Archives of the Balkan Medical Union
vol. 56, no. 4, pp. 408-412
December 2021

ORIGINAL PAPER

NEUROENDOCRINE TUMOURS IN PATIENTS OPERATED FOR ACUTE APPENDICITIS: A RETROSPECTIVE CLINICAL STUDY

Kalbim ARSLAN[1]✉, Feyzi KURT[2]

[1] General Surgery Clinic, Near East Unıversity, Lefkoşa, Cyprus
[2] General Surgery Clinic, Seyhan State Hospital, Adana, Turkey

Received 04 March 2021, Accepted 10 June 2021
https://doi.org/10.31688/ABMU.2021.56.4.03

Abstract

Introduction. The objective of the study was to determine the incidence of neuroendocrine tumours in patients undergoing appendectomy because of acute appendicitis and to investigate the treatment and follow-up of these tumours.
Materials and methods. The data of 6592 patients who were operated for acute appendicitis in two different health centers, between January 2012 and May 2020, were obtained from an electronic database. Fourteen patients with neuroendocrine pathologies were included in the study.
Results. Of the 6592 patients undergoing appendectomy, 14 had neuroendocrine tumours. Of these 14 patients, six were male and eight were female. The mean age of the patients was 36.71 years. Six of the tumours were distal, seven were medial and one was in the appendix radix. The mean tumour size was 1.17 cm. Right hemicolectomy was performed in two patients with appendix radix tumours (2 cm in size) and the remaining 12 patients underwent appendectomy. The mean follow-up duration was 36.4 months.
Conclusions. The pathologies of the patients who undergo appendectomy for acute appendicitis should be closely monitored, cases with neuroendocrine tumours

Résumé

Tumeurs neuroendocrines chez les patients opérés pour une appendicite aiguë: une étude clinique rétrospective

Introduction. L'objectif de l'étude était de déterminer l'incidence des tumeurs neuroendocrines chez les patients subissant une appendicectomie due à une appendicite aiguë et d'étudier le traitement et le suivi de ces tumeurs.
Matériels et méthodes. Les données de 6592 patients opérés d'une appendicite aiguë dans deux centres de santé différents entre janvier 2012 et mai 2020 ont été obtenues grâce à un scan réalisé sur une base de données électronique. Quatorze patients atteints de pathologies neuroendocriniennes ont été inclus dans l'étude.
Résultats. Parmi les 6592 patients subissant une appendicectomie inclus dans l'étude, 14 avaient des tumeurs neuroendocrines. Sur ces 14 patients, six étaient de sexe masculin et huit de sexe féminin. L'âge moyen des patients était de 36,71 ans. Six tumeurs étaient distales, sept médiales et une radicale. La taille moyenne des tumeurs était de 1,17 cm. Une hémicolectomie droite a été réalisée chez deux patients avec tumeurs

✉ Address for correspondence: Kalbim ARSLAN
Near East University, Faculty of Medicine General Surgery Department, Nicosia, Cyprus
E-mail: kalbimarslan@hotmail.com; Phone: 0533 8742950/ 0392 6751000

should be reevaluated, and treatment and follow-up of these cases should be done based on the tumour characteristics.

Keywords: acute appendicitis, neuroendocrine tumour, carcinoid tumour, surgery, histopathology.

localisées en radix (taille de 2 cm) et les 12 patients restants ont subi une appendicectomie. La durée moyenne du suivi était de 36,4 mois.

Conclusions. Les pathologies des patients ayant subi une appendicectomie pour appendicite aiguë doivent être étroitement surveillées, les cas de tumeurs neuroendocrines doivent être réévalués et le traitement et le suivi de ces cas doivent être effectués en fonction des caractéristiques de la tumeur.

Mots-clés: appendicite aiguë, tumeur neuroendocrine, tumeur carcinoïde, chirurgie, histopathologie.

