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A Low-Grade Appendiceal Mucinous Neoplasia and Neuroendocrine Appendiceal Collision Tumor: A Case Report and Review of the Literature

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Data Interpretation D
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Patient: Female, 31-year-old
Final Diagnosis: Appendiceal neuroendocrine tumor • low-grade appendiceal mucinous neoplasm
Symptoms: Abdominal pain • dysuria
Medication: —
Clinical Procedure: Laparoscopic appendicectomy • laparoscopic right hemicolectomy
Specialty: Oncology • Surgery

Objective: Rare co-existence of disease or pathology

Background: Incidental appendiceal neoplasms account for 1-2% of appendectomies. Mucinous neoplasms and carcinoids are the most frequent lesions, with an incidence of 0.6% and 0.3-0.9%, respectively. Appendiceal collision tumors are extremely rare and result from the proliferation of 2 different cellular lines. This report describes a young woman with a collision tumor composed of a low-grade appendiceal mucinous neoplasia (LAMN) and an appendiceal neuroendocrine tumor (ANET).

Case Report: A 31-year-old woman was admitted to our institution presenting with abdominal pain and dysuria. After ultrasound assessment of a dilated appendix with wall thickening and distension by anechogenic material, a diagnosis of acute appendicitis was made. The patient, after a period of antibiotic therapy and observation, underwent an urgent laparoscopic appendectomy due to worsening condition. Surprisingly, the histological exam revealed a Tis LAMN extending from the base of the appendix to the resection margins, and a T3 grade-1 ANET, chromogranin-A and synaptophysin-positive, with a Ki67 less than 1%. On the basis of histological examination and European Neuroendocrine Tumor Network guidelines, in light of the positive LAMN resection margin and ANET mesoappendiceal invasion, after multidisciplinary team discussion, an elective laparoscopic hemicolectomy was indicated. The patient is now in good condition following a regular 5-year follow-up.

Conclusions: A collision LAMN and ANET is an exceedingly rare condition. The heterogeneity of clinical presentation and lack of solid evidence seem to recommend a tailored management. Laparoscopy is a safe and useful tool in localized mass excision.

Keywords: Adenocarcinoma, Mucinous • Appendiceal Neoplasms • Carcinoma, Neuroendocrine

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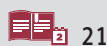
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Background

Primary appendiceal neoplasms are infrequent tumors, found in around 1-2% of all appendectomy specimens [1,2]. Most benign and malignant appendiceal neoplasms are discovered incidentally during appendectomy with preoperative diagnosis of appendicitis. Malignant appendiceal neoplasms can present with distant spread, peritoneal involvement, or direct invasion, although this is an uncommon presentation [1].

The most common clinical onset is acute appendicitis caused by appendicular luminal obstruction by the neoplastic mass. A carcinoid syndrome is rarer and is caused by vasoactive peptides produced by appendiceal neuroendocrine tumors (ANETs), while mucocele and pseudomyxoma peritonei are a typical finding of mucinous neoplasms [1].

Mucinous neoplasms and carcinoids are the most frequent benign and malignant appendiceal lesions, respectively found in 0.6% and 0.3-0.9% of appendectomy specimens [3].

Rarely, collision or combined neoplasms can occur. The former are the result of 2 distinct but adjacent neoplasms, without any transition zone, resulting from the proliferation of 2 different cellular lines (biclinal malignant transformation), while the latter are the result of a multidirectional differentiation of cells from a single tumor [4,5]. Since combined and collision tumors are exceptional cases, a consensus on their treatment has not yet been reached.

Here, we present the case of a 31-year-old woman undergoing laparoscopic appendectomy for assumed appendicitis and afterward, a laparoscopic right hemicolectomy for a collision low-grade appendiceal mucinous neoplasm (LAMN) and an ANET. In addition, a review of similar cases reported in the literature was performed.

Case Report

A 31-year-old woman presented at the emergency room of our institution with abdominal pain associated with dysuria. She had had 2 pregnancies, no comorbidities, and no previous history of surgery. Physical examination revealed a painful and tender abdomen, particularly in the right iliac fossa with local peritonism, a positive Blumberg's sign, and no signs of bowel occlusion. The patient was afebrile and vitals were normal, as were blood sample tests that showed a slight neutrophilia with a normal white blood cell count. A pelvic ultrasound scan revealed a 5.5-cm-long appendix with wall thickening, without any surrounding free fluid, that was distended by an anechogenic material (Figure 1).

