Low-Grade Appendiceal Mucinous Neoplasia and Neuroendocrine Appendiceal Synchronous Tumor: A Rare Case Report and Review of Literature for 13 Cases

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Abstract

Appendiceal neoplasms are a rare cause of gastrointestinal cancers, comprising a small percentage of cases . The coexistence and synchronization of appendiceal neoplasms are rare occurrences. . Two separate but nearby neoplasms that have undergone bi-clonal malignant transformation give rise to Synchronous neoplasms. It is uncommon for appendiceal neuroendocrine tumours (ANET) and low-grade appendiceal mucinous neoplasms (LAMN) to coexist simultaneously; however, they are regularly found after appendectomy. A 52-year-old woman presented to the emergency room with right iliac fossa pain for several days. She had a history of cholecystectomy and was otherwise healthy. Physical examination revealed mild tenderness in the right iliac fossa. Abdominal ultrasound and CT scan showed a cystic lesion adherent to the cecum, likely representing an appendicular mucocele. Planned laparoscopic appendectomy became an open surgery due to an enlarged mesenteric lymph node and suspicion of neoplasm. A right hemicolectomy was performed instead. The postoperative course was uneventful, except for an elevated white blood cell count that normalized after antibiotic treatment. Histopathological examination revealed a low-grade neuroendocrine tumour at the tip of the appendix and a well-differentiated mucinous neoplasm at the base, both with early-stage classifications. Follow-up ultrasound showed no signs of recurrence. The patient is in good condition and scheduled for regular 5-year follow-up. Our case contributes to the existing knowledge by presenting a novel manifestation of a synchronous tumor.. Collisions between LAMN and ANET are relatively rare, but the fact that it is commonly discovered after an appendectomy makes management challenging. Because there is a dearth of reliable data, we recommend tailored case-by-case planning for postoperative treatment and follow-up.

Keywords: *Adenocarcinoma; Mucinous; Appendiceal Neoplasms; Carcinoma; Neuroendocrine*

Introduction

Approximately 0.4%–1% of all gastrointestinal cancers are thought to be caused by appendiceal neoplasms.[1] In addition, many patients develop appendicitis caused by luminal blockage, although their clinical presentation varies.[2] Appendiceal neoplasms can be rationally categorized.[3] There are several types of appendicular tumours. Hyperplastic polyps, adenomas, malignant low-grade appendiceal mucinous neoplasms, malignant high-grade appendiceal mucinous neoplasms, and adenocarcinomas are examples of appendicular epithelial tumours.[4] Carcinoid or mesenchymal tumours are non-epithelial neoplasms that fall within this category. The jelly belly is a colloquial term for peritoneal pseudomyxomas that can develop from appendiceal mucinous lesions.[5] However, the most prevalent primary neoplasm described in the appendix, carcinoid tumours, develop from neuroendocrine cells distributed in many parts of the gastrointestinal tract.[6] The coexistence of appendicular neoplasms is uncommon. Two separate but nearby neoplasms that have undergone bi-clonal malignant transformation give rise to Synchronous neoplasms. A single tumour results in many neoplasms that have undergone multidirectional cell differentiation.[7,8] It is very uncommon for appendiceal neuroendocrine tumours (ANET) and low-grade appendiceal mucinous neoplasms (LAMN) to coexist simultaneously, but they are regularly found after appendectomy which makes management challenging. Unfortunately, the optimal course of action has not yet been authorized.[9] Here, we describe a case of a 52-year-old woman who underwent a laparoscopic appendectomy that turned into an open right hemicolectomy because of appendicular lumps that were later identified as a combination of a carcinoid tumour and a low-grade appendiceal mucinous neoplasm (LAMN). Additionally, we reviewed similar cases published in the literature. This case report has been reported in line with the SCARE criteria[10]

