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Management and outcomes of appendicular neuroendocrine tumours: Retrospective review with 5-year follow-up

B. Amr, F. Froghi*, M. Edmond, K. Haq, R. Thengungal Kochupapy

Surgical Department, Derriford Hospital, Plymouth Hospitals NHS Trust, United Kingdom

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Abstract

Background: Neuroendocrine (NEN) tumours are the commonest type of tumours affecting the appendix. The majority of cases are diagnosed incidentally on post-operative histopathological examination of the resected appendicectomy specimen. Preoperative diagnosis remains a challenge, unless the patient presents with obvious features of carcinoid syndrome or signs of metastatic disease. Hence, the authors present our five-year experience in diagnosing and managing NEN tumours of the appendix.

Methods: Retrospective review of all patients underwent an emergency appendicectomy with intention to treat clinically suspected appendicitis at Derriford Hospital (Plymouth, Devon, UK) was undertaken. Patients with diagnoses other than NEN of the appendix were excluded. For patients with appendicular NEN, demographic data, pre-operative inflammatory markers, post-operative histology results as well as follow-up investigations were obtained using patients' electronic records. Case notes were reviewed for clinical presentation, operative details and follow-up information.

Results: 2724 patients underwent emergency appendicectomy between January 2009 and May 2014. Carcinoid tumours were identified in 17 histologically examined appendicectomy specimens. Clinically, all patients presented with acute appendicitis with raised inflammatory markers in 58.5% of patients. Median tumour size was 5 (1–20) mm. Median postoperative follow up was 2.9 (0.92–5.8) years. All patients remained tumour free with no evidence of metastasis or recurrence during the entire study period.

Conclusion: Appendicular NEN are rare and usually diagnosed incidentally; hence precise examination of routine appendicectomy specimens is fundamental in the diagnosis. Simple appendicectomy is sufficient for tumours less than 1 cm for adequate clearance, whilst right hemi-colectomy is recommended for larger tumours.

Keywords: Appendicitis; Neuroendocrine tumours; Carcinoid

Introduction

First described by Oberndorfer in 1907, neuroendocrine (NEN) tumours are slow growing rare tumours arising from enterochromaffin cells found throughout the gastrointestinal tract and the broncho-pulmonary system.[1] The appendix is the most common site for gastrointestinal carcinoid tumours. NEN represents 60% of all appendicular tumours, making it the most common tumour type affecting the appendix.[2] However, appendicular NEN tumours are very rare with a reported annual incidence of 0.15/100,000 that has increased to 0.4–0.6/100,000 with a slight female predominance.[3]

The preoperative diagnosis of dormant appendicular NEN is challenging unless patients present with symptoms and signs of carcinoid syndrome or features of metastatic disease.[5] The majority of cases are diagnosed incidentally in 3–5/1000 performed appendicectomy operations.[4] Currently, a simple appendicectomy is advocated for tumours less than 2 cm and a formal right hemicolectomy for tumours greater than 2 cm due to the higher risk of mesenteric lymph node metastasis.[4] Patients with appendicular NEN diagnosis have had good outcomes with a five-year survival rate of 85–100%.[3,6,7]

Given their rare nature and difficulty in preoperative diagnosis of appendicular NEN, there is a scarcity of large

* Corresponding author. Plymouth Hospitals NHS Trust, Derriford Hospital, Derriford Road, PL6 8DH, Plymouth, United Kingdom. Tel.: +44 01752431486.
E-mail address: farid.froghi@nhs.net (F. Froghi).

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case series or studies in the literature. The authors therefore present a single-center case series of appendicular NEN identified from a retrospective analysis of all the appendicectomy specimens in the last five years to explore our experience in the diagnosis and management of patients with these rare tumours as well as identifying metastatic behaviour and tendency to recur.