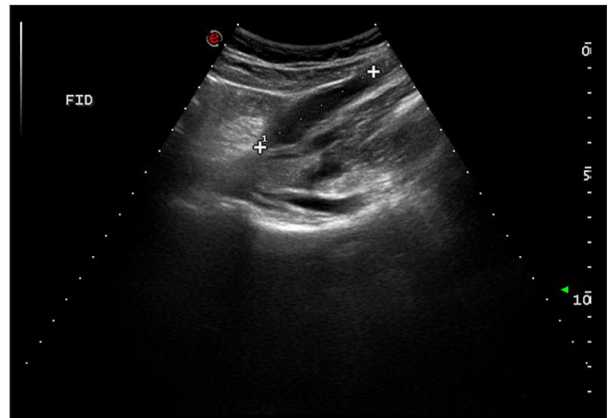


Figure 1. Abdominal ultrasound showing an appendix 5.5 cm long, dilated, and distended by an anechogenic material with wall thickening.

Our first-line treatment was conservative management with antibiotics (ceftriaxone and metronidazole) and analgesic therapy. Two days after admission, the patient's condition worsened, with increasing C reactive protein and leukocytosis prompting an urgent laparoscopic appendectomy. Intraoperatively, the appendix was covered with fibrin, adherent to the right salpinx with concomitant cecal, uterine, and anterior rectal inflammation and reactive pelvic inflammation. Intraoperatively, there were no signs of appendiceal perforation or extracellular mucin. The postoperative course was regular and the patient was discharged in good condition on the fourth postoperative day.

Macroscopic specimen examination showed a 4-centimeter-long appendix, filled with a dense acellular mucoid fluid, with a 1.5-centimeter yellowish bulk on its tip. This was found to be a well-differentiated ANET that was chromogranin-A- and synaptophysin-positive, with a Ki67 of less than 1% (ANET-1, WHO 2010 guidelines), no perineural or lymphovascular infiltration, and full-thickness invasion extended to the periappendiceal fat tissue (pT3Nx). Surprisingly, the histopathological examination also revealed a synchronous Tis LAMN (Armed Forces Institute of Pathology (AFIP) 2017 and WHO 2010 guidelines) at the appendiceal base with total mucosal substitution and involved surgical margins (Figure 2).

Three months later, a complete colonoscopy showed no pathological findings and a staging abdominal contrast computed tomography (CT) scan revealed no pathological enhancements but some subcentimetric paraortic and interaortocaval nodes. After multidisciplinary team discussion of the case, a laparoscopic right hemicolectomy was planned as suggested by American Joint Committee on Cancer (AJCC) guidelines [6], since the resection margins were involved by the LAMN and the ANET was extended to the periappendiceal fat tissue. Intraoperatively, no further macroscopic lesions were seen, and a right hemicolectomy with a latero-lateral isoperistaltic

