

**Appendiceal Mucinous Neoplasms-LAMN and HAMN: A Case Series and Review of Literature**Jaison J<sup>\*1</sup>, Zope R<sup>2</sup>, Murgod P<sup>3</sup>, Kate P<sup>4</sup>, Wankhade S<sup>5</sup>, Bhide S<sup>6</sup><sup>1</sup>Department of Pathology, MAEER MIT Pune's MIMER Medical College & Dr. BSTR Hospital, Talegaon D, Pune, India<sup>2</sup>Department of Pathology, MAEER MIT Pune's MIMER Medical College & Dr. BSTR Hospital, Talegaon D, Pune, India<sup>3</sup>Department of Pathology, KLE JGMM Medical College & Hospital, Huballi, India<sup>4</sup>Department of Pathology, MAEER MIT Pune's MIMER Medical College & Dr. BSTR Hospital, Talegaon D, Pune, India<sup>5</sup>Department of Pathology, MAEER MIT Pune's MIMER Medical College & Dr. BSTR Hospital, Talegaon D, Pune, India<sup>6</sup>Department of Pathology, MAEER MIT Pune's MIMER Medical College & Dr. BSTR Hospital, Talegaon D, Pune, India

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**Abstract:**

According to the WHO Digestive System Tumors 5<sup>th</sup> ed, Appendiceal Mucinous Neoplasms (AMNs) are defined as mucinous epithelial proliferations with extracellular mucin and pushing invasion pattern. They are further classified into Low-grade appendiceal mucinous neoplasms (LAMN) and High grade appendiceal mucinous neoplasms (HAMN) based on cytological grading.

The classification of these tumors has undergone significant refinement over the years and so there is a need to be abreast with the new guidelines published in the World Health Organization Classification of Digestive System Tumors 5th edition, AJCC 8th Cancer Staging Manual, Peritoneal Surface Oncology Group International (PSOGI) modified Delphi consensus and College of American Pathologists (CAP) protocol regarding AMNs.

In the present article, we discuss three cases of LAMN and one case of HAMN in the light of the recent diagnostic criteria, terminologies, tumor grading, pathologic staging, biologic behaviour, treatment, and prognosis of AMNs. The accurate diagnosis of AMNs is clinically important because management may include treatment modalities such as cytoreductive surgery and hyperthermic intraperitoneal chemotherapy etc. and post treatment follow up in certain cases.

**Keywords:** Appendix, Mucinous Neoplasms, LAMN, HAMN.

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**Introduction**

Appendiceal Mucinous Neoplasms (AMNs) are uncommon appendiceal epithelial neoplasms. They are defined as mucinous epithelial proliferations with extracellular mucin and pushing invasion pattern. They are further classified into Low grade appendiceal mucinous neoplasms (LAMN) and High grade appendiceal mucinous neoplasms (HAMN) based on cytological grading. The classification of these tumors has undergone significant changes over the years and so there is a need to be abreast with the new guidelines. [1], [2], [3], [4]

In the present article, we discuss three cases of LAMN and one case of HAMN with respect to the current guidelines.

**Case Presentation****Case No 1**

A 25-year-old male patient, brought to casualty with pain in abdomen for 2-3 hours and 3 episodes of vomiting. History of similar episodes in past. USG abdomen revealed an inflamed appendix. Laparoscopic appendectomy was performed. On gross, appendix measured 7 cm in length, tip was intact but dilated. The dilated part measured 2x0.8x0.8 cm. The cut surface of this dilated part showed blocked lumen with inspissated mucin. Histopathology report: LAMN Grade 1, AJCC staging: pT3

**Case No 2**

An 8-year-old male patient, presented with pain in right iliac fossa and around umbilicus, 20 days back, history of fever on and off, non-bilious vomiting on and off. History of similar episodes in past. USG abdomen revealed inflamed appendix with adhesions to lateral abdominal wall and caecum. Open appendectomy was performed. On gross, the appendix measured 5 cm in length. The external surface appeared congested with intact tip. On cut surface, lumen filled with mucinous material. Histopathology report: LAMN Grade 1, AJCC staging: pT3

