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CASE REPORT | SMALL BOWEL

A Case of Familial Appendiceal Neuroendocrine Tumor

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ABSTRACT

The risk of developing appendiceal neuroendocrine tumor (aNET) may be attributed to multiple factors. A familial clustering is found in less than 1% of the cases. We report the case of a 25-year-old woman who initially presented with a clinical presentation of acute appendicitis and was subsequently diagnosed with aNET by histopathological examination after an emergency appendectomy. While revealing the result to the patient, she was found to have a positive family history of appendiceal carcinoid tumor. Although rare and only found in 1% of the cases, aNET found in family history should raise the suspicion of neuroendocrine tumors in other family members.

KEYWORDS: appendiceal neuroendocrine tumor; carcinoid tumor; family history; right hemicolectomy

INTRODUCTION

Neuroendocrine tumor is a rare slow growing tumor with both neural and endocrine characteristics, which arise from the diffuse system of neuroendocrine cells.[1] They can be found everywhere in the body, and they constitute only 0.5% of all malignant conditions and 2% of all malignant tumors of the gastrointestinal tract.[2] They are classified as foregut (respiratory tract, thymus, thyroid, stomach, duodenum, and pancreas), midgut (small bowel, appendix, and ascending colon), and hindgut (transverse, descending colon, and rectum) according to the embryological origin.[3] The incidence of appendiceal neuroendocrine tumor (aNET) is 0.2% of all neuroendocrine tumor.[4] The majority of neuroendocrine tumors are sporadic, and only 10% are familial, arising in the context of autosomal dominant inherited syndromes (MEN type 1–2, neurofibromatosis type 1).[5] We report here a case of a young female individual with familial aNET. The aim of this case report is to increase awareness of the familial aNETs to have a diagnosis and an appropriate treatment early on.

CASE REPORT

A 25-year-old woman, previously healthy with no surgical history, presented to the emergency department with 3-day history of right lower-quadrant pain. The patient denied any episodes of nausea, vomiting, fever, or chills. Vitals were within normal limits. On physical examination, abdomen was soft with positive bowel sounds and mild right lower-quadrant tenderness. Laboratory tests showed slightly elevated white cell count of 10.2×10^9 cells/L, neutrophils 70%, hemoglobin 14.2, platelet count 461,000, and C-reactive protein of 2.52 mg/L.

A computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast showed a dilated appendix up to 12 mm showing thickened enhancing wall with no significant adjacent fat streaking or enlarged lymphadenopathy (Figure 1). Findings are suggestive of acute uncomplicated appendicitis.

After preoperative preparation, the patient underwent an uncomplicated laparoscopic appendectomy. During the operation, the appendix was found to be inflamed with notable swelling in the head and body. No obvious perforations were observed, and the root of the appendix was otherwise noninflamed. The patient passed gas day 1 postoperatively, clear fluid diet was started and well tolerated, and the patient was discharged home.

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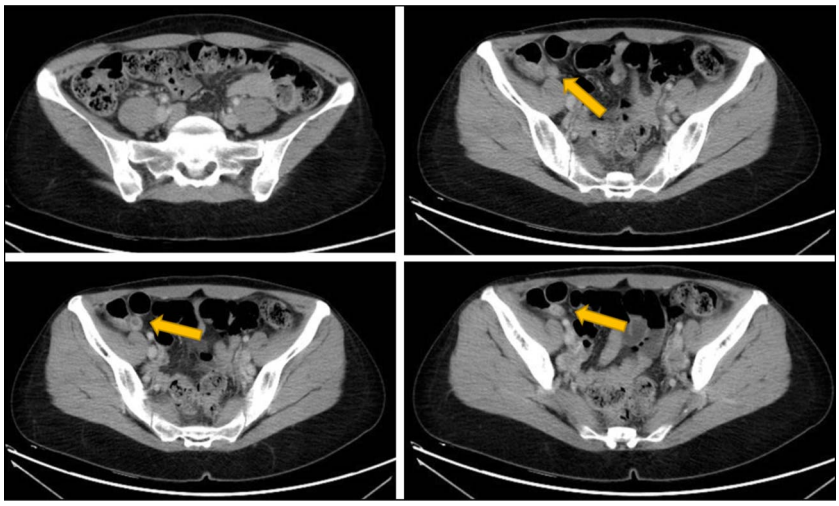

Figure 1. Computed tomography scan of the abdomen and pelvis, transversal view, showing thickened enhancing wall dilated appendix (yellow arrow).

One week later, the pathology result showed the presence of well-differentiated neuroendocrine tumor of 4.4 cm in length, grade 2/grade 3. The tumor is present at the resection margin of the appendix with invasion of the muscularis propria, subserosal adipose tissue, and mesoappendix with a deep invasion more than 3 mm. So, stage was found to be PT3N1, metastatic well-differentiated neuroendocrine tumor in 3 of 4 regional lymph nodes.

