

Mucinous neoplasms of the appendix – A clinicopathologic study of 21 cases with special insight into current classification and controversies



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ABSTRACT

Background: Appendiceal mucinous neoplasms are rare and heterogeneous disease which often clinically present as appendicitis. There are many controversies regarding the classification of mucinous neoplasms of the appendix. **Aims and Objectives:** Our aim of this study was to study different types of mucinous neoplasms of appendix based on current (WHO 2019) classification, their clinical and radiological presentations and controversies regarding their diagnosis. **Materials and Methods:** This was a retrospective study done in a tertiary care hospital. We studied clinical presentations of 21 cases along with the histopathological study of respective appendectomy specimens. **Results:** Out of 21 cases, 3 (14.28%) cases were serrated polyp, 9 cases (42.85%) were low grade appendiceal mucinous neoplasm, 3 cases (14.28%) were high-grade appendiceal mucinous neoplasm, and 6 (28.57%) cases were mucinous adenocarcinoma. In this study, we have discussed in brief about regarding the current classification and controversies of appendiceal mucinous neoplasms. **Conclusion:** Mucinous neoplasms of the appendix are complex lesions with many controversies. Oversimplification in the recent classification may add to more complexity. Reintroduction of the old terminology of mucinous tumor of uncertain malignant potential might save histopathologists from potential litigation.

Key words: Mucinous neoplasm; Appendix; Low-grade appendiceal mucinous neoplasm; High-grade appendiceal mucinous neoplasm

INTRODUCTION

Mucinous neoplasm of the appendix are heterogeneous group of neoplasms ranging from mucocoeles to Pseudomyxoma Peritonei. Primary neoplasms of the appendix are present in < 2% of surgical appendectomies specimen.¹ Appendiceal mucinous neoplasms are rare entities seen only in <1% of appendectomy specimens.²

According to the current WHO classification of tumors of the digestive system (IARC/WHO, 2019), the major categories of primary neoplasms of appendix are

epithelial tumors, mesenchymal tumors, and lymphoma. Mucinous neoplasms of the appendix are a complex diverse group of epithelial tumors often causing cystic dilation of appendix. Among the epithelial tumors adenocarcinoma of the appendix occurs in 0.1–0.2% of appendectomies.³

According to the WHO-2010 classification, there are three main categories of appendiceal mucinous neoplasms.⁴

1. Mucinous adenoma
2. Low-grade appendiceal mucinous neoplasm (LAMN)
3. Appendiceal adenocarcinoma.

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However, according to the 2019 WHO classification of tumors of the digestive system, neoplastic appendiceal mucinous lesions are classified as follows –

1. Serrated lesions with or without dysplasia and hyperplastic Polyps
2. LAMN
3. High-grade appendiceal mucinous neoplasm (HAMN)
4. Mucinous adenocarcinoma.

Hyperplastic polyps of the appendix are rare lesions and morphologically resembles those of the colonic polyps.⁵

Serrated lesions of the appendix are relatively recently described entity, most commonly seen in the colon and rarely seen in the appendix.⁶ Serrated lesions typically exhibit the histology of saw tooth like dysplastic epithelium found in >50% of basal crypts.⁷

Mucinous adenoma which was a distinct category of appendiceal mucinous neoplasm (In the WHO-2010 classification but not in WHO-2019 classification) is usually low grade confined to the mucosa of the appendix and is classified into tubular, tubulovillous, and villous types.⁸

LAMN characterized by villous or flat proliferation of mucinous epithelium with low-grade atypia.⁹

HAMN, this terminology was introduced by PSOGI in 2016 which was later distinctly categorized under appendiceal mucinous neoplasms by the WHO in 2019.¹⁰

Mucinous adenocarcinoma is a very rare malignant neoplasm seen in 0.05–0.2% in all appendectomy specimens and only in 6% of all malignant tumors of the appendix.¹¹ It is characterized by infiltrative invasion and by desmoplastic stroma.

