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A Case of Familial Appendiceal Neuroendocrine Tumor: Case Report and Literature Review

***(Running Title:** familial appendiceal neuroendocrine tumor)*

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Abstract

The risk of developing appendiceal neuroendocrine tumor may be attributed to multiples factors. A familial clustering is found in less than 1% of the cases.
We herein report the case of a 25-year-old female who initially presented with a clinical presentation of acute appendicitis and was subsequently diagnosed with appendiceal neuroendocrine tumor (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, appendiceal neuroendocrine tumor 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 with familial appendiceal neuroendocrine tumor. The aim of this case report is to increase awareness of the familial aNETs in order to have a diagnosis and an appropriate treatment early on.

Case

A 25-year-old female patient, previously healthy with no past surgical history, presented to the emergency department with 3 days history of right lower quadrant pain. Patient denied any episodes of nausea, vomiting, fever or chills. Vitals were within normal limits. On physical exam, abdomen was soft with positive bowel sounds and mild right lower quadrant tenderness. Laboratory tests showed slightly elevated white cell count of 10.2 $x10^9$ cells/l, neutrophils 70%, hemoglobin 14.2, platelet count 461000 and CRP of 2.52 mg/l.

A computed tomography (CT) scan abdomen pelvis with intravenous (IV) 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.

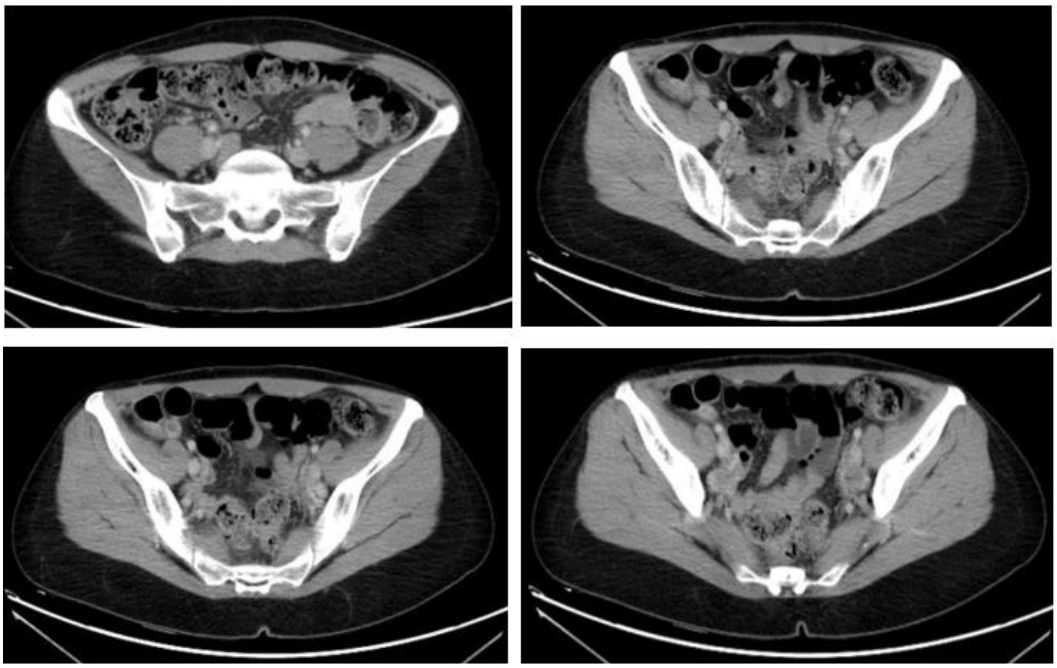

Figure 1: CT Scan abdomen pelvis, transversal view, showing thickened enhancing wall dilated appendix.

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 non-inflamed. Patient passed gas day 1 post operatively, clear fluid diet was started, well tolerated and patient was discharged home.

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 found to be PT3N1, metastatic well differentiated neuroendocrine tumor in 3 out 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 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 0.7cm. No invasion of the subserosa was seen. Patient then underwent right hemicolectomy. Margins were found to be negative of tumor involvement at ileum and colon sites. 50 lymph nodes were harvested and zero were affected. Patient did not require any further adjuvant treatment postoperatively and is followed-up to date.

