Case series

Diagnostic pitfalls in low grade appendiceal mucinous neoplasms

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ABSTRACT

Primary neoplasms of the appendix are present in less than 2% of appendicectomy specimens. Appendiceal mucinous neoplasm is a rare malignancy which is found in less than 0.3% of appendicectomy specimens and accounts for around 1% of gastrointestinal neoplasms. These have varying malignant potential and include a heterogeneous group of diseases. According to the WHO 5th edition (2019), the neoplastic spectrum of appendiceal mucinous neoplasms comprise of low-grade appendiceal mucinous neoplasms (LAMNs), high grade appendiceal mucinous neoplasms (HAMNs), and mucinous adenocarcinoma of the appendix. The patients with mucinous appendiceal lesions are frequently operated for symptoms resembling acute appendicitis as they lack specific clinical and imaging presentation. Categorisation of these neoplasms with attention to extent of mucin and neoplastic cells is crucial to stage the disease as well as to assess the risk of pseudomyxoma peritonei (PMP), a life-threatening complication with poor prognosis. We present 8 LAMNs including a rare case of synchronous mucinous cystadenoma of ovary and LAMNs. We discuss the different clinical presentations and the challenges faced in diagnosis.

Keywords: LAMNs; appendix; mucinous neoplasms.

INTRODUCTION

Primary neoplasms of the appendix are present in less than 2% of appendicectomy specimens. Appendiceal mucinous neoplasm is a rare malignancy which is found in less than 0.3% of appendicectomy specimens and accounts for around 1% of gastrointestinal neoplasms (1,2). These have varying malignant potential and include a heterogeneous group of diseases as reflected by different classification systems.

In the past, different classifications of appendiceal mucinous neoplasms were proposed due to the frequent disparities between the clinical behaviour and histological findings. In 2003, Misdraji *et al.,* first classified these lesions into low-grade appendiceal mucinous neoplasms (LAMNs) and mucinous adenocarcinoma based on degree of cytological atypia and complexity of architecture. This was further adopted by the World Health Organization classification in 2010. According to the WHO 5th edition (2019), the neoplastic spectrum of appendiceal mucinous neoplasms comprise of LAMN, HAMN and mucinous adenocarcinoma of the appendix (3).

The mucinous appendiceal lesions lack specific clinical or imaging presentation and the symptoms resemble those of acute appendicitis. Categorisation of these lesions based on extent of mucin and presence of neoplastic cells is pivotal for staging the disease and to assess the risk of pseudomyxoma peritonei (PMP), a life-threatening complication with poor prognosis (4,5).

We present 8 cases of LAMNs including a rare case of synchronous mucinous cystadenoma of ovary and LAMN. We discuss the different clinical presentations and the challenges faced in diagnosis.

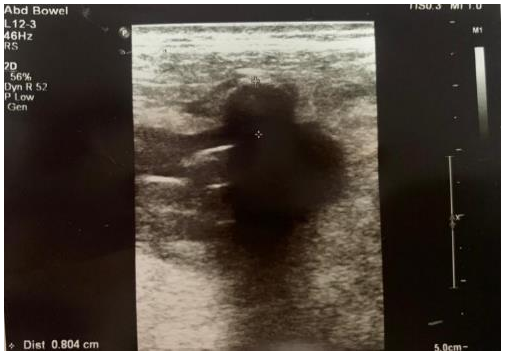

Fig. 1: Ultrasound abdomen showing enlarged appendix

Case 1

A 55-year-old female presented with complaints of right lower abdominal pain, nausea and low-grade fever. On examination tenderness was present in the right iliac fossa. Hematological parameters revealed Neutrophilic leucocytosis. USG abdomen and pelvis showed 8 mm inflamed appendix with some free fluid in abdomen (Fig. 1). Patient underwent appendicectomy with a preoperative diagnosis of acute appendicitis. Intraoperatively, appendix was enlarged and distended (Fig. 2A). No rupture seen. A diagnosis of Mucocele was considered and sample was sent for histopathology. Grossly, appendix was distended, no rupture seen (Fig. 2B). Cut surface showed a dilated lumen filled with mucin. Microscopically, lumen of appendix was dilated and lined by epithelium exhibiting villiform appearance. The lining cells were columnar, having basally located nuclei. Acellular pools of mucin were seen in subserosa (Fig. 3). Base of appendix was uninvolved by LAMN.

