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Primary Neuroendocrine Carcinoma of the Appendix: A Case Report

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List of Abbreviations:

NEC: Neuroendocrine carcinoma; WHO: World Health Organization; NETs: Neuroendocrine Tumors; MANEC: Mixed Adenoneuroendocrine Carcinoma; CT: Computed tomography; NEN: Neuroendocrine Neoplasm; ENETS: European Neuroendocrine Tumor Society; UICC: Union for International Cancer Control; AJCC: American Joint Committee on Cancer; SEER: Surveillance Epidemiology and End Results; GCC: Goblet cell carcinoid

1. Abstract

1.1. Background: Neuroendocrine Carcinoma (NEC) of the appendix is extremely rare and its clinical characteristics and treatment strategy have not been well established. Here we present a case of appendiceal NEC with very rapid progression, in which complete remission was achieved by radical surgery followed by systemic chemotherapy.

1.2. Case presentation: A 50-year-old woman presented with right lower quadrant abdominal pain and low-grade fever. She underwent laparoscopic appendectomy based on the diagnosis of acute appendicitis with mucinous cystadenoma of the appendix. The resected specimen showed a 2.5-cm tumor at the base of the appendix. Immunohistochemistry revealed diffuse staining for synaptophysin and a Ki-67 labeling index of >90%. The case was diagnosed as NEC according to the 2010 World Health Organization classification. One month after appendectomy, we performed right hemicolectomy with extended lymph node dissection for metastatic lymph nodes around the ileocolic and superior mesenteric vessels. Pathological examination revealed metastases in 27 of 42 dissected lymph nodes, including lymph nodes around the root of the superior mesenteric artery and superior mesenteric vein. One month after right hemicolectomy, metastasis to Virchow's lymph node was detected. After six cycles of chemotherapy with etoposide and cisplatin, complete remission was achieved and was maintained at the 3-year follow-up after initial surgery.

1.3. Conclusion: Right hemicolectomy with extended lymph node dissection followed by chemotherapy with etoposide and cisplatin may be a viable treatment strategy for appendiceal NEC.

2. Introduction

The World Health Organization (WHO) diagnostic criteria for neuroendocrine tumors (NETs) and neuroendocrine carcinoma (NEC) of the gastrointestinal tract were published in 2010 [1]. NEC is defined as a small cell or large cell carcinoma with a mitotic rate of more than 20 per 10 high power fields and/or a Ki-67 labeling index of >20%. Thus, all poorly differentiated neoplasms are classified as NEC, which constitutes a separate group from NET given its invariable high-grade malignant potential. NEC is characterized by diffuse immunostaining for synaptophysin, and only infrequent and sparse immunostaining for chromogranin A [1, 2]. Appendiceal NEC, which is distinct from mixed adenoneuroendocrine carcinoma (MANEC), is extremely rare, and its clinical characteristics are not well established. A literature review in PubMed revealed only two case reports on appendiceal NEC [3, 4]. In this report, we describe a case of

appendiceal NEC with very rapid progression, in which complete remission was achieved by radical surgery followed by systemic chemotherapy.

3. Case Presentation

A 50-year-old woman was referred to our hospital with complaints of right lower quadrant abdominal pain and prolonged fever for over a week. Her medical history was unremarkable. On physical examination, we noted tenderness at McBurney's point with mild rebound tenderness. Computed tomography (CT) revealed an enlarged appendix, with wall thickening and a cystic lesion at the appendiceal tip (Figure 1A, B). Under the diagnosis of acute appendicitis with mucinous cystadenoma of the appendix, she underwent laparoscopic appendectomy. During the operation, there were no findings indicative of malignancy (Figure 1C). There were no postoperative complications, and she was discharged six days postoperatively.

Analysis of the resected specimen revealed wall thickening at the base of appendix, and the peripheral side was filled with mucous (Figure 1D). The cut end was intact. The tumor size was 2.5 × 2.5 cm, and microscopic observation showed tumor cells with hyperchromatic nuclei forming a sheet-like structure in the submucosa, with low- and high-grade tubulo-villous adenoma in the mucosa. The tumor invaded the muscularis propria.

Immunohistochemical analysis of the tumor revealed a neuroendocrine tumor with positive staining for synaptophysin (Figure 2) and CD-56. Based on these findings, neuroendocrine neoplasm (NEN) was suspected. Chromogranin A staining was negative. The Ki- 67 labeling index was ≥90%, confirming that the tumor was a NEC according to the 2010 WHO classification. Focal squamous differentiation was observed, as well as lymphatic and venous invasion. The T-stage of the appendiceal NEN was T3 according to European Neuroendocrine Tumor Society (ENETS) staging [5] and T2 according to Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging [6].

