

Confined Low Grade Appendiceal Mucinous Neoplasm With Coexisting Distant Metastasis

JUWAIIRIYA ARSHI¹, AMARJIT DAVID PETER², YUANXIN LIANG³ and YANSHENG HAO¹

¹Department of Pathology & Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, U.S.A.;

²General Surgery, UR Medicine-F.F.Thompson Hospital, Canandaigua, NY, U.S.A.;

³Department of Pathology, Yale University School of Medicine, New Haven, CT, U.S.A.

Abstract. *Background/Aim:* Appendiceal mucinous neoplasms (AMNs) are tumors with dysplastic mucinous epithelium, a pushing growth pattern but no infiltrative invasion to the appendiceal wall. Some AMNs are associated with pseudomyxoma peritonei, characterized by intraperitoneal mucinous involvement. Recent studies have demonstrated that LAMNs confined to the appendix have low or no risk for disease recurrence, progression, and peritoneal involvement during follow up. *Case Report:* Here, we present two extremely rare cases with confined low grade appendiceal mucinous neoplasm (pTis and pT3) and simultaneous extraperitoneal subcutaneous or ovary involvement at the time of diagnosis. *Conclusion:* Our cases demonstrate that although the primary tumor is limited to the appendix, coexisting distant metastasis may occur on very rare occasions.

Appendiceal mucinous neoplasms (AMNs) are mucinous neoplasms of the appendix which are characterized by mucinous epithelial proliferation with extracellular mucin and pushing tumor margins. These neoplasms commonly occur in adults in their sixth decade of life. AMNs can cause pseudomyxoma peritonei, which is manifested by intra-abdominal mucinous ascites, tumor deposits on peritoneal surface, omentum and viscera of pelvic organs. Compared to acellular mucin, cellular mucin is associated with higher risk

for recurrence or progression; the cytological grade of extra-appendiceal epithelium is an important prognostic indicator (1). Heated intra-peritoneal chemotherapy and early postoperative intra-peritoneal chemotherapy have improved the survival of patients with pseudomyxoma peritonei (2, 3).

Based on cytological features, AMNs are divided into low grade appendiceal mucinous neoplasms (LAMNs) and high grade appendiceal mucinous neoplasms (HAMNs). In the presence of infiltrative-type invasion, the mucinous lesion should be diagnosed as invasive mucinous adenocarcinoma. HAMN is rare and related studies are limited. AMNs commonly harbor *GNAS* and *KRAS* mutations, while *p53* mutations are associated with HAMNs or adenocarcinoma (4).

Recent studies have demonstrated that AMNs confined to the appendix have extremely low to absent risk of post-operative malignant progression (5). According to the AJCC cancer staging manual, LAMN confined by muscularis propria is staged as pTis and belongs to the overall prognostic Stage Group 0 (6). Nowadays, it is generally believed that a confined low grade appendiceal mucinous neoplasm is a benign disease. Here, we present two unusual cases of confined LAMNs with simultaneous distant metastasis at the time of diagnosis.

Case Report

Case 1. A 48-year-old female had a medical history of gastroesophageal reflux disease (GERD) and migraines. She also had a history of adjustable gastric banding surgery 10 years ago, with a reservoir placed beneath the skin of the upper abdominal wall. This was subsequently removed 5 years ago. The patient presented to the surgery office with a bulging abdominal wall and pain at a previous surgical site, suspicious for incisional hernia. She was planned for a minimally invasive exploration and hernia repair.

Prior to the operation, an abdominal and pelvic CT scan was performed. The CT study showed a 4 cm loculated fluid collection in the subcutaneous fat of the anterior abdominal wall. Radiological differentials include subcutaneous sebaceous

Correspondence to: Yansheng Hao, MD, Ph.D., Department of Pathology & Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, U.S.A. Tel: +1 5852765934, e-mail: yansheng_hao@urmc.rochester.edu

Key Words: Appendix, LAMN, confined, metastasis, Pseudomyxoma peritonei.