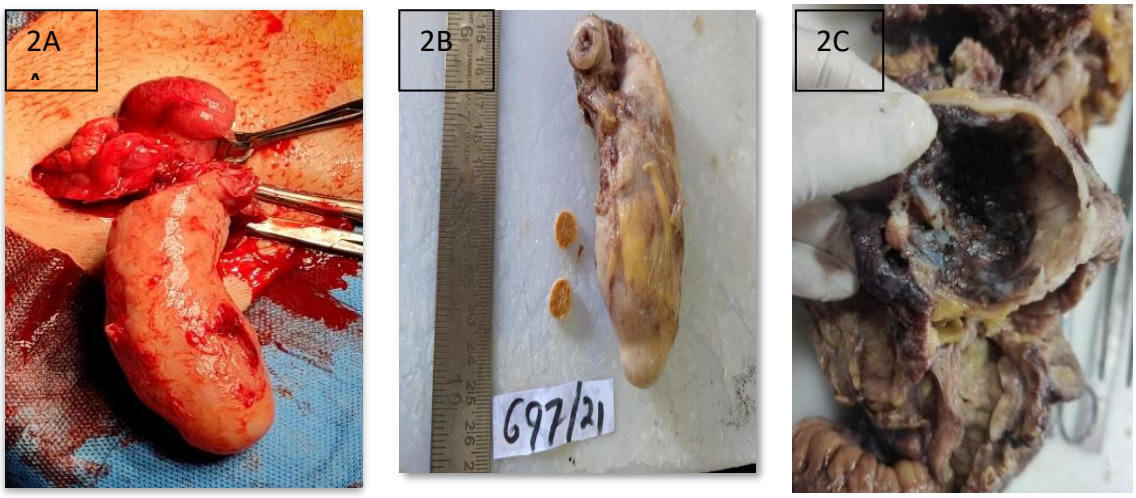

Fig. 2A: Intraoperative findings – Distended appendix; **2B:** Gross image of distended appendix; **2C:** Hemicolectomy specimen showing dilated appendix.

Case 2

A 37-year-old female, presented with severe abdominal pain. On examination, abdominal guarding, and tenderness present in the right iliac fossa. Hematological parameters revealed neutrophilic leucocytosis. Ultrasound abdomen showed ruptured appendix with Pseudomyxoma peritonei. Patient underwent right hemicolectomy and specimen was sent for histopathological study, and peritoneal fluid was sent for cytology. Grossly, Right hemicolectomy showed an enlarged appendix with mucin over serosa. Cut surface lumen was dilated and filled with mucoid material (Fig. 2C). Histopathology showed predominantly ulcerated mucosa with focal areas showing neoplastic epithelium exhibiting undulating villiform architecture and papillary tufts (Fig. 3). Lining cells were tall columnar, having hyperchromatic nuclei exhibiting stratification. Submucosal fibrosis and mural hyalinization noted. Serosa showed acellular pools of mucin. Cytology of the fluid revealed pools of thick acellular mucin (Fig. 4A & 4B).