Aims and objectives

Our aim of this study was to study different types of mucinous neoplasms of appendix based on current (WHO 2019) classification, their clinical and radiological presentations and controversies regarding their diagnosis.

MATERIALS AND METHODS

Study design

This was a retrospective study done in a tertiary care hospital (COMSDH, Kolkata) of West Bengal.

Duration

The study was conducted from April 2017 to April 2022 over a period of 5 years.

Ethical clearance

The study was approved by the Institutional Ethics Committee (IEC) of our institute.

Inclusion criteria

All the appendectomy specimens showing histopathological features of any one of the category of neoplastic appendiceal mucinous lesions according to the WHO 2019 classification are included in the study.

Exclusion criteria

Appendectomy specimens showing features of appendicitis or mucocele (retention cyst) are excluded from the study.

Case definition

According to the 2019 WHO classification of neoplastic appendiceal mucinous lesions are following –

1. Serrated lesions and polyp – Mucosal epithelial polyps having serrated (saw tooth on stellate) architecture of the crypt lumen with or without atypia.
2. LAMN
 - Pushing invasion/expansile growth confined to muscularis propria
 - Monolayered mucinous cells or pseudostratified mucinous cells
 - Dissection of mucin in to the wall (acellular mucin)
 - Fibrosis
 - Low-grade nuclear cytological features
3. HAMN – These lesions have all the features similar to LAMN except presence of high-grade nuclear features at least focally.
4. Mucinous Adenocarcinoma
 - Infiltrative invasion
 - Tumor budding, discohesive single cells or clusters (up to 5 cells), and or small irregular glands typically within a desmoplastic stroma
 - Mucin pool with atypical cells
 - Mucin pool covering >50% of the lesion.

All the cases falling under any one of the above categories were studied. All the cases were studied retrospectively. We collected the clinical history (clinical presentation, radiological findings, operative procedures) of the patients from the department of surgery. Histopathology slides and reports were collected from achieved records of pathology department of our institute. Histopathology slides were re-evaluated by two pathologists from our department and definitive diagnosis were re-established according to the current 2019 WHO classification.

Statistical analysis

The study done using IBM software version SPSS V20.0. The variables (qualitative) were reported as number and percentage (%).

RESULTS

The clinical and pathological records of 21 appendectomy specimens (Figure 1) reviewed which showed abdominal/pelvic pain as the most common clinical presentation (Table 1).

Out of the total 21 cases, 9 cases (42.85%) showed features of LAMN (Figure 2a), 3 cases were of HAMN (Figure 2b), and serrated polyp each (14.28%), six cases were mucinous adenocarcinoma (28.57%) (Figure 2c and Table 2).

DISCUSSION

Appendiceal tumors are rare tumors constituting 0.5% of all gastrointestinal tumors.¹² Mucinous tumors account for 8% of the appendiceal tumors.¹³

There are many controversies and lack of consensus for classifying appendiceal mucinous tumors, ever since Rokitsky first described appendiceal mucocele in 1842.¹⁴

Mucocele of appendix is a descriptive term for an abnormal mucous accumulation distending the appendiceal lumen irrespective of the underlying cause.¹⁵ According to Higa *et al.*,¹⁶ mucocele is a clinicopathologic spectrum comprising of mucosal hyperplasia, mucinous cyst adenoma, and mucinous cyst adenocarcinoma. However, in the 2019 WHO classification, no such entity is included under appendiceal mucinous neoplasms. Since simple mucocele/simple retention cyst/inflammatory mucocele/obstructive mucocele do not refer to a neoplastic lesion, the only term simple retention cyst was used in the study of appendiceal mucinous lesions by Koç *et al.*¹⁷

The next controversy is regarding the entity mucinous cyst adenoma/mucinous adenoma of the appendix.

Initially, the appendiceal mucoceles were classified into four categories: Simple retention cysts, mucosal hyperplasia, mucinous cyst adenoma, and mucinous cystadenocarcinoma. Recently mucosal hyperplasia terminology has been replaced by hyperplastic polyps and serrated polyps with or without dysplasia (WHO, 2019).