While delivering the result to the patient, she was found to have a positive family history of appendiceal carcinoid tumor. Her brother was admitted 12 years ago at the age of 18 years with the same presentation for acute appendicitis and was found to have carcinoid tumor of the appendix, involving the margins at its base. This tumor involved the submucosa and the muscular layer and measures 0.7 cm. No invasion of the subserosa was seen. The patient then underwent right hemicolectomy margins, which were found to be negative of tumor involvement at ileum and colon sites. Fifty lymph nodes were harvested, and zero were affected; they did not require any further adjuvant treatment postoperatively and were followed up to date.

A DOTA positron emission tomography (PET) scan returned negative for distant metastasis. The patient was scheduled for right hemicolectomy. Operation was performed 2 weeks after appendectomy, followed by smooth operation recovery and stay. The patient was discharged on day 3 postoperatively. Final pathology result showed suture granulomas and fat necrosis at the site of the appendix with no residual tumor, a 1-mm microscopic deposit of well-differentiated neuroendocrine tumor (NET) in the mesentery, negative proximal and distal colonic margins negative for tumor, and 2 metastatic pericolic lymph nodes of 57 lymph nodes. Immunohistochemical stains of the neoplastic cells showed strong diffuse expression of both chromogranin A (CgA) and synaptophysin and Ki-67 labeling index of 3%. Based on the immunohistochemistry result, the diagnosis of well-differentiated neuroendocrine tumor, grade 2/3 was confirmed (Figure 2). The patient was doing well on follow-up, and after referring to her oncologist, no further adjuvant treatment was advised.

DISCUSSION

Appendiceal neoplasms are rare and can be divided into epithelial that are adenocarcinomas and nonepithelial that consist of neuroendocrine or lymphoma. The incidence of aNET is 0.2% of all neuroendocrine tumors and arise from subepithelial neuroendocrine cells lying on the lamina propria mucosae and the submucosal layer of the appendix wall. These neoplasms are usually benign and occur at a younger age.[4]

In a large study for Alkhayyat et al including 2020 patients diagnosed from 2014 till 2019, the majority were White adults aged between 18 and 65 years. The prevalence was also higher in female individuals 7.4/100,000 compared with male individuals 5.7/100,000.[4] Several articles have noted that the incidence of aNET is higher in the female population, which may be an effect of higher appendectomy rates in younger women.[6]

The risk of developing aNET may be attributed to multiple factors. Most patients were more likely to have a history of smoking, alcohol abuse, obesity, diabetes, ulcerative colitis, Crohn's disease, MEN type 1, neurofibromatosis type 1, and a family history of gastrointestinal cancer.[7]

Taal et al found a familial clustering in neuroendocrine tumor in less than 1% of the cases. A family history of carcinoid tumors was found to be associated with a greater risk of developing neuroendocrine tumors and other cancers. The predisposition in neuroendocrine tumor patients to other tumors is not increased, but there was an excess of some tumor's types, such as thyroid cancer, non-Hodgkin lymphoma, and brain tumors. In case of familial neuroendocrine tumors, the age distribution in the children is slightly different. The relative risk of

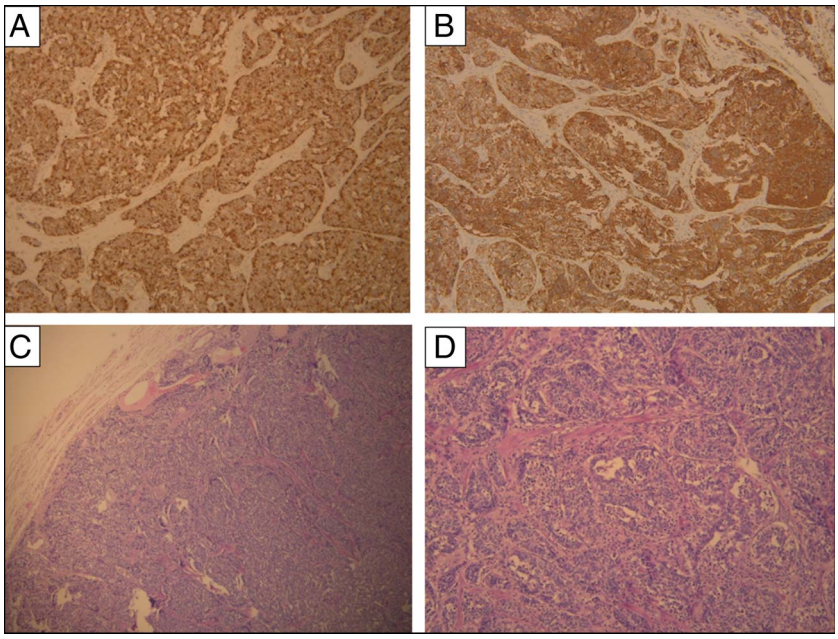

Figure 2. A, Chromogranin A stain. B, Synaptophysin stain. C, Lumen of the appendix obliterated by the neuroendocrine tumor cells. D, High resolution, lumen of the appendix obliterated by the neuroendocrine tumor cells.

synchronous tumors is increased in case of neuroendocrine tumors up to 15, and the overall relative risk of a second primary more than 1 year after the neuroendocrine tumor was 2. The presence of a second primary can be a treatment-related effect, chemotherapy, or irradiation.[8]