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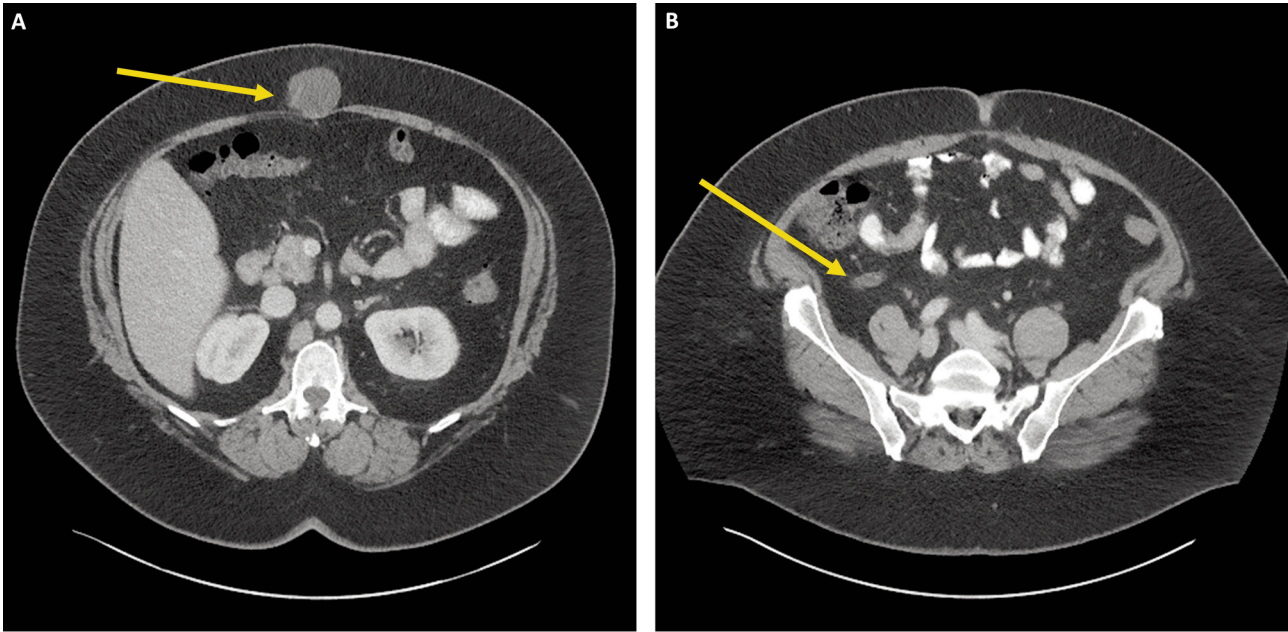


Figure 1. Computerized tomography (CT) images of low grade appendiceal mucinous neoplasm and abdominal wall involvement. (A) A loculated cystic fluid collection in the subcutaneous fat of the anterior abdominal wall at the midline. No obvious fascial defect. (B) Appendix is dilated to 1 cm and filled with fluid, without fecalith. There is no inflammatory change of the surrounding tissue.

cyst, seroma or resolving hematoma. Abscess or necrotic tumors were considered less likely (Figure 1A). The appendix was found to be distended and filled with fluid. However, there was no wall thickening or inflammatory change of the surrounding fat. Early appendicitis was not excluded (Figure 1B). There was no intra-abdominal ascites, free air, abscess, or adenopathy.

Laparoscopic appendectomy and excision of the abdominal wall cystic mass were performed. During the surgery, the appendix was found to be thickened and chronically inflamed. The cystic mass appeared to be a fibrous sac, which was completely separated from the anterior sheath. No anterior sheath or fascial defects were identified.

Gross examination of the abdominal wall specimen showed a fibrous cyst containing clear mucinous material. No discrete lesions or perforations were identified grossly in the appendix. Microscopic examination revealed villous proliferation of hypermucinous epithelial cells with low grade nuclear atypia, confined within the muscularis propria of the appendix. No diverticula were seen (Figure 2A and B). The tumor cells were positive for SATB2 and negative for PAX8 (Figure 2C and D). Similar morphologic features and immunohistochemical profiles were found in the tumor cells of the subcutaneous cystic mass, confirming metastasis from the appendiceal primary (Figure 2E-H). A pathological diagnosis of LAMN, pTisM1, was made.

Case 2. A 69-year-old female had a medical history of asthma, hypercholesterolemia, liver disease, Lyme disease, and pneumonia. She presented with lower abdominal pain and ultrasound exam found a 12.8 cm complex posterior midline mass with cystic and solid components. An ovarian origin neoplasm was suspected. Additionally, a 6.7 cm soft tissue density without internal color flow in the right lower quadrant was also identified. Serological CEA levels were elevated.