Introduction

Neuroendocrine tumours (NETs), also known as carcinoid tumours, develop from neural crest cells and are mostly (95%) located in the gastrointestinal tract[1]. More rare, these tumours may be located outside the gastrointestinal tract, such as bronchi, ovary, and thymus[2]. Appendiceal NETs developed from neuroendocrine cells of the appendix[1,3] are benign tumours that metastasize very rarely, and are the most common appendiceal tumours[4]. Such tumours can be seen in about 0.33% of appendectomy specimens[5]. They are more common in women than in men[5]. Other appendiceal tumours include adenocarcinomas, mucinous neoplasms, and goblet cell carcinoid (GCC) tumours. Most of the appendiceal NETs are asymptomatic. When they are symptomatic, they mimic acute appendicitis[6]. When tumours grow, they may cause abdominal pain, abdominal distension, and ileus. Sometimes, symptoms suggestive of carcinoid syndrome (diarrhea, flashing) may appear. The diagnosis is usually made after histopathological examination of appendectomy specimens[7]. These tumours are often located distally to the appendix, have usually less than 1 cm in size and are rarely larger than 2 cm[8]. Although incidentally detected, NETs have a good prognosis, and they may rarely recur[9]. The probability of recurrence increases if the tumour is located in the radix, it has 1-2 cm in size, and if there is mesoappendiceal invasion. In such cases, a more comprehensive surgical intervention can be planned, although there is a limited number of studies in the literature on this subject[10]. Neuroendocrine tumours can immunohistochemically release neuroendocrine markers such as chromogranin A, synaptophysin, non-specific enolase (NSE), CD56 and glucagon[11].

The objective of the study was to determine the incidence of neuroendocrine tumours in patients undergoing appendectomy because of acute appendicitis and to investigate the treatment and follow-up of these tumours.

Material and methods

The data of 6592 patients who had surgery for acute appendicitis between January 2011 and May 2019 were obtained retrospectively from an electronic database of the Near East University Hospital, Nicosia, Cyprus and Seyhan State Hospital Adana, Turkey. The histopathological results of all the patients were analysed. From these patients, 14 patients with a histopathological diagnosis of NET were included in the study. Gender, age, physical examination findings, laboratory results, radiology reports and pathology results of these patients were examined in detail.

The study was approved by the Clinical Research Ethics Committee of Adana Training and Research Hospital, date 08/04/2020, number 54/784.

Results

Fourteen patients from a group of 6592 patients who underwent appendectomy for acute appendicitis had a diagnosis of NET at the histopathological exam (0.21%). Eight of the patients (57.14%) were female and six (42.86%) were male. The average age was 36.71 years (42.51 years in male patients and 29.87 years in female patients) (Tables 1 and 2). Eight patients were diagnosed with acute appendicitis by computed tomography (CT) in addition to physical examination and laboratory findings, while four patients were diagnosed by ultrasonography (USG), and two patients were diagnosed clinically. None of the patients had a diagnosis of NET before the operation. None of the patients had symptoms of carcinoid syndrome (such as diarrhea and flushing). All patients underwent emergency surgery as open surgery. During the operation, six patients had phlegmon and

Table 1. Demographic characteristics of the patients and treatments applied.

N	*Gender*	*Age*	*Tumour localization*	*Tumour size (cm)*	*Surgical treatment*
1	F	24	Distal	0.8	Appendectomy
2	M	18	Distal	0.6	Appendectomy
3	F	22	Medial	1.3	Appendectomy
4	F	36	Distal	1.2	Appendectomy
5	M	41	Medial	1.6	Appendectomy
6	F	45	Medial	0.8	Appendectomy
7	F	32	Distal	1.4	Appendectomy
8	F	20	Medial	2	Right hemicolectomy
9	M	56	Radix	1.8	Right hemicolectomy
10	M	42	Medial	0.6	Appendectomy
11	F	38	Distal	0.4	Appendectomy
12	F	42	Medial	1.1	Appendectomy
13	M	51	Medial	1.3	Appendectomy
14	M	47	Distal	1.6	Appendectomy

Table 2. The ratio of age, tumour localization and tumour sizes.

