



Case Report

Multidisciplinary Management of a Mixed Neuroendocrine and Nonneuroendocrine Neoplasm of the Appendix: A Case Report

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Abstract

Introduction: Mixed neuroendocrine and nonneuroendocrine neoplasms (MiNENs) are the rarest neuroendocrine appendiceal neoplasms, for which no standard treatment guidelines are available. Here, we present a case report of a pelvic MiNEN.

Case description: A 41-year-old woman underwent clinical evaluation to determine the causes of her infertility. Medical tests revealed a massive cystic mass in the left pelvis and a small fluid-filled nodule originating from the appendix. Fertility-sparing surgery evidenced an appendiceal MiNEN, with a low-grade neuroendocrine component in the context of a low-grade mucinous neoplasm (LAMN). Pathological stage was pT4 N0 M1 (according to the AJCC VIII ed.), as the tumour reached the visceral peritoneum, showing no metastatic lymph node involvement. A single metastatic nodule expressing neuroendocrine features was found in the omentum. Instrumental re-evaluation performed after surgery revealed two additional abdominal spots, suspicious for metastases. After multidisciplinary discussion, a second surgery was performed, followed by intraperitoneal intraoperative hyperthermia (HIPEC). Three months later, CT scan revealed a neoformation between the stomach and the pancreas tail, suspicious for disease progression. Surgical biopsy was deemed unfeasible. Since LAMN was the main component of the pelvic mass previously removed, the patient underwent oral fluoropyrimidine-based chemotherapy. Simultaneously, patient was treated with somatostatin analogues (SAs), after assessing a moderate 68Ga-PET scan positivity. The patient is currently on treatment, alive and progression-free after 28 months.

Conclusion: Our case highlights the importance of multidisciplinary approach and literature review to guarantee the most appropriate management of rare diseases such MiNENs, underlining the unmet need of common guidelines.

Keywords: MiNENs; Multidisciplinary; HIPEC; Neuroendocrine; LAMN, NET.

Introduction

Appendiceal neuroendocrine tumours are typically discovered incidentally in 0.3-0.9% of appendectomy specimens and are usually removed for acute appendicitis. These tumours are classified based on pathological features as well-differentiated neuroendocrine tumours (NETs), poorly differentiated neuroendocrine carcinomas (NECs) and mixed neuroendocrine and nonneuroendocrine neoplasms (MiNENs). The latter typically have a nonneuroendocrine mucinous component, which distinguishes them from MANEC (mixed adenoneuroendocrine carcinoma), in which the nonneuroendocrine component is typically poorly differentiated [1]. Since MiNENs are the rarest type of neuroendocrine appendiceal neoplasm, there are no standard guidelines for their diagnosis and treatment, as well as no clear surgical recommendations or universally recognized therapeutic regimens [2]. Therefore, expert and multidisciplinary management is strongly recommended to deal with the complexities of these ultrarare disease. Here, we present a case report of a patient with pelvic MiNEN who underwent surgical resection and treatment via a polypharmacological approach. The administered treatments included HIPEC (intraperitoneal intraoperative hyperthermia), oral chemotherapy and somatostatin analogues. This report aims to provide a comprehensive description of the multidisciplinary management and outcomes of this patient.

Case Description

In October 2020, a 41-year-old woman who desired pregnancy underwent medical investigation and imaging assessments to determine the cause of her infertility. An ultrasound (US) scan revealed a massive lesion in the left ovary that was suspicious for malignancy. As a result, contrast-enhanced pelvic magnetic resonance imaging (MRI) was conducted (Figures 1,2), revealing a cystic mass in the left pelvis, measuring 92x71x112 mm, as well as a smaller fluid-filled mass originating from the appendix. No significant symptoms were reported, except for occasional self-limiting episodes of diarrhea in the previous 30 days, which did not require any medication. Subsequently, the patient was referred for surgical consultation. As she expressed a firm desire for pregnancy, fertility-sparing surgery was offered, involving left adnexectomy, omentectomy and lymphadenectomy of the pelvis, obturator and lumbosacral nodes. Additional right ovary biopsy, multiple peritoneal biopsies, peritoneal washing, appendicectomy and resection of the appendicular neof ormation were performed. The surgical procedure took place in December 2020. Histological examination revealed a MiNEN of the appendix, with a low-grade neuroendocrine component (G1 NET) in combination with a low-grade appendiceal mucinous neoplasm (LAMN). The pathological