A diagnostic and therapeutic laparoscopic sacral colpopexy with bilateral salpingo-oophorectomy and tumor debulking procedure was performed. During the surgery, there was a small uterus that was displaced anteriorly by an approximately 10 cm right adnexal and another 3 cm left adnexal mass. Both these two mass lesions contained gelatinous mucinous fluid. An enlarged appendix (approximately 3.5 cm in size) was found, and an appendectomy was performed.

There was a 1.7 cm mucinous neoplasm, located at the distal half of the appendix. No gross perforation was identified on the appendiceal specimen. Microscopically, a cystic lesion with hypermucinous epithelial lining and low-grade nuclear atypia was identified in the appendix. The tumor had invaded through the muscularis propria into the mesoappendix (Figure 2I and J). All surgical margins were clear of tumor. Bilateral ovaries were positive for the mucinous tumor, which demonstrated similar histological morphology to the appendiceal neoplasm, supporting a diagnosis of metastatic appendiceal LAMN (Figure 2K and L). A final pathological diagnosis was LAMN with pT3 N0 M1.

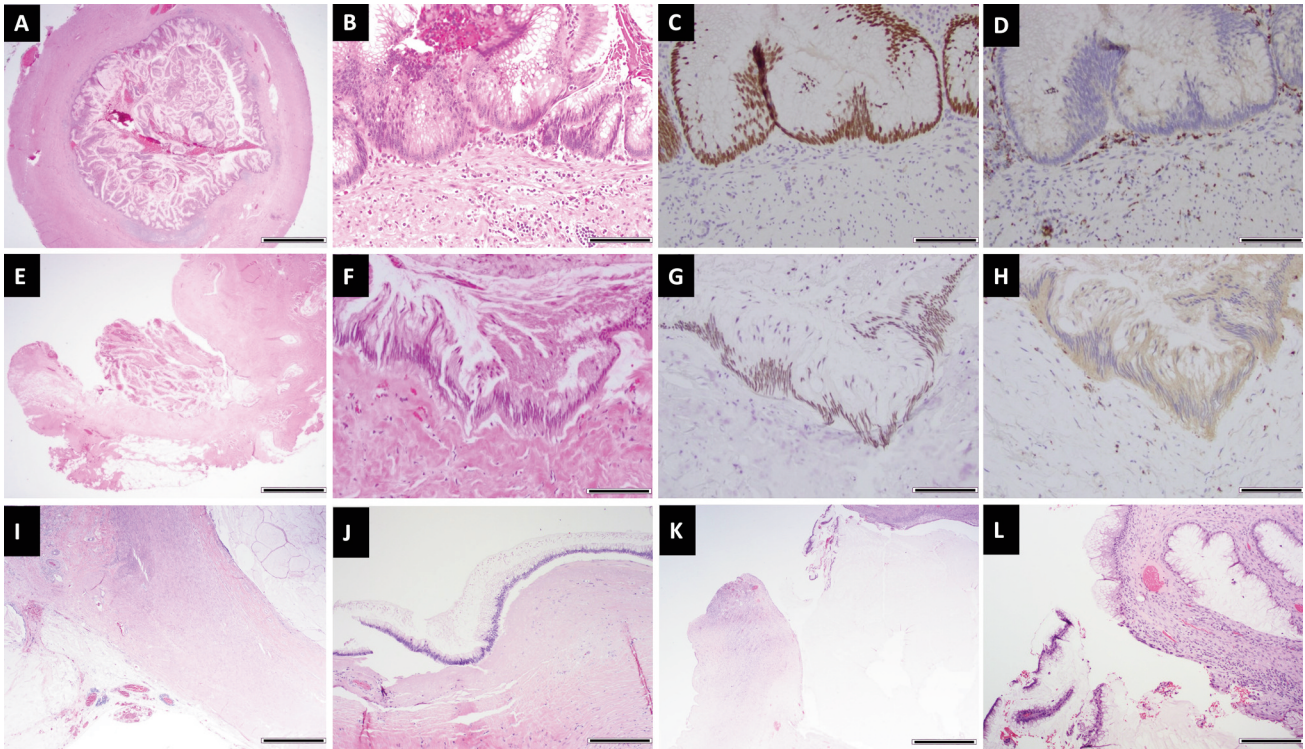


Figure 2. Low grade appendiceal mucinous neoplasm with distant involvement. Case 1. Appendiceal low grade appendiceal mucinous neoplasm: (A) H&E staining (scale bar, 2,000 μm), (B) H&E staining (scale bar, 100 μm), (C) SATB2 immunohistochemical DAB staining (384R-16, Cell Marque) (scale bar, 100 μm), (D) PAX8 immunohistochemical DAB staining (AC1438C, Biocare Medical) (scale bar, 100 μm). Abdominal wall lesion: (E) H&E staining (scale bar, 2,000 μm), (F) H&E staining (scale bar, 100 μm), (G) SATB2 (scale bar, 100 μm), (H) PAX8 staining (scale bar, 100 μm). Case 2. Histology of low grade appendiceal mucinous neoplasm in appendix (right upper corner) and mesoappendix (left lower corner) at low (scale bar, 1000 μm) (I) and high magnification (scale bar, 200 μm) (J). Histology of ovarian lesion at low (scale bar, 1000 μm) (K) and high magnification (scale bar, 200 μm) (L).

Discussion

AMNs are composed of a spectrum of morphologically and prognostically different diseases. According to the 2019 WHO classification, three tiered categories were established (7). Mucinous adenocarcinoma is localized at one end with infiltrative invasion, while low grade appendiceal mucinous neoplasm with a “push” pattern of growth is at the other end. Between them, high grade appendiceal mucinous neoplasm is termed as lesions with high-grade architectural and cytologic atypia without infiltrative invasion (8). The classification and nomenclature of these mucinous tumors is controversial and keeps evolving (9, 10).

LAMNs are far more common than the other two entities (11). Diverticula were found to be coexistent in 42% of LAMNs. Diverticulum-like herniation or mucin dissection through the appendiceal wall can lead to peritoneal cavity dissemination as pseudomyxoma peritonei (12). Recent studies have shown LAMNs confined to the appendix without breaching the serosa (<T4) have negligible post-op risk of