Gender	*Age (%)*	*Distal*	*Medial*	*Radix*	*Size (cm)*
M	42.51	2	3	1	1.25
F	29.87	4	4	-	1.09
M + F	36.71	6	7	1	1.17
		(42.83%)	(50%)	(7.14%)	

Table 3. Details of histopathology results of the patients.

Table 3/A. Tumour localization

Distal	6 (42.83%)
Medial	7 (50 %)
Radix	1 (7.14%)

Table 3/B. WHO classification 2010

G1	12 (85.71%)
G2	2 (14.28%)
G3	0

Table 3/C. TNM classification

T1 N0 M0	8 (57.14%)
T1b N0 M0	5 (35.71%)
T2 N0 M0	1 (7.14%)

Table 3/D. Tumour infiltration

Submucosa	5 (35.71%)
Muscularis propria	3 (21.42%)
Subserosa	4 (28.57%)
Mesoappendix	2 (14.28%)

Table 3/E. Lymphovascular invasion.

Positive	1 (7.14%)
Negative	13 (92.85%)

Table 3/F. Surgical margin

Positive	1 (7.14%)
Negative	13 (92.85%)

three patients had gangrene. No tumour findings were found in any of the patients.

According to the 2010 World Health Organization (WHO) classification, 12 patients (85.71%) had well-differentiated G1 histology and two patients (14.28%) had moderately differentiated G2 histology. According to the Europen Neuroendocrine Tumour Society (ENETS) guideline, eight patients had T1aN0M0, five patients T1BN0M0 and one patient T2N0M0 stage. The average tumour size was 1.17 cm (0.4-2 cm). Surgical margin was found to be positive in one patient with lymphovascular involvement (Table 3). The tumour was located distally in six patients (42.83%), medial in seven patients (50%) and in the radix in one patient (7.14%). Two patients with a positive surgical margin and a tumour size of

2 cm underwent right hemicolectomy later. Surgical margin of these two cases was reported as negative. No lymphovascular invasion was observed. There was no metastasis or lymph node involvement. The mean follow-up duration of the patients was 36.4 months. The patients were followed by CT and colonoscopy. None of our patients had recurrence or died during the follow-up period.

Discussion

Appendectomy is the most performed emergency operation. In our study, of the 6592 patients who underwent appendectomy within eight years, 14 (0.21%) had NET, a rate slighlty lower than that reported in the literature (0.33%)[12]. The average age of our patients was 36.71 years, which was compatible with the literature[13]. Such tumours are more common in women[5,14]. About 70% of appendiceal NETs are located distally to the appendix[10]. This rate was 42.83% in the present study. In half of the other cases, the tumour was located medially to the appendix. If the tumour size is 1 cm or less, appendectomy is enough for the treatment of NETs. However, tumours bigger than 2 cm require right hemicolectomy. The most appropriate approach for tumours with a size of 1–2 cm is still a matter of debate[10]. All tumours were well-differentiated (G1 and G2), according to the 2010 WHO classification. Furthermore, our cases had T1N0M0 and T2N0M0 stages, according to TNM classification. No lymph node involvement and metastasis were observed in patients from our study and therefore a second operation was not necessary. Raoof et al.[15] reported a rate of 2.7% of lymph node involvement, even if the tumour size is less than 1 cm, and this rate has been reported to increase up to 31% and 64% in tumours with a size of 1-2 cm and 2 cm, respectively. These authors suggested that lymph node involvement was the best prognostic factor in such cases. There are numerous studies in the literature reporting that appendectomy is sufficient and no other surgical procedure is needed for the treatment of tumours smaller than 2 cm in patients with NET[16,17].

No additional procedure is required following appendectomy in incidentally-detected appendiceal NET cases. Imaging methods may be used for high-grade tumours smaller than 1 cm, tumours with a size of 1-2 cm, tumours larger than 2 cm, and metastatic tumours[18]. Computed tomography and indium-111-labeled octreotide scintigraphy can be used for such cases[19]. Plasma chromogranin A level was found to be high in 80-100% of patients with NETs[20].

