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Case report

Treatment and management of 1,5 cm diameter appendiceal neuroendocrine tumors: A gray zone

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Abstract. Appendiceal neuroendocrine tumours are rare and often diagnosed as incidentalomas after an appendectomy for acute appendicitis. Appendiceal tumours can cause appendiceal torsion, eventually resulting in acute appendicitis. In the international guidelines (NANTS and ENETS), tumour size is the main prognostic factor and is associated with os and lymph node relapse (LNM). Right hemicolectomy for tumours >2 cm in diameter and simple appendicectomy for those <2 cm, and linfadenectomy are generally recommended. Management of tumors between 1 and 2 cm, is still a matter of debate. With this case report we try to deepen this debate, about which clinical and surgical choice to undertake.

Key words: appendiceal neuroendocrine tumors, appendectomy, surgical treatment

Introduction

More than 80% of appendiceal neuroendocrine tumors (aNETs) are unexpectedly diagnosed in appendectomy specimens and are found in approximately 0.5% to 1% of all appendectomies (1, 2). These tumors have several features that differ from other gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Approximately 80% of aNETs have a maximum diameter less than 1 cm, 15% between 1,5 and 2 cm and only 5% a diameter greater than 2 cm (3). aNETS usually run an indolent clinical course and are more common in the third-forth decade of life with a predilection for female genre (4-7). The last finding probably reflects the increased use of explorative laparoscopy with concomitant appendectomy performed among women as a diagnostic tool for lower abdominal pain (1, 3). Sporadically aNETS have aggressive behavior with early liver and mesenteric lymph node metastasis (LNM).(8) Unlike mixed-type goblet cells or adenocarcinoids, pure appendiceal carcinoids are associated with a highly favourable prognosis, with five-year survival approximating 90%. Such prolonged survival depends on treatment by adequate surgical resection – a topic which is a matter of literature debate (1-3). Management is based on surgical resection. However, controversy arises when deciding whether an appendectomy alone is sufficient or whether the patient should undergo a completion right hemicolectomy (CRH) after appendectomy, as it is recommended for > 2 cm tumours. Indications for tumours between 1-2 cm are where the controversy lies (5, 8). Current guidelines (NANTS, ENETS) recommend risk factors beyond tumor size: mesoappendix invasion, positive margins, vascular and lymph node involvement, and tumor grade. However, these recommendations are not supported by strong evidence (3).

Case report

We are reporting a 43-year-old Caucasian female admitted with a clinical picture of acute appendicitis. In her past medical history: HBV infection, left

safenectomy, and 4 c-sections. She was transferred to ER, with abdominal pain in the right iliac fossa. Blood tests on admission showed WBC: 8 x 10^3 u/L, PCR 44 mg/L. Abdominal-CT scan showed ptotic caecum and a distended appendix with a hyperdense appearance, pericecal fat vascular congestion and nearby lymph nodes <1 cm (Figure 1). An Abdomen-MRI scan showed a solid thickening of the appendix with a fusiform shape and homogeneous contrast enhancement. The patient underwent antibiotic therapy and an elective laparoscopic appendicectomy was planned. During the procedure, there were no signs of peritoneal carcinomatosis or ascites. An ultrasound energy device achieved successful appendicectomy with total mesoappendix excision (Figures 2, 3). Histological testing revealed a well-differentiated appendicular