Case Report

A 52-year-old single woman presented at the emergency room of our institution with right iliac fossa pain for several days. It was vague, with no other symptoms. The patient reported that her last menstrual cycle was irregular, occurring twice a month. She had no comorbidities and a history of cholecystectomy. Physical examination was unremarkable, except for mild right iliac fossa tenderness, no rebound tenderness, a negative Rovsing's sign, a negative obturator sign, and a negative Psoas sign. The patient was afebrile and had normal vital signs. Abdominal US showed the presence of a cystic lesion of the right iliac fossa, 3 cm in diameter, and an abdominal CT scan revealed evidence of a cystic-like structure measuring approximately 3.20 cm in diameter (Figure 1) with a thickened enhanced wall (0,48 cm) (Figure 2) adherent to the cecum extending downward, probably representing appendicular mucocele. No free fluid could be seen at the time of the exam; also, there was a renal cortical cyst measuring about 5.5*6 cm. The impression was mucocele appendix vs. cystic neoplasm; therefore, laparoscopic appendectomy was planned on the same admission. Her white blood count (WBC) was 11.0 $x10^3$/uL. She was administered antibiotics and analgesic therapy before surgery.

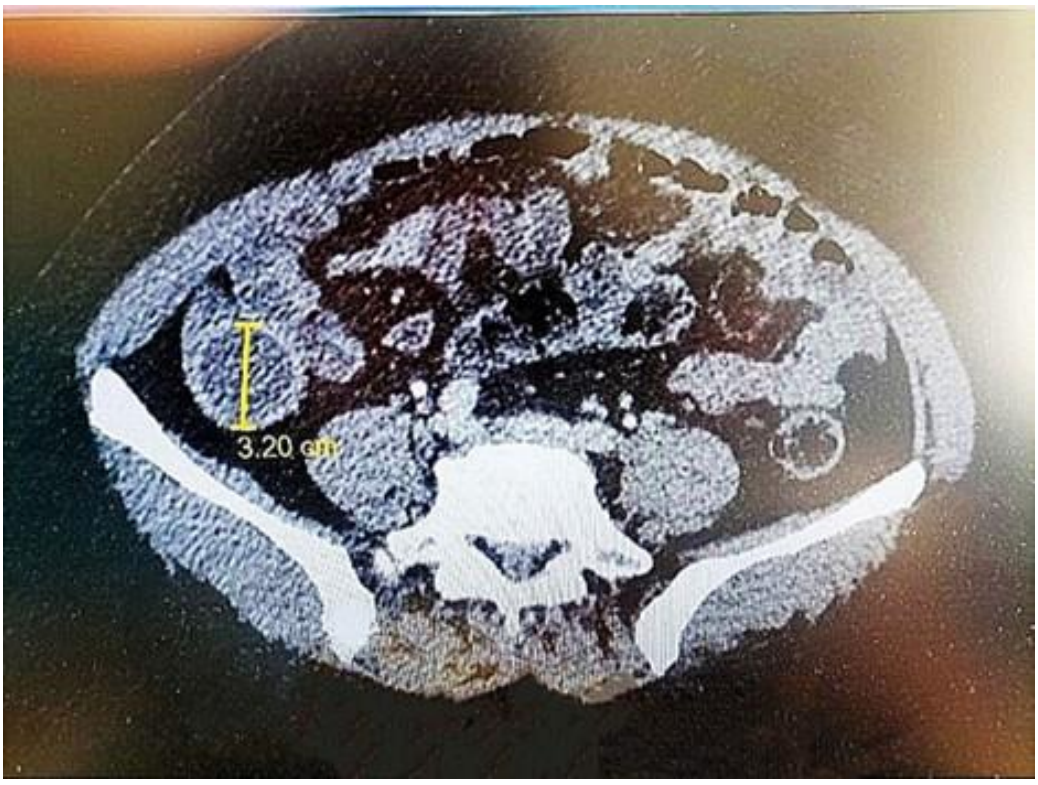

Figure 1: CT findings- cystic-like structure measuring approximately 3.20cm in diameter.