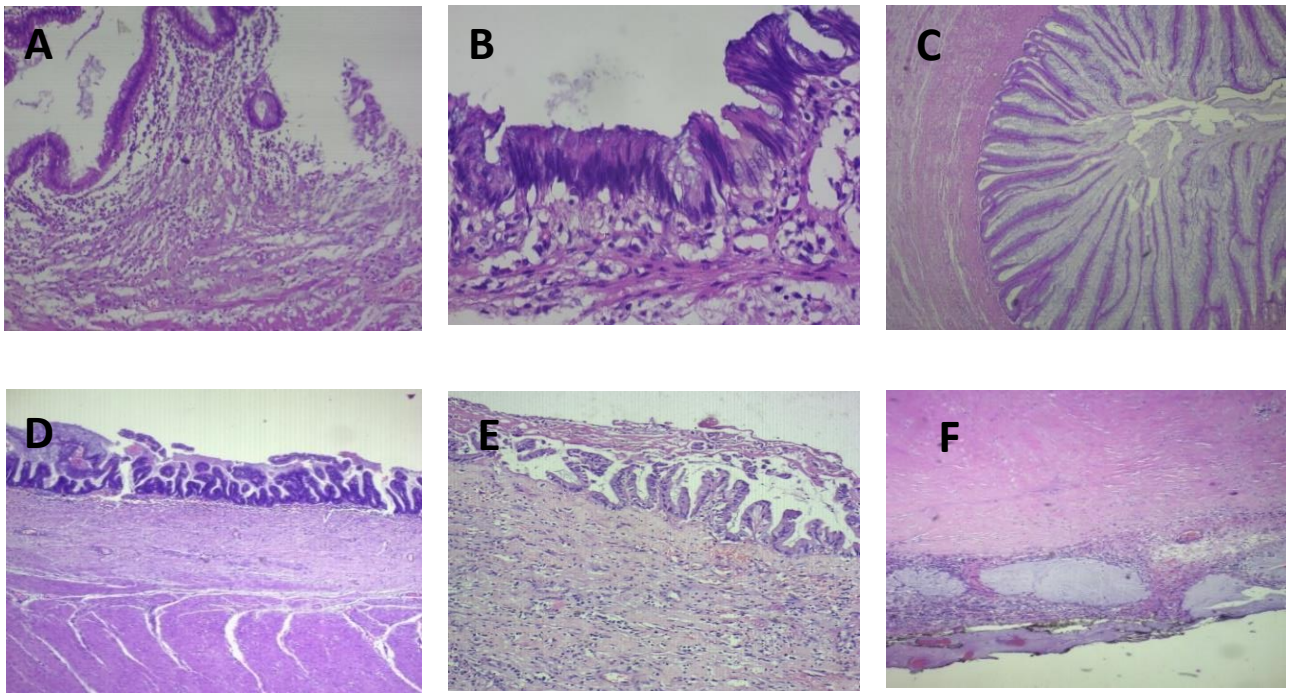

Fig. 3: Microscopic appearance of LAMN: A. Low power view showing appendix lined by single layer of mucin secreting cells, H & E, 100 x B. Lining cells exhibiting low grade dysplasia, H & E, 400 x C. Appendiceal mucosa replaced by slender villi with hypermucinous epithelium, H & E, 400 x D. Lining cells exhibiting undulating villiform architecture, H & E, 100 x E. Lining cells exhibiting villiform architecture, lamina propria shows fibrosis. H & E, 100 x F. Serosa showing pools of acellular mucin (Arrow) (H & E, 100 x)

