Mucinous neoplasm of the appendix: management according to reviewed histologic spectral aspects

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Abstract

Of the diseases affecting the cecal appendix, mucinous neoplasms, although rare, are the most common epithelial tumor. They are often asymptomatic and diagnosed by anatomopathological exams of sections, collected during appendectomies due to acute appendicitis. These tumors have the potential to become malignant, and their early surgical handling are the most important prognostic factor. So, clinical, image, operatory and histologic spectral aspects should always take into account. The present study reports a case of mucinous neoplasm of the appendix that manifested with intestinal partial obstruction and suggests the need for a comprehensive and uniform classification, which could address the best disease first approach. The information was obtained through a patient records review, photographic documentation of the diagnostic tests and histologic study of operative specimen. In addition, the manuscript opens a discussion about the approach of choice of this complex neoplasia, since great variability persists in clinical and pathological records, due to variations in classifications and definitions. This variability in disease nomenclature may significantly impact the treatment and prognosis.

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Introduction

Mucinous neoplasms of the appendix are rare lesions characterized by progressive distension of the viscera due to mucus production and accumulation in the glandular tissue. Although it is the most common epithelial tumor, it is often asymptomatic (25-50% of cases) and commonly found during clinical imaging investigations. In other cases, such tumors manifest with acute appendicitis and recurrent abdominal pain at the right iliac fossa. Mucinous neoplasms may also result from fecal impaction or the presence of cecal polyps obstructing the appendiceal ostium. Endometriosis and metastatic melanoma are other rare causes of mucinous neoplasms.[1-6]

From an epidemiological point of view, mucinous neoplasms of the appendix have a higher incidence after the sixth decade of life and are predominant in women (4/1). They correspond to 0.2-0.5% of all tumors of the gastrointestinal tract and approximately 1% of colorectal neoplasms. Other neoplasms of the gastrointestinal tract, ovaries (cystadenoma and cystadenocarcinoma), breast, and kidney may be associated with mucinous neoplasms of the appendix. Therefore, colonoscopy is recommended in these patients.[7]

These tumors have the potential to become malignant, and

their early surgical handling are the most important prognostic factor and clinical, image, operatory and histologic spectral aspects should always take into account. Perhaps the most important aspect, and that which should be highlighted, is the variability among pathology reports due to different disease classifications and/or definitions.

Mucoceles of the appendix have been historically classified as: simple retention cyst; mucous hyperplasia; mucinous cystadenoma; and mucinous cystadenocarcinoma. The most characteristic examples are lesions diagnosed as adenocarcinomas and labelled by others as *low-grade appendiceal mucinous neoplasm* or *mucinous tumor of uncertain malignant potential*. The same lesion can, therefore, be diagnosed as malignant, having uncertain biological behavior, or benign, the differences among which have significant treatment implications.[8]

The present study aims to report a case of mucinous neoplasm of the appendix, that manifested as a recurrent partial obstruction of the intestines due to repeated cecal-appendiceal intussusception; and at same time, revises the current uniform nomenclature that allow subsequent propose a standard of care for operative management of mucinous neoplasm of appendix.

Case Report

A 49-year-old woman sought gynecological care for the evaluation of submucous myomas. The attending physician ordered an ultrasound of the abdomen, which showed findings suggestive of an ileocecal intussusception measuring 5.5×3.2×4.1 cm. Computed tomography of the abdomen with oral and intravenous contrast was ordered for diagnostic complementation and revealed a large mucinous tumor of the appendix with invasion of the cecum wall, but the absence of inflammatory signs suggestive of a mucocele of the appendix (Figures 1 and 2). Thickening of the cecal wall, possibly related to chronic inflammation, was also evident.

Two weeks later, the patient experienced sudden abdominal pain in the periumbilical region that lasted for 72 h until she received medication in the emergency room. A physical examination revealed that the patient was in good general condition, lucid and oriented, hydrated, acyanotic, anicteric, and afebrile; and had reddish mucosae. An abdominal examination showed a distended abdomen, increased hydro-aerial noises, hypertympanism on percussion, and pain on deep palpation but no peritoneal reaction.

First, laparoscopy was performed. An intraoperative evaluation showed a mucinous tumor located at the base of the appendix and cecal wall close to the ileal papilla (Figure 3). It caused episodes of intestinal partial obstruction due to obstruction of the ileal papilla using a valvular mechanism. Monoblock resection of the appendix, mesoappendix, and distal end of the cecum was achieved by dissection and stapling of the cecal wall parallel to the ileal papilla (Figure 4). The patient progressed well in the postoperative period, resumed eating 4 hours after surgery, and was discharged within 24 h.

