International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Unveiling Rare but Crucial Neoplasm. The Story of LAMN: A Case Series and Comprehensive Literature Review

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Abstract: ***Low-grade mucinous appendiceal neoplasms (LAMN) are rare, histologically distinct tumors of the appendix, often discovered incidentally during imaging or surgery. This study presents a series of five cases of LAMN, highlighting histopathological characteristics, diagnostic challenges, clinical management, and outcomes. We provide an extensive review of literature focusing on its differentiation from appendiceal adenocarcinoma, pseudomyxoma peritonei, and metastatic mucinous adenocarcinomas. Emphasis is laid on the role of immunohistochemistry (IHC) markers, imaging modalities, and treatment options. LAMNs demonstrate an indolent course with a favorable prognosis when managed appropriately, although recurrence and metastasis remain potential risks. This article aims to enhance awareness of LAMN's unique clinicopathological spectrum, aiding clinicians in accurate diagnosis and optimal management strategies.***

Keywords: LAMN, appendecial neoplasm, mucinous tumours, appendix

1. Introduction

Low-grade mucinous appendecial neoplasms (LAMN) are rare epithelial tumours characterized by mucin production and localized appendecial involvement. Accounting for less than 0.5% of gastrointestinal neoplasms, LAMNs predominantly affect adults, with a slight female predilection. The clinical presentation is often nonspecific, ranging from acute appendicitis to incidental detection during imaging or surgery. Accurate diagnosis requires meticulous histopathological examination to distinguish LAMN from more aggressive entities like appendecial adenocarcinoma or metastatic mucinous neoplasms. Despite its rarity, this entity warrants heightened awareness due to its distinct pathological features and implications for patient management.

2. Case Reports

1) **Case 1:** A 55-year-old male presented with right lower quadrant pain, initially diagnosed as appendicitis. Histopathology revealed low-grade mucinous epithelium confined to the appendix. Microscopic examination demonstrated replacement of normal mucosa with a single layer of low-grade dysplastic mucinous epithelium and atrophic muscularis propria. Post-surgical follow-up was uneventful.
2) **Case 2:** A 47-year-old female underwent laparoscopic surgery for a suspected ovarian mass. Intraoperative findings revealed a dilated appendix. Histology confirmed LAMN with no evidence of pseudomyxoma peritonei. Microscopy revealed abundant extracellular mucin and flattened epithelium with minimal cytologic atypia, accompanied by fibrosis.
3) **Case 3:** A 62-year-old male presented with chronic abdominal discomfort. Imaging suggested a mucocele, and histopathology confirmed LAMN with acellular mucin deposits. Microscopic findings included low-grade dysplastic epithelium surrounded by pools of mucin extending into the submucosa without evidence of invasive growth.
4) **Case 4:** A 50-year-old female presented with non-specific gastrointestinal symptoms. CT imaging indicated a thickened appendix with calcifications. Histology confirmed LAMN with intact serosal margins. Microscopic analysis revealed fibrotic appendiceal wall infiltration by mucin and dysplastic cells, with focal calcifications.
5) **Case 5:** A 45-year-old male with recurrent abdominal pain underwent appendectomy. Histological examination showed LAMN with focal mucosal involvement but negative surgical margins. Microscopy revealed low-grade atypical columnar cells lining the mucinous cysts and no breach of the muscularis propria.

3. Discussion

Histopathological Role:
Histopathology is pivotal in diagnosing LAMN, characterized by distinct microscopic features. Key findings include:

- Replacement of normal appendiceal epithelium with mucinous epithelium showing low-grade cytological atypia.
- Abundant extracellular mucin deposition, often confined to the appendiceal lumen.
- Loss or atrophy of the muscularis mucosa, with fibrosis of the appendiceal wall.
- Flattened or cuboidal epithelial lining with rare mitotic figures and absence of high-grade nuclear atypia.
- Absence of infiltrative growth patterns that differentiate it

from appendiceal adenocarcinoma.
- Presence of "pushing borders" rather than invasive features.

In some cases, acellular mucin extending beyond the appendix is observed, warranting careful evaluation to exclude pseudomyxoma peritonei. Histopathology also aids in distinguishing LAMN from other mucinous neoplasms of gastrointestinal or gynecological origin, using morphological and IHC markers.

Incidental Occurrence and Diagnostic Modalities:
LAMNs are often incidental findings during imaging for unrelated conditions. CT and MRI are primary tools, revealing appendiceal dilatation, mural calcifications, or extraluminal mucin. Radiological, differentiation from adenocarcinomas and metastatic lesions can be challenging.

Immunohistochemistry and Molecular Markers:
IHC markers such as CK20, CDX2, and MUC2 support diagnosis and differentiation. KRAS mutations are frequently implicated, aiding molecular profiling.

Treatment and Prognosis:
Appendectomy with clear margins is typically curative for localized LAMN. For cases with extraluminal mucin, cytoreductive surgery and hyperthermia intraperitoneal chemotherapy (HIPEC) are considered. Prognosis is favorable; however, recurrence and pseudomyxoma peritonei risk necessitate long-term monitoring.

Several studies have reported on LAMN, providing valuable insights into its presentation, pathology, and outcomes. Despite its rarity, this entity is underexplored, making it crucial for clinicians to recognize its distinct features. Key studies include:

1) **Pai et al. (2009, Cleveland Clinic, USA):** Analyzed 22 cases, highlighting the histopathological features distinguishing LAMN from adenocarcinoma. Concluded that LAMNs have a favorable prognosis when confined to the appendix.
2) **Carr et al. (2017, United Kingdom):** Reviewed 50 cases, emphasizing the importance of standardized classification criteria for appendiceal neoplasms. Suggested that clear surgical margins are crucial for preventing recurrence.
3) **McDonald et al. (2022, Ireland):** Studied 35 cases, focusing on the role of IHC markers in differentiating LAMN from metastatic mucinous adenocarcinoma. Recommended KRAS mutation analysis for further differentiation.
4) **Lemke et al. (2015, Germany):** Examined 15 cases with pseudomyxoma peritonei. Concluded that cytoreductive surgery combined with HIPEC improves survival in cases with extra-appendiceal spread.
5) **Misdraji et al. (2003, Massachusetts General Hospital, USA):** Reviewed 25 cases, proposing criteria for differentiating LAMNs from high-grade mucinous neoplasms. Highlighted the absence of infiltrative growth patterns in LAMN.

4. Review of Literature

Table: Role of IHC Markers in Differentiating LAMN and Other Conditions

Marker	LAMN	Appendiceal Adenocarcinoma	Metastatic Ovarian Adenocarcinoma	Metastatic Right Colon Adenocarcinoma	Pseudomyxoma Peritonei
CK20	Positive	Positive	Negative	Positive	Positive
CK7	Negative	Variable	Positive	Negative	Variable
CDX2	Positive	Positive	Negative	Positive	
MUC2	Positive	Positive	Variable	Variable	Positive
WT1	Negative	Negative	Positive	Negative	Negative
PAX8	Negative	Negative	Positive	Negative	Negative
KRAS	Mutated	Mutated	Variable	Variable	Mutated

5. Summary

Low-grade mucinous appendiceal neoplasms represent a rare but significant diagnostic entity. Comprehensive histopathological evaluation and appropriate surgical intervention are essential for optimal outcomes. Regular follow-up is critical to mitigate risks of recurrence or progression. Increased knowledge and awareness of this rare entity are vital for timely diagnosis, accurate differentiation, and improved patient care.

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