



Appendiceal Carcinoid Tumors—A Single-Center Case Series Analysis of 2415 Appendectomies

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Abstract

We aimed to report our experiences about the appendiceal carcinoid tumor (ACT) detected incidentally in patients who operated with the diagnosis of acute appendicitis (AA). A case series analyses from historical patients who had undergone elective and emergency appendectomies from January 2015 to August 2019 and registered on accrual and for whom histopathological records were well preserved have been analyzed. Those cases with histopathologically proven ACT were extracted, and demographics, clinicopathological characteristics, treatment modalities, and follow-up results were evaluated. Among the 2415 appendectomy specimens, 14 carcinoid tumors were detected (0.58%), 9 being male and 5 female patients, with a mean age of 31.5 years (21–72). The clinical presentation was AA in all cases. In twelve patients, appendectomy was sufficient, but complementary right hemicolectomy was needed in the remaining two cases. The size of the tumor was less than 1 cm in 12 (86%), and the median tumor size was 0.62 (range, 0.2–1.7). Tumor localization was an appendiceal apex in 10 (71%), midportion in 3 (21%), and base in 1 (7%). There was no need for any adjuvant therapy. During the mean follow-up time of 36.6 months (range, 24–46), all patients were disease-free and alive. An ACT is generally diagnosed incidentally with the histopathological analysis in patients undergoing surgery for suspected AA. This emphasizes the value of the histopathological analysis of every removed appendix. The long-term prognosis of incidentally found ACT is good.

Keywords Appendiceal carcinoid · Appendectomy · Treatment · Histopathological analysis

Introduction

Appendiceal carcinoid tumor (ACT) is a unique carcinoid tumor and when compared with those encountered elsewhere in the gastrointestinal system has a relatively common frequency, small size, usually indolent behavior, occurrence in middle-aged patients with female predominance [1]. Primary tumors of the appendix were identified in 0.5% of all appendectomy specimens. ACT is the most common primary tumor of the appendix representing > 50% of all appendiceal neoplasms [2]. ACTs are rare neuroendocrine neoplasms that usually behave as benign

tumors, while certain lesions possess the potential for malignancy and are therefore be able to metastasize [4]. The probability of metastasis of ACTs is low, nearly 4.7% of all ACTs [4]. Lymphatic spread is the primary route, and hepatic metastases are rare [3]. ACT has no specific clinical presentation but usually presents as acute appendicitis and mainly diagnosed incidentally in the histopathological analysis of appendectomy specimens [3].

In this retrospective study, we aimed to report a case series analysis of 14 ACTs detected after urgent appendectomy in a single tertiary referral center and to review our results in the light of current literature.

Materials and Methods

The data of patients who underwent an appendectomy at the General Surgery Clinic of Health Sciences University, Kanuni Sultan Süleyman Education and Research Hospital, Istanbul, Turkey, from January 2015 to August 2019, were reviewed and collected retrospectively from the computerized hospital

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database, patient files, and phone calls. Detailed surgery and histopathological reports were recorded. Further surgery and treatment if any was also recorded. Follow-up data is investigated.

Patients with the diagnosis of histopathologically proven ACT were analyzed for demographics (age, gender), histopathological results, operation reports, and follow-up times, and findings, localization, diameter, depth of invasion of the tumor, histopathological cell type, mitotic activation rate, and level of Ki67 were defined.

This study was carried out according to the principles of the Helsinki Declaration. All the patients were routinely informed and provided their written consent.

Statistical Analysis

A descriptive analysis was used. For uniform distributions, mean and standard deviation, and diverse distributions, median and range were used.

Results

A total number of 2475 appendectomies were performed during the study period. Sixty appendectomies found to be in conjunction with other operations were extracted from the study. Among these 2415 cases, 14 (0.58%) patients had histopathologically proven carcinoid tumors of the appendix. Patients consisted of 9 (64%) males and 5 (36%) females with a mean age of 31.5 years (range, 21–72). Preoperative diagnosis was acute appendicitis in all cases.

Initial operations were open appendectomy with Mcburney incision in 9 patients and laparoscopic appendectomy in the

remaining 5 cases. In two patients with a tumor size of greater than 1 cm and with mesoappendiceal involvement, a complementary right hemicolectomy was performed (Table 1). In these two patients, mesoappendiceal lymph node metastasis and in patient with ACT at the base of the appendix, cecal tumor infiltration was detected in histopathological examination.

