



Neuroendocrine Tumors of the Appendix in Adolescents and Young Adults

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Abstract

Neuroendocrine tumors involving the appendix in young people are uncommon. A retrospective review of appendiceal NET at Cleveland Clinic Children's was completed, 14 patients were identified, 3 cases were classified as intermediate grade tumors, lymph node metastasis was present in 2 cases. The largest size tumor measured 4.5 cm, 5 patients underwent right hemicolectomy per NANETS criteria, 3 patients who met this criteria did not undergo hemicolectomy. No disease recurrence. Appendiceal NET is associated with an excellent prognosis in localized disease and has low metastatic potential. A multicenter review will be beneficial in better defining criteria for a second surgery.

Abbreviations

RHC: Right Hemicolectomy; NANETS: North American Neuroendocrine Tumor Society; NET: Neuroendocrine Tumor; PT: Patient; AYA: Adolescents and Young Adults; RX: Treatment; LN: Lymph Node; PT: Patient; NO: Number

Introduction

Neuroendocrine tumors (NET) are rare in the pediatric population and originate from the neuroendocrine cells of the gastrointestinal tract, the appendix being the most common site.

A summary of existing series reports an incidence between 2 and 5 per 1000 cases in pediatric appendectomies [1]. Despite their low incidence, NET represent the most frequent tumor involving the gastrointestinal tract in children and adolescents [2-4].

Most appendiceal NET are incidental findings in a post-appendectomy specimen and therefore have no characteristic tumor-specific symptoms. Clinical presentation of appendiceal NET is similar to acute appendicitis, but it can be an incidental intra-operative finding during appendectomy or other surgical procedures [5].

The metastatic potential depends on the size, depth, and site of the tumor [6].

We reviewed our institutional experience concerning treatment and outcomes and compared to current NANETS guidelines.

Methods and Results

We performed a retrospective review of adolescent and young adult (age 15-23) patients diagnosed with appendiceal NET between January 2010 to May 2016. Data which included demographics, presenting symptoms, mode of imaging, pathologic review, disease workup, treatment, post treatment surveillance were collected and analyzed, 14 patients were identified as diagnosed with appendiceal NET (Table 1). Females were in the majority (9/14). The most common presenting symptom was abdominal pain.

All patients underwent appendectomy, with post-operative diagnosis from pathology examination. Mean age at diagnosis was 17.2 years (age 15-23 years), 5 patients underwent right hemicolectomy with indications being tumor size >2 cm, perineural invasion and lymph node metastasis; PT 2 TS 4.5 cm, tumor invasion, LN involvement; PT 8 TS 2 cm, Grade 1, No invasion /LN involvement, PT 9 TS 1.8 cm, no invasion, positive LN, PT 11 TS 0.4 cm, Grade 1, Perineural invasion, No LN involvement and PT 14 with tumor size of 3 cm.

PT 7 had TS >2 cm while patient 12 TS could not be determined, both did not undergo RHC;

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Table 1: Characteristics of Carcinoids involving the appendix in AYA.

PT NO	AGE	SEX	TUMOR SIZE (CM)	METASTASIS /INVASION	LN	Grade	RX
1	17	F	0.8	No	No	1	A
2	17	F	4.5	Yes ^a	Yes	1	A + RHC
3	14	F	1.4	No	No	1	A
4	19	F	1	No	No	1	A
5	16	M	1	No	No	1	A
6	21	F	0.1 cm	No	No	1	A
7	19	F	3	No	No	1	A
8	15	M	2	No	No	1	A + RHC
9	15	F	1.8	Yes ^b	Yes	2	A + RHC
10	20	M	0.6	No	No	2	A
11	19	M	0.4	Yes ^{b,c}	No	1	A + RHC
12	13	F	NM	No	No	2	A
13	19	F	0.1 cm	No	No	1	A
14	23	F	3 cm	Yes ^a	No	1	A + RHC

Appendectomy only A + RHC Appendectomy + Right hemicolectomy (RHC)

^amesoappendix, ^bperineural invasion, ^clymphovascular invasion

Table 2: Surgical Approaches from NANETS consensus guidelines for the management of well differentiated NETs of the Appendix [7].