However, there are several authors who do not find this treatment approach adequate and recommend more aggressive surgical resection[23]. In the literature, there are studies suggesting that right hemicolectomy should be performed in patients with high-grade malignant NET, particularly in tumours located in the root of the appendix[24]. In one patient in the present study, the tumour was located in the appendix radix and the surgical margin was positive; therefore, right hemicolectomy was performed for this patient as the second operation. The histopathological result of this patient revealed that the surgical margin was negative and there was no lymph node involvement (G1, T1N0M0).

The risk of metastasis is high in patients with NET with a size of 2 cm or larger[10,15]. More aggressive surgery should be performed for these patients[25]. Right hemicolectomy is the most commonly recommended and performed surgical approach in such cases. However, there are also studies in the literature indicating that ileocecal resection is sufficient[26].

In the literature, there are studies suggesting pharmacological control and cytoreductive chemotherapy for tumour-secreted bioactive products in metastases of NET cases and in carcinoid syndrome[27]. The response rate to short-acting chemotherapy combined with streptozotocin and 5-fluorouracil or doxorubicin is reported to be about 40%[28]. Although octreotide, which is a somatostatin analogue, is the most effective pharmaceutical agent, the success rate does not exceed 60%[29]. Hepatic artery chemoembolization can be tried in patients with unresectable liver metastases who cannot recover with these treatments[30].

Conclusions

In the present study, no NET diagnosis can be made neither before nor during the surgery in any of the patients with acute appendicitis who underwent surgery. All patients were incidentally diagnosed as NET. No recurrence occurred in any of our patients during the follow-up period. In conclusion, the histopathology results of patients undergoing appendectomy surgery should be examined in detail. Patients diagnosed with NET should be re-evaluated and their treatment and follow-up should be planned carefully.

Author contribution:

Formal analysis: K.A. and F.K.; Investigation: K.A. and F.K.; Resources: F.K. and K.A.; Data curation: F.K. and K.A.; Writing–original draft preparation: K.A. and F.K.; Writing–review and editing: K.A. and F.K.; Visualization: K.A. and F.K.; Supervision: K.A. and F.K.; Project administration: K.A. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

"No funding for this study"

Acknowledgements:

