Primary Neuroendocrine Carcinoma of the Appendix: A Case Report and Review of the Literature

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Abstract. Aim: We report on a rare case of appendiceal primary neuroendocrine carcinoma (NEC) and discuss three cases previously described. Case Report: A 58-year-old woman presented with acute abdominal pain and a low-grade fever. She was diagnosed with acute appendicitis and underwent laparoscopic appendectomy. Pathological examination of the resected specimen revealed NEC. Immunohistochemical analyses were positive for synaptophysin, chromogranin, and CD-56. The tumour was high grade and the Ki-67 index was >20%. Primary NEC of the appendix is extremely rare. To our knowledge, this is the first case report of an appendiceal NEC that meets the 2010 diagnostic criteria of the World Health Organization. Conclusion: Due to its non-specific clinical presentation, NEC is often misdiagnosed as appendicitis; however, it can advance rapidly and carries a very poor prognosis, despite chemotherapy. In the future, a treatment protocol for immunohistochemical analyses should be established to improve the survival rate.

Neuroendocrine cells exist throughout the human body (1). Neuroendocrine tumours (NETs) are a heterogeneous group of neoplasms composed of cells containing dense-core neuroendocrine secretory granules in the cytoplasm (2). The World Health Organization (WHO) grouped high-grade NETs with neuroendocrine carcinoma (NEC) in the 2010 classification of the NETs (3). The gastrointestinal tract has the largest proportion of neuroendocrine cells (1), i.e. approximately two-thirds of NETs; one-quarter of these cells are present in the lungs and the remainder, in other endocrine tissues (4, 5). However, NETs account for only 2% of all gastrointestinal tract malignancies (2). The small intestine is most commonly affected, followed by the rectum and then the appendix (6). Here, we describe a very rare case of NEC in the appendix without any metastases and present a review of the literature. To our knowledge, this is the first case reported which meets the 2010 WHO diagnostic criteria.

Case Report

A 58-year-old woman was referred to our hospital with acute severe pain in the right lower quadrant of the abdomen and a low-grade fever. Computed-tomography (CT) of the abdomen showed an enlarged appendix and thickening of the appendiceal wall, with fluid accumulation, suggestive of an abscess (Figure 1). She was clinically diagnosed with acute appendicitis and underwent laparoscopic appendectomy. During the operation, the ileocecal region was noted to be severely inflamed and thickly covered with omentum. The appendix was noticeably enlarged (Figure 2). The patient had an uneventful postoperative course and was discharged from the hospital on postoperative day 7. Pathological examination of the resected specimen showed a poorly-differentiated adenocarcinoma intermingled with signet ring-like cancer cells mainly located in the muscle layer. A few tumour cells were present in the mucosa. On the basis of these results, metastasis from an occult cancer was strongly suspected. Laboratory tests, including those for carcinoembryonic antigen (CEA) and CA19-9, were normal. Whole-body 18F-fluorodeoxyglucose positron-emission tomography was performed to identify a primary focus, but no abnormal accumulations were detected. Colonoscopy did not yield any findings either. As some cancer cells were observed in the resection facer, ileocecal resection with lymphadenectomy was performed after a few weeks. The patient was discharged on postoperative day 13 without any complications. Immunohistochemical analysis of the specimen revealed neuroendocrine neoplasia with positive expression of synaptophysin, chromogranin, and CD-56. It was a high-resolution image. This article is freely accessible online.

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grade neoplasia, in terms of mitotic count, with a low degree of differentiation, and the Ki-67 index was 51.8%. According to the WHO classification and European Neuroendocrine Tumor Society (ENETS) (7), the final diagnosis was a primary NEC of the appendix (stage IIa; T2, ly0, v0, N0, M0 according to TNM classification by ENETS). Although some studies recommend adjuvant or intraperitoneal chemotherapy to prolong survival (8-10), the patient declined chemotherapy. The patient is currently well and has had no tumour recurrence for five months since the first surgery.