Appendectomy only	Small tumors , well differentiated (<1 cm) confined to tip of appendix without lymphovascular invasion or invasion into mesoappendix < 2 cm tumors with the above features
Right hemicolectomy	Tumors >2 cm, tumor size cannot be determined, incompletely resected tumors, evidence of lymphovascular invasion, invasion of the mesoappendix, intermediate to high grade tumors, mixed histology (goblet cell carcinoid, adenocarcinoid). Mesenteric nodal involvement

and are alive and well at follow-up periods of 36 months and 14 months respectively.

Overall, tumor size ranged from microscopic foci to 4.5 cm, 2 patients had metastatic disease involving the regional lymph nodes only and 1 patient had lymphovascular involvement (Table 1). The patients with lymph node involvement had additional findings of mesoappendix involvement (PT 2) and intermediate grade (PT 9), 3 patients had intermediate risk disease per NANETS consensus guidelines for the diagnosis and management of NET, 1 patient had a perforated appendix; patient did report flushing and diarrhea occurring prior to presentation (15 year old female who presented with 4 days of vomiting, diarrhea, occasional flushing with shivering & intermittent fever and abdominal pain).

This patient was found to have regional lymph node involvement and underwent right hemicolectomy.

Post-surgery surveillance included imaging utilized CT abdomen more commonly, octreotide scan, Chromogranin A and 5 HIAA. Follow-up duration ranged from 2 - 77 months (median = 12 months). Relapses did not occur.

Discussion

The first case of an appendiceal NET was described by Berger in 1882, but it was not until 1907 that the term carcinoid was coined by Sigfried Oberndorfer at the German Pathological Society Summit in Dresden ([7]).

Appendiceal NET represent tumors with a low metastatic potential and in the majority of patients, surgery is curative. Majority in children arise in the appendix; however they can also occur in other primary sites including the small intestine, bronchus and others [8,9].

These lesions are more likely to be found in females, as reported in several publications [6,10].

Classic carcinoid syndrome which consists of some combination of wheezing, flushing, diarrhea, hypotension and /or abdominal pain is rare in young patients with NETs as they rarely have metastasis to the liver or other sites ([7]).

Incidence at our institutions concurs with the rare occurrence of this tumor in pediatric patients.

Carcinoid syndrome occurrence was rare (1/14); abdominal pain in contrast was 100% (14/14).

Majority of patient (10/14) had low grade tumors with tumor size being less than 2 cm.

Pediatric management of NET is derived from an adult medicine based guideline- The NANETS guidelines [11] which is elaborated in Table 2: small (<1cm) well differentiated carcinoids confined to the tip of the appendix that are excised are considered cured if there is no evidence of lymphovascular invasion or invasion into the mesoappendix, and do not require any follow-up; <2 cm tumors (without regional involvement) also do not require any follow up. Right hemicolectomy is being recommended for appendiceal NET with evidence of tumor invasion at the base of the appendix, in patients with tumors greater than 2 cm, in those with tumor where size cannot be determined, incompletely resected tumors, intermediate to high grade tumors, evidence of lymphovascular invasion, invasion of the mesoappendix, and mixed histology, 5 patients underwent right hemicolectomy; PT 2 TS 4.5 cm, tumor invasion, LN involvement; Patient 8 TS 2 cm, Grade 1, No invasion/LN involvement, PT 9 TS 1.8 cm, intermediate grade, PT11 TS 0.4 cm, Grade 1, lymphovascular invasion and PT 14 with tumor size of 3 cm.

Interestingly PT 7 had TS >2cm while PT 12 TS could not be determined, both did not undergo RHC; and are alive and well, 6 patients did not meet criteria for RHC and appropriately did not undergo surgery. Of the five that underwent RHC two patients had positive regional lymph nodes.

Three patients who meet NANETS criteria for RHC did not undergo further surgery (Patient 7, 10, 12); and remain alive/disease free with a total combined follow-up duration of 41.5 months. Our report is limited by number of patients and duration of follow up.

A multicenter review will be beneficial in better defining criteria for a second surgery in AYA.

Disease workup after diagnosis and surveillance in our institution consisted of computed tomography abdominal & lung scans, Octreotide scans, Chromogranin levels and 5-HIAA levels.

Follow up schema has been difficult to standardize, generally we have recommended proposed NANETS guidelines of reassessment between 3 and 6 months after complete resection; and every 6 to 12 months for at least 7 years.

Our report adds to existing literature to pediatric patients with appendiceal NET and regional lymph node metastases [12-15].

In conclusion, a larger patient series is needed to better define which patients with appendiceal NETs will benefit most from undergoing a right hemicolectomy.

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