

Prevalence and clinicopathological characteristics of appendiceal carcinoids in Sharjah (United Arab Emirates)

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Abstract

AIM: To determine the incidence and clinico-pathological profile of appendiceal carcinoids in a cohort of patients undergoing emergency appendicectomies for clinically suspected acute appendicitis in Sharjah, United Arab Emirates (UAE).

METHODS: The study included the retrospective data of 964 patients operated for clinically suspected acute appendicitis, and the resected specimens were received at Al-Qasbi Hospital (Sharjah) from January 2010 to December 2010. The data of the patients who were histologically reported to have carcinoid tumors of the appendix were extensively evaluated for the patient's demographics, indication for surgery, surgical procedure, tumor localization in the appendix, diameter of the lesion, concomitant appendicitis, immunohisto-

chemistry studies and clinical follow-up.

RESULTS: Out of the 964 patients included in the study, 9 (0.93%) were found to have appendiceal carcinoids. The mean age reported was 28.7 years with a male to female ratio of 2:1. Eight tumors were located near the tip of the appendix with a mean diameter of 3.3 mm, while the remaining one was near the proximal end of the appendix. All the cases were associated with concomitant suppurative appendicitis. In seven reported cases, tumors were confined to the muscular layer while in one case each there was an extension to the serosa and mesoappendix, respectively. All tumors were found to be positive for chromogranin A, synaptophysin and neuron-specific enolase on immunohistochemistry but negative for cytokeratin-7. None of the patients developed recurrence or any reportable complications in the short follow-up period (12-26 mo) that was arranged as a six-monthly re-evaluation by abdominal ultrasonography.

CONCLUSION: Our study found a higher incidence of appendiceal carcinoids in patients undergoing emergency appendectomy for acute appendicitis in Sharjah, UAE compared to two previous studies from the Persian Gulf region. Interestingly, tumors were found to be more commonly in young males, which is in contrast to previous studies. Moreover, all the tumors were positive for common neuroendocrine markers.

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Key words: Appendix; Carcinoid; Prevalence; Sharjah United Arab Emirates

Core tip: Incidence of appendiceal carcinoids is higher in patients undergoing emergency appendectomy for acute appendicitis in Emirate of Sharjah compared to two previous studies from the same geographical region. Moreover, tumors were found more commonly in

young males in contrary to previous studies.

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INTRODUCTION

Carcinoid tumors are rare, slow-growing neuroendocrine tumors arising from the enterochromaffin cells disseminated throughout the gastrointestinal and bronchopulmonary systems^[1]. The biological behavior of these tumors is poorly understood. Carcinoid tumors are considered indolent tumors as compared to adenocarcinoma, yet they have a potential to exhibit highly aggressive behavior. Although in 2004 they accounted for 1.25% of all malignancies, their frequency is augmenting by 6% annually^[2]. In an American study the most common primary tumor site varied by race, with the lung being the most common in white patients, and the rectum as the most common site in Asian/Pacific Islander, American Indian/Alaskan Native, and African American patients^[3].

The incidence of gastrointestinal carcinoids in both males and females has concurrently increased. A recent study from England analyzing the anatomic distribution of the tumors in 10324 cases revealed the commonest site to be the appendix, small intestine, colon, stomach and rectum in the decreasing order of frequency^[4]. Additionally, the largest absolute increase in incidence of the carcinoid was also reported at the site of the appendix^[4]. Recent data report the overall incidence of carcinoid tumors among patients undergoing emergency appendectomies between 0.27% and 1.6%^[5,6].

Appendiceal carcinoid tumors are clinically silent and are usually an incidental finding in patients undergoing surgery for suspected acute appendicitis or during incidental appendectomy in the course of relevant abdominal surgery procedures^[7]. Most appendiceal carcinoids are located at the tip of the organ. They are usually diminutive, measuring less than 1 cm, and rarely grow beyond than 2 cm in diameter^[8]. Immunohistochemically carcinoid tumors of the gastrointestinal tract including the appendix express general neuroendocrine markers, such as chromogranin A, synaptophysin, non-specific enolase (NSE), CD56 and glucagon^[9]. The gold standard treatment is surgical treatment by resection of the whole appendix for carcinoids located around the tip. In cases where the tumor is larger than 2 cm or located at the base of the appendix, a wider resection has to be performed with right hemicolectomy^[1,2,4].