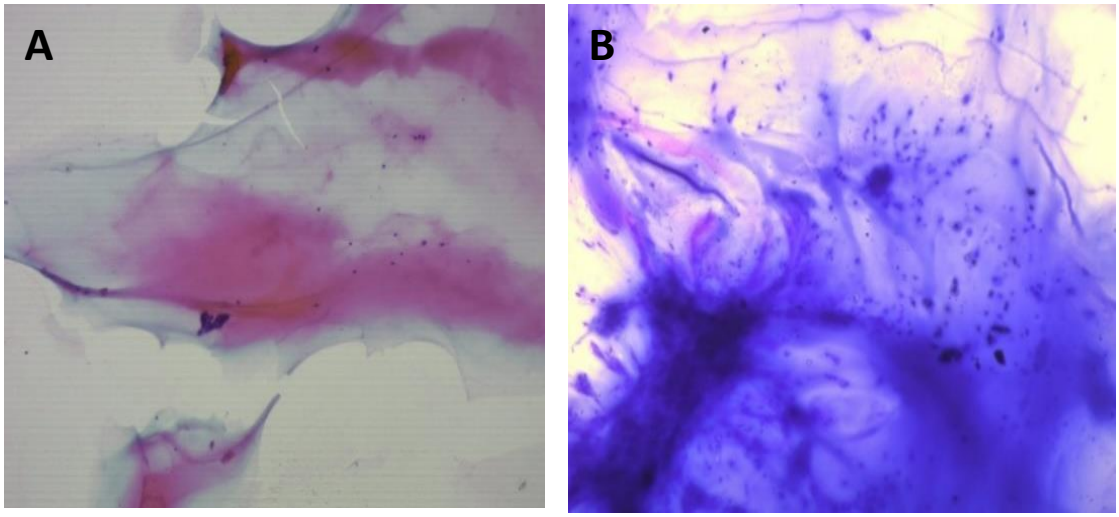

Fig. 4A & **4B**: Cytology smears showing thick pools of acellular mucin (3A - Pap stain, 100 x, 3B – MGG stain, 100 x)

Case 3

A 59-year-old female patient came with complaints of abdominal pain and loose stools for a duration of 3 weeks. Ultrasound abdomen revealed a right adnexal mass and small uterine fibroid along with dilated appendix. Patient underwent a total abdominal hysterectomy, right salpingoophorectomy, with appendicectomy and omental biopsy. Grossly, appendix was dilated and measured 6 x 4 x 4 cm. Lumen was filled with mucoid material. Microscopically, mucosa appeared flattened and lined by single layer of tall columnar mucin secreting cells (Fig. 3). Atrophy of the underlying lamina propria was noted. Grossly, right ovary was enlarged and measured 10 x 8 x 8 cm. Outer surface – capsule was intact. Cut surface showed a multiloculated cyst filled with mucoid material. Microscopically, cysts were lined by single layer of columnar mucin secreting cells with basally located nuclei. Periphery showed remnant ovarian stroma (Fig. 5A & 5B). Hence, a diagnosis of concurrent Low grade appendiceal mucinous neoplasm with mucinous cystadenoma of ovary was given.