Methods

A retrospective review of all patients who underwent emergency appendicectomy with the intention to treat clinically suspected appendicitis between January 2009 and May 2014 at a teaching hospital (Derriford Hospital, Plymouth, Devon, UK) was undertaken. Patients with histological findings other than NEN of the appendix and those who underwent surgery for reasons other than suspected appendicitis were excluded. Demographic data, preoperative diagnoses, investigations and operative findings for patients with the diagnosis of NEN tumours of the appendix were reviewed. Pathological reports were reviewed for tumour type, tumour size, and depth of invasion, the degree of differentiation, resection margin and lymph node involvement. Follow-up records and survival data were also examined from the hospital case notes. The study protocol has been reviewed and approved by Plymouth Hospitals NHS Trust audit department.

Results

Between January 2009 and May 2014, 2724 patients (47.2% M) with a median age of 24 years underwent emergency appendicectomy with the intention to treat clinically suspected appendicitis at our institution. The diagnosis of appendicular NEN tumours was histologically confirmed in 17 appendicectomy specimens. For this cohort of patients, there were 11 females (64.7%) with a median age of 20 years (range: 8–69) and 6 males (35.3%) with median age of 29.5 years (range: 16–73).

During the study period we diagnosed eighteen cases with appendicular NEN, however, one case did not meet the inclusion criteria as the patient underwent a right hemicolectomy for a caecal volvulus.

All patients presented with clinically suspected acute appendicitis. Laboratory investigations revealed raised white cell count (WCC) in 10 patients (58.8%). Emergency laparoscopic appendicectomy was successfully performed in 7 patients (41.2%) while 10 patients (58.3%) had their appendix surgically removed via the traditional open approach.

The incidence of appendicular NEN in our series was 0.62% with a median tumour size of 5 mm (range: 1–20). 64.7% of the tumours measured less than 1 cm. Median tumour size was larger among female patients with no statistical significance ($p = 0.071$). The histopathological characteristics of the resected tumours are shown in (Table 1). The tip of the appendix was the most common tumour site being identified in 64.7% of the cases.

Complete resection was successfully achieved in 16 patients, whereas one patient had a perforated appendix at the time of surgery and hence the exact identification of the resection margin was not possible. Two patients with 18 mm and 12 mm tumours at the appendicular base subsequently underwent a right hemicolectomy at 80 days and 72 days respectively following the initial appendicectomy operation. For these two patients, the final histological examination did not reveal evidence of disease remnants or other lesions within the resected specimen.

Serosal invasion was reported in six patients while five patients had invasion of the mesoappendix. Only one patient had a single positive lymph node deposit for a well-differentiated, completely resected, 2 mm tumour at the centre of the appendix. Large cell type was identified in 8 cases while goblet cell was found in only two cases. None of our patients were found to have features of carcinoid syndrome and the median hospital stay was 2 days (range: 1–16).

Based on the TNM classification of appendicular carcinoid (Table 2),[16] 11 patients (64.7%) were staged T1a and

Table 1
Histopathological characteristics for the resected 17 appendicular NEN specimens.

N	17	
Tumour size (%)	≤1 cm	11 (64.7)
	>1 < 2 cm	4 (23.5)
	= 2 cm	1 (5.9)
	Missing (perforation)	1 (5.9)
Tumour site (%)	Tip	11 (64.7)
	Base	2 (11.8)
	Middle	2 (11.8)
	Whole appendix	2 (11.8)
Depth of invasion (%)	Mucosa	6 (35.3)
	Serosa	6 (35.3)
	Mesoappendix	5 (29.4)
R0 (%)		16 (94.1)
Node positive (%)		1 (5.9)
Large cell NET (%)		8 (47)
Goblet cells (%)		2 (11.8)
Carcinoid features (%)		0
Well diff (%)		13 (76.5)
Low grade (%)		2 (1.8)
T4 (%)		1 (5.9)

Table 2
Summary of TNM classification-7th edition of appendicular NEN (well differentiated neuroendocrine tumour).

T1a	≤1 cm
T1b	>1–2 cm
T2	>2–4 cm OR with extension to the caecum
T3	>4 cm OR with extension to the ileum
T4	Perforates peritoneum OR other organs or structures
N1	Regional