The anatomopathological exam resulted in the diagnosis of low-grade mucinous neoplasm of the appendix with the presence of expansive invasion up to the muscularis propria without perforation, angiolymphatic invasion, or perineural invasion or sclerosis, fibrosis, or hyalinization of the appendiceal wall; and all margins were free of disease (Figure 5).

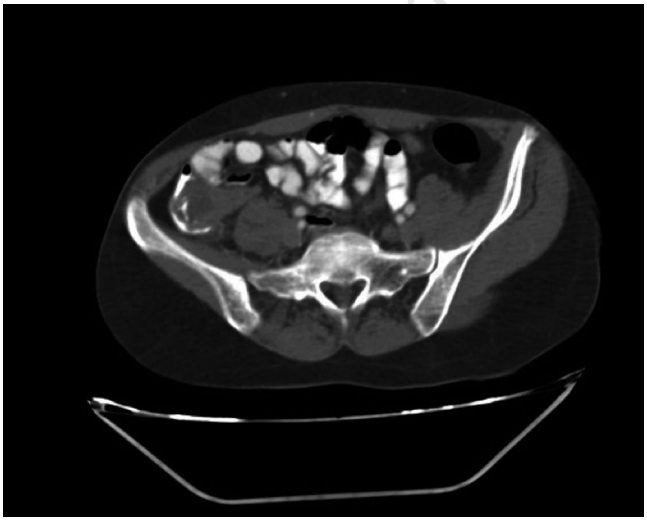

Figure 1. Abdominal tomography (axial plane) image showing a large mucinous tumor of the appendix with invasion of the cecum wall causing invagination and valvular obstruction of the ileal papilla.

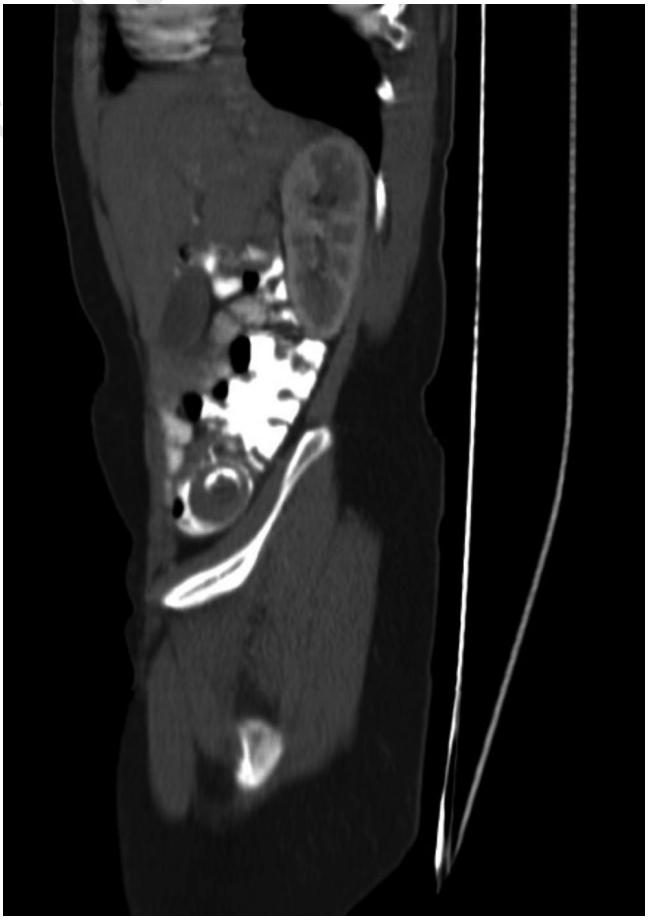

Figure 2. Abdominal tomography (sagittal plane) image showing a large mucinous tumor of the appendix with typical target sign appearance of intestinal intussusception (cecal-appendiceal).