The term mucinous cyst adenoma was used by Carr *et al.*,¹⁸ which did not exist in their subsequent modified Delphi classification according to other studies,¹⁹ mucinous cystadenoma has no risk of developing pseudomyxoma and therefore not related to LAMN. The WHO 2010 classification contains the entity mucinous adenoma but the WHO-2019 classification does not have any such entity. According to our observation that cases which were previously diagnosed as mucinous cyst adenomas after

Table 1: Clinical features of appendectomy specimens (n=21)

1	Age, mean (range) in years	51 (26–72)
2	Sex (Male:female)	3:4
3	Presenting Symptoms	Number of cases (%)
	Abdominal pain	12 (51.14)
	Abdominal distention	3 (14.28)
	Abdominal mass	2 (9.5)
	Incidental finding	4 (19.04)
4	Imaging	Number of cases (%)
	Retention cyst	10 (47.63)
	Appendicitis	6 (28.57)
	Pseudomyxoma peritonei	4 (19.04)
	No data available	1 (4.76)
5	Surgical procedure	Number of cases (%)
	Appendectomy only	17 (80.95)
	Appendectomy with cecetomy	3 (14.28)
	Total colectomy	1 (4.76)

Table 2: Histopathological categories of appendiceal mucinous neoplasms (n=21)

S. No.	Histopathological category	Number of cases (%)
1.	Serrated polyp	3 (14.28)
2.	LAMN	9 (42.85)
3.	HAMN	3 (14.28)
4.	Mucinous adenocarcinoma	6 (28.57)

LAMN: Low-grade appendiceal mucinous neoplasm, HAMN: High-grade appendiceal mucinous neoplasm



Figure 1: Dilated appendix specimen of 4 cm diameter. Cut section showing pool of mucin and thin wall

re-evaluation of the HP slides were diagnosed as that of LAMN in terms of WHO-2019 classification.

Appendiceal mucinous neoplasms include a spectrum of tumors, which challenge our very definition of malignancy and force us to consider whether biology, morphology, or both should form the basis of tumor classification.¹⁵

Although occurring in all age groups, LAMNs are commonly seen in the 5th–6th decades of life with a high occurrence rates in women.^{2,20-22}

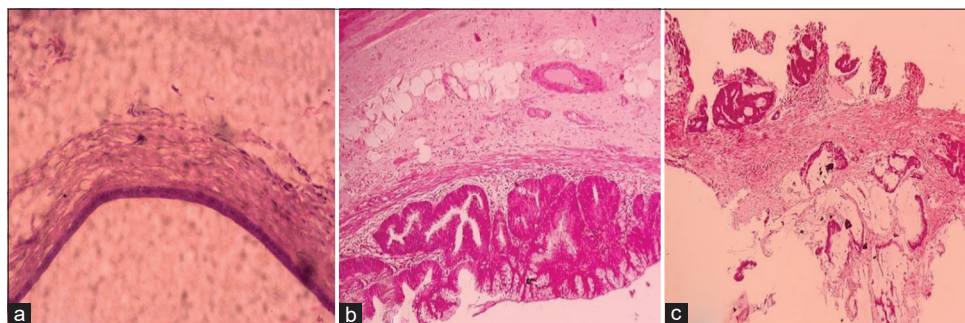


Figure 2: (a) Photomicrographs of low grade mucinous neoplasm showing flattened mucosal epithelium lining with thickened submucosa (H and E Stain $\times 100$). (b) Photomicrograph of high-grade mucinous neoplasm showing pushing invasion of mucinous glands with high-grade nuclear feature (H and E Stain $\times 40$). (c) Photomicrograph of mucinous adenocarcinoma showing infiltrative invasion of glands and mucin pool with atypical cells (H and E Stain $\times 40$)