**Case No 3**

A 38-year-old female patient presented with pain in abdomen. USG abdomen revealed an inflamed appendix. Laparoscopic appendectomy was performed. Histopathology report: LAMN Grade 1, AJCC staging: pTis

**Case No 4**

A 70-year-old female patient presented with pain in abdomen. On examination, tenderness present in umbilical region and right iliac fossa. USG abdomen revealed possibility of perforated appendix with adjacent abscess and mesenteritis. Open appendectomy performed. Histopathology report: HAMN Grade 2, AJCC staging: pT4a

**Table 1: Summary of AMNs in the present study**

Sr.No	Age (in years)	Sex	Clinical Diagnosis	Histopathological Diagnosis
1.	25	Male	Acute Appendicitis	LAMN Grade 1, pT3
2.	8	Male	Acute Appendicitis	LAMN Grade 1, pT3
3.	38	Female	Acute Appendicitis	LAMN Grade 1, pTis
4.	70	Female	Acute Appendicitis	HAMN Grade 2, pT4a

**Discussion**

According to the WHO Digestive System Tumors 5th ed, Appendiceal mucinous neoplasms (AMNs) are rare appendiceal epithelial tumors, characterized by mucinous epithelial proliferation with extracellular mucin. or pushing tumor margins. Pushing invasion is defined as a tongue-like protrusion, diverticulum-like growth or a broad-front spread of the epithelium into the appendiceal wall. Destructive invasion or desmoplastic infiltration characteristic of invasive carcinoma is however not evident in AMNs.[1] The appendiceal mucinous neoplasms (AMNs) constitute about 0.2%–0.3% in the specimens of the appendix.[3],[4],[5] Most AMNs develop in middle-aged or elderly patients. Slight female predominance is noted.[2],[3],[6]However, in our case series a wide age distribution was noted with no particular sex predilection. Patients may present with non-specific symptoms such as acute or chronic right lower quadrant abdominal pain.[1],[3]Laboratory findings for appendiceal mucinous lesions are nonspecific and may include anemia or elevated levels of tumor markers eg, carcinoembryonic antigen (CEA), CA 19-9, and CA-125. [2]All the patients presented with features of acute appendicitis in our series. AMNs are further classified into low grade appendiceal mucinous neoplasm (LAMN) and high-grade appendiceal mucinous neoplasm (HAMN) based on cytological grading.

**Low-Grade Appendiceal Mucinous Neoplasm (LAMN)**

LAMN is a mucinous neoplasm with low-grade cytology associated with effacement of lamina propria, decreased or absent mucosal lymphoid

tissue, obliteration of the muscularis mucosae, fibrosis of the submucosa but without overt features of the invasion. Typically, circumferential proliferation of low-grade mucinous epithelium is noted.

The epithelium may show a papillary, villous, undulating, or flat architecture with monolayered lining epithelial cells.[1]The features of low-grade epithelial dysplasia are mildly enlarged hyperchromatic nuclei with minimal mitotic activity. [2]

The minimum criterion for diagnosis is at least focal obliteration or loss of the lamina propria and muscularis mucosa. LAMN may show a serrated architecture and can be mistaken for a serrated lesion.

Diffuse serrations and basal crypt dilatation favor a serrated lesion over LAMN. If a lesion shows overlapping features of serrated lesion and LAMN, it should be classified and staged as LAMN if pushing invasion and obliteration of lamina propria/muscularis mucosae are present.[7]LAMN are Low grade or Grade I tumors. [1]

On Gross examination, typical LAMNs usually have thin fibrotic walls and abundant intraluminal mucin, and less commonly, calcification of the wall. Visible rupture with mucin extravasation occurs in patients with disseminated peritoneal mucinous disease.

Low-grade appendiceal mucinous neoplasm should be differentiated from appendiceal diverticulum, appendiceal retention cysts, appendiceal endometriosis and mucosal hyperplasia seen in acute appendicitis. The reactive cellular atypia in

the acute suppurative appendicitis may also mimic the neoplastic atypia in LAMN.