stage was pT4 N0 M1 (according to the AJCC VIII ed.), as the tumor reached the visceral peritoneum, and none of the nineteen resected lymph nodes showed metastatic invasion. A single distant metastasis was histologically reported as a 2 mm nodule of the omentum with neuroendocrine characteristics. Tumour epithelial (CEA, CA19.9, CA50, CA15.3, CA125) and neuroendocrine (NSE, chromogranin) marker levels were measured in serum samples. NSE levels were slightly above the upper limit of the reference interval (19.3 ng/mL; upper limit of the reference interval: 18.3 ng/mL), whereas all the remaining markers were within the limits. Imaging reassessment by contrast-enhanced CT scan was performed after surgery and revealed two additional lesions suspicious for metastases. One was located in the spleen and had a polylobate appearance and irregular margins (Figure 3), and the other one was located between the right iliac vessels and ipsilateral psoas muscle and measured 21x15 mm (Figure 4). The case was discussed by our interinstitutional multidisciplinary neuroendocrine tumour board to evaluate the best management strategy. The board recommended surgical resection of the two suspicious nodules, followed by intraperitoneal intraoperative hyperthermia (HIPEC). Therefore, in September 2021, the patient underwent exploratory laparotomy, right adnexectomy, splenectomy, omentectomy, multiple peritoneal biopsies and resection of the falciform ligament. Histologic examination did not show presence of disease on the resection margins and confirmed the dual nature of the neoplasm, revealing LAMN infiltration of the spleen and a neuroendocrine origin of the iliac lesion. Mitomycin C was intraperitoneally administered (58.8 mg) as part of the HIPEC procedure. Since the neoplasm has two distinct biological components, namely, mucinous and neuroendocrine characteristics, HIPEC was tailored to the main component of the disease in-loco (LAMN). After 3 months, clinical and imaging re-evaluations were performed, revealing an exophytic neof ormation (31x30 mm) between the stomach and the tail of the pancreas (Figure 5). In a subsequent 18FDG-PET scan, no pathological uptake of the radiotracer was detected, whereas a 68GA-edotreotide-PET scan revealed slight uptake. NSE levels were once again slightly above the upper limit of the reference interval (20.1 ng/mL; upper limit of the reference interval: 18.3 ng/mL). As disease relapse was suspected, the case was discussed again at the Neuroendocrine Tumour Board, which proposed surgical biopsy of the newly found lesion to determine its origin and offer the patient tailored systemic treatment. Nevertheless, surgical biopsy was deemed unfeasible due to its location and size. Therefore, systemic treatment was selected based on the predominant histologic component of the main lesion after external review of the examination that confirmed the initial diagnosis. Since LAMN was the main component of the pelvic mass removed first, the patient was prescribed fluoropyrimidine-based chemotherapy, but she refused intravenous administration and requested oral treatment. Therefore, treatment with 1500 mg

of capecitabine per day 2 weeks on/1 week off was started in September 2021. Additionally, given the positive results shown by 68GA-edotreotide-PET scan, the patient was prescribed a long-acting somatostatin analogue (SSA-LAR) by intramuscular administration (30 mg every 28 days). Imaging re-evaluations were performed every 4 months during follow-up. The last whole-body contrast-enhanced CT scan was performed in January 2024 (Figure 6), showing dimensional shrinkage of the known lesion (24x19 mm vs 31x30 mm). Within twenty-eight months of treatment with a combination of capecitabine and SSA-LAR, no new lesions were found, and no dimensional increase in the known lesion was observed. The patient remained asymptomatic and in excellent clinical condition, although her desire for a pregnancy could not be fulfilled.

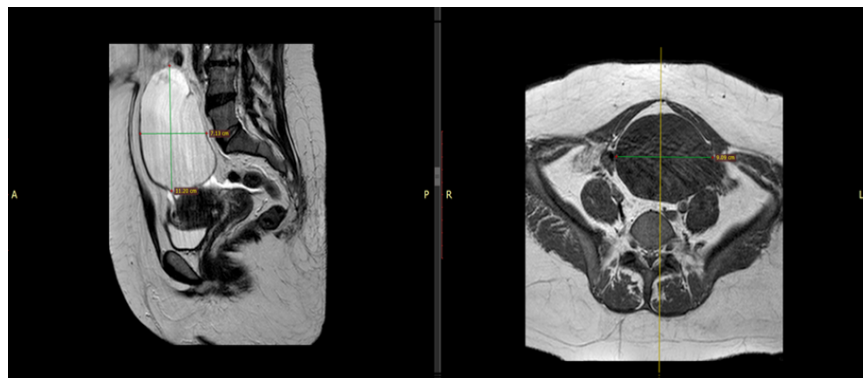


Figure 1: Contrast-enhanced MRI evidences a cystic mass in the left pelvis, measuring 92x71x112 mm.