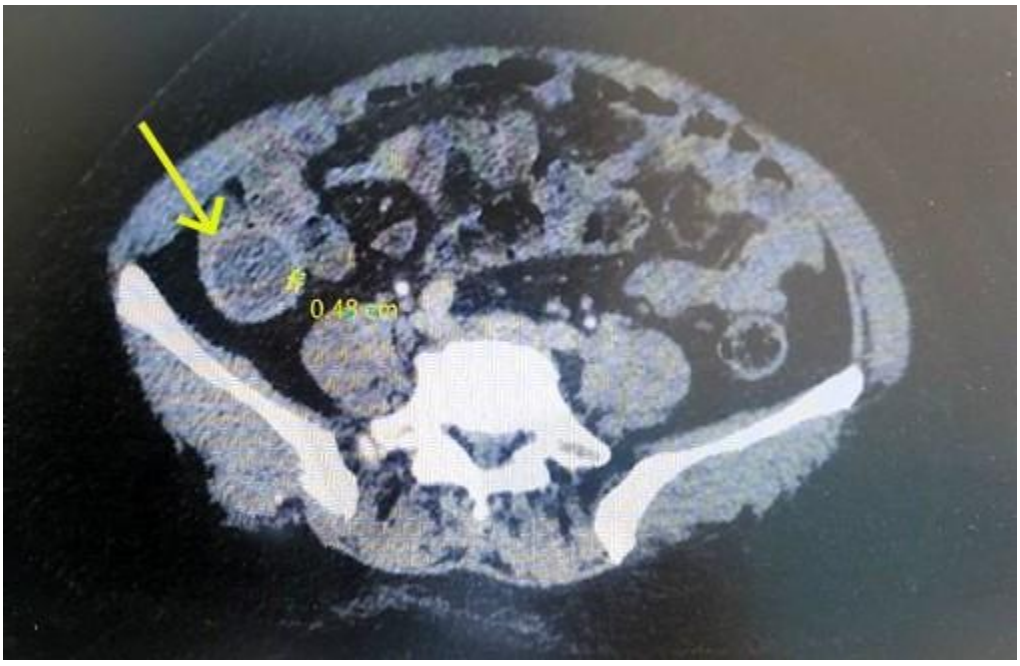

Figure 2: CT findings- cystic-like structure with a thickened enhanced wall (0,48cm).

Intraoperatively, a cystic lesion was observed at the base of the appendix, making intussusception with the cecum. In addition, enlarged mesenteric lymph nodes were also observed. A Slightly distended distal part of the appendix was

observed but with no prominent signs of inflammation, perforation, or extraluminal mucin. The cecal wall and terminal ileum were unremarkable.

It was difficult to mobilize the appendix or release the intussusception during the surgery. However, the surgery was converted to open surgery because of the enlarged mesenteric lymph nodes and the high suspicion of neoplasm, and a right hemicolectomy was performed.

The postoperative course was uneventful except for an elevated WBC of 26.3 $x10^3$/uL with a shift to the left of 92%. Follow-up postoperative US was performed and showed no fluid collection. Her abdominal drain output was unremarkable, with a minimal amount of serosanguinous fluid, and her WBC count improved and returned to normal over several days with antibiotic administration. The patient was discharged in good condition on the fifth postoperative day.

The right hemicolectomy specimen was sent to the histopathological department, and the gross description was as follows: right hemicolectomy specimen composed of part of the terminal ileum measuring 5 × 4 cm, cecum measuring 8 × 5 cm, and appendix measuring 6 × 3.3 cm. The Appendiceal base was dilated and filled with mucin confined grossly within the lumen and measured 3.5 × 2 cm. The remainder of the appendix contains an intraluminal mass measuring 3 × 1.8 cm. No gross appendiceal perforations were observed (Figure 3).

Figure 3: Dilated appendix with intraluminal mucin.

After the resected specimen was fixed in formaldehyde solution (10%), processed, and converted to Formalin-Fixed Paraffin-Embedded (FFPE) tissue, the histological sections were placed onto glass slides and stained with routine H&E staining. The findings regarding the two lesions are as follows:

The first appendiceal (tip) mass was a low-grade well-differentiated neuroendocrine tumour that invaded the muscularis propria with less than 2 mitoses per 2 mm2 (Figures 4,5). There was Lympho-vascular Invasion, but no Perineural Invasion and all examined regional lymph nodes were negative for the tumor. According to the American Joint Committee on Cancer-AJCC 9th version classification, the pathological stage was pT2NO. The secondary appendiceal base mass was a well-differentiated low-grade mucinous neoplasm confined to the muscularis propria. According to the American Joint Committee on Cancer-AJCC 9th version classification, the pathological stage was pTisN0.