None

References

1. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13715 carcinoid tumors. *Cancer* 2003:97:934-59
2. Sweeney JF, Rosemurgy AS. Carcinoid tumors of the Gut. *Cancer Control* 1997;4(1):18-24.
3. Birkness J, Lam-Hilmlin D, Byrnes K, Wood L, Voltaggio L. The inverted appendix – a potentially problematic diagnosis:clinicopathologic analysis of 21 cases. *Histopathology.* 2019;74(6):853-860.
4. Gu Y, Wang N, Xu H. Carcinoid tumor of he appendix: A case report. *Oncol. Lett.* 2015; 9(5):2401-2403.
5. Spallitta SI, Termine G, Stella M, Calistro V, Marozzi P. Carcinoid of the appendix. A casereport. *Minerva Chir.* 2000; 55(1-2):77-87.
6. Senel F, Karaman H, Demir H. Neuroendocrine tumors detected in appendectomy specimens: ten –year single –center experience.*Turk J Med Sci.* 2018:48(1):68-73.
7. Murray SE, Lloyd RV, Sippel RS. Chen H, Oltmann SC. Postoperative surveillance of small appendiceal tumors. *Am. J. Surg.* 2014;207(3): 342-345.
8. Debnath D, Rees J, Myint F. Are we missing diagnostic opportunities in cases of carcinoid tumors oft he appendix? *Surgeon.* 2008;6(5):266-272.
9. Shapiro R, Eldar S, Sadot E, Papa MZ, Zippel DB. Appendiceal carcinoid at a large tertiary center: pathologic findings and long-term follow-up evaluation. *Am. J. Surg.* 2011;201(6):805-8.
10. Pape UF, Niederle B, Costa F, et al. ENETS Consensus Guidelines for Neuroendocrine neoplasms of the appendix (Excluding Goblet Cell Carcinomas). *Neuroendocrinology.* 2016;103(2):144-52.
11. Tadashi T. Carcinoid tumors of digestive organs: a clinicopathologic study of 13 cases. *Gastroent Res* 2009; 2(1):35-37.
12. Mahajan H, Gosselink MP, Di Re AM, Larcos G, Ping CH, Ctercteko G. A multifocal pattern of neuroendocrine neoplasms along the appendix: A series of six cases. *Int J Surg Pathol.* 2019;27(6):613-618.
13. Zehani A, Aloui, Chelly I, Haouet S, Kchir N. Gastrointestinal neuro-endocrine tumors, retrospective study of 36 cases. *Tunis Med.* 2017;95(6):393-400.
14. McCusker ME, Cote TR, Clegg LX, Sobin LH. Primary malignant neoplasma of the appendix: a population based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer* 2002;94(12):3307-12.
15. Raoof M, Dumitra S, O`Leary MP, Sing G, Fong Y, Lee B. Mesenteric lymphadenectomy in well-differentiated appendiceal neuroendocrine tumors. *Dis Colon Rectum* 2017;60(7):674-681.
16. Tchana-Sato V, Detry O, Detroz B, et al. Carcinoid tumor of the appendix:a consecutive series from 1237 appendectomies. *World J Gastroenterol* 2006;12 (41): 6699-701.
17. Rothmund M, Kisker O. Sugical treatment of carcinoid tumors of small bowel, appendix, colon and rectum. *Digestion* 1994;55 Suppl 3: 86-91.
18. Goede AC, Caplin ME, Winslet MC. Carcinoid of the appendix. *Br J Surg.* 2003;90(11):1317- 22
19. Roggo A, Wood WC, Ottinger LW. Carcinoid tumors of the appendix. *Ann Surg* 1993;217(4):285-90.
20. Oberg K. Neuroendocrine gastrointestinal tumors – a condensed overview of diagnosis and treatment. *Ann Oncol* 1999;10 Suppl 2:S3-58.
21. Fornaro R, Frascio M, Sticchi C, et al. Appendectomy on right hemicolectomy in the treatment of appendiceal carcinoid tumors. *Tumori* 2007;93(6):587-90.
22. Gore RM, Berlin JW, Mehta UK, Newmark GM, Yaghmai V. GI carcinoid tumors: appearance of the primary and detecting metastases. *Best Pract Res Clin Endocrinol Metab.* 2005;19(2):245-63.
23. Amr B, Froghi F, Edmond M, Haq K, Kochupapy TR. Management and outcomes of appendicular neuroendocrine tumors: retrospective review with 5-year follow-up. *Eur. J. Surg. Oncol.* 2015;41(9) 1243-6.
24. Mitra B, Pal M, Paul B, Saha TN, Maiti A. Goblet cell carcinoid of appendix: a rare case with literature review. *Int. J. Surg. Case Rep.* 2013;4(3):334-7.
25. Safioleas MC, Moulakakis KG, Kontzoglou K, et al. Carcinoid tumors of the appendix. Prognostic factors and evaluation of indications for right hemicolectomy. *Hepatogastroenterology.* 2005;52(61):123-7.
26. Corpron CA, Black CT, Herzog CE, Sellin RV, Lally KP, Andrassy RJ. A half century of experience with carcinoid tumors in children. *Am J Surg* 1995;170(6) :606-8.
27. Sweeney JF, Rosemurgy AS. Carcinoid tumor of the gut. *Cancer Control* 1997;4(1):18-24.
28. Kvols LK. Metastatic carcinoid tumors and the carcinoid syndrome. A selective review of chemotherapy and hormonal therapy. *Am J Med* 1986;81(6B):49-55.
29. Kvols LK, Moertel CG, O`Connell MJ, Schutt AJ, Hahn RG. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *N Engl J Med* 1986;315(11):663-6.
30. Therasse E, Breittmayer F, Roche A, et al. Transcatheter chemoembolization of progressive carcinoid liver metastasis. *Radiology* 1993;189(2):541-7.