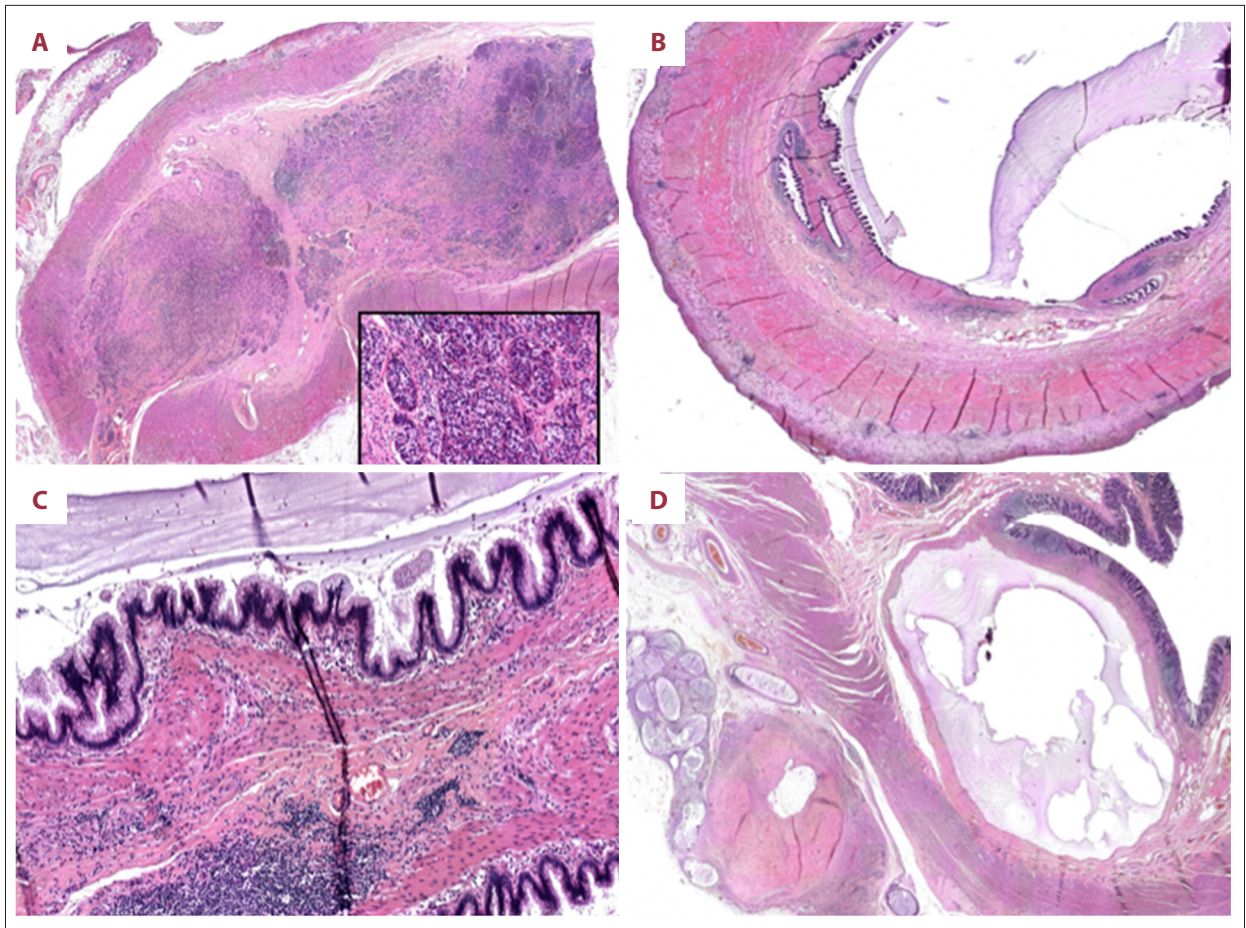


Figure 2. (A) H&E, 10×: Neuroendocrine tumor, grade 1 (carcinoid) at tip. Large and small nests composed of polygonal cells with salt-and-pepper chromatin and cytoplasmic brightly eosinophilic basally-located granules (insert; H&E 200×). Muscularis propria and subserosal tissue were infiltrated. In immunohistochemistry analysis (not shown), these cells were positive for chromogranin-A and synaptophysin. No mitosis was observed, and the Ki-67 proliferation index was less than 1%. (B) H&E 10×, and (C) H&E 100×: Low-grade appendiceal mucinous neoplasms (LAMN). At the corpus, the lumen was dilated by mucus accumulation. Mucosa-associated lymphoid tissue was absent. The normal mucosa was replaced with an undulating epithelial monolayer of uniform columnar cells with apical mucin and basal hyperchromatic nucleus. Muscularis mucosae were maintained. (D) H&E 10×. On subsequent right hemicolectomy, the specimens showed a residual appendix partially occluded by extensive fibrosis. The lumen was filled with acellular mucus. In the caecum wall there was a lake of extracellular mucus in the submucosa without evidence of epithelial cells.

ileocolic anastomosis was performed. At the histopathological examination, margins were negative as were the 6 lymph nodes retrieved. Extracellular mucinous fluid was found in the colic submucosal layer, surrounded by a fibrotic nodular area in the site of the previous resection.