Discussion

Neuroendocrine cells are distributed throughout the body and can be found in the gastrointestinal tract, pancreas, lung, thyroid, adrenal gland, etc. The gastrointestinal tract has the highest proportion of neuroendocrine cells. NETs in the gastrointestinal tract occur predominantly in the small intestine (44.7%), followed by the rectum (19.6%), appendix (16.7%), colon (10.6%), and stomach (7.2%) (6). According to a Swedish study, the incidence of all gastrointestinal NETs is approximately 2.0 per 100,000 in men and 2.4 per 100,000 in women (11). Moreover, the annual incidence of NETs of the appendix is 0.15-0.6 per 100,000 persons according to the Surveillance Epidemiology and End Results (SEER) database. The incidence of appendectomies performed for any indication is approximately 2.0 per 100,000 in men and 2.4 per 100,000 in women (11). Moreover, the annual incidence of NETs of the appendix is 0.15-0.6 per 100,000 persons according to the Surveillance Epidemiology and End Results (SEER) database. The incidence of appendectomies performed for any indication is approximately 3-9 per 1,000 persons, and thus, this is a relatively common surgery (7). However, NEC of the colon and rectum are very rare (1). In particular, NEC accounts for 0.1-3.9% of all colorectal malignancies (1, 10). Moreover, it is extremely rare in the appendix. A literature review in PubMed revealed only three similar case reports, including mixed adenoneuroendocrine carcinoma (MANEC). A few case reports have described NETs of the appendix, but they were almost all cases of carcinoid tumours without any Ki-67 examination. Therefore, to our knowledge, our case is the first to present NEC of the appendix meeting the 2010 WHO diagnostic criteria for NETs and NEC (Table I) (3, 12-14).

It can be difficult to diagnose NEC preoperatively. On haematoxylin-eosin staining, NEC can be quite similar to poorly-differentiated adenocarcinoma (15) and hence requires further immunohistochemical analyses, such as those for synaptophysin, chromogranin, and CD-56. Although an early diagnosis is important to ensure appropriate management, it can be exceedingly difficult since the clinical presentation mimics acute appendicitis with right lower-quadrant abdominal pain and the lack of specific symptoms. In fact, most cases have been diagnosed as acute appendicitis, including that of our patient, and following pathological examination, patients have required additional operations such as ileocecal resection or right hemicolecotomy.

NET is a low-grade malignancy and in general, no additional therapy is required (16). Although the prognosis of appendiceal NETs is generally excellent, NEC or MANEC have very poor outcomes and can progress very rapidly (7). The lymph node metastasis rate is 58%, while the hepatic metastasis rate is 39–66%; the one-year survival rate was 37-46% (1,17,18). Its biological characterization is similar to that of pulmonary small cell carcinoma, and some reports recommend adjuvant chemotherapy with cisplatin+irinotecan (19, 20). Other studies suggest cytoreductive surgery with adjuvant or intraperitoneal chemotherapy (8-10). In our case, the patient declined chemotherapy following the second operation. Due to its high-grade nature, NEC has an extremely poor prognosis regardless of therapy, and the most important prognostic predictors are disease stage, tumour size, and nodal status (7). Therefore, malignancy should always be excluded in any appendectomy, and careful follow-up should be arranged in case any additional operations or therapies are required.

In conclusion, NEC of the appendix is an extremely rare and aggressive disease. In many cases, it may be erroneously diagnosed as acute appendicitis. When encountering acute
appendicitis, malignancy and NETs should be considered in the differential diagnosis. If any unusual findings are noted perioperatively, pathological examination should be conducted thoroughly and potentially include immunohistochemical analyses, such as those for synaptophysin, chromogranin, and CD-56. As more cases of NEC are diagnosed, we hope that a treatment protocol will be established to improve the survival rate of such patients.

Figure 2. Laparoscopic appendectomy. a: The ileocecal region is severely inflamed and covered with omentum. b: After dissecting the mesoappendix, the appendix was found to be enlarged. c: Handling of the roots of the appendix. d: Removal of the resected appendix.

Figure 3. a: Macroscopic imaging of the appendix. b: Poorly-differentiated neuroendocrine carcinoma (hematoxylin-eosin) (x40). c: Positive synaptophysin expression (x20). d: Positive chromogranin expression (x20). e: Positive CD-56 expression (x20). f: A high cell-proliferation index (Ki-67) (x20).
Table I. Literature review of primary NEC and MANEC of the appendix.

<table>
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<th>Year</th>
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<th>Operation</th>
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<th>Language</th>
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<td>2006</td>
<td>70</td>
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<td>Malignant cecal polyp</td>
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<td>2</td>
<td>Couvelard (13)</td>
<td>FR</td>
<td>2010</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>MANEC?</td>
<td>-</td>
<td>French</td>
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<td>Tanaka et al. (14)</td>
<td>JP</td>
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<td>53</td>
<td>M</td>
<td>Ileus (post operation)</td>
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<td>MANEC</td>
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<td>Our case</td>
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<td>51.8%</td>
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References


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