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 pour appendicite aiguë dans deux centres de santé différents, entre janvier 2012 et mai 2020, ont été obtenues à partir d’un scanner 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 des tumeurs étaient distales, sept étaient médiales et une était radicale. La taille moyenne des tumeurs était de 1,17 cm. Une hémostomie droite a été réalisée chez deux patients avec tumeurs
INTRODUCTION

Neuroendocrine tumours (NETs), also known as carcinoid tumours, develop from neural crest cells and are mostly (95%) located in the gastrointestinal tract. More rare, these tumours may be located outside the gastrointestinal tract, such as bronchi, ovary, and thymus. Appendiceal NETs developed from neuroendocrine cells of the appendix are benign tumours that metastasize very rarely, and are the most common appendiceal tumours. Such tumours can be seen in about 0.33% of appendectomy specimens. They are more common in women than in men. 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. When tumours grow, they may cause abdominal pain, abdominal distension, and ileus. Sometimes, symptoms suggestive of carcinoid syndrome (diarrhea, flushing) may appear. The diagnosis is usually made after histopathological examination of appendectomy specimens. These tumours are often located distally to the appendix, have usually less than 1 cm in size and are rarely larger than 2 cm. Although incidentally detected, NETs have a good prognosis, and they may rarely recur. 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. Neuroendocrine tumours can immunohistochemically release neuroendocrine markers such as chromogranin A, synaptophysin, non-specific enolase (NSE), CD56 and glucagon.

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...
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 European 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

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 hemicolecysty |
| 9  | M      | 56  | Radix               | 1.8             | Right hemicolecysty |
| 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     | 1.09      |
| M + F  | 36.71   | 6      | 7      | 1     | 1.17      |

Table 3. Details of histopathology results of the patients.

| Table 3/A. Tumour localization         | Table 3/B. WHO classification 2010 |
|----------------------------------------|-----------------------------------|
| Distal                                 | G1                                |
|                                        | (57.14%)                          |
| Medial                                 | G2                                |
|                                        | (14.28%)                          |
| Radix                                  | G3                                |
|                                        | 0                                 |

| Table 3/C. TNM classification          | Table 3/D. Tumour infiltration    |
|----------------------------------------|-----------------------------------|
| T1 N0 M0                               | Submucosa                         |
|                                        | (57.14%)                          |
| T1b N0 M0                              | Muscularis propria                |
|                                        | (35.71%)                          |
| T2 N0 M0                               | Subserosa                         |
|                                        | (28.57%)                          |
|                                        | Mesoappendix                      |
|                                        | (14.28%)                          |

| Table 3/E. Lymphovascular invasion.   | Table 3/F. Surgical margin        |
|---------------------------------------|-----------------------------------|
| Positive                              | Positive                          |
|                                      | (7.14%)                           |
| Negative                              | Negative                          |
|                                      | (92.85%)                          |
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 slightly 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 literature3. Such tumours are more common in women5,14. About 70% of appendiceal NETs are located distally to the appendix40. 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 debate50. 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 NET46,51.

No additional procedure is required for 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 tumours58. Computed tomography and indium-111-labeled octreotide scintigraphy can be used for such cases59. Plasma chromogranin A level was found to be high in 80-100% of patients with NETs38.

However, there are several authors who do not find this treatment approach adequate and recommend more aggressive surgical resection23. 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 appendix24. 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 larger10,15. More aggressive surgery should be performed for these patients23. Right hemicolectomy is the most commonly recommended and performed surgical approach in such cases. However, there are also studies in the literature indicating that ileorectal resection is sufficient26.

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 syndrome27. 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 treatments30.

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“

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