Discussion and Conclusions

Mucocele of the appendix is a nonspecific term describing obstructive dilatation of the vermiform appendix accompanied by an abnormal accumulation of mucus. Chronic obstruction of the appendix may be due to mucus or hyperplasia of the mucosa. Both benign and malignant hyperplasia may obstruct the appendiceal ostium and cause symptoms, although benign hyperplasia is more common, representing 63-84% of cases.[1,6,8,9]

The disease may manifest as acute appendicitis in 8-14% of cases. Other rare complications include intussusception, bleeding, and peritonitis. Even less described is the diagnosis of intestinal partial obstruction caused by valvar mechanism (cecal-appendiceal segment) on the ileal papilla as documented in the present report. Another important aspect is that approximately 30% of patients may develop appendiceal perforation, either spontaneous or during surgery, with spillage of mucus into the peritoneum, which may lead to its most fearsome complication, pseudomyxoma peritonei.[10-12]

Iatrogenesis is a complication of mucinous tumors with potential high morbidity that is characterized by multiple mucinous implants in the peritoneal cavity. Pseudomyxoma peritonei is difficult to treat, and it has a reserved prognosis. It occurs both in benign and malignant lesions and presents with survival rates of 53-75% after 5 years in centers specialized in its treatment. The differential diagnosis should be performed together with other intraperitoneal (ovarian, intestinal duplication, mesenteric cysts) and extraperitoneal (inflammation, hemorrhage, renal cyst, pancreatic pseudocyst) lesions.[10]

A recent consensus among pathologists, although not unanimous, reclassified mucoceles of the appendix and indicated the possibility of standardization of anatomopathological reports, which ultimately will endorse adoption of the therapeutic conduct. Experts postulate that the term *mucocele* is inadequate and should be replaced by terms that address the degrees of invasion and cellular atypia while unifying the terminology and contributing to decreased dubious interpretations and the possibility of conflicting reports.[8]

The term *mucinous adenocarcinoma* should be reserved for infiltrative lesions with severe cellular atypia. In addition, the term *cystadenoma* is no longer recommended, and the following classi-

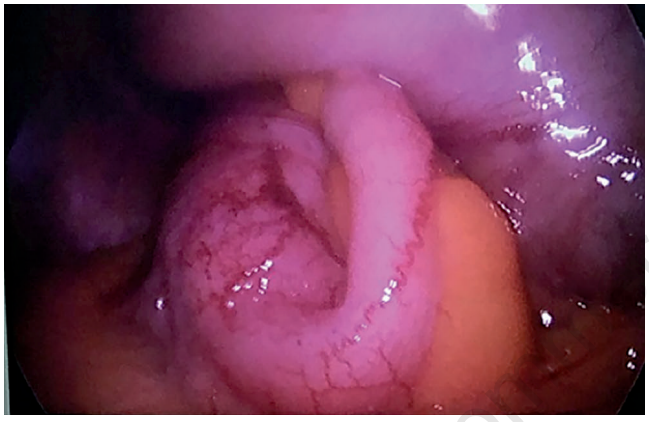

Figure 3. Laparoscopic image showing a mucinous tumor of the vermiform appendix (base) and invasion of the distal end of the cecum. Inflammatory process and cecal-appendiceal intussusception are also visible.

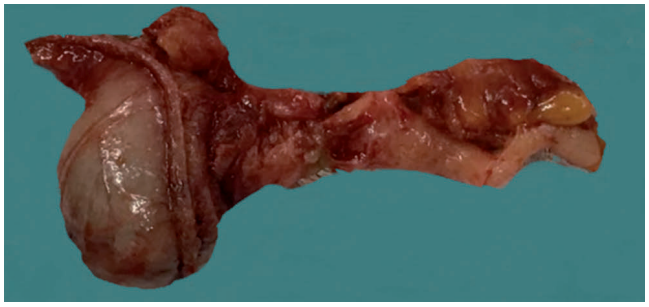

Figure 4. Photograph of a section taken from laparoscopic cecal-appendectomy showing a large mucinous tumor enveloping the base of the appendix and the distal end of the cecum that was obstructing the ileal papilla by a valvular mechanism.

