with increased frequency of diarrhea	Granulomatous appendicitis of tubercular etiology	a. ZN stain - non-contributory. b. Culture - positive for <i>Mycobacterium tuberculosis</i> bacillus.	For 10-month period - put on antitubercular therapy and was doing well
5.	50/Female	Acute RIF pain, fever, vomiting	Xanthogranulomatous appendicitis	--	For 3-month period - uneventful
6.	15/Male	Acute RIF pain, fever, nausea	Acute appendicitis with pinworm infestation	--	Anthelmintic treatment given
7.	48/Female	Progressive abdominal distention	Pseudomyxoma peritonei with synchronous LAMN and borderline mucinous tumor of the ovary	Serum CEA - 22 ng/mL (Raised) Serum CA-125-10 units/mL (Normal) IHC for CK20 - positive; IHC for CK7 - negative	For 6-month period - doing well and was put on chemotherapeutic regimen.
8.	60/Female	Acute RIF pain, low-grade fever	LAMN, pTis	--	6-month follow-up period - uneventful.

RIF: Right iliac fossa, LAMN: Low-grade appendiceal mucinous neoplasm

DISCUSSION

Appendicular NETs have shown a substantial increase by 70–133%, with a predominance of younger age group as compared to other epithelial malignancies like adenocarcinomas.^{10,11} The symptoms may mimic that of acute appendicitis as was seen in the study cases of this series or may rarely present as carcinoid syndrome, namely flushing, bronchoconstriction, and diarrhea caused by release of vasoactive substances.¹² Histopathological diagnosis is usually straightforward but substantiated by ancillary tests like IHCs for synaptophysin or chromogranin A in certain cases. For categorization into G1, G2, and G3 histologic grades, mitotic count and KI-67 index plays a significant role and has a bearing on the prognosis and long-term outcome of these patients. Tumors <1 cm in dimension as in both of our cases are simply treated by appendectomy alone with a 100% 5-year survival rate. However, the treatment approaches for larger tumors may include extended right hemicolectomy and lymphadenectomy, where the risk is weighed against long-term survival outcome and metastatic potential of the tumor.¹³

Neurogenic appendicopathy is an ambiguous entity that clinically simulates acute appendicitis but lacks histopathological features of acute inflammation. The key diagnostic feature is obliteration of lumen by hypertrophic

neural bundles or neuroendocrine cells without any definite insular growth pattern, as was seen in this study case. Its importance lies in the fact that it may often be mistaken as NETs, neurofibromas, or neuromas and a definite distinction from these entities is essential, so as to determine future prognostication of these cases.¹⁴ Neurogenic appendicopathy is a non-neoplastic entity that must never be overdiagnosed as a neoplasm, as appendectomy is the only sufficient treatment necessary in this case with no requirement for long-term follow-up.

Granulomatous inflammation can involve any system and vermiform appendix is no exception. Such inflammation may exclusively affect the appendix or may be involved as a part of systemic disease. Tuberculosis is definitely one of the causes of such inflammation, this being a rare extrapulmonary manifestation of the same.¹⁵ The presentation may be similar to acute abdominal pain or even have chronic long-standing features of fever, cough, nausea, weight loss, pulmonary lesions on chest X-ray, or studding of peritoneum and mesentery.¹⁶ Histology is the gold standard for diagnosis of these cases with other supportive tests to evaluate the cause of granulomas.

Xanthogranulomatous inflammation is a form of chronic inflammation that may affect any organ system, kidneys, and gallbladder being the most commonly affected ones.¹⁷

Although a rarely encountered pathology in the appendix, it is important to make an appropriate diagnosis on histopathology as they may cause false elevation of serum tumor markers like CA 19-9 and may clinically mimic colonic malignancy.¹⁸ Furthermore, histopathological study is necessary to rule out other entities with overlapping features such as malakoplakia and Crohn's disease.¹⁹

Gastrointestinal infection due to *E. vermicularis* (or pinworm) occurs worldwide as the most common helminthic infection, especially amongst people belonging to lower socioeconomic strata.²⁰ This may be a lesser encountered pathogen in the developed nations, as opposed to the Indian subcontinent. Pinworm is a standalone entity that may cause lower abdominal pain, even in the absence of histopathologic features of acute inflammation in the appendix. It should be reported in appendectomy sections if present, as the patient may require antihelminthic therapy to prevent future complications. However, the incidence of pinworm infections is gradually falling, even in developing nations, due to better sanitary habits, availability of safe and clean drinking water, and awareness among general population regarding health and hygiene.

PMP is an extremely rare condition, which occurs when a mucin-producing tumor of the abdomen or pelvis spreads within the abdominal or pelvic cavity. Appendix is the primary source in majority of the cases, as has been described above. Ovarian origin is quite rare, whereas synchronous ovarian and appendiceal involvement is an exceptional situation that was seen in this study series. Considering raised serum CEA versus CA-125, the tumor was thought to be primarily of appendicular origin with secondary ovarian involvement. This theory is further justified by positive CK20 and negative CK7 staining in IHC.²¹ Surgical cytoreduction combined with hyperthermic intraperitoneal chemotherapy has been the recommended standard of care for PMP,²² which was followed in this case. Long-term prognosis and disease-free survival depend on histologic grade of the tumor, stage, and extent of dissemination.²³

Appendiceal mucinous tumors are a heterogeneous group of tumors with rising incidence.²⁴ Often, they may present as luminal dilatation or cystic changes and sometimes they may be deceptively normal on gross examination. Histopathology is the main diagnostic modality and subsequent treatment is dependent on the grade and stage of the neoplasm.²⁵ The treatment and long-term prognosis of LAMN drastically changes with staging. Early-stage disease requires only watchful follow-up as for this study case, whereas high-stage disease with peritoneal involvement may require chemotherapy due to increased chances of recurrence.²⁶

Limitations of the study

This study has been conducted on fewer number of cases highlighting the rare histopathological diagnosis. This paves the way for further studies with large sample size and for longer duration to effectively predict the trend of occurrence of these cases in routine histopathology reporting.

CONCLUSION

Appendix is one of the most commonly reported specimens by the histopathologist. In certain rare cases, it may pose diagnostic challenges with some rare histomorphologic pictures, some of which have been discussed here. Appropriate diagnosis is essential to plan the future course of management and predict the long-term outcome of the patients.

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DECLARATION OF PATIENT CONSENT

Written informed consent was obtained from the patients for publication of this manuscript and any accompanying images.

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