Since the tumor was a T3 stage (ENETS) NEC, and given its location at the base of the appendix, complementary right-sided hemicolectomy with

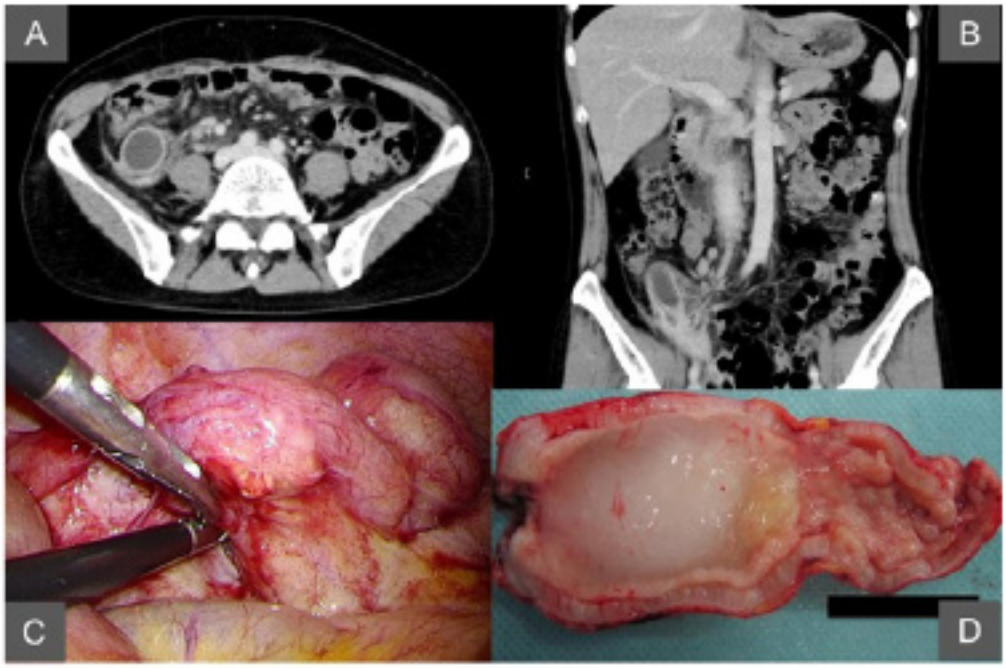

Figure 1: CT scan on arrival at hospital and intraoperative findings. CT scan revealed a cystic lesion at the tip of the appendix, with wall thickening and swelling of the lymph nodes (A, B). Intraoperatively, the appendix was swollen, but there were no signs of metastasis or dissemination (C). Resection of the specimen revealed that the appendix was filled with mucous and that the wall at the base was swollen (D).

lymph node dissection was strongly recommended given the high probability of lymphatic metastases. Accordingly, the patient underwent right hemicolectomy about one month after the previous operation. During the operation, lymph node swelling that extended through the ileocolic vessels and superior mesenteric vessels was observed, indicating metastases beyond the locoregional lymph nodes. All swollen lymph nodes were resected (Figure 3). Pathological examination revealed metastases in 27 of 42 dissected lymph nodes, including lymph nodes around the root of the superior mesenteric artery and superior mesenteric vein. Most of the metastatic lymph nodes were invaded by the NEC, with focal squamous differentiation. There was no evidence of dissemination or other metastatic disease, and the margin of the primary lesion was negative. According to the 2010 WHO classification, the final diagnosis of the primary appendiceal NEC was Stage IV (T3, ly+, v+, N1, and M1 (LYM) according to TNM classification by ENETS staging [5], and T2, ly+, v+, N1, and M1 (LYM) according to TNM classification by UICC/AJCC, 8th edition, staging [6]). The patient had an uneventful postoperative course and was discharged on postoperative day 11. Given the tumor's massive and rapid lymphatic spread, a CT scan was performed one month after right hemicolectomy in order to check for remnant disease. CT revealed swelling of Virchow's lymph node which was not detected before initial surgery, suggesting distant metastasis. The patient underwent chemotherapy with etoposide and cisplatin. After six cycles of chemotherapy, complete remission was achieved, which was maintained at the 3-year follow-up after initial surgery.