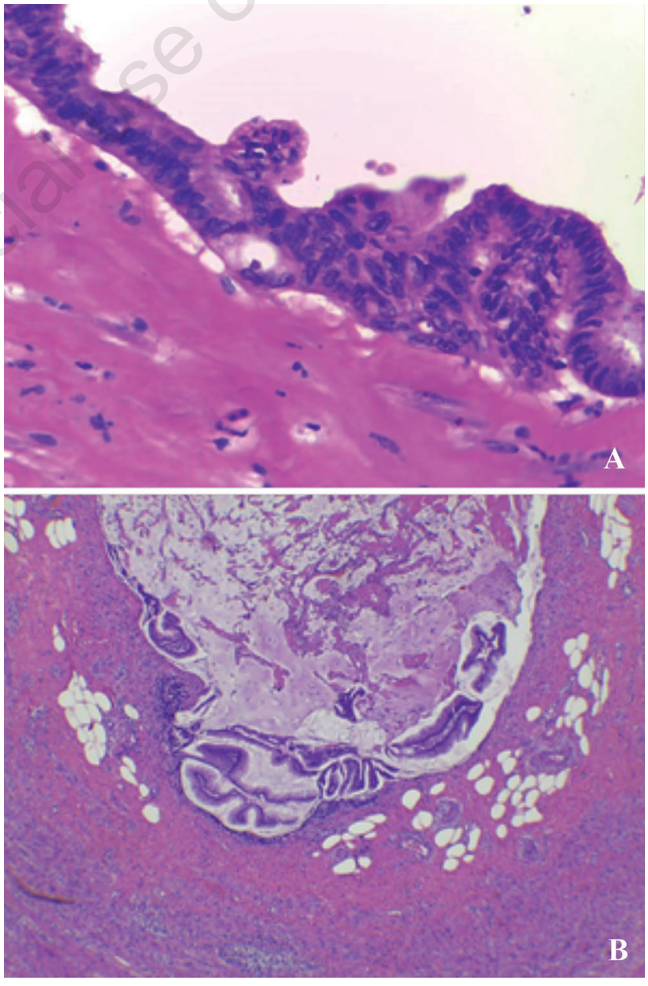

Figure 5. A) Histological image of a mucinous tumor of the appendix showing the absence of an infiltration process and the presence of an expanding margin. Micrograph (25×). Hematoxylin eosin staining. B) Presence of cellular atypia. Anatomopathological report: low-grade appendiceal mucinous neoplasm. Micrograph (400×). Hematoxylin eosin staining.

fication is proposed: adenomas, low-grade mucinous neoplasm (LAMN), high-grade mucinous neoplasm (HANM), and adenocarcinomas. Adenomas are neoplasia confined to the mucosa, *i.e*., the muscularis mucosae is intact throughout the lesion and there is no mucin dissecting into the appendix wall. The classification of tumors as LAMN or HAMN considers tumor biology and morphology. The defining characteristic of LAMN is the *pushing invasion* of the appendix wall (with loss of muscularis propria, submucosal fibrosis, acellular mucin dissecting into the wall and villous or flat epithelial growth, and the absence of high-grade dysplasia). It is a rare disease with an incidence of approximately 0.2–0.7% during appendectomy. Approximately 25-50% of LAMN cases are discovered accidentally during imaging exams, endoscopies, or laparotomies.[11]

The prognosis of LAMN[1] depends on its stage. When it is disseminated into the peritoneum, it follows a progressive and serious clinical course. However, when the tumor is limited to the appendix or ruptures but remains confined to the lower right quadrant, the prognosis is related to the presence of neoplastic mucinous epithelium outside in the peritoneum. Cases of LAMN[1] that are confined to the appendix without extra-appendiceal mucin are essentially cured by appendectomy. Cases of LAMN[1] associated with acellular mucin confined to the right lower quadrant present with a low risk of recurrence or progression to peritoneal pseudomyxoma, whereas those associated with mucin and neoplastic mucinous epithelial cells present with a high risk of recurring as disseminated disease (50%).[1,13,14]

In the evaluation of LAMN,[1] the entire appendix should be examined to identify the presence of mucin on the serosa and, more importantly, the presence of mucinous epithelium within the extra-appendiceal mucin. Another designation, with a lower rate of agreement among pathologists (30/44 [68%]), is HANM.[2] According to pathologists, this term should be used for cases with LAMN[1] histological characteristics, without infiltration, but with high-grade cellular dysplasia. The terms unspecified adenocarcinoma, mucinous adenocarcinoma, signet ring adenocarcinoma, and undifferentiated carcinoma complete the range of mucinous diseases of the appendix. Mucinous adenocarcinoma is responsible for 40% of all adenocarcinomas, although it is not clear which proportion can be classified as LAMN[1] according to the current World Health Organization terminology. The survival rates for appendiceal adenocarcinoma after 5 years varies (18.7-55%), and patients with mucinous adenocarcinomas have better prognosis.[8,14]

