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Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO: 7367).

"Title: Prevalence and clinicopathological correlation of carcinoid in appendectomy specimens in Sharjah, United Arab Emirates (UAE)".

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The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated and a few grammatical errors have been corrected.
2. Revision has been made according to the suggestions of the reviewer and all the changes have been highlighted in yellow.
3. References and typesetting were corrected. DOI and PMID has been added to each reference where available. For those references that have not been indexed by PubMed, a printed copy of the article of the reference has been submitted.

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Oncology*.

Sincerely yours,

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Please note one of the authors of this manuscript “Farhan Sacchal Cyprian” is a native English speaker and he has taken care of ENGLISH language in this paper.

Prevalence and clinicopathological correlation of carcinoid in appendectomy specimens in Sharjah (UAE)

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Author contributions:

Khurshid Anwar designed and performed the research, reported the pathological specimens, analyzed data and wrote paper

Dr. Munaf Desai reported the pathological specimens and provided clinical information of the cases.

Ms. Noura Al-Bloushi collected and organized the data.

Dr. Farheen Alam reported the pathological specimens and provided clinical information of the cases.

Dr. Farhan Sachal Cyprian analyzed the data, wrote paper and revised it for any English grammatical errors

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ABSTRACT

Background. Carcinoid tumors, although rare, are considered to be one of the commonest tumors in the appendix. Their incidence has been shown to vary in different studies.

Aimes, Setting & Design. This seminal study was carried out 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).

Materials and methods. The study included the retrospective data of 964 patients operated for clinically suspected acute appendicitis, the resected specimens were received in the department of pathology at Al-Qasmi hospital Sharjah from January 2010 to December 2010. The data of the patients that were histologically reported to have carcinoid tumors of the appendix was extensively evaluated for the patient's demographics, indication for surgery, surgical procedure, tumor localization in the appendix, diameter of the lesion, concomitant appendicitis, immunohistochemistry 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 appendix with 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 muscular layer while in one case each there was an extension to serosa and mesoappendix. All tumors were found to be positive for chromogranin A, synaptophysin and neuron-specific enolase on immunohistochemistry (IHC) but negative for cytokeratin-7 (CK-7). None of the patients developed recurrence or any reportable complications in the short follow up period (12 – 26 months) that was arranged by a six monthly re-evaluation via abdominal ultrasonography.

Conclusions. 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 that is in contrast to previous studies. Moreover all the tumors were positive for common neuroendocrine markers.

Keywords: Appendix, Carcinoid , Prevalence, Sharjah UAE.

Running title: Appendicular carcinoid in Sharjah, UAE.

INTRODUCTION

Carcinoid tumors are rare, slow-growing neuroendocrine tumors (NETs) 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 adenocarcinomas, yet they have a potential to exhibit highly aggressive behavior. Although in 2004 their incidence was reported as 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].

Incidence of gastrointestinal carcinoid in both males and females has concurrently increased. The anatomic distribution of tumors in a recent study from England analyzing 10,324 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 a 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 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 clinico-pathological characteristics of appendiceal carcinoids along with their immunohistochemical profile in a cohort of patients undergoing emergency appendectomies for clinically suspected acute appendicitis in Sharjah, UAE.

Material & 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 patients who underwent consecutive appendectomies between January 2010 to December 2010 in Sharjah UAE and their specimens received at the hospital for analysis. Only the data of the patients that 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, immunohistochemical analysis of the following: chromograninin A, synaptophysin, NSE, serotonin, carcinoembryonic antigen (CEA), CK-7 and cytokeratin-20 (CK-20). Patient follow up was conducted for those diagnosed with carcinoid only at every 6 months and recurrence evaluated via abdominal ultrasonography.

RESULTS

Nine hundred and sixty four patients underwent appendectomy during the study period out of which, 9 (0.93%) cases were found to have histological evidence of carcinoid tumors of the appendix. The clinicopathological data in relation to carcinoids is shown in Table.1. There were 6 male and 3 female patients with a mean age of 28.7 years ranging between 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 mean diameter of the tumors was 3.3 mm (range: 1 – 8 mm) associated with concomitant suppurative appendicitis in all cases. Seven tumors were confined to muscular layer while one case exhibited an extension to serosa and another extended to the mesoappendix. The margins of all the resected tissue samples received for histological analysis, however, were free of tumor.

In one case the tissue sample from the tip was very infinitesimal to be evaluated by immunohistochemistry (IHC). The rest of the 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 months (range, 12-26 months).

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 carcinoid in gastrointestinal tract^[3,10]. The reason for this rise remains, as yet, obscure nevertheless an increase in 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 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 malignant potential with the ability to metastasize^[7].

Our present study reports the incidence of carcinoid tumors at 0.93% per annum from the pathological specimens analyzed during emergency appendectomies. This incidence is quite high compared to two other studies under taken 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 the female preponderance in our patients with carcinoid as suggested in many previous studies^[12,13,14]. We are unable to explain this gender disparity in our study where males were affected with 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 year of age) and their preferential location in the tip of the appendix, the later being attributed to the increased concentration of subepithelial neuroendocrine cells near the tip^[16,17]. Our observations in present study confirm these findings (Table 1). The average age for males is 31.3 years while for females it is 23.3 years. The mean overall age of the patients is in accord at 28.7 years.

Approximately 80% of appendiceal carcinoids are less than one cm 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 cm, 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 serosal layer and another one was located in mesoappendix (Table 1).

All carcinoid tumors evaluated in this series showed positive IHC staining with common neuroendocrine markers. Interestingly all the samples identified were positive for chromogranin A, synaptophysin and neuron-specific enolase (Table 2). However, four carcinoids were positive for serotonin and one each for CEA and CK-20, all of them had size between 1-4 mm. A previous study has demonstrated variable staining with these markers (62%-85%) in gastrointestinal carcinoids^[9]. The staining characteristics observed in our study were not associated with any other clinicopathological characteristic.

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

CONCLUSION

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 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.

ACKNOWLEDGEMENTS

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COMMENTS

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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 UAE.

Innovations and breakthroughs

This is the first study from the region that shows that the incidence of appendiceal carcinoid tumors have 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 environmentally associated due 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 prespective.

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TABLES

Table 1 : Clinicopathological correlation in patients with appendiceal carcinoid from Emirates of Sharjah.

Patient number #	Age (yrs)	Gender	Tumor size (mm)	Extension*	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

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

* No vascular invasion was identified in any case

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

Patient #	Age (yrs)	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.