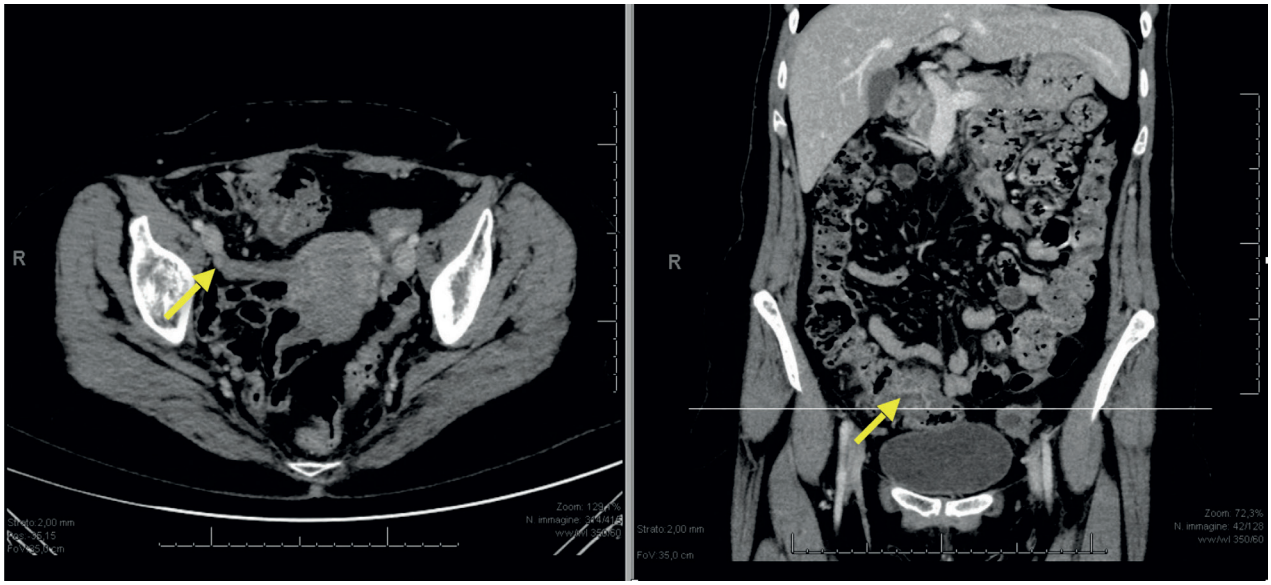

Figure 1. Abdominal CT-scan that describes ptosic caecum and distended appendix. As indicated by the yellow arrows