The aim of the current study was to determine the incidence and clinicopathological characteristics of appendiceal carcinoids along with their immunohistochemical

Table 1 Clinicopathological characteristics of patients with appendiceal carcinoids from Emirates of Sharjah

Patient number ¹	Age (yr)	Gender	Tumor size (mm)	Extension ²	Tumor localization
1	25	M	8	Serosal layer	28 mm from proximal end
2	29	M	4	Mesoappendix	Tip
3	33	M	4	Muscular layer	Tip
4	19	M	2	Muscular layer	2 mm from tip
5	28	M	1	Muscular layer	Tip
6	54	M	1	Muscular layer	6 mm from tip
7	25	F	4	Muscular layer	13 mm from tip
8	18	F	3	Muscular layer	Tip
9	27	F	3	Muscular layer	10 mm from tip

¹All cases underwent open appendectomy for clinical diagnosis of appendicitis which was further confirmed on microscopic examination;

²No vascular invasion was identified in any case. M: Male; F: Female.

profile in a cohort of patients undergoing emergency appendectomies for clinically suspected acute appendicitis in Sharjah, United Arab Emirates (UAE).

MATERIALS AND METHODS

This retrospective study was carried out at the Pathology Department of Al-Qasmi Hospital, Sharjah, UAE, which is the only tertiary care government facility in the region for the histopathological analysis of the surgical specimens. This study includes all consecutive patients who underwent appendectomies between January 2010 and December 2010 in Sharjah, UAE, and their specimens were received at the hospital for analysis. Only the data of the patients who were histologically reported to have carcinoid tumors of the appendix was reviewed for the patient's age, gender, indication for surgery and surgical procedure. The histological analysis included tumor localization in the appendix, evaluation of the diameter of the lesion after fixation with formaldehyde, concomitant appendicitis, and immunohistochemical analysis of chromogranin A, synaptophysin, NSE, serotonin, carcinoembryonic antigen (CEA), CK-7 and cytokeratin-20 (CK-20). Patient follow-up was conducted for those diagnosed with carcinoids only every 6 mo and recurrence evaluated by abdominal ultrasonography.

RESULTS

Nine hundred and sixty-four patients underwent appendectomies during the study period, of whom 9 (0.93%) were found to have histological evidence of carcinoid tumors of the appendix. The clinicopathological data in relation to carcinoids are shown in Table 1. There were 6 male and 3 female patients with a mean age of 28.7 years (range, 18-54 years). All the cases were operated for a clinical suspicion of appendicitis. Histologically 4 carcinoid lesions were demonstrated at the tip, another 4 ranged from 2-13 mm away from the tip and one lesion was located 28 mm from the base of the appendix. The

Table 2 Immunohistochemical characterization of appendiceal carcinoid tumors in patients from Emirates of Sharjah

Patient number	Age (yr)	Sex	CG	Synaptophysin	NSE	5-HT	CEA	CK20	CK7
1	25	M	+	+	+	-	-	-	-
2	29	M	+	+	+	+	-	-	-
3	33	M	+	+	+	-	-	-	-
4	19	M	+	+	+	-	-	+	-
5	28	M	N/D	N/D	N/D	N/D	N/D	N/D	N/D
6	54	M	+	+	+	+	+	-	-
7	25	F	+	+	+	+	-	-	-
8	18	F	+	+	+	-	-	-	-
9	27	F	+	+	+	+	-	-	-

CG: Chromogranin; NSE: Non-specific enolase; 5-HT: Serotonin; CEA: Carcinoembryonic antigen; CK-20: Cytokeratin 20; CK-7: Cytokeratin 7; N/D: Not determined as the tissue sample was unavailable for the staining procedure; M: Male; F: Female.

mean diameter of the tumors was 3.3 mm (range, 1-8 mm). Concomitant suppurative appendicitis was present in all cases. Seven tumors were confined to the muscular layer, while one case exhibited an extension to the serosa and another extended to the mesoappendix. The margins of all the resected tissue samples received for histological analysis, however, were free of tumor cells.

In one case the tissue sample from the tip was very infinitesimal to be evaluated by immunohistochemistry (IHC). The rest eight tumors were positive for chromogranin A, synaptophysin and NSE as shown in Table 2. Four tumors were additionally found to be positive for serotonin and one each for CEA and CK-20. None of the tumors was positive for CK-7.

All patients remained disease-free after a median follow-up duration of 22 mo (range, 12-26 mo).