disease recurrence, peritoneal involvement, or disease-specific mortality (5, 13). Thus, contrary to HAMN and mucinous adenocarcinoma, LAMN confined by the muscularis propria is staged as pTis and belongs to an overall prognostic stage group 0. T1 and T2 are not applicable to LAMN. T3 or T4a is assigned when acellular mucin or mucinous epithelium extends into the subserosa or serosa. Peritoneal involvement is stratified into pM1a and pM1b staging categories based on the absence or presence of neoplastic epithelium in the mucin, and extraperitoneal involvement is classified as pM1c (6). It is generally accepted that patients with pTis LAMN do not develop tumor recurrence and are essentially cured by appendectomy (10).

In female patients, it is difficult to differentiate appendiceal primary from metastasis or involvement from ovarian mucinous tumors, based on morphology alone without immunohistochemical staining. It has been reported that a combination of CK7 and SATB2 has a greater than 95% accuracy to determine the origin. PAX8 and CDX2 can be used as second-line markers (14).

The risk of distant metastasis with primary LAMNs is very low. Distant involvements of lung, spleen, stomach, para-aortic lymph nodes and brain have been rarely reported. Of note, most of these patients present with concurrent pseudomyxoma peritonei (15).

Here, we present two confined appendiceal LAMN cases with coexistent distant involvement. One pTis LAMN with extraperitoneal subcutaneous metastasis at the time of diagnosis. The other is pT3 LAMN with simultaneous ovary metastasis. The mechanisms of this distant involvement are still elusive. No clear evidence of lymphovascular invasion of LAMN has been reported. One hypothesis is that the distant spreading might be associated with prior appendiceal rupture caused by surgical procedure, diverticulum, or other injuries.

Conclusion

Combined with recent studies, our two cases demonstrate that coexisting distant metastasis could rarely be identified when appendectomy is performed for a confined LAMN, even a pTis tumor. However, if no extra-appendiceal involvement is identified during the appendectomy, there is no risk of disease recurrence or progression after the primary tumor is removed by a complete resection.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

JA: Acquisition of data; drafting of the manuscript. ADP: acquisition of data; revision of the manuscript. YL: acquisition of data; revision of the manuscript. YH: acquisition of data; drafting figure; drafting the manuscript; administrative support.

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Received October 3, 2023
 Revised October 26, 2023
 Accepted November 2, 2023