The earlier terms like Mucinous cystadenoma and mucocele should not be used as synonyms for LAMN due to their ambiguous and misleading nature.[4]

### High-Grade Appendiceal Mucinous Neoplasm (HAMN)

The term HAMN is coined for Mucinous neoplasms with the architectural features of LAMN but with high-grade cytologic atypia but no infiltrative invasion. On microscopy, cribriform growth pattern, loss of nuclear polarity, high-grade cytology (i.e., enlarged, hyperchromatic, pleomorphic nuclei, and atypical mitotic figures), single-cell necrosis and sloughing of necrotic cells into the lumen may be noted. HAMNs are Grade 2 tumors according to the three tier grading system. HAMNs and have an intermediate risk between LAMNs and mucinous adenocarcinomas. They have an aggressive clinical behavior than LAMNs, but being extremely rare their prognosis is still not very clear. HAMN should also include lesions with high-grade cytologic atypia that is seen only focally, provided it is unequivocal; however, there has been no accepted consensus on the quantification of focal lesions.[1]The Peritoneal Surface Oncology Group International (PSOGI) recommends that the percentage of high-grade dysplasia present should also be reported.[2]High-grade features are often seen on a background of LAMN, supporting the fact that HAMN develops from LAMN. Molecular studies also support the hypothesis that HAMN develops from LAMN. Similar to LAMNs, HAMNs frequently show mutations in KRAS, GNAS, and RNF43. However, in addition HAMNs also show mutations in TP53, ATM, and APC, and these additional alterations may be responsible for their more aggressive phenotype. [7], [8]

### Staging of Appendiceal Mucinous Neoplasms

Significant changes to the staging criteria of AMNs, particularly for LAMN has been proposed by the AJCC 8th Cancer Staging Manual

- pTis(LAMN): LAMN confined to the appendiceal wall after histologic examination of the entire appendix. Acellular mucin or

mucinous epithelium may interrupt the muscle propria.

- pT3(LAMN): LAMN with acellular mucin or mucinous epithelium extending into the subserosa or mesoappendix but no involvement of the serosa after histologic examination of the entire appendix.
- pT4(LAMN): LAMN invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix (pT4a), and/or directly invades adjacent organs or structures (pT4b). pT4a does not include luminal or mural spreading into the cecum.

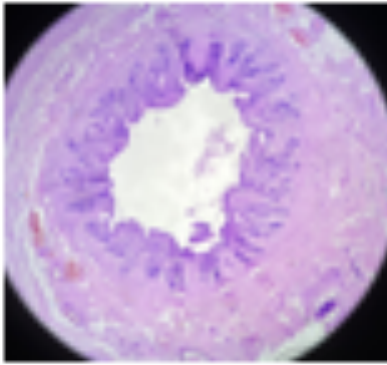
pT1 and pT2 do not apply to LAMN. In most LAMNs, there is no well-preserved mucosal architecture; therefore, assessment of the involvement of the mucosa and submucosa is not possible, and therefore pT1 designation cannot be applied to LAMNs. Also, studies evaluating the outcomes in LAMN have proved that pushing invasion into the appendiceal wall is not associated with tumor recurrence and so pT2 designation does not apply to LAMN.[1], [9]

Mucinous deposits on the appendiceal serosa are associated with a granulation tissue-like response and neo-vascularization.

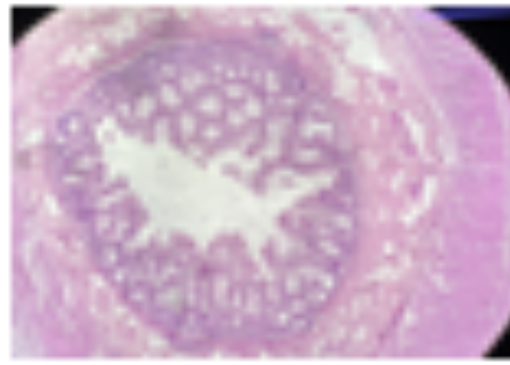
- M1a: Peritoneal dissemination is limited to acellular mucin only.
- M1b: metastases confined to the peritoneum only.
- M1c: metastases outside the peritoneum, such as pleuropulmonary metastasis.