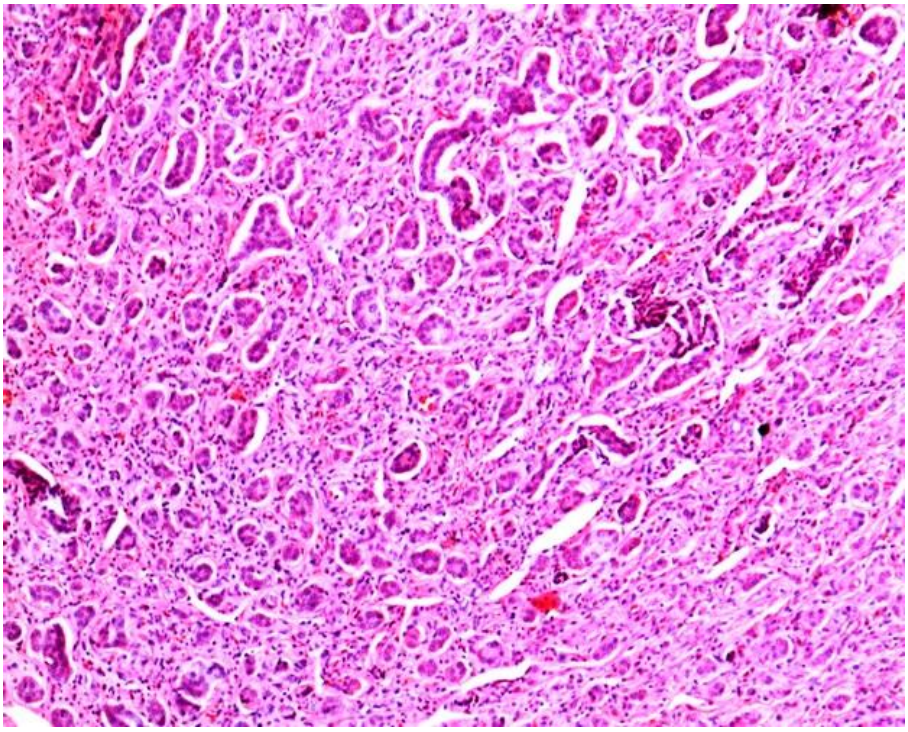

Figure 4: H&E-stained sections revealed that the appendiceal wall was infiltrated by numerous tumorous cells arranged as acini and nests.

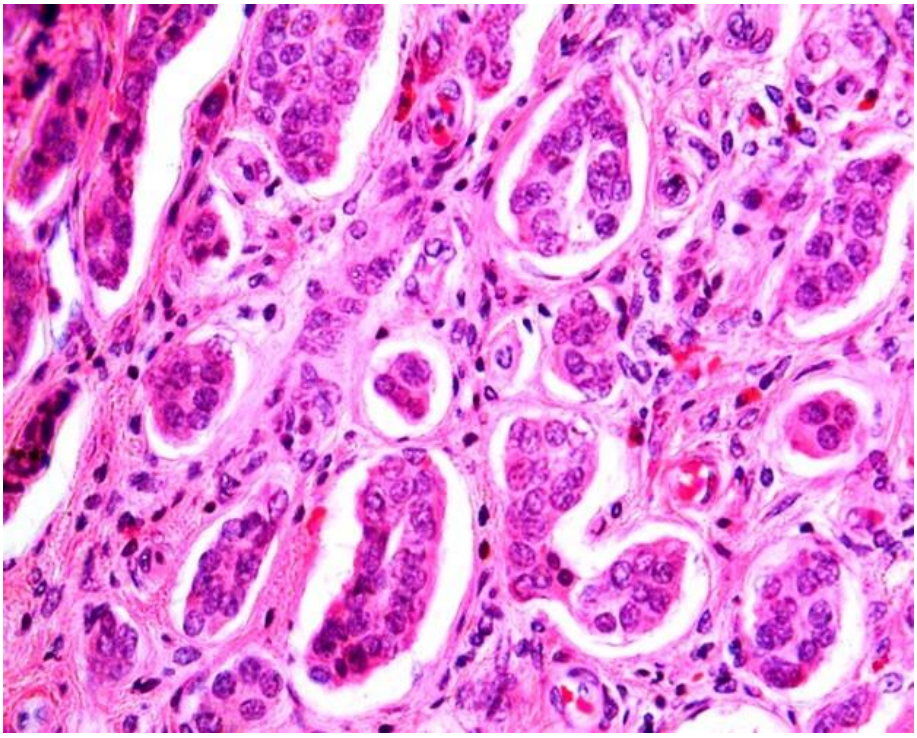

Figure 5: H&E-stained sections at higher power, these cells had monotonous round nuclei with salt and pepper chromatin.