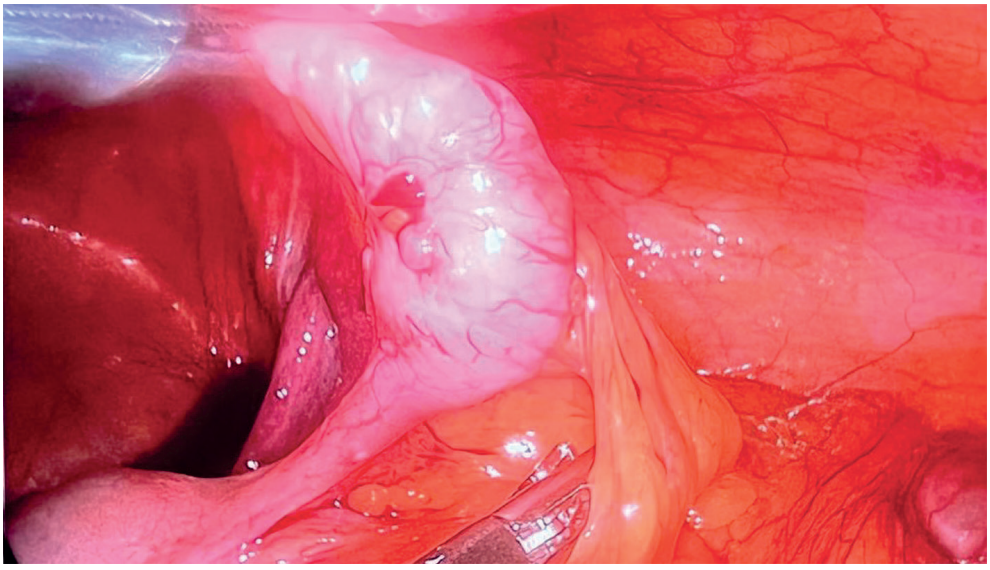

Figure 2. Intraoperatory image of the appendix during videolaparoscopy

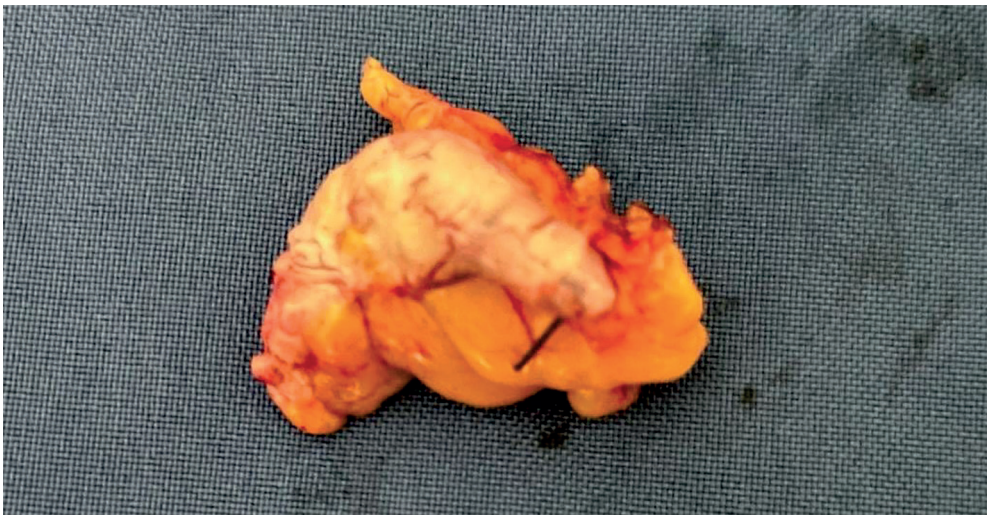

Figure 3. Resected appendix with mesoappendix. The longitudinal and transverse diameters were respectively 6 and 1,5 cm.

NET (G1) infiltrating the entire wall (pT3). The patient was discharged on day 2.

Discussion

Current guidelines (9-11) propose simple appendectomy as adequate and curative for the treatment of appendiceal NETs <1 cm. Right hemicolectomy (within 3 months from the appendicectomy) should be reserved for patients in whom at least one of the following criteria is present:

- tumor size > 2 cm
- location of the tumor at the base of the appendix
- infiltration of the cecum
- positive surgical resection margins
- appendiceal mesentery invasion
- metastatically infiltrated mesoappendiceal lymph node
- presence of undifferentiated or low differentiated cells or the presence of goblet cells.

While for tumors 1-2 cm, a simple appendectomy followed by periodic postoperative follow-up for 5 years is recommended (2) and CRH should be considered when there are affected margins in tumors located at the base, when there is invasion of the mesoappendix that measures greater than 3 mm, or when there are other risk factors. However, several studies have challenged these recommendations, mainly in tumors smaller than 2 cm, arguing that CRH offers no benefits in terms of survival in smaller tumors (12, 13). Furthermore a colectomy should be avoided owing to a poorer quality of life for these patients. A decision regarding a hemicolectomy in an aNET between 1 and 2 cm should be discussed by a multidisciplinary oncological meeting. The opinions of pathologists, surgeons, gastroenterologists, endocrinologists, radiologists, medical oncologists, and nuclear medicine specialists should be taken into consideration before making a recommendation. Long-term issues related to a hemicolectomy should be discussed with the patient, particularly with younger ones (8). The rarity of aNETS, paucity of data, and ambiguity of the guidelines may be contributing to the variability of practice. This casts some doubt on the need for aggressive surgical resection of appendiceal carcinoids and calls for a reassessment of the treatment guidelines (1). The staging of aNETs is mainly based on tumor size and serosal or mesoappendix invasion. The pathology report should also include pTNM staging (according to either American Joint Committee on Cancer classification, ENETS classification, or both), margin status,

and vascular and lymphatic vessel involvement (8). Mesoappendix invasion is usually associated with a higher rate of vascular and lymphatic vessel involvement (8). In current practice the mesoappendix is not systematically resected during a laparoscopic appendectomy (simple or classic appendectomy): once the appendix has been isolated,dividing the mesoappendix from the tip to the base , the meso is left in place tied or coagulated. From the technical point of view in the case of aNETS, since mesoappendix invasion is an important prognostic factor, it should be preferred after an accurate examination performing an appendicectomy with total mesoappendix resection rather than using the simple appendicectomy technique. Contrary to the classic mesoappendix dissection, some advanced sealing devices can be useful to ligate the appendix meso from the appendicular artery root securely, and mesoappendix section is safely performed (14, 15). This technique would give the possibility for a careful histopathological evaluation of the surgical specimen providing crucial information for determining management (8).

Conclusions

Decisions related to the indication of an appendicectomy rather than a completion right hemicolectomy (CRH) resection for T1b aNETS should be made by a multidisciplinary oncological meeting to offer each patient a better treatment approach. The factors that should be discussed include:

- tumor size
- mesoappendix invasion
- positive margins
- vascular and lymphatic vessel involvement
- tumor grade

In case of appendectomy, it should be preferred to perform a total mesoappendix excision and not a simple appendectomy, which leaves in place the mesoappendix and prevents local staging. Prospective studies regarding optimal treatment for aNETs between 1 and 2 cm in diameter are unmet needs in the NET field and should be addressed in the future.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethics Statement: The patient gave informed written consent agreement before inclusion to the study.

Authors Contribution: FM conceived and wrote the manuscript; EV and RC supervised and corrected the project; EV corrected the formal English; FD reviewed the pertinent literature; AA and AR analyzed and validated the data.

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