DISCUSSION

Carcinoid tumors were not considered to be common tumors, but recent studies suggest an abrupt increase in their incidence and prevalence over the last few decades. Additionally, the appendix has been identified as one of the most common sites for carcinoids in the gastrointestinal tract^[3,10]. The reason for this rise remains, as yet, obscure, although an increase in the number of elective appendectomies was considered to be one of the contributing factors. Contrary to this belief, a recent study demonstrated that the number of surgeries did not actually influence the incidence of appendiceal carcinoids^[6]. However, more extensive pathological examination including multiple sections from different parts of the appendix may have played a part in detecting even the tiny foci of the tumors. Our present findings validate this hypothesis since most of the carcinoids identified were relatively small in size (1-4 mm in diameter). Carcinoid tumors are generally asymptomatic due to their small size and specific location in the appendix and are commonly diagnosed as an incidental finding in emergency or elective appendectomy specimens^[11]. Although the majority of the carcinoids exhibit benign behavior, they do have a malignant potential with the ability to metastasize^[7].

Our present study reports the incidence of carcinoid

tumors at 0.93% per annum in the pathological specimens obtained during emergency appendectomies. This incidence is quite high compared to that reported by two other studies conducted in the same geographical region. The reported incidence in appendectomy specimens from Iran was 0.2% and that from Saudi Arabia 0.6%^[12,13]. However, in most studies from other geographical regions the incidental histological diagnosis of carcinoid ranged from 0.3%-0.9% in patients undergoing appendectomy^[8]. In a recent study conducted in a community teaching hospital in South Australia, appendiceal carcinoids were even found to occur in 1.6% of emergency appendectomies performed for acute appendicitis^[6].

We did not observe a female preponderance in our patients with carcinoids as suggested in many previous studies^[12-14]. We are unable to explain this gender disparity in our study where males were affected by this neoplastic lesion twice as frequently as females. There may be, however, a strong environmental bias in the UAE for this discrepancy. The gut microbiome influences both the development of the mucosal immune system as well as the regulation of epithelial regeneration^[15]. Previous literature has indicated carcinoid tumors to be distributed among younger age groups (20-30 years of age) and their preferential location in the tip of the appendix, with the latter being attributed to the increased density of subepithelial neuroendocrine cells near the tip^[16,17]. Our observations in the present study confirm these findings (Table 1). The average age for males was 31.3 years while for females it was 23.3 years. The mean overall age of the patients was 28.7 years.

Approximately 80% of appendiceal carcinoids are less than one centimeter in diameter^[8]. Our present findings are consistent with previous studies as the tumor size in all cases in our study were less than one centimeter, with eight cases measuring between 1 and 5 mm and one 8 mm in diameter. Seven carcinoids were confined to the muscular layer, while one extended into the serosal layer and another one was located in the mesoappendix (Table 1).

All carcinoid tumors evaluated in this series showed positive IHC staining for common neuroendocrine markers. Interestingly, all the samples identified were positive for chromogranin A, synaptophysin and neu-

ron-specific enolase (Table 2). However, four carcinoids were positive for serotonin and one each for CEA and CK-20, respectively, all of them had a size between 1-4 mm. A previous study has demonstrated variable staining for these markers (62%-85%) in gastrointestinal carcinoids^[9]. The staining characteristics observed in our study were not associated with any other clinicopathological characteristics.

Although some carcinoids have been reported to be aggressive, none of the patients had recurrence or any reportable complications in the short follow-up period (12-26 mo). Histological analysis of the draining lymph nodes or the liver was not performed due to gross normal appearance and unremarkable abdominal ultrasonographic findings in these patients. The metastatic potential of carcinoids cannot be accurately assessed based on the follow-up duration, and this is a limitation of the current study.

Our seminal study from this region shows the incidence of appendiceal carcinoids in patients undergoing emergency appendectomies for clinically suspected acute appendicitis from Sharjah, UAE to be higher than that reported by two previous studies from the same geographical region. Contrary to other studies, young males were involved two times more commonly than the females. All tumors were found positive for common neuroendocrine markers.

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COMMENTS

Background

Carcinoid tumors are considered to be one of the commonest tumors in the appendix. Their incidence has been shown to vary in different studies and this seminal study details the prevalence of these tumors in the United Arab Emirates.

Innovations and breakthroughs

This is the first study from the region that shows that the incidence of appendiceal carcinoid tumors has augmented as compared to the previous studies from the region. Interestingly, this rise is observed in the young male population instead of the females, as highlighted in previous studies.

Applications

Such a difference in incidence necessitates an investigative research into the etiology and further monitoring to evaluate the trend of these tumors that may be associated with environmental factors due to changes in the gut microbiome. Repetitive evaluations are fundamental to assess incidence rates in cancer demographics. In addition data from other countries in the Persian Gulf region can provide a better global perspective.

Peer review

The authors present a subject of importance for the surgical community: the carcinoids of the appendix.

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