In 2019, the World Health Organization published a new classification for the aNETs. The well-differentiated NETs are G1 low grade, G2 intermediate grade, and G3 high grade. The mitotic rate and Ki-67 index are, respectively, $<$2% and $<$3% for G1, 2%–20% and 3%–20% for G2, $>$20 and $>$20% for G3. The poorly differentiated aNETs were divided into small-cell neuroendocrine carcinoma and large-cell neuroendocrine carcinoma. The mitotic rate and Ki-67 index for neuroendocrine carcinoma are $>$20%. And finally, the well or poorly differentiated, mixed neuroendocrine non-neuroendocrine neoplasm with variable grade, mitotic rate, and Ki-67 index.[9]

Neuroendocrine tumors can be functional in 40% of the cases or nonfunctional depending on the excess of hormones namely serotonin, substance P and/or peptides, CgA, and synaptophysin secretion. CgA is raised in both nonfunctioning and functioning NETs and is the most commonly used biomarker to assess the disease burden and monitor treatment response, but its role in aNETs is unclear.[10]

There are no classic symptoms that are attributed to aNETs. The common symptoms at presentation were abdominal pain, diarrhea, nausea, vomiting, flushing, GI bleeding, obstruction, perforation, acute appendicitis, intussusception, and volvulus. Most patients present with acute appendicitis as the result of appendiceal luminal obstruction by the tumor frequently in the distal third. Diagnosis is usually made incidentally in appendectomy specimens.[4] Some patients may present with NET syndrome such as intermittent flushing, purple face, diarrhea, asthma attacks, and shock. NET frequently indicates that the tumor has already progressed to advanced stages.[10]

Management of aNET is dictated by the size of the tumor, mesoappendix invasion, margins, and lymphatic involvement.[11] After a complete resection of an incidentally diagnosed well-differentiated aNET measuring less than 1 cm, no further diagnostic testing or intervention is required. When aNET is between 1 and 2 cm, an abdominal CT scan or magnetic resonance imaging to evaluate the presence of lymphatic involvement or distant metastasis is indicated. For tumors larger than 2 cm or with mesoappendix infiltration or vascular or lymphatic vessel invasion, somatostatin receptor scintigraphy or PET scan using gallium 68–labeled somatostatin analogs should be considered with a right hemicolectomy to be performed afterward.[11]

For tumors between 1 and 2 cm, after diagnosis of aNET, controversy arises when deciding whether an appendectomy is sufficient or the patient will have better outcomes with right hemicolectomy. The main purpose to complete a right hemicolectomy is to complete the regional lymph node dissection that was found to be involved in 6%–9% of cases. For tumors between 1 and 2 cm, an appendectomy followed by periodic postoperative follow-up for 5 years is advised. In cases of more advanced disease, patients with either tumor located at the base of the appendix, infiltration of the cecum, positive surgical resection margins, mesoappendix invasion, metastatically infiltrated mesoappendiceal lymph node, or the presence of undifferentiated or low differentiated cells or presence of goblet

cells are advised to have further surgical intervention involving a right hemicolectomy.[11]

A large meta-analysis showed a survival rate ranging from 95.6% reaching 100% in a 10-year follow-up period.[11] No specific recommendations on follow-up after resection of an aNET and no adjuvant therapy are needed after complete resection of a well-differentiated midgut NET.[11] The initial evaluation for patients with metastatic relapse or progression should include CT scan, magnetic resonance imaging, or somatostatin receptor PET scan imaging and an assessment for carcinoid syndrome. The somatostatin analogs are the first therapy for symptomatic control in functional tumors. After progression in somatostatin analogs, the patient with positive imaging may receive peptide receptor radionuclide therapy.[11]

Recent advances in therapeutics developed to target aberrations in known oncogenic genes have revolutionized medical oncology. Erkut et al analyzed 588 tumor samples from patients with appendiceal cancer, identified genomic alteration patterns, patterns in gene expression, and aberrations in protein expression that distinguish appendiceal cancers from colorectal cancers, and found that the patient with aNETs has patterns of genomic alterations in APC, GNAS, and SMAD4 that resemble to pancreatic adenocarcinomas, with the exception of KRAS alterations being significantly lower.[12] The low expression of MGMT and TS by immunohistochemistry can be used as a basis to consider the combination of capecitabine and temozolomide for the treatment of aNET.[12]

No screening or testing was reported in the literature concerning familial aNET, so no consensus management in the familial aNET was reported. Thus, a strong family history should be kept in mind while dealing with aNET to have an optimal management of this disease.

Appendiceal neoplasms are rare, and the incidence of aNET is 0.2% of all neuroendocrine tumors. The development of aNET may be attributable to multiples factors including family history. Although rare and found only in less than 1% of the cases, family history of appendiceal carcinoid tumors should raise the suspicion of neuroendocrine tumors in other family members. Testing and a possible screening should be established for future considerations in the management of this neuroendocrine disease.

DISCLOSURES

Author contributions: All authors participated in the writing and editing of the article. ZE Rassi is the article guarantor.

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