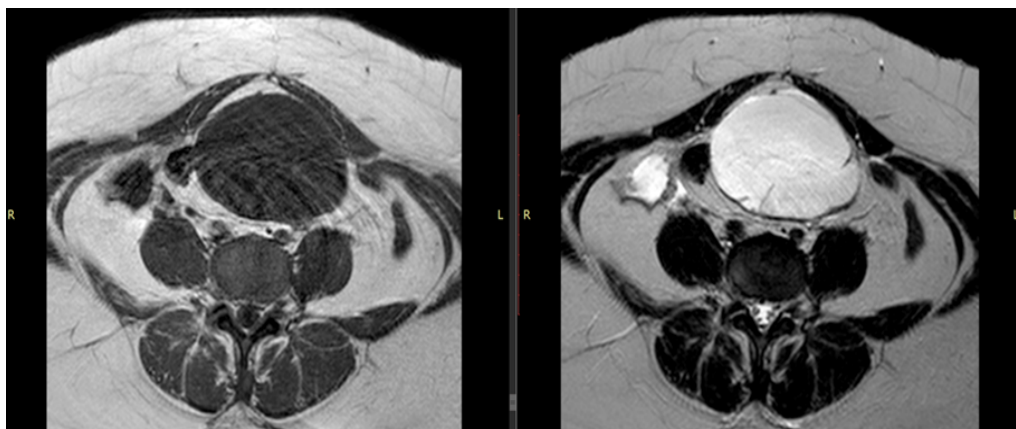


Figure 2: Contrast-enhanced MRI evidences a suspicious fluid-filled lesion originating from the appendix.

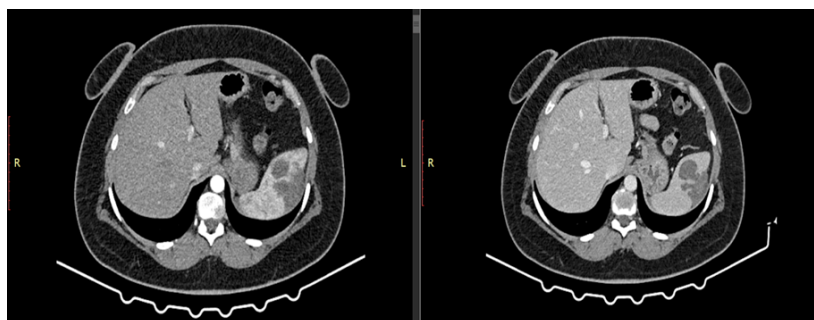


Figure 3: Contrast-enhanced CT scan shows a suspicious lesion in the spleen, with polylobate appearance and irregular margins.

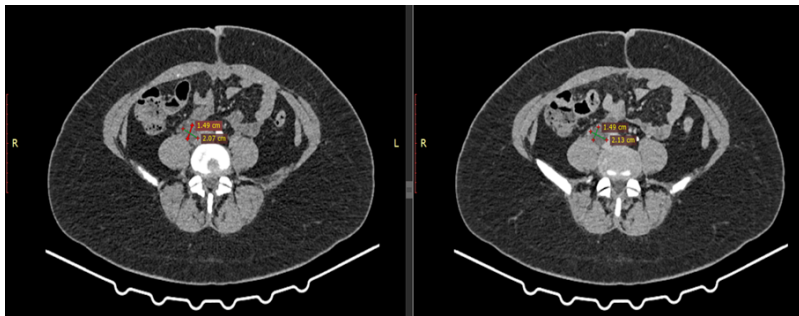


Figure 4: Contrast-enhanced CT-scan shows a suspicious lesion localized between the right iliac vessels and ipsilateral psoas muscle, measuring 21x15 mm.

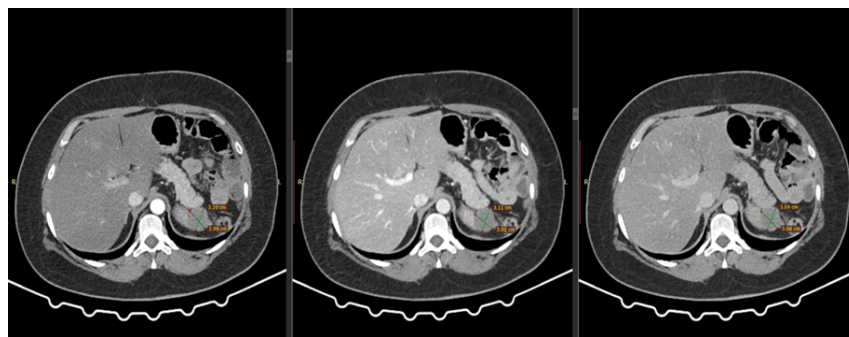


Figure 5: Contrast-enhanced CT scan, performed 3 months after pelvic surgery and HIPEC, shows an exophytic neoplasm measuring 31x30 mm between the stomach and the tail of pancreas, suspicious for disease relapse.