The issue is much more complex and other elements can be added to achieve consensual disease report avoiding misinterpretation. Valasek *et al*. (2017) reviewed 46 appendiceal specimens with diagnosis of primary neoplasia. The authors observed a significative discordance between originating and reference pathologist in the diagnosis of LAMN (50% to 63.0%) and adenocarcinoma (50% to 28.3%), respectively and propose an interesting checklist, which can contribute to diagnosis (Table 1). They concluded that appendiceal mucinous lesions diagnosis remain a challenging area. Recently published guidelines (Table 2) and the checklist may help improvement of diagnostic concordance, reduce over-interpretation and potential overtreatment.[15]

Surgery is the treatment of choice for mucinous tumors of the appendix. However, the surgical approach (laparotomy *vs* laparoscopy) and indication for complementary right hemicolectomy remain controversial. Although the laparoscopic approach has gained terrain, some authors have indicated the laparotomy approach because of the lower risk of appendiceal rupture. However, the advantages of minimally invasive surgery, experienced teams, safe mobilization of the ileal-cecal-appendiceal segment, and constant preoccupation with the risk of perforation result in excellent postoperative results.[16]

Gonzalez Moreno *et al.* suggested that right hemicolectomy should be avoided in cases of malignant tumors unless there is lymph node involvement. Otherwise, appendectomy alone or accompanied by typhlectomy should be adopted to obtain free resection margins. Appendectomies should be accompanied by resection of the mesoappendix and collection of all periappendiceal fluid. Although the presence of four to eight lymph nodes at the mesoappendix has been described, this number is not used as a criterion for determining the need for right hemicolectomy. In the case of benign tumors, appendectomies are curative. As a rule, this is determined post-appendectomy and following anatomopathological examination of the sectioned piece. Right hemicolectomy should not be performed based only on intraoperative suspicion of mucinous tumor of the appendix, since only 10-20% of the cases are malignant tumors, except in the case of presumptive diagnosis and possibility of frozen section examination.[5,16]

For perforated mucinous neoplasia's of the appendix, another

Table 1. Review of the current nomenclature of mucoceles of the appendix, their most characteristic histological aspects, and recommended therapeutic approach.

Nomenclature	Histological finding	Treatment
Adenoma	Benign lesion	Appendectomy
LAMN	*Pushing invasion* Intact serosa Negative lymph nodes	Appendectomy
HAMN	Presence of severe cellular atypia	Appendectomy
Perforated	Negative peritoneal cytology Free margins Free lymph nodes Other	Intraperitoneal chemotherapy Cytoreductive surgery Intraperitoneal chemotherapy Hyperthermia
Mucinous adenocarcinoma	Malignant tumor	Right hemicolectomy plus 1 or 2

Adapted from Carr *et al.*, 2016.[8] LAMN, low-grade appendiceal mucinous neoplasm; HAMN, high-grade appendiceal mucinous neoplasm.

Table 2. Proposed checklist for appendiceal neoplasia.

Appendix entirely submitted:	___ Yes, entirely submitted ___ No, representative sections only ___ Unknown
Definitive luminal neoplastic epithelium:	___ Present ___ Not identified ___ Cannot be determined
Loss of lamina propria/muscularis propria and stromal hyalinization:	___ Present ___ Not identified ___ Cannot be determined
Extra-appendiceal mucin:	___ Present ___ Not identified ___ Cannot be determined
Extra-appendiceal neoplastic epithelium*	___ Present ___ Not identified ___ Cannot be determined
Destructive or infiltrative invasion/tumor budding°	___ Present ___ Not identified ___ Cannot be determined
Surgical evaluation for peritoneal disease	___ Yes, peritoneal disease present ___ Yes, peritoneal disease absent ___ Evaluation not performed or incomplete ___ Unknown

From Valasek *et al.*, 2017.[15] * If present, confers high risk of recurrence in LAMN; °small, irregular glands in a desmoplastic stroma and/or discohesive single cells or clusters of up to 5 cells; if present = diagnostic of adenocarcinoma.

therapeutic approach should be adopted. If, following appendectomy, the peritoneal cytology is negative, the margins are free, and the ileocecal lymph nodes are not affected, intraperitoneal wash and chemotherapy should be administered. If the cytology is positive, cytoreductive peritoneal surgery with early postoperative intraperitoneal chemotherapy and hyperthermia should be adopted. Perioperative chemotherapy includes mitomycin and 5-fluorouracil. It is also recommended that these patients be referred and treated in reference centers.[5]

Mucinous neoplasms of the appendix are rare lesions with not fully defined nomenclature that have been reviewed with the aim of achieving a more consensual anatomopathological diagnosis, decreasing the variability of terms, and contributing to uniform and contextualized therapeutic conduct.

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