After the surgical procedure and multidisciplinary team discussion, no further treatment was considered necessary, so the patient was referred to an oncologic specialist who scheduled a 5-year follow-up period. There was no sign of recurrence after 1 year.

Discussion

Since collision tumors are such rare entities, one hypothesis is that the blind-ended tubular structure of the appendix favors prolonged exposure to carcinogens, although a common agent able to promote both LAMN and ANET is still unknown [7].

There are other situations in which 2 concomitant appendiceal pathologies can occur, such as ANET and endometriosis. As with collision tumors, the incidence of this condition is extremely rare [8].

LAMNs are found in 0.6% of all appendectomies and account for around 20% of appendiceal neoplasms. Women are more

often affected and the peak incidence is in the sixth decade of life. The usual clinical presentation is as a palpable mass or tenderness in the right iliac fossa [1]. LAMNs represent up to 73% of mucinous epithelial neoplasms. They are usually non-invasive and have a good prognosis, although up to 18% of cases present with peritoneal mucinous deposits or pseudomixoma peritonei. Their treatment depends on different neoplastic features such as the grade of their cellular atypia, nodal involvement, and peritoneal spread, and LAMNs confined to the appendix mainly require only appendectomy. However, if nodes are involved or R0 resection is not achieved, a right hemicolectomy is required. In the case of peritoneal involvement, without extraperitoneal masses, patients should undergo cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, while extraperitoneal metastatic disease is treated with the same regimens used for metastatic colorectal chemotherapy [3,9,10].

ANETs comprise approximately 30-80% of all appendiceal tumors [11] and are the most frequent among all kinds of NETs. Most of these neoplasms have an excellent prognosis, with a 5-year survival rate close to 100% in the lower tumor stages [12]. Usually detected intraoperatively or during histological examination after appendectomy, ANETs typically do not present with tumor-related symptomatology [11].

For well-differentiated ANETs between 1 and 2 cm, further treatment after appendectomy is still recommended. In our case, the negative prognostic factors of mesoappendiceal invasion and LAMN extension to the resection margin indicated

a laparoscopic right hemicolectomy, which was carried out after multidisciplinary team discussion and patient consent.

Retrospectively reviewing the literature, to the best of our knowledge, only 9 other cases of collision LAMN and ANET are reported in the literature (see **Table 1**) [2,7,13-17]. Of the cases reported, the patient age ranged between 23 and 60 years, with a mean age of 38.5 years and no significant differences in sex (6 female and 4 male). In none of these cases was preoperative workup able to diagnose both neoplasms: in 6 cases, the diagnosis was made postoperatively after appendectomy performed in an acute setting; in 3 cases, it was an incidental finding during surgery performed for other reasons; and in 1 case, a high level of carcinoembryonic antigen (CEA) prompted a diagnostic laparoscopy.

A pathognomonic ultrasound-scan sign for mucinous appendiceal neoplasms is the “onion-skin appearance” typical of mucocoele. CT scan is furthermore able to detect mucocoele as low-attenuated material filling the appendix, and is useful in detecting mucinous distant implants as low-attenuated deposits [18-20]. ANETs in CT scan appear like small submucosal masses or nodular wall thickenings and can eventually show calcifications; usually these lesions are difficult to visualize radiologically because of their small size, and are difficult to discriminate from appendicitis [21].

In 3 of the reported cases, the patients were simply treated with appendectomy; 2 cases further required a right hemicolectomy; and in the remaining 5 cases, peritoneal mucin invasion required extensive surgery and chemotherapy.

Table 1. Cases of collision ANET and LAMN.