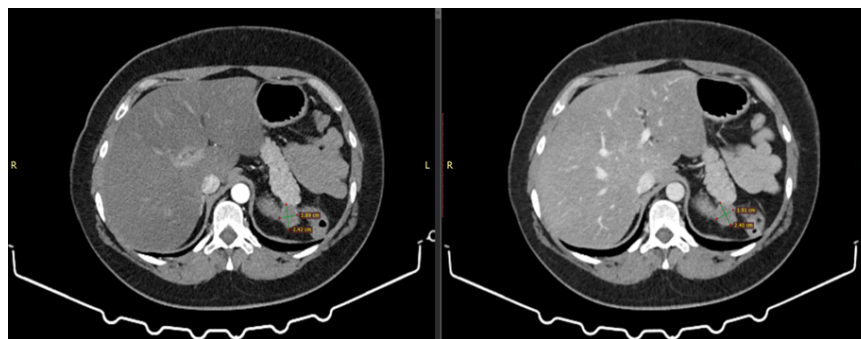


Figure 6: The latest whole-body contrast-enhanced CT scan performed by the patient, showing disease control and dimensional reduction of the known site of disease (24x19 vs 31x30 mm) within 2 years of treatment combining capecitabine and SSA-LAR.

Discussion

Appendiceal MiNENs are complex histopathological entities often discovered incidentally during appendectomies performed in the context of acute appendicitis. A recent study by Song and Yang [3] analysed information collected from a 17-year program database (2000-2017) to understand the epidemiological and clinical evolution of this disease. Despite their rarity, the incidence of MiNENs is rapidly increasing, highlighting the need to perform clinical and translational studies to better describe the clinical behaviour of these malignancies, identify the molecular drivers of tumour growth, and ultimately define effective treatment strategies. Similarly, Zheng et al. [4] evaluated data from a 12-year database (2004-2016) to extract information on the outcomes and prognostic factors of MiNENs, confirming their aggressive behaviour and poor prognosis. These data were consistent with those reported by Shi et al. [5], who retrospectively compared the characteristics and survival between patients affected by GEP-NEC or MiNEN. The authors reported a worse prognosis in the patients with MiNEN compared to those affected by pure small intestine and appendiceal NEC, whereas no significant survival difference between MiNEN and NEC was found in other parts of the digestive system. Since standard treatment guidelines are not yet available, in recent years, the combination of surgical and systemic treatments has been considered a potential strategy for managing these malignancies. Indeed, the combination of cytoreductive surgery and HIPEC has been largely used to treat peritoneal dissemination of the primary disease. In 2020, Garach et al. [6] compared the effects of this combination in both mucinous and nonmucinous appendiceal neoplasms and reported that mucinous features lead to a better treatment response and a more favourable prognosis. In the same year, Sluiter et al. [7] performed a meta-analysis to assess whether combining HIPEC with cytoreductive surgery in peritoneally metastatic goblet cell carcinomas, which are histologically comparable to MiNENs and MANEC, could lead to better outcomes than surgery alone. The results showed an improved median overall survival (OS) in the surgery + HIPEC group compared to the surgery alone group. These data support our decision in the management of this case.

Conclusion

Given the rarity and poor prognosis of MiNENs, guidelines for the diagnosis and treatment of these diseases are needed. Moreover, due to their complex biology, treatment chosen for one component may not be appropriate for controlling the evolution of other tumour types. This case highlights the importance of a multidisciplinary approach, literature review and discussion based on clinical expertise to guarantee the selection of the best management strategies. Since there are no standard available guidelines, case reports are very useful for overcoming the lack of clinical data and supporting clinical decisions.

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Ethics statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Clinical data were collected within the study approved from the Ethics Committee of the University of Naples Federico II (approval no. 186/2023). The patient provided written informed consent for the use of all the reported data, including accompanying images. Anonymity was assured.

Conflict of interest: The authors have no conflict of interest to declare.

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