Histopathologically tumor was located at the apex of appendix in 10 (71%) patients, in the midportion in 3 (21%) cases, and at the base of the appendix. Mean diameter of tumor size was 0.62 cm (range, 0.2–1.7) (Table 1). Depth of invasion was detected as submucosa in 8 (57%), muscularis propria in 4 (29%), and mesoappendix in 2 (14%) cases. Ki67 proliferation and mitotic index levels were < 3 in all cases (Table 2).

During a mean follow-up of 36.6 months (range, 24–46), all patients were alive and had no tumor recurrence. Our results are shown in Table 1.

Discussion

Carcinoid tumors of the appendix are rare neoplasms. It has been previously reported that the incidence of ACTs ranges between 0.3 and 0.9%, as determined incidentally by using histopathological examination performed on excised appendectomy specimens [5]. However, ACTs are the most frequent tumors arising from the appendix, comprising between 32 and 57% of all appendiceal tumors [5]. Our study could be considered as a large volume sample size with a similar incidence rate of ACTs in line with previous studies [5, 7–10]. The incidence of ACTs that have been reported in the former studies is shown in Table 3.

Table 1 Demographics, histopathological results, operation types, and follow-up time of patients

Mean age (range) (year)	31.5 (21–72)
Male/female ratio	9/5
Incidence (compared with appendectomy cases) (%)	0.58%
Pathology	Classical carcinoid tumor (100%)
Location of tumor (n, %)	Apex (10, 71%) Midportion (3, 21%) Base 1 (1, 7%)
Mean diameter mean (range) (cm)	0.62 (0.2–1.7)
Depth of invasion (n, %)	Submucosa (8, 57%) Muscularis propria (4, 29%) Mesoappendix (2, 14%)
Operative approach (n, %)	Appendectomy (12, 86%) Complementary right hemicolectomy (2, 14%)
Mean follow-up mean (range) (month)	36.6 (range, 24–46)

n, number of patients, %, percentage; mean number (range)

Table 2 Tumor localization and histopathological properties

No	Tumor site	Depth of invasion	Size of tumor (cm)	Mitosis	Ki67
1	Apex	Submucosa	0.2	<3	<3
2	Midportion	Muscularis propria	0.4	<3	<3
3	Apex	Submucosa	0.5	<3	<3
4	Apex	Submucosa	0.7	<3	<3
5	Apex	Submucosa	0.6	<3	<3
6	Apex	Muscularis propria	0.5	<3	<3
7	Base	Mesoappendix	1.3	<3	<3
8	Midportion	Muscularis propria	0.8	<3	<3
9	Apex	Submucosa	0.3	<3	<3
10	Apex	Muscularis propria	0.5	<3	<3
11	Midportion	Mesoappendix	1.7	<3	<3
12	Apex	Submucosa	0.5	<3	<3
13	Apex	Submucosa	0.4	<3	<3
14	Apex	Submucosa	0.3	<3	<3

Appendiceal carcinoid tumors are usually asymptomatic and have no specific clinical symptoms or signs, but the tumor can occasionally obstruct the appendiceal lumen much like a fecalith and result in acute appendicitis, and diagnosis is made incidentally on histopathological analysis [6]. In a retrospective study of 1570 cases, it is reported that there was a marked female predominance (M/F ratio, 0.47), and the mean age of diagnosis was 42.2 years [1]. In our study, all patients were presented with the signs and symptoms of acute appendicitis, and ACT diagnosis was made only after histological analysis of the appendectomy specimen. On the contrary to the literature, surprisingly, there was a male predominance in our study (male/female, 9/5), and mean age was 31.5 (21–72).

The majority of ACT is located at the apex of the appendix, and the majority of the cases are smaller than 1 cm [7]. The malign potential of ACT is directly related to tumor size, and metastasis is very rare for the tumors smaller than 1 cm [7]. In our series, the tumors were localized at the tip of the appendix in 10 (71%) cases, at the midportion of appendix in 3 (21%), and the base in 1 (7%). The tumor was smaller than 1 cm in 86% of cases with a median diameter of 0.62 cm (range, 0.2–1.7).

ACT exhibits little metastatic potential and therefore rarely presents with metastases [11]. Characteristics of the tumor predicting aggressive behavior include size, histological subtype, and mesoappendiceal involvement [12]. The predictive value of tumor size is supported by many studies [13]. The calculated risk of metastasis from tumors ≤ 1 cm is zero, while a definite increase of risk occurs with tumor size ≥ 2 cm, the rate of metastasis ranges from 20 to 85% [13]. In our series, tumors were less than 1 cm in 12 (87%) cases who were treated with simple appendectomy. In two cases with mesoappendiceal involvement, tumor size was 1–2 cm (13%) and right hemicolectomy was the treatment of choice. Histopathological examination of hemicolectomy specimens demonstrated the regional mesoappendiceal but no distant lymph node metastasis.