4. Discussion and Conclusions

Here, we describe a rare case of appendiceal NEC. Despite having rap-

idly progressed through the lymphatic system, complete remission was achieved by radical surgery followed by systemic chemotherapy. Right hemicolectomy with extended lymph node dissection followed by chemotherapy with etoposide and cisplatin may be a viable treatment for appendiceal NEC.

According to the Surveillance Epidemiology and End Results (SEER) database, appendiceal NEN has an incidence rate of approximately 0.15–0.6 cases per 100000 people per year, with a slight female preponderance and a mean patient age of 38–48 years [7]. Approximately 60-75% of appendiceal NENs occur in the tip of the appendix [5, 8]. Most appendiceal NENs are diagnosed incidentally during appendectomy for acute appendicitis, at a rate of 3-5/1000 appendectomies [5]. According to the WHO classification scheme, appendiceal NENs are classified as gastrointestinal NENs, and evaluated according to tumor size, mitotic index, and prolifer-

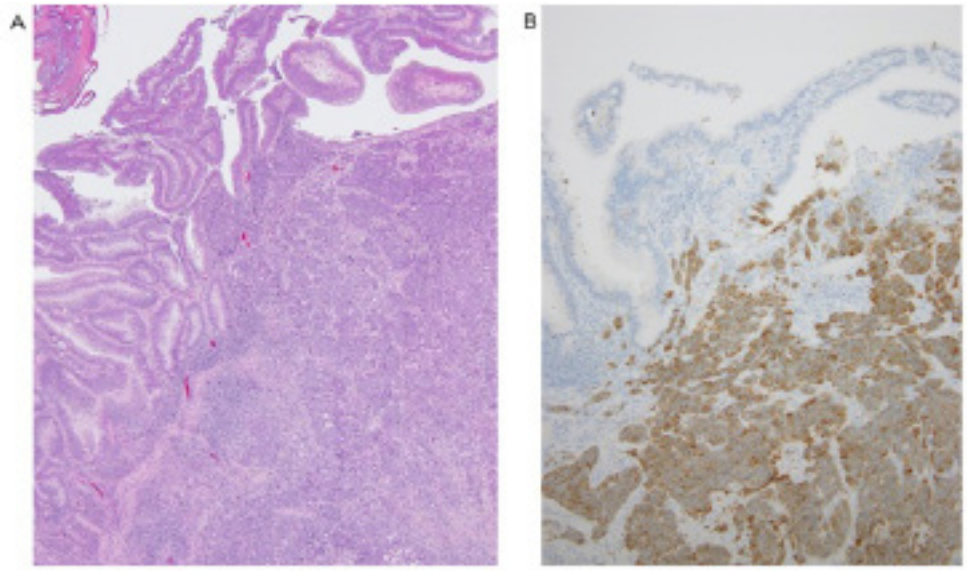

Figure 2: Microscopic findings. Hematoxylineosin staining revealed the neuroendocrine carcinoma forming a sheet-like structure in the inner portion of the tumor (A). The tumor was positive for synaptophysin (B), but the adenoma was negative (no figure).