Follow-up US performed 3 months later showed no free fluid in the abdomen and no signs of recurrence. The patient was scheduled for a follow-up CT during the same month. Subsequently, multidisciplinary team discussions will determine the need for further treatment. The patient will be referred to an oncological specialist scheduled for a 5-year follow-up period.

Discussion

According to our knowledge, after looking back at the literature, only 12 additional examples of LAMN and ANET Synchronous have been documented (Table 1).[9,11-19] Patients in the reported cases ranged in age from 23 to 60 years, with a mean age of 43 years and no appreciable sex differences (six females and seven males). Preoperative workup failed to detect both neoplasms in any of these cases; in nine of them, the diagnosis was made postoperatively following an urgent appendectomy. Regarding geographic distribution, 38.5% of the cases were in North America, and 23.1% were in South America. The remaining cases were distributed in Europe, Asia, and Africa with percentages of 15.4%, 15.4%, and 7.6%, respectively. The only treatment needed in three of the reported instances was appendectomy; in four cases, a right hemicolectomy was also necessary; in the other five cases, peritoneal mucus invasion necessitated extensive surgery and chemotherapy. Finally, due to the intraoperative findings in one case, laparoscopic appendectomy was required, which also involved the resection of a distal piece of the cecum.

Table 1: An up-to-date review of the literature.

Authors	Sex	Age (years)	Country	Presentation	Histology	Surgical treatment	Follow-up
Sugarbaker PH[9]	Female	39	USA	right lower quadrant pain	primary low-grade appendiceal mucinous neoplasm (PT3N0M1a) the second primary tumour was also found to be a neuroendocrine tumour (PT1BN0)	open right hemicolectomy	2 years later, the patient got an exploratory laparotomy which showed mucin in the right hemidiaphragm, falciform ligament, and the right paracolic sulcus. Since that, she has been operated on with greater omentectomy, lesser omentectomy, cholecystectomy, hysterectomy, and bilateral salpingo-oophorectomy. Also, she systematically took Hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C and doxorubicin intraperitoneally and 5-fluorouracil and leucovorin for 90 min. The patient had not shown any prolapse 5 years after her definitive cytoreduction with HIPEC.
	Male	32	USA	Mucin in the hernia sac during left hernia repair. Later, Large mucin deposits were seen on the right	low-grade mucinous neoplasm of the appendix The stage was PT3N0M1a. Well-differentiated neuroendocrine tumour.	Visceral resections were right colon, greater and lesser omentum, and gallbladder. Peritonectomy procedures were right subphrenic,	Chromogranin A and 5-HIAA were in the normal range postoperatively. The patient is being followed at 3-month intervals.

				hemidiaphragm, left upper quadrant, and pelvis, with a large tumour mass in the right lower quadrant of the abdomen	Ki67 of 5%.	left subphrenic, omental bursa, parietal and pelvic peritonectomy. Complete cytoreduction (CC-0) was reached. HIPEC was performed with mitomycin C for 90 min	He is fully active without evidence of disease recurrence
Baena-del-Valle J [11]	Female	49	Colombia	epigastric hernia	LAMN, NEN Positive for chromogranin and synaptophysin positive for cytokeratin 20 and CDX-2 and negative for cytokeratin 7	radical cytoreduction and hyperthermic intraperitoneal chemotherapy.	Discharged from the hospital on day 11 without complications.
	Male	42	Colombia	3 years of progressive abdominal distension ended by epigastric hernia	LAMN, NEN Positive for chromogranin and synaptophysin positive for cytokeratin 20 and CDX-2 and negative for cytokeratin 7	An appendectomy and omentectomy	Year after, the patient took radical and hyperthermic intraperitoneal chemotherapy cytoreduction. A year later, the patient presented with progressive abdomen disease; since they couldn't conduct full cytoreduction, they only used chemotherapy.
Ruiz SG [12]	Male	54	USA	Right lower quadrant abdominal pain It is radiating to the right inguinal area. It is associated with right flank	A well-differentiated LAMN invading the subserosa without involving the visceral peritoneum or lymphovascular invasion,	A laparoscopic appendectomy includes a distal segment of the cecum in the resection.	Surgical resection was considered appropriate, and no further treatment was required.

				pain, nausea, and vomiting.	A well-differentiated NET		
Ekinci N [13]	Male	60	Turkey	Right lower quadrant and stomach discomfort dating back two months. Moderate anaemia A slight rise in the leukocyte count and carcinoembryonic antigen level.	The diagnosis of a low-grade mucinous tumour WHO Grade I neuroendocrine neoplasm ki67 <1%	The first appendectomy and second right hemicolectomy were indicated but refused by the patient.	The patient was free of the disease six months after the operation when being followed up.
Cafaro MA [14]	Female	35	Argentina	Twenty-four hours of continuous epigastric pain with migration to the right iliac fossa. Showed leukocytosis with neutrophilia	well-differentiated neuroendocrine neoplasia and low-grade mucinous epithelial neoplasia.	Appendectomy	follow-up with postsurgical tumour markers was performed with normal results, in addition to computed tomography and postoperative colonoscopy without alterations.
Hajjar R [15]	Male	50	Canada	abdominal pain	The coexistence of mucinous and neuroendocrine appendicular tumors	right hemicolectomy and cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) were performed five months after the appendectomy.	The patient recovered uneventfully after the surgery and remains cancer-free after 20 months of follow-up.
Sholi AN [16]	Female	23	USA	Right lower quadrant pain.	a LAMN An intermediate-grade	laparoscopic appendectomy Robotic right hemicolectomy	At the 2-year follow-up, surveillance MRI showed no evidence of disease, and the patient continues to be

					neuroendocrine tumor Extensive vascular invasion (T4Nx). Immunohistochemistry determined a Ki-67 proliferation index of 8%.	(RHC) with lymph node dissection and right lower peritonectomy.	followed with expectant management. Tumor markers were not collected and given to management at an outside centre. At the last follow-up, her abdominal complaints and panic attacks resolved.
Tan HL [17]	Male	52	Singapore	Two years earlier, an elevated serum level of carcinoembryonic antigen (CEA) was discovered during a routine health checkup.	low-grade mucinous appendiceal tumour with an unplanned discovery of a unique carcinoid centre with a maximum diameter of 3 mm	laparoscopic appendicectomy	Less than three months have passed since the patient's surgery, and a surveillance CT scan of his abdomen and pelvis is scheduled for six months from now.
Bouhafa A [18]	Male	40	Tunisia	Three months history of intermittent hypogastric pain.	Well-differentiated endocrine carcinoma and a low-grade mucinous neoplasm	Right colectomy, Adjuvant chemotherapy.	No recurrence after 10 months of monitoring.
Villa M [19]	Female	31	Italy	abdominal pain, dysuria.	Well-differentiated ANET Chromogranin-A- and synaptophysin-positive, Ki67 of less than 1% a synchronous Tis LAMN	Failed first-line conservative treatment, then laparoscopic appendectomy; three months later, an elective laparoscopic hemicolectomy was carried out.	The patient was referred to an oncologic specialist who scheduled a 5-year follow-up period after the right hemicolectomy. There was no sign of recurrence after 1 year.

LAMN – low-grade appendiceal mucinous neoplasia; ANET – appendiceal neuroendocrine tumor; NEN – appendiceal neuroendocrine neoplasm; NET – neuroendocrine tumor; CRS– colorectal surgery; HIPEC – hyperthermic intraperitoneal chemotherapy; CEA – carcinoembryonic antigen; CT – computed tomography; CgA – chromogranin-A; HIAA–5-Hydroxyindoleacetic acid;Robotic right hemicolectomy (RHC).

The incidence of appendiceal neoplasm is predicted to be 1% of the incidence of colon and rectal cancers.[10] About 5% of the time, primary appendiceal neoplasms—rare clinical entities—are unintentionally found after an emergency appendectomy for appendicitis.[1] Less than five cases of actual appendiceal Synchronous tumours, defined as the coexistence of two tumour forms with different clonal origins that are histologically distinct from one another, have been documented in the literature.[11,20,21]

The appendiceal mucosa has a surface area much smaller than 1% of that of the colonic and rectal mucosa. Prolonged exposure to retained intestinal carcinogens may have affected the appendix, which is a tubular structure with a blind end. The 0.5% frequency of epithelial neoplasms and neuroendocrine tumours, often tiny and benign, may also indicate higher levels of carcinogens in the appendix. There are probably different carcinogens for adenomatous and neuroendocrine cancers of the appendix. The discovery of carcinoid and adenomatous tumours in the same appendix raises the possibility that the same carcinogen may be responsible for both appendiceal malignancies.[9]

Neuroendocrine neoplasms (aNENs), which are appendix cancers, are frequently discovered in patients in their fourth and fifth decades of life.[22] Mucinous neoplasm diagnosis peaked during the fifth and seventh decades of life.[23-25] Patients with ACTs appear clinically in various ways. A right lower quadrant tumour that was accidentally palpated,[20] growing abdominal distention over time,[11] or acute appendicitis symptoms are examples of current symptoms.[17] Here, the patient presented with pain in the right iliac fossa for several days.

The histological spectrum of appendiceal mucinous neoplasms includes mucinous adenomas, low-grade mucinous neoplasms, high-grade mucinous neoplasms, and mucinous adenocarcinomas.[26] The first two entities can be managed using a straightforward appendectomy.[23] Like other carcinoid tumours, appendiceal carcinoids can be treated with straightforward appendicectomy with clear margins if the tumour is less than 2 cm in size and there is no sign of mesoappendiceal invasion.[22]

The term "appendiceal mucinous neoplasms" refers to a group of benign or malignant tumours that can manifest as a variety of diseases. Adenomas, LAMNs, and mucinous adenocarcinomas are the three types of mucinous neoplasms defined according to the 2010 WHO guidelines.[27] In contrast to LAMN, which is composed of well-differentiated glands that pierce the muscularis mucosa with dissecting mucin or epithelium, adenomas are benign lesions restricted to the mucosa.[23] Surgical excision with negative margins is appropriate for appendiceal adenomas and low-grade mucin-based tumours.[23,24] In this case, the LAMN was entirely removed during the initial surgery, and the neuroendocrine component guided the later staging and reoperation. Right Hemicolectomy RHC should be considered when there are additional metastatic risk indicators, such as serosal involvement, a Ki-67 proliferative index greater than 2%, placement at the base of the appendix, and angio- or neuroinvasion.[22]

Given their capacity to release vasoactive peptides, they can result in "carcinoid syndrome," which is characterized by flushing and diarrhoea. If no nodal or distant illness is present, NETs 2 cm in size seldom metastasize and have a five-year survival rate of >90%.[28] For tumours> 2 cm in size and those < 2 cm with vascular or mesoappendiceal invasion, positive margins, or mixed histology, right hemicolectomy is recommended as the cornerstone of treatment.[28] Otherwise, appendectomy appears sufficient. Because the tumour was 3.4 cm and there was lymph node enlargement in addition to the presence of intussusception, which prevented us from performing laparoscopic appendectomy, accordingly, the right hemicolectomy was performed. Only a few carefully reported cases of the coexistence of mucinous and neuroendocrine appendiceal tumours have been published.[17] These may manifest as "combined" tumours or "collision" tumours. The margins of collision tumours are well-defined, and the space between them is devoid of features.[29] Cell populations are mixed in combined tumours.[29]

The "onion-skin look" typical of mucocele is a pathognomonic ultrasound-scan marker for mucinous appendiceal neoplasms. Additionally, a mucocele can be seen as a low-attenuated material filling the appendix on a CT scan, and it can be used to identify distant mucinous implants as low-attenuated deposits. When observed on a CT scan, ANETs resemble small submucosal masses or nodular wall thickening and may later develop calcifications. Owing to their small size, these lesions are typically challenging to visualize radiologically and are difficult to distinguish from appendicitis.[19]

Only one of the component tumour types is present in the metastases from Synchronous tumours, whereas both component neoplasms are present in the metastases from composite tumours.[30] In our case, there weren't any metastases, whereas it was in the Sholi study[16] in which there were at the time of the hemicolectomy, metastases from the neuroendocrine component were found in 4 of the 26 lymph nodes.

It is important to note that there is a continuous discussion surrounding the treatment of peritoneal carcinomatosis (PC) that develops from NET neuroendocrine tumours. Unfortunately, there is still a dearth of research on treating the unique appearance of this tumour. Surgical cytoreduction alone has been recommended as a viable method to treat NET-derived PC because of the considerable morbidity associated with HIPEC. The optimal therapeutic strategy in this circumstance may not yet be a combination of Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC).[31]

However, given the enormous therapeutic benefit of HIPEC in managing the PMP component, it would have been warranted if our patient also had peritoneal neuroendocrine metastases. Aggressive CRS and HIPEC continue to be the cornerstones of a curative surgical approach for combined mucinous and neuroendocrine appendiceal tumours with peritoneal dissemination. However, the effectiveness of such a comprehensive procedure greatly depends on several non-modifiable factors, such as the grade of the mucinous neoplasm and associated PCI.[32-34]

The laparoscopic method also seems to be a safe and practical choice for some appendiceal tumours, as shown in our second case, and comparable findings have been described in the literature for both appendiceal carcinoids and appendiceal mucinous neoplasms.[24]

Before surgery, a diagnosis of both primary neuroendocrine tumour and primary mucinous appendiceal tumour can be made. However, in many cases, cross-sectional imaging frequently reveals the appendix mucocele but not the neuroendocrine tumour. Only the final pathology reveals this finding. Low-grade appendiceal neoplasms have a low likelihood of lymph node metastasis.[35] Lymph node metastasis is more likely to occur in neuroendocrine tumours of the appendix that are > 20 mm and have lymphovascular invasion or tumours that invade the mesoappendix. As a result, right hemicolectomy has been suggested and is frequently performed, as has already been done in our case.[36] However, no survival advantage with right colon resection has been previously reported.[36] Additionally, the search for better survival with right hemicolectomy was unsuccessful in two recent cases.[37,38] Recent research suggests performing radical appendectomy with ileocolic and appendiceal lymph node sampling to aid in the selection of individuals undergoing right colon resection. It has not been demonstrated that improving survival would result from right hemicolectomy to remove occult positive lymph nodes.[39]

Both tumour forms should be subjected to long-term surveillance, and cross-sectional imaging at regular intervals is recommended for both LAMN[23] and aNEN.[28] On the whole, aNENs have far better outcomes than other appendiceal neoplasms and have a very low chance of returning.[22] However, for aNENs confined to the base of the appendix or aNENs with nodal involvement, surveillance MRI or CT is advised, and MRI should be strongly preferred over CT to reduce radiation exposure.[40] When lesions are radiographically occult, CEA and CgA may be particularly helpful tools to manage postoperative follow-up and assess potential recidivism for LAMN and ANETas, an internal test to detect recurrence.[19] In our case, conducting an immuno-histochemistry wasn't possible due to a lack of resources.

In the case of finding a Mets, doing second-step surgery via laparoscopy in the event of localized presentation is safe, practical, and leads to a quicker postoperative recovery. It is difficult to establish a standard of care and follow-up because there are no clear clinical patterns and only a few patients. Although a key indicator at this point appears to be whether LAMN has spread, therapy should be customized for each patient.[19] Regarding the follow-up in our case, Observe US Three months later showed no sign of recurrence, and there was no free fluid in the abdomen. In the same month, the patient had a planned follow-up CT scan. A multidisciplinary team discussion will determine whether additional therapy is required. The patient will be referred to an oncologist and will have a 5-year follow-up period.

Conclusion

Two tumours with distinct histology were evaluated independently to determine the most effective treatment. Our patient was thought to require a simple appendectomy with clear margins because both cancers were found to be low-grade, inactive, and restricted to the appendix but were converted to open right hemicolectomy due to previously mentioned indications... Because there is a dearth of reliable data and a large variety of clinical patterns, we recommend tailored case-by-case planning for postoperative treatment and follow-up.

Disclosure

The study was exempt from ethnical approval in my institution as the data used in this report can be accessed with the explicit consent obtained from the patient involved.

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