According to the AJCC 8th Cancer Staging Manual, HAMN should be staged using the same staging system as invasive mucinous adenocarcinoma

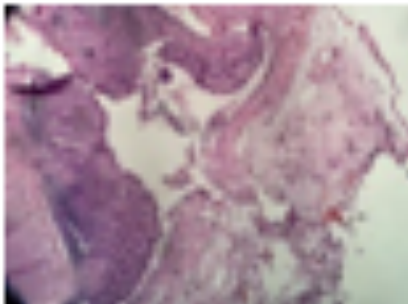
Of the 3 cases of LAMN in our series, two cases were staged as pT3 as they showed histological features of LAMN (Fig.1&Fig.2) with acellular mucin extending into the subserosa (Fig.3) and one case was staged as pTis as LAMN features were confined to the mucosa. The single case of HAMN was staged as pT4a as the lining epithelium showed features of HAMN (Fig.4) and the acellular mucin was seen invading the serosa of the appendix.



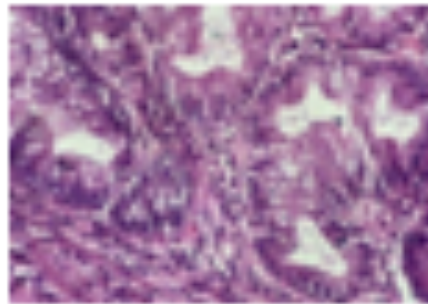
**Figure 1: Microphotograph of LAMN showing absent mucosal lymphoid tissue. (H&E 5X)**



**Figure 2: Microphotograph of LAMN showing papillary architecture with monolayered lining epithelial cells. (H&E 10X)**



**Figure 3: Microphotograph showing acellular mucin extending into the subserosa (H&E 10X)**



**Figure 4: Microphotograph of HAMN showing mucosal glands lined by cells showing enlarged nuclei. (H&E 45X)**

#### Disseminated Peritoneal Mucinous Disease

The term Pseudomyxoma peritonei is a clinical term and should be avoided in pathological diagnosis instead the term disseminated peritoneal mucinous disease should be used for a neoplastic condition characterized by the grossly persistent accumulation of mucinous ascites in the peritoneal cavity.

Most cases of disseminated peritoneal mucinous disease are due to the perforation of AMNs. Rarely, mucinous neoplasms from other organs, including the colon, pancreas, ovary, and urachus, may also show similar presentation.[10],[11] Immunohistochemical stains of cytokeratin 20, and CDX2 is helpful in the diagnosis of the appendiceal origin. [4],[12]

For completely resected LAMN or HAMN that has not ruptured, appendectomy alone is sufficient. Low-grade appendiceal mucinous neoplasms (LAMNs) and high-grade appendiceal mucinous neoplasms (HAMNs), have excellent prognosis with complete resection, Histopathologic features such as the presence of extra-appendiceal neoplastic epithelium, high-grade cytology, architectural complexity, and invasion are important predictors of recurrence. The standard of care for the treatment of peritoneal involvement of LAMN is cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy

(HIPEC). Cytoreductive surgery is performed to remove macroscopic peritoneal disease, whereas the HIPEC allows for a high concentration of chemotherapy to control microscopic residual disease. [7],[13],[14] CRS and HIPEC provide long-term survival. The combined treatment modality including CRS and hyperthermic intraperitoneal chemotherapy has led to a 5-year survival ranging from 5% to 100% in low-grade disease, and a survival ranging from 0 to 65% for high-grade disease.[3]

Involvement of the proximal appendiceal margin by LAMN in a simple appendectomy specimen by neoplastic epithelium or acellular mucin has not been shown to predict recurrence of disease, even if no follow-up surgery is performed. The Chicago Consensus on Peritoneal Surface Malignancies however, recommends cecectomy or ileocecectomy in cases with positive resection margin.[7] Post-treatment surveillance using cross-sectional imaging modalities like abdominal and pelvic CT or MRI and tumor markers, should be advocated as per the recurrence risk based on pathology and the completeness of surgical resection. [15],[16]

In our study, in all 3 cases of LAMN and 1 case of HAMN, there was no involvement of the proximal appendiceal margin and only appendectomy was performed. However, 6 monthly follow-up is advised for the patient with HAMN.

## Conclusion

The present article provides a comprehensive update on the diagnostic criteria, terminologies, tumor grading, pathologic staging, biologic behavior, treatment, and prognosis of AMNs.

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