

Carcinoid tumors of the appendix

Our experience in a university hospital

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ABSTRACT

Objective: To present our experience of carcinoid tumors of the appendix managed at a university teaching hospital. Complex symptomatology, varied biochemical affections and different surgical therapeutic modalities are discussed.

Methods: The medical records of all the patients who underwent consecutive appendectomies at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia from 1994 to 1999 were retrospectively analyzed. The data of patients identified to have histological evidence of carcinoid tumors of the appendix were further reviewed for the demographic details, indications for surgery, surgical procedure, tumor localization in the appendix and size; concomitant appendicitis and further surgical procedures were considered.

Results: During the study period, 1547 appendectomies were performed and, out of these, 9 (0.6%) cases were reported to have carcinoid tumors of the appendix. There were 4 male and 5 female patients, age range 17-51 years (median 29.8 years). Seven subjects had a clinical

evidence of appendicitis while 2 presented with chronic abdominal pain. There were 6 open and 3 laparoscopic appendectomies. Six carcinoid tumors were encountered at the appendiceal apex, 2 at the midportion, and one at the base with a mean diameter of 9.5 mm (range, 4-19 mm). One patient had histologically confirmed residual tumor, which necessitated a right hemicolectomy 3 weeks later. All patients remained disease-free during a mean follow up of 7 years (range, 4-10 years).

Conclusion: Carcinoid tumors of the appendix are extremely rare and invariably remain asymptomatic. Simple appendectomy offers adequate relief while the need for further extensive surgery depends on tumor characteristics and dissemination. Despite an excellent prognosis, all reported patients should be followed up with urinary 5-hydroxyindoleacetic acid and abdominal ultrasonography.

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Carcinoid tumors are among the most challenging tumors in clinical practice. Carcinoids are neuroendocrine tumors derived predominantly from enterochromaffin cells and are capable of amine precursor uptake and decarboxylation (APUD cells). The prevalence is estimated to be approximately

0.05 per 100,000 although autopsy reports suggest that it may be as high as 2 per 100,000.¹ Seventy-four percent of the carcinoids occur in the gastrointestinal tract (GIT), 25% in bronchopulmonary system² while the remaining 1% is reported in ovary,³ thymus,⁵ testis,⁵ liver,⁶ spleen⁷

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and breast.⁸ Within the GIT, 26% are found in the appendix, 15% in ileum, 11.3% in rectum, and 4.1% in the cecum.⁹ A substantial number of carcinoids clinically remain silent and 10-18% declare due to their mass effect or carcinoid syndrome,¹⁰ characterized by flushing, diarrhea, wheezing, valvular insufficiency and sexual dysfunction. Appendicular carcinoids have the most favorable prognosis of all carcinoid tumors and the tumors are identified as incidental lesions in 0.3% appendectomies¹¹ which reaffirm the premise that the diagnosis of the majority of carcinoids is made after surgery. We report a series of 9 appendiceal carcinoids, which were diagnosed by the histological analysis of the surgically removed specimens.

Methods. This retrospective survey was conducted at the College of Medicine, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia. The medical charts of all patients who underwent consecutive appendectomies from 1994 to 1999 were analyzed. The data of the patients histologically reported to have carcinoid tumors of the appendix were further reviewed for patient's age, gender, indication for surgery, surgical procedure, tumor localization in the appendix, diameter of the lesion after fixation with formaldehyde, concomitant appendicitis, the need for extended surgery and follow up.

Results. One thousand five hundreds and forty-seven patients underwent appendectomy during the study period and out of these, 9 (0.6%)

cases were found to have histological evidence of carcinoid tumors of the appendix. There were 4 male and 5 female patients with a mean age of 29.8 years (range, 17-51 years). Open appendectomy (OA) was performed in 6 and laparoscopic appendectomy (LA) in 3 cases (Table 1). Seven subjects were operated with the clinical suspicion of appendicitis and 2 for chronic abdