Synchronous Low-Grade Appendiceal Mucinous Neoplasia and Neuroendocrine Appendiceal Tumor: A Case Report with Literature Review

Eman M. Kreishan[1], Ibraheem M. Alkhawaldeh[2], Jehad Feras AlSamhori[3], Jalal G. Almaaiteh[1], Almutazballlah B. Qablan[4], Alaa Ramadan[5]* and Abdulqadir J. Nashwan[6]

[1]Faculty of Medicine, AL-Karak Government Hospital, Mutah University, Al-Karak, Jordan

[2]Faculty of Medicine, Mutah University, Al-Karak, Jordan

[3]Faculty of Medicine, University of Jordan, Amman, Jordan

[4]Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan

[5]Faculty of Medicine, South Valley University, Qena, Egypt

[6]Nursing Department, Hamad Medical Corporation, Doha, Qatar

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*Corresponding author: Alaaramadan251@gmail.com

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Abstract

Appendiceal neoplasms are rare gastrointestinal cancers. Synchronous neoplasms—where two adjacent neoplasms undergo bi-clonal malignant transformation—are even rarer. Simultaneous coexistence of appendiceal neuroendocrine tumors (ANET) and low-grade appendiceal mucinous neoplasms (LAMN) is unusual; they are usually discovered after appendectomy. We present a rare case of a 52-year-old woman who presented with right iliac fossa pain that was tender to touch. Imaging revealed a cystic lesion adherent to the cecum, likely representing an appendicular mucocele. The initially planned laparoscopic appendectomy was transformed into an open surgery due to the finding of an enlarged mesenteric lymph node and suspicion of neoplasm. A right hemicolectomy was performed instead. Histopathological examination revealed a low-grade neuroendocrine tumor at the tip of the appendix and a well-differentiated mucinous neoplasm at the base, both with early-stage classifications. The patient recovered uneventfully and is scheduled for 5-year follow-up. Our case contributes to the existing knowledge by reporting a novel coexistence of LAMN and ANET in an individual. Because there is a dearth of reliable management data, we recommend individualized treatment and follow up in such cases.

Keywords: Adenocarcinoma; Mucinous; Appendiceal Neoplasms; Carcinoma; Neuroendocrine; Jordan.

Introduction

Appendiceal neoplasms are considered to account for approximately 0.5% of all gastrointestinal cancers.[1] In addition, many patients develop appendicitis caused by luminal blockage, although their clinical symptoms can vary.[2] Appendiceal neoplasms can be categorized into distinct types.[3] Epithelial neoplasms include hyperplastic polyps, adenomas, appendiceal mucinous neoplasms with high- or low grade malignancy, and adenocarcinomas.[4] Non-epithelial neoplasms include carcinoid or mesenchymal tumors. Peritoneal pseudomyxoma, colloquially known as 'jelly belly,' develops from appendiceal mucinous lesions.[5] The most prevalent primary neoplasm described in the

appendix is the carcinoid tumor, which develops from neuroendocrine cells distributed in many parts of the gastrointestinal tract.[6]

Synchronous appendicular neoplasms occur when two distinct neoplasms develop near each other, each undergoing bi-clonal malignant transformation. A single tumor results in many neoplasms that have undergone multidirectional cell differentiation.[7,8] It is rare for appendiceal neuroendocrine tumors (ANET) and low-grade appendiceal mucinous neoplasms (LAMN) to coexist simultaneously. They are regularly found after appendectomy, which makes management challenging. Additionally, no standard approach for managing such cases has been established.[9]

We describe a case of a middle-aged woman with a synchronous low-grade LAMN and ANET. We have also supplemented the case report with a review of similar cases available in the literature. This paper is compliant with the Surgical Case Report (SCARE) criteria.[10]

Case Report

A 52-year-old single Jordanian woman presented at the emergency room of our institution with vague pain in the right iliac fossa for several days. She reported no other symptoms except that her last menstrual cycle was irregular and was occurring twice in a month. She had no comorbidities and a history of cholecystectomy. Physical examination was unremarkable, except for a mild non-rebound tenderness around the right iliac fossa, a negative Rovsing's sign, a negative obturator sign, and a negative Psoas sign. The patient was afebrile and had normal vital signs. Laboratory tests revealed a slightly elevated white blood count (WBC) of $11.0 \times 10^3/\mu L$.

Abdominal ultrasound (US) showed the presence of a cystic lesion of the right iliac fossa, 3 cm in diameter. Abdominal computed tomography (CT) revealed a cystic-like structure 3.2 cm in diameter [Figure 1A] with a thickened (0.48 cm) enhanced wall [Figure 1B] adhering to the cecum extending downward, suggesting an appendicular mucocele. No free fluid could be seen at the time of the examination. The scan also revealed a renal cortical cyst measuring about 5.5 × 6 cm. The differential diagnosis included mucocele of the appendix versus cystic neoplasm. A laparoscopic appendectomy was scheduled during the same admission.

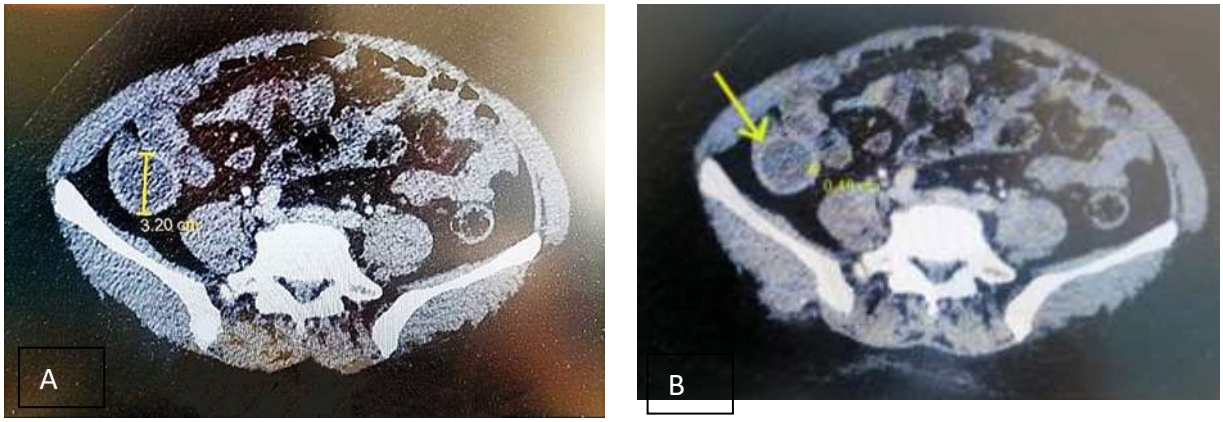

Figure 1: A. Abdominal computed tomography (CT) image showing a cystic-like structure measuring approximately 3.2 cm in diameter. B. The thick (0.48 cm) enhanced wall of the cystic-like structure.

Intraoperatively, a cystic lesion was observed at the base of the appendix, intussuscepting with the cecum. Enlarged mesenteric lymph nodes were also observed. The distal part of the appendix was slightly distended, but without prominent signs of inflammation, perforation, or extraluminal mucin. The cecal wall and terminal ileum were unremarkable. It was difficult to laparoscopically mobilize the appendix or release the intussusception. There were also concerns of enlarged mesenteric lymph nodes and the high suspicion of neoplasm. Therefore, we converted the procedure to an open surgery and a right hemicolectomy was performed.

The postoperative course was uneventful except for an elevated WBC count of 26.3 × 10^3/µL with a 92% shift to the left. A follow-up postoperative US showed no fluid collection. The abdominal drain output was unremarkable, with a minimal amount of serosanguinous fluid, and the WBC count returned to normal over several days with antibiotic therapy. The patient was discharged in good condition on the fifth postoperative day.

The right hemicolectomy specimen that was sent to the histopathological department comprised part of the terminal ileum (5 × 4 cm), cecum (8 × 5 cm), and appendix (6 × 3.3 cm). The appendiceal base was dilated and filled with mucin (3.5 × 2 cm). The remainder of the appendix contained an intraluminal mass (3 × 1.8 cm). No gross appendiceal perforations were observed [Figure 2].

Figure 2: The excised appendix (6 × 3.3 cm). The base is dilated (3 × 1.8 cm) and filled with intraluminal mucin.

At the histopathology lab, the specimen was fixed in10% formaldehyde solution, processed into formalin-fixed paraffin-embedded (FFPE) tissue, and slides of the lesions made. As per histological report, the first appendiceal (tip) mass was a low-grade well-differentiated neuroendocrine tumor that invaded the muscularis propria with < 2 mitoses per 2 mm^2 [Figure 3]. There was lympho-vascular Invasion, but no perineural invasion, and all the examined regional lymph nodes were negative for the tumor. The pathological stage was pT2NO, as per the American Joint Committee on Cancer 9th Version (AJCC-9) classification.

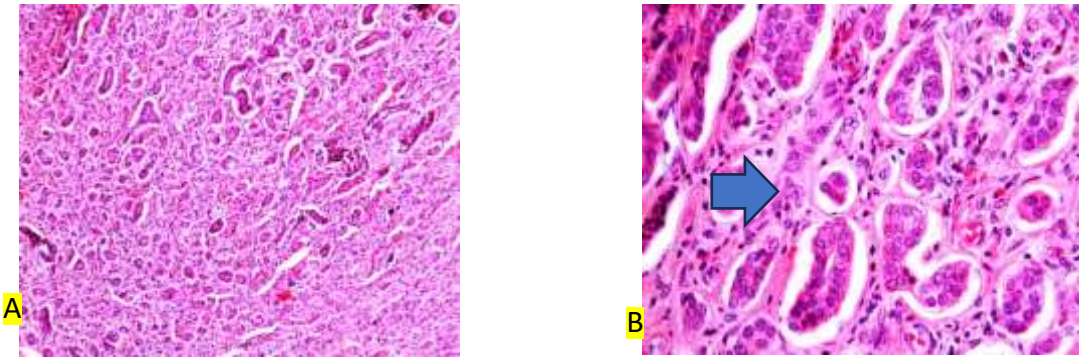

Figure 3: Hematoxylin and eosin-stained slides of the appendiceal (tip) mass. A: A low-grade well-differentiated neuroendocrine tumor is visible with the appendiceal wall infiltrated by numerous tumorous cells arranged as acini and nests.
B: At higher magnification, monotonous round nuclei with salt and pepper chromatin are visible within the tumorous cells.

The secondary appendiceal base mass was described in the pathology report as a well-differentiated low-grade mucinous neoplasm confined to the muscularis propria. Its AJCC-9 pathological stage was pTisN0.

A follow-up ultrasound performed three months later showed no free fluid in the abdomen and no signs of recurrence of tumors. After a follow-up CT scheduled for the same month, our multidisciplinary team will determine further management strategy. If the CT report is clear, the patient will be referred to an oncological specialist who may schedule five-year follow-ups.

Discussion

The extreme rarity of the present case is made clear by the fact that despite meticulous literature search, we could find only 13 previously published cases of synchronous occurrence of LAMN and ANET [Table 1].[9,11–19] The mean age of these patients was 43 years (range: 23–60 y) with no appreciable sex differences (six females and seven males). Preoperative workup had failed to detect neoplasm in any of these cases. In nine cases, the correct diagnosis was made postoperatively following an urgent appendectomy. Regarding geographic distribution, 38.5% of cases were in North America, and 23.1% were in South America. The remaining cases were distributed in Europe, Asia, and Africa.

The only treatment needed in three of the reported cases was appendectomy. In four, a right hemicolectomy was also performed. In five cases, peritoneal mucus invasion necessitated extensive surgery and chemotherapy. In one case, due to the intraoperative findings, laparoscopic appendectomy was required, which also involved the resection of a distal piece of the cecum.

Table 1: A comparative review of the current case of synchronous appendiceal neuroendocrine tumor with previous 13 cases reported in the literature.

Authors	Sex & age in years	Country	Presentation	Histological finding	Surgical treatment	Follow-up
Kreishan et al. 2024 (Present Study)	Female, 52	Jordan	Several days' pain in the right iliac fossa.	Low-grade neuroendocrine tumor at the tip of the appendix and a well-differentiated mucinous neoplasm at the base, both at early-stages.	Appendectomy, during which both tumors were identified and treated.	Follow-up ultrasound showed r recurrence. The patient recovered and is scheduled for regular 5-yea
Gupta et al. (2023)	Male, 64	United Kingdom	Acute appendicitis.	Pseudomyxoma peritonei (PMP), low-grade appendiceal mucinous neoplasm (LAMN), and a neuroendocrine tumor within the LAMN.	Cytoreductive surgery, which included right hemicolectomy and cholecystectomy.	The patient declined chemotherap months after the diagnosis du progression, which included a morphology to grade 3 mucino peritonei with signet ring cells.
Sugarbaker et al. (2020)[9]	Female, 39	USA	Right lower quadrant pain	Primary LAMN (PT3N0M1a) The second primary tumor was also a neuroendocrine tumor (PT1BN0)	Open right hemicolectomy	Two years post-surgery, an laparotomy showed mucin in hemidiaphragm, falciform ligamen paracolic sulcus. Patient under omentectomy, lesser cholecystectomy, hysterectomy, salpingo-oophorectomy. She a HIPEC with mitomycin C and intraperitoneally, and 5-fluor leucovorin for 90 min.

						No relapse noted 5 years after HIP
	Male, 32	USA	Mucin in hernia sac during left hernia repair. Later, Large mucin deposits were seen on the right hemidiaphragm, left upper quadrant, and pelvis, with a large tumor mass in the right lower quadrant of the abdomen	LAMN stage PT3N0M1a, with well-differentiated NET (Ki67 of 5%).	Visceral resections of right colon, greater and lesser omentum, and gallbladder. Peritonectomy: right subphrenic, left subphrenic, omental bursa, parietal, and pelvic. HIPEC with mitomycin C for 90 min.	Complete cytoreduction (CC-0 Chromogranin A and 5-HIAA retu range. Followed up at 3-month interv evidence of disease recurrence.
Baena-del-Valle et al. (2015)[20]	Female, 49	Colombia	Epigastric hernia	Synchronous LAMN and NEN (positive for chromogranin, synaptophysin, cytokeratin 20, and CDX-2; negative for cytokeratin 7.)	Radical CRS and HIPEC.	Discharged on day 11 without com
	Male, 42	Colombia	3 years of progressive abdominal distension ended by epigastric hernia	Synchronous LAMN and NEN (positive for chromogranin, synaptophysin, cytokeratin 20 and CDX-2; negative for cytokeratin 7).	Appendectomy and omentectomy.	After one year, the patient unde HIPEC with cytoreduction. A presented again with progress disease. Administered chemotherap cytoreduction could not be conduc
Ruiz et al. (2021) [12]	Male, 54	USA	Right lower quadrant abdominal pain It is radiating to the right inguinal area. It is associated with right flank pain, nausea, and vomiting.	A well-differentiated LAMN invading the subserosa without involving the visceral peritoneum or lymphovascular invasion, synchronous with a well-differentiated NET.	Laparoscopic appendectomy resection along with a distal segment of the cecum.	No further treatment was required.
Ekinci et al. (2021) [13]	Male, 60	Turkey	Right lower quadrant and stomach discomfort dating back two months. Moderate anemia. Slightly elevated WBC count and CEA level.	Synchronous LAMN with ANET Grade I (ki67 <1%)	Appendectomy performed. Though a right hemicolectomy was indicated, patient refused.	Disease free at six-month follow-u
Cafaro et al. (2020) [14]	Female, 35	Argentina	Continuous epigastric pain for 24 hours, migrating to the right iliac fossa. Showed leukocytosis with neutrophilia.	Well-differentiated ANET and LAMN.	Appendectomy	Follow-up with postsurgical tumor with CT and postoperative colon normal results.
Hajjar et al. (2019)	Male, 50	Canada	abdominal pain	Coexistence of ANET and LAMN	Emergency appendectomy.	The patient recovered uneventfully cancer-free after 20 months of follo

[15]					Five months later: right hemicolectomy, CRS, and HIPEC,	
Sholi et al. (2019) [16]	Female, 23	USA	Right lower quadrant pain.	LAMN and intermediate-grade ANET with extensive vascular invasion (T4Nx with 8% Ki-67).	Laparoscopic appendectomy, RHC, lymph node dissection, and right lower peritonectomy.	At 2-year follow-up, MRI showed r disease. At the last follow-up, h complaints and panic attacks resolv her management was continued at a
Tan HL [17]	Male, 52	Singapore	Two years earlier, an elevated CEA was discovered during a routine health checkup.	LAMN synchronous with a unique carcinoid center (3 mm diameter).	Laparoscopic appendicectomy	A surveillance CT scan of abdom was scheduled for six months post-
Bouhafa et al. (2015) [18]	Male, 40	Tunisia	Three months history of intermittent hypogastric pain.	Well-differentiated ANET synchronous with LAMN	Right colectomy, Adjuvant chemotherapy.	No recurrence after 10 months of r
Villa et al. (2021) [19]	Female, 31	Italy	Abdominal pain, dysuria.	Well-differentiated ANET (chromogranin-A- and synaptophysin-positive, Ki67 < 1%), synchronous with Tis LAMN.	Failed first-line conservative treatment, then laparoscopic appendectomy. Three months later, an elective laparoscopic right hemicolectomy was conducted.	After hemicolectomy, the oncologi 5-year follow-up period. No recurr year.

Note. *ANET: Appendiceal neuroendocrine tumor; CEA: Carcinoembryonic antigen; CRS: Cytoreductive surgery; CT: computed tomography; CgA: chromogranin-A; HIAA: 5-hydroxyindoleacetic acid; HIPEC: Hyperthermic intraperitoneal chemotherapy; LAMN: Low-grade appendiceal mucinous neoplasia; MRI: Magnetic resonance imaging; NEN: Appendiceal neuroendocrine neoplasm; NET: Neuroendocrine tumor; RHC: Robotic right hemicolectomy; Tis: Tumor in situ; WBC: White blood cells.*

Appendiceal neoplasms are rare clinical entities, representing around 1% of all colon and rectal cancers.[10] Approximately 5% of primary appendiceal neoplasms are incidentally discovered post emergency appendectomies.[1] Thirteen cases of true appendiceal synchronous tumors—defined as the coexistence of two histologically distinct tumors, each with different clonal origin—have been documented in the literature.[11,20,21]

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

Appendiceal neuroendocrine neoplasms (aNENs) are often discovered in individuals in their fourth and fifth decades of life.[22] Mucinous neoplasms tend to be diagnosed during the fifth and seventh decades.[23–25] ACTs may present clinically in various ways. Examples include a right lower quadrant tumor that was accidentally palpated,[20] growing abdominal distention over time,[11] or acute appendicitis symptoms.[17] In the current case, the patient presented with several days' pain in her right iliac fossa.

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 tumors, appendiceal carcinoids can be treated with straightforward appendicectomy with clear margins if the tumor 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 tumors 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 tumors.[23,24] In this case, the LAMN was entirely removed during the initial surgery, and the neuroendocrine component guided the later staging and reoperation. [24] Right hemicolectomy RHC should be considered when there are additional metastatic risk indicators such as serosal involvement, a Ki-67 proliferative index > 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 diarrhea. If no nodal or distant illness is present, NETs up to 2 cm in size seldom metastasize and have a five-year survival rate of > 90%.[28] For tumors > 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. In our patient, the tumor was 3.4 cm and there was lymph node enlargement in addition to the presence of intussusception. This prevented us from performing laparoscopic appendectomy, leading us to opt for a right hemicolectomy. Only a few carefully reported cases of the coexistence of mucinous and neuroendocrine appendiceal tumors have been published.[17] The lesions may manifest as 'collision tumors,' where each tumor is distinct, with clear boundaries and no mixing of cell types, or as 'combined tumors,' where both cell types are intermixed within the same tumor.[29]

The 'onion-skin' appearance of a 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 calcification. Due to their small size, these lesions are typically challenging to visualize radiologically and are difficult to distinguish from appendicitis.[19]

In metastases from synchronous tumors, only one of the component tumor types will be present, whereas in metastases from composite tumors, both component neoplasms will be present.[30] In our case, no metastases were found. However, Sholi et al.[16] describes finding at the time of hemicolectomy, metastases from the neuroendocrine component in four of the 26 lymph nodes.

Research on the treatment of peritoneal carcinomatosis (PC) associated with NET remains limited. Surgical cytoreduction alone has been recommended as a viable alternative to HIPEC to avoid the unpleasantness of chemotherapy. The optimal therapeutic strategy in this circumstance may not yet be a combination of cytoreductive surgery (CRS) and HIPEC, which calls for more research.[31]

Aggressive CRS and HIPEC continue to be the cornerstones of a curative surgical approach for combined mucinous and neuroendocrine appendiceal tumors with peritoneal dissemination. HIPEC has enormous therapeutic benefit for patients with pseudomyxoma peritonei (PMP) component. However, the need and effectiveness of this combined procedure would depend on several non-modifiable factors, such as the grade of the mucinous neoplasm and associated peritoneal cancer index (PCI).[32–34] As our patient did not have PMP, HIPEC was not indicated for her.

The laparoscopic method is considered a safe and practical choice for some appendiceal tumors, as shown in the case described by Baena-del-Valle et al.[20] and there are comparable findings in the literature for both appendiceal carcinoids and appendiceal mucinous neoplasms.[24]

It would be ideal if a diagnosis of both primary neuroendocrine tumor and primary mucinous appendiceal tumor is available before surgery. In practice, however, cross-sectional imaging often reveals the appendix mucocele but misses the much smaller neuroendocrine tumor, which tends to be revealed in the final pathological analysis. Low-grade appendiceal neoplasms have a low likelihood of lymph node metastasis.[35] Lymph node metastasis is more likely to occur in neuroendocrine tumors of the appendix that are > 20 mm and have lymphovascular invasion or tumors that invade the mesoappendix. Therefore, right hemicolectomy has been suggested and is frequently performed, as had previously been done in our patient.[36] However, no survival advantage with right colon resection has been reported.[36] Additionally, the search for better survival with right hemicolectomy was unsuccessful in two recent cases.[37,38] A 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 tumor forms should be subjected to long-term surveillance, and cross-sectional imaging at regular intervals is recommended for both LAMN[23] and aNEN.[28] Generally, 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, assessments of carcinoembryonic antigen (CEA) and chromogranin-A (CgA) levels 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 present case, immuno-histochemical analysis was not possible due to a lack of resources.

Where a metastasis is found, performing a second-step surgery via laparoscopy in the event of localized presentation is considered safe and is likely to lead to a quicker postoperative recovery. It is difficult to establish a standard of care and follow-up due to a lack of clear clinical patterns and the extreme rarity of cases. Although a key indicator at this point appears to be whether LAMN has spread, therapy should be customized for each patient.[19]

Conclusion

This case highlights the complexity of managing multiple comorbid conditions, including obesity, T2DM, and chronic liver disease, in a patient with comorbid conditions. The multifaceted management required underscores the importance of a multidisciplinary approach, personalized care, and adherence to treatment guidelines for optimal outcomes. it becomes evident that several previous cases reported similar complexities in the management of patients with overlapping cardiometabolic disorders, although none presented with the same combination of factors. This underscores the growing need for targeted research and interventions in this population.

Disclosure

This study was exempt from institutional ethical approval, as the data used in this report can be accessed with the explicit consent obtained from the patient. The authors declare no conflicts of interest. Informed consent was obtained from the patient for publishing this case.

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