Authors and year	Sex	Age (years)	Presentation	Histology	Surgical treatment	Follow-up
Baena-del-Valle et al 2015 [14]	F	49	Acellular mucin during epigastric hernia repair	Appendiceal perforation, PCI 27 + LAMN (cytokeratin 20 and CDX-2 +, cytokeratin 7 –) and NET (CgA and synaptophysin +)	First appendectomy + CRS + HIPEC	Not available
	F	45	Epigastric hernia and free abdominal fluid	Multiple abdominal mucinous implants + tumor-like lesion on the tip of the appendix + LAMN (cytokeratin 20 and CDX-2 +, cytokeratin 7 –) and NET (CgA and synaptophysin +)	First diagnostic laparoscopic appendectomy + omentectomy + CRS + HIPEC	One year later: progression of disease with perihepatic and pleural recurrences
Tan et al 2015 [13]	M	52	Elevated CEA trend	LAMN (3.5-5 cm diameter) without involvement of either the appendiceal base nor the surrounding structures + absence of peritoneal disease + carcinoid 3 mm	Appendectomy	Regular CT scan at 6 months after the surgery

Table 1 continued. Cases of collision ANET and LAMN.

Authors and year	Sex	Age (years)	Presentation	Histology	Surgical treatment	Follow-up
Hajjar et al 2018 [11]	M	50	Abdominal pain	5.5 cm LAMN + perforation with PMP + 1.6 cm well-differentiated NET, infiltrating muscularis propria and mesoappendix, ki67 3%, grade of G2/3 + perineural invasion, no vascular invasion, free resection margins, no lymph nodes	First appendectomy, second right hemicolectomy, omentectomy, cholecystectomy, peritoneal stripping, CRS, and HIPEC	DFS at 20 months after surgery
Ekinci et al 2018 [2]	M	60	Abdominal discomfort, RIF pain, mild anemia, elevated WBC, elevated CEA	LAMN + NET WHO grade 1, infiltrating the entire thickness of the appendiceal wall, ki67 <1%	First appendectomy, second right hemicolectomy indicated but refused by the patient	DFS at 6 months after surgery
Sholi et al 2019 [12]	F	23	Constipation and abdominal fullness	LAMN + well-differentiated NET	First appendectomy, second right hemicolectomy	DFS at 24 months after surgery
Sugarbaker et al 2020 [7]	F	39	Right iliac fossa pain	Ruptured LAMN with extrusion of mucin + foci of mucin and epithelial cells on the surface of the small bowel, but no involvement of the lymph nodes (pT3N0M1) +1.7 cm pT1BNO NET	First appendectomy + right hemicolectomy, second greater omentectomy, lesser omentectomy, cholecystectomy, hysterectomy, and bilateral salpingo-oophorectomy + HIPEC	DFS 5 years after surgery
	M	32	Mucin fluid during left inguinal hernia repair	LAMN pT3N0M1a + well-differentiated NET G2T2N1MX (ki67 5%)	Right hemicolectomy, greater omentectomy, lesser omentectomy and cholecystectomy + HIPEC	Follow-up scheduled every 3 months, DFS 1 year after surgery
Cafaro et al 2020 [16]	F	35	Epigastric pain with migration to right iliac fossa + >WBC	LAMN + well-differentiated NET	Appendectomy	DFS at 15 months after surgery

LAMN – low-grade appendiceal mucinous neoplasia; ANET – appendiceal neuroendocrine tumor; NET – neuroendocrine tumor; CRS – colorectal surgery; HIPEC – hyperthermic intraperitoneal chemotherapy; CEA – carcinoembryonic antigen; CT – computed tomography; DFS – disease-free survival; WBC – white blood cell; CgA – chromogranin-A.

In our experience, in the case of localized presentation, the use of laparoscopy to perform second-step surgery is safe, feasible, and results in a faster postoperative recovery. The lack of a linear clinical pattern and the rarity of cases makes it difficult to trace a standard of care and follow-up. At this stage, management should be tailored to each patient, although a landmark seems to be whether the LAMN is disseminated. CEA and chromogranin-A could be useful tools to manage

postoperative follow-up and check potential recidivism for LAMN and ANET, respectively [1].

Conclusions

The presence of a collision LAMN and ANET is exceedingly rare. Often diagnosed as an incidental finding after appendectomy,

optimal management remains a challenge. We recommend tailoring the postoperative treatment and follow-up on a case-by-case basis, since solid evidence is lacking and clinical patterns differ greatly. In our case, laparoscopy has proven to be an excellent tool in performing appendectomy and right hemicolectomy for localized appendiceal collision neoplasms.

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Conflict of Interest

None.