A Dota positron emission tomography (PET) scan returned negative for distant metastasis. And patient was scheduled for right hemicolectomy. Operation was done two weeks post appendectomy. Smooth operation recovery and stay. Patient discharged on day 3 post operatively. And 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 NET in the mesentery, negative proximal and distal colonic margins negative for tumor and 2 metastatic pericolic lymph nodes out of 57 lymph nodes. 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 non-epithelial 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 Caucasian adults aged between 18 and 65 years. The prevalence was also higher in females 7.4/100000 compared to males 5.7/100000 [4]. Several articles have noted that the incidence of appendiceal neuroendocrine tumor is higher in the female population, which may be an effect of higher appendectomy rates in younger women [6].

The risk of developing appendiceal neuroendocrine tumor may be attributed to multiples factors. The majority of the patients were more likely to have a history of smoking, alcohol abuse, obesity, diabetes, ulcerative colitis, Crohn 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. And a family history of carcinoid tumors was found to be associated with a greater risk of developing neuroendocrine tumors as well as 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 for synchronous tumors is increased in case of neuroendocrine tumors up to 15 and the overall relative risk for 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 2010, the World Health Organization classified aNETs into: well-differentiated NETs/G1 (NET-G1), intermediately differentiated NETs/G2 (NET-G2), poorly differentiated neuroendocrine carcinomas (NET-G3), and mixed adenoneuroendocrine carcinomas. Poorly differentiated NETs can be further subdivided into large-cell and small-cell carcinomas [9].

Neuroendocrine tumors can be functional in 40% of the cases or non-functional depending on the excess of hormones namely serotonin, substance P and/or peptides, chromogranin (CgA), synaptophysin secretion. CgA is raised in both non-functioning 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. The majority of the 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 MRI 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 afterwards [11].

For tumors between 1 and 2 cm, after diagnosis of appendiceal neuroendocrine tumor, controversy arises when deciding whether an appendectomy is sufficient or 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 were found to be involved in 6 to 9% of cases. For tumors 1 to 2 cm an appendectomy followed by periodic post operative 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 is recommended after complete resection of a well-differentiated midgut NET [11]. The initial evaluation for patients with metastatic relapse or progression should include CT scan, MRI 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 analogues patient with positive imaging may receive peptide receptor radionuclide therapy [11].

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 in order to have an optimal management of this disease.

Conclusion

Appendiceal neoplasms are rare and the incidence of aNET is 0.2% of all neuroendocrine tumors. The development of appendiceal neuroendocrine tumor 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.

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References

1. Howe JR, Cardona K, Fraker DL, et al. The surgical management of small neuroendocrine tumors: Consensus Guidelines of the North American Neuroendocrine Tumor Society (NANETS) Pancreas. 2017;46(6):715–31.
2. Moertel CG. Karnofsky memorial lecture. An odyssey in the land of small tumors. J Clin Oncol. 1987; 5:1502–1522.
3. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008; 26:3063–3072.
4. M. Alkhayyat et al. epidemiology of neuroendocrine tumors of the appendix in the USA: a population-based national study (2014-2019), Annals of Gastroenterology (2021) 34, 713-720.
5. Gut P, Komarowska H, et al. Familial syndromes associated with neuroendocrine tumours. Contemp Oncol (Pozn) 2015;19(3):176–183.
6. Hassan et al. Risk factors associated with neuroendocrine tumors: A U.S.-based case–control study, Int. J. Cancer: 123, 867–873 (2008).
7. E. Hiripi1, J. Lorenzo Bermejo et al. Familial gastrointestinal carcinoid tumours and associated cancers, Annals of Oncology 20: 950–954, 2009 doi:10.1093/annonc/mdn706.
8. B.G. Taal et al. Epidemiology of Neuroendocrine Tumors, Neuroendocrinology 2004,80, DOI:10.1159/000080731
9. Moris et al. Neuroendocrine Neoplasms of the Appendix: A Review of the Literature, Anticancer Research February 2018, 38 (2) 601-611
10. Capdevila J, Meeker A, et al. Molecular biology of neuroendocrine tumors: from pathways to biomarkers and targets. Cancer Metastasis Rev. 2014; 33:345–351.
11. Muñoz de Nova JL et al. Management of incidentally discovered appendiceal neuroendocrine tumors after an appendicectomy, World J Gastroenterol 2022 April 7; 28(13): 1304-1314, DOI: 10.3748/wjg. v28.i13.1304.