ACT usually metastasizes to the regional lymph nodes rather than to the liver [14]. Carcinoid syndrome develops in less than 10% of patients with carcinoid tumors [15]. Clinically, this syndrome develops when vasoactive substances produced by carcinoid tumor escape hepatic degradation and gain access into the systemic circulation. Its clinical features include facial flushing, bronchospasm, diarrhea, and

Table 3 The review of literature of appendiceal carcinoid tumors in terms of years, number of cases enrolled, and incidence

Lead author	Years	Number of AA enrolled	ACT detected	Incidence
Beyrouiti et al.	1995–2001	9584	46	0.48%
Connor et al.	1979–1994	7970	74	0.9%
Butte et al.	1980–2007	8903	40	0.44%
Tchana-S et al.	2000–2004	1237	5	0.4%
Egin et al.	2006–2012	3769	10	0.26
Current series	2015–2019	2415	14	0.58%

AA, acute appendicitis; ACT, appendiceal carcinoid tumor

right-sided cardiac valvular fibrosis. This syndrome can be seen in ACT patients with liver metastases (<2% of all ACTs) [16]. In our series, during the follow-up period, we did not encounter any carcinoid syndrome episode.

A simple appendectomy is enough treatment for ACT < 1 cm in diameter because metastasis is unlikely [15]. In our study, twelve ACT patients with tumor size of 0.2–0.9 cm underwent a simple appendectomy, and there was no mesoappendiceal lymph node involvement. Controversy exists over the management following an appendectomy, especially about the role of right hemicolectomy in patients with tumors 1 to 2 cm in size [15]. Some acceptable indications for right hemicolectomy in these controversial cases have been proposed including histological evidence of mesoappendiceal extension, tumor at the base of the appendix with positive margins or involvement of the caecum, high-grade malignant ACT with a raised tumor prognostic index as measured by mitotic index, and Ki67 proliferation index [11]. In our series, reoperation with complementary right hemicolectomy was performed in two patients whose tumor sizes were 1.3 and 1.7 cm with mesoappendiceal invasion. Formal right hemicolectomy must be the treatment of choice for ACT > 2 cm in size due to the increased incidence of regional and distant metastasis [17]. Thus, the results of the histopathological analysis are so important for deciding whether additional curative treatment is needed or not.

The prognosis of ACT seems to be much better than other gastrointestinal carcinoid tumors [17]. The 5-year survival rate of patients with local disease is reported to be 92%, 81% of those with regional metastases, and 31% of those with distant metastases, respectively [18]. In our series, all the patients were alive without recurrence during a mean follow-up of 36.6 months.

Relations of ACTs with other synchronous or metachronous colorectal cancers have attracted a lot of concern and reported in the literature [19]. Secondary primary cancer and carcinoid tumor association was first reported by Pearson by the autopsy series in nearly 55% of frequency rates [20]. Although these secondary neoplasms can originate from any tissue in the body, they usually originate from the gastrointestinal tract [20]. Multicentric prospective studies with large case series are needed to determine the exact frequency of association and the need for early colorectal cancer screening programs for these patients. In our series, no ACT patients had concomitant secondary primary tumor at the time of diagnosis and during follow-up period.

The study has some limitations. First of all, it is a single-center study and has a retrospective design. But its relatively large cross-sectional data softens its limitations.

Conclusions

Appendiceal carcinoid tumor usually presents itself as an acute appendicitis and diagnosed incidentally on

histopathological examination. Hemicolectomy should be considered in carcinoid tumors 1–2 cm in size if the mesoappendix is involved, angioinvasion is demonstrable, a high mitotic index, and Ki67 level is apparent. We have aimed to raise awareness of the importance of the results of histopathological analysis of appendectomy specimens. The increased likelihood of coexisting neoplasms and relative risk of metastasis should warrant careful evaluation and postoperative follow-up of such lesions.

Authors' Contributions Study conception and design: Yasin Kara, Mustafa Uygur Kalaycı

Acquisition of data: Yasin Kara

Analysis and interpretation of data: Yasin Kara

Drafting of manuscript: Yasin Kara and Mustafa Uygur Kalaycı

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent This study was carried out according to the principles of the Helsinki Declaration. All the patients were routinely informed and provided their written consent.

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