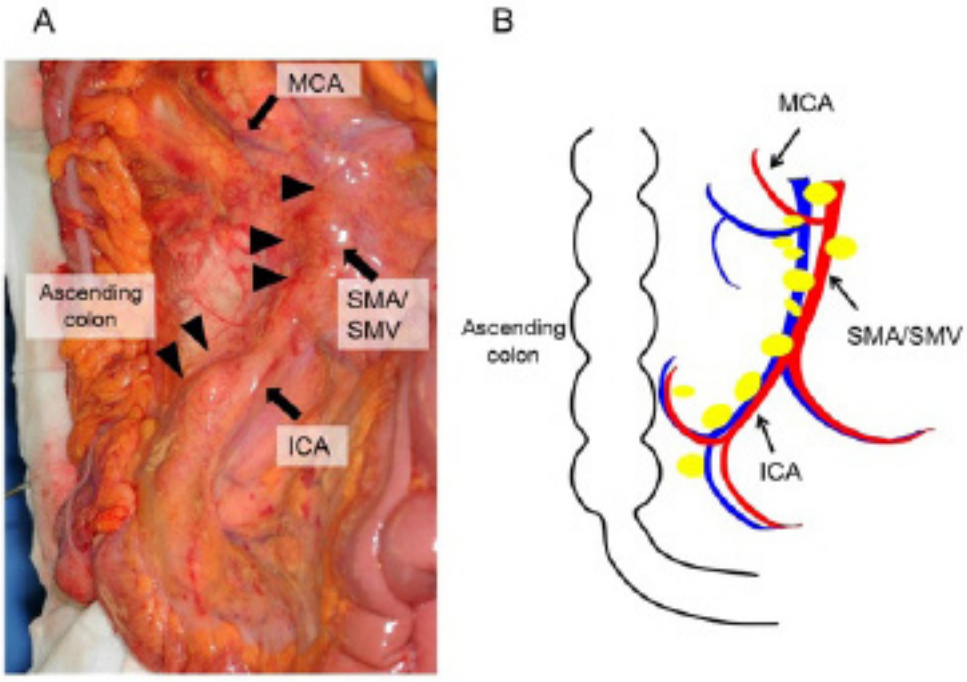

Figure 3: Intraoperative findings from the second operation. Lymph node swelling (arrowheads) was observed around the ileocolic artery and vein, and superior mesenteric artery (SMA) and superior mesenteric artery vein (SMV)(A). Pathological examination revealed metastasis in 27 of 42 dissected lymph nodes, including the lymph node around the root of the SMA and SMV. The scheme shows the range of swelling of the lymph nodes (yellow circles) (B). MCA; middle colic artery, ICA; ileocolic artery.

ative index [1]. Regarding staging, two different TNM staging systems are used: the one proposed by ENETS [5] and the one proposed by the UICC/AJCC [6]. Whereas most NETs with localized lesions have a very good prognosis [5, 9,10], NEC has a very poor prognosis [11]. So far, very few cases of appendiceal NEC have been reported in the literature. O'Kane *et al.* [3] reported a case of small cell carcinoma of the appendix with multiple liver metastasis and para-aortic lymphadenopathy. Despite undergoing right hemicolectomy and palliative chemotherapy, the patient died two months after surgery. The tumor was positive for synaptophysin by immunohistochemistry, and the Ki-67 staining index was approximately 90%. Thus, the diagnosis was NEC according to the 2010 WHO classification. Tomioka *et al.* [4] reported a case of appendiceal NEC without any metastasis. The tumor was diagnosed after appendectomy for acute appendicitis, and a few weeks later, ileocecal resection with lymphadenectomy was performed. No regional lymph node metastasis was observed. The patient declined adjuvant chemotherapy and was disease free at five months after initial surgery. Another case reported as appendiceal NEC in 2006 does not appear to be currently classified as NEC according to the 2010 WHO classification because the tumor was a well-differentiated NET [12].

ENET consensus guidelines for appendiceal NEC state that "appendiceal NEC should, irrespective of the tumor size, be treated using an oncological right-sided hemicolectomy and be managed as adenocarcinoma cases" [5]. In the present case, complementary right hemicolectomy was performed one month after appendectomy. Moreover, our case had multiple lymph node metastases. Thus, right hemicolectomy with lymph node dissection for appendiceal NEC appeared to be an appropriate strategy.

NENs arise from neuroendocrine cells located throughout the human body. G1/G2 NETs are well-differentiated and slow-growing tumors. However, NEC is poorly differentiated and aggressive, and has clinicopathological characteristics that are similar to those of small cell carcinoma of the lung. On this basis, NEC cases are often treated using the same regimen as that for small cell carcinoma of the lung, i.e., chemotherapy with cisplatin [13-15]. The Japanese Clinical Oncology Group is currently conducting a randomized phase III study of etoposide plus cisplatin combination therapy versus irinotecan plus cisplatin combination therapy in patients with advanced NEC of the digestive system (JCOG1213; UMIN000014795). Our case was registered in this study and assigned to the group of etoposide plus cisplatin combination therapy. Complete remission was achieved after six months of chemotherapy, which has now been maintained for three years. Our findings suggest that chemotherapy with etoposide and cisplatin may be an effective treatment for appendiceal NEC.

In conclusion, we presented a very rare case of primary appendiceal NEC. NEC progressed very rapidly through the lymphatic system in this case, but complete remission was achieved by radical surgery followed by systemic chemotherapy. Although clinical characteristics of NEC are not well established given its rarity, right hemicolectomy with lymph node dissection followed by chemotherapy with etoposide and cisplatin may be a viable treatment strategy.

5. Acknowledgements

SM and DS designed the report and wrote the initial draft of the manuscript; HT performed the pathological diagnosis and assisted in the preparation of the manuscript; and TO, MI, and YK contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be 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.

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