In nine diagnosed LAMN cases, all were of 5–6 decades and eight cases were female and two cases were male like that of study of Collins *et al.*¹⁵

Problem of LAMN is to identify pushing type of invasion which may be misinterpreted as benign entity. Another problem is that appendix may be grossly unremarkable or cystically dilated.¹⁵

Moreover, in our cases, all (100%) were dilated. Diagnostic feature of LAMN is presence of neoplastic epithelium over fibrotic or hyalinized stroma rather than lamina propria or muscularis mucosa.¹⁵ Main diagnostic challenge is adenoma or adenocarcinoma. LAMNs that perforate wall of appendix may be mistaken as ruptured adenoma, but any tumor with mucin and or epithelium dissecting inside or outside the wall of appendix should not be taken as adenoma.

The real problem is when bland looking mucinous epithelium of LAMN without infiltrative invasion reach to the peritoneal cavity diagnosis is still LAMN not Adenocarcinoma as per the WHO classification. It is a difficult moment for histopathologist as it is contrary to our traditional histomorphologic features and may chase the fear of under diagnosis as repeated deeper sections may reveal tiny invasive foci which may have been missed and patient may present with obvious Adenocarcinoma in the future as treatment approach does differ in both cases and thus histopathologist may face litigation. This area needs to be addressed meticulously and may be with other nomenclature or entity.

Mucinous adenocarcinoma

The incidence of appendiceal mucinous adenocarcinoma is 0.01–0.08%.^{23,24} Due to this low incidence, the rate of misdiagnosis is very high.

Real problem is to differentiate between the neoplasms extending beyond appendix but with low cytological atypia and with other features of LAMN. This is of great

clinical significance as these entities have separate treatment approach as well as different prognosis.

LAMNs show prominent fibrosis of the wall with pushing invasion. Sometimes the real problem is to differentiate low-grade mucinous adenocarcinoma from LAMNs. If it is infiltrative invasion, it is adenocarcinoma but even without infiltrative invasion low-grade adenocarcinoma may present with pushing invasion and on repeated deeper section infiltrative foci may be seen. This is the real grey zone which needs to be answered. That is why though mucinous adenocarcinoma accounts for 40% of appendiceal adenocarcinoma although it is not clear what proportion of these might be classified as LAMN according to current WHO terminology.

HAMN

About 14.28% of all our cases were HAMNs.

As per the WHO classification, this entity was described as pushing invasion through appendiceal wall with breach of muscularis mucosa where cytologic atypia is of high grade but do not have infiltrative invasion as that of appendiceal mucinous adenocarcinoma. Now, in search of microinvasion in a case of HAMN, how many sections need to be given from wall of Appendix? EnBlock? More sectioning needs more money which is a constraining factor in a poor country. Another scenario may be that in a case of HAMN there is mucin within wall but not tumor cells. What we will call it?

Serrated polyp

In the first case series reported by Rubio,⁵ most of the serrated lesions of the appendix were diagnosed as incidental findings during evaluation of appendectomy specimens.

Although serrated lesions were diagnosed incidentally in our case most of them presented with features of acute appendicitis.

Limitations of the study

Due to relative rarity of appendiceal mucinous neoplasm, the total number of cases studied were low (sample size =21). Though we have tried to include wide variety of different pathologic entities following WHO guidelines, more number of cases could have enhanced the overall credibility of this study.

CONCLUSION

Sometimes, oversimplification may add more complexity.

Can we reintroduce the old terminology of mucinous tumor of uncertain malignant potential to save histopathologists from potential litigation as remarkable variation in prognosis and recurrence rate between LAMN versus HAMN, and HAMN versus adenocarcinoma exist and as really sometimes treacherous bland morphology, difficult to find invasive foci, complex criteria, and subjective variation between histopathologists add more difficulties.

Mucinous neoplasms of the appendix are complex lesions with many controversies and with dissent voices in respect to classification and nomenclature which possibly will evolve even in the future to give a definite and consensus classification.

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