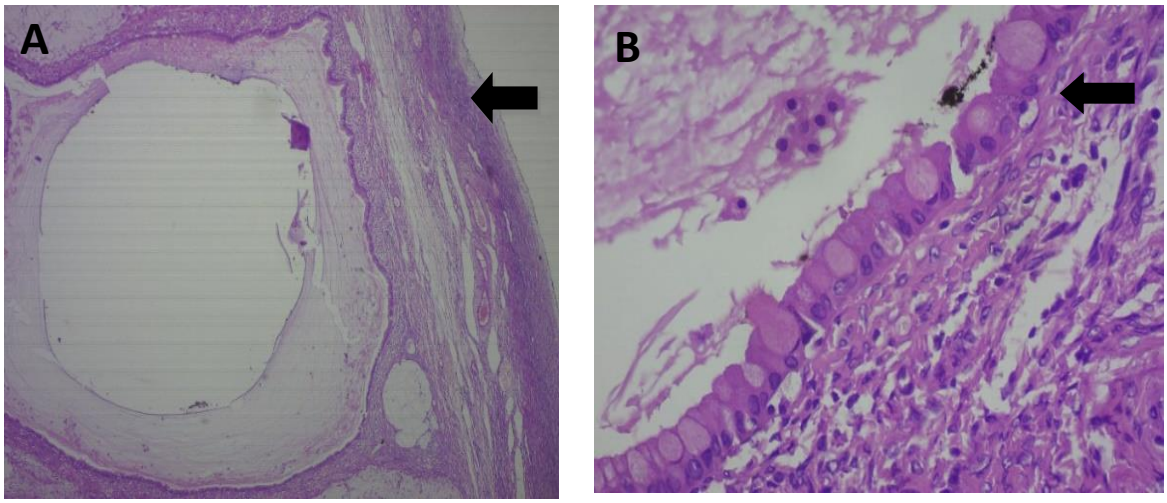

Fig. 5: A) Ovarian cyst with luminal mucoid material. Periphery shows remnant ovarian stroma (Arrow) B) High power view showing single layer of columnar mucin secreting cells with basally located nuclei (H&E, 400x)

Case 4

A 55-year-old female patient presented with complaints of pain abdomen, nausea, vomiting and loss of appetite for 2 weeks. MRI of pelvis revealed features suggestive of ruptured appendix. Mild ascites present. Patient underwent an appendicectomy. Grossly, appendix was enlarged, lumen was dilated and filled with mucin. Microscopically, the mucosa was ulcerated and focally showed villiform appearance with cells exhibiting low grade dysplasia. Submucosal fibrosis was present (Fig 3). Acellular mucin was seen extending to serosa.

Case 5

A 46-year-old female patient presented with complaints of pain in the umbilical region, fever and vomiting for 4 days. On examination abdomen was distended and guarding was present. CT abdomen revealed edematous bowel loops with adjacent fat stranding and mild to moderate free fluid in right iliac fossa- likely sequelae of ruptured appendicitis. Patient

was taken up for emergency laparotomy and appendicectomy was done. Grossly, appendix was enlarged, showed dilated lumen filled with mucin. Serosa showed mucoid material. Microscopically, the appendiceal mucosa showed slender villi, with lining cells being tall columnar, exhibiting low grade cytological atypia (Fig. 3).

Case 6

A 77-year-old male patient came with complaints of recurrent episodes of pain abdomen. On examination Tenderness present in right iliac fossa. USG revealed an appendicular mass. Patient was taken up for appendicectomy. Intraoperatively appendix revealed a sealed off perforation with focal mucin collection at the tip of appendix. Appendicectomy was done and sent for histopathological examination. Grossly, appendix measures 6 cm in length. Outer surface showed exudate. The was no gross dilatation of appendix. Representative sections were given which revealed normal mucosa, however acellular mucin was noted at the serosa. Hence, extensive sampling of rest of the appendix was done which focally showed neoplastic epithelium comprising of single layer of columnar cells having hyperchromatic nuclei exhibiting stratification (Fig. 3).

Cases 7 and 8

Here we have a 40-year-old male and a 74-year-old female patient with similar presentations. Both the patients came with complaints of pain abdomen and underwent laparoscopic appendicectomy for a clinical diagnosis of acute appendicitis. Grossly, appendix was distended, and lumen was filled with mucin. Microscopy revealed features of LAMN.

DISCUSSION

In our study, LAMNs were more common in older women, which is consistent with studies by Pai *et al.,* Umetsu *et al.,* and Mary *et al.,* (6-8). Female to male ratio was 3:1. The age of patients ranged from 37 to 77 years with mean age being 55 years. Pain abdomen was the most common presenting symptom, which was seen in all cases, along with other symptoms like nausea, vomiting, fever and loose stools. A preoperative diagnosis of acute appendicitis was considered in 6 cases. Similar findings were noted in other studies (6-9). Grossly, appendix was enlarged in 7 out of 8 cases, cut surface showed dilated lumen filled with mucin. In one of the cases, no gross dilatation of appendix was noted. Microscopically, the most common architectural pattern was undulating appearance of lining epithelium, followed by filiform and flattened lining. The summary of clinicopathologic features of LAMNs in this study is described in Table 1.

Table 1: Clinicopathological features of LAMNs in this study

Characteristics	No. of patients
Sex	
Male	2 (25%)
Female	6 (75%)
Mean age (range)/Years	55 (37–77 years)
Presenting complaints	
Pain abdomen	8 (100%)
Nausea and vomiting	3 (37.5%)
Fever	2 (25%)
Loose stools	1 (12.5%)
Admitting diagnosis	
Appendicitis	6 (75%)
Mucocele	2 (25%)
Gross appearance	
Distended appendix	7 (87.5%)
Normal	2 (12.5%)
Microscopy	
Flat epithelial lining	1 (12.5%)
Undulating or scalloped	4 (50%)
Filiform	3 (37.5%)
Degree of fibrosis	
Confined to mucosa	7 (87.5%)
Full thickness	1 (12.5%)
Additional pathological findings	
Pseudomyxoma peritonei	1 (12.5%)
Mucinous cystadenoma of ovary	1 (12.5%)
pT stage	
pTis	4 (50%)
pT3	1 (12.5%)
pT4a	3 (37.5%)
pT4b	0

As seen in our study, microscopically LAMNs can show varied morphology. The most common and classic appearance is presence of filiform mucinous epithelial proliferation, replacing the normal appendiceal mucosa. The tumour cells appear hyper mucinous but are cytologically bland. The morphological patterns include an undulating or scalloped appearance whereas in some cases the epithelium can be attenuated or flattened monolayered. This rests on fibrotic submucosal tissue and lymphoid tissue are usually absent. Mucin can dissect through the appendiceal wall, extend to peritoneal surface or even cause rupture of appendix (3). In this study we encountered cases with all of the above-mentioned morphological patterns. Many a times, the epithelium can be completely denuded making the diagnosis difficult as seen in one of our cases. In such cases, extensive sampling of appendix should be done till neoplastic epithelium is seen. Another challenge in diagnosis of LAMN is distinguishing these from High grade appendiceal mucinous neoplasms (HAMN) and mucinous adenocarcinomas. HAMNs are rare lesions and show similar histological features as those of LAMN, however, the neoplastic epithelium has high grade features with presence of frequent mitotic figures including atypical ones. LAMNs can be distinguished

from mucinous adenocarcinomas by pattern of invasion. LAMNs invade with a broad tumour front and exhibit fibrosis and hyalinisation of underlying tissue. However, mucinous adenocarcinomas exhibit infiltrative pattern, expansile mucin pools containing glands, clusters and detached strips of atypical neoplastic cells (10). LAMNs and HAMNs are considered *in situ* (pTis) if confined to the submucosa and muscularis propria. However, staged pT3 if tumour extends into subserosa. Tumours that involve the serosa are considered pT4a (3). In our study, 50% of the cases had pTis, similar results were seen in a study by Lu *et al.,* (9).

Pseudomyxoma peritonei (PMP), a life-threatening complication of mucinous neoplasms is characterized by the presence of intraperitoneal mucin. This may or may not be associated mucin-producing epithelium (11). The actual mechanism of mucin traversing the appendiceal wall in LAMN is not fully understood, however, most commonly it occurs as a result of appendiceal rupture, as we saw in one of our cases. Pseudomyxoma peritonei can also result due to mucinous neoplasms of the ovary, however it is very rare. Hence, it should be kept in mind that, all cases of PMP in females with ovarian mucinous neoplasm, appendix should be meticulously examined for presence of mucinous neoplasm and *vice versa.*

CONCLUSION

Appendiceal mucinous neoplasms are a heterogeneous group of tumours ranging from low grade mucinous neoplasms to mucinous adenocarcinomas. In most of the cases pre-operative diagnosis is difficult as they lack specific clinical and imaging findings. Proper histological staging is crucial in prognostication and to guide further management. Hence, a precise diagnosis is very important which requires multiple sections of the appendix as well as comprehensive analysis of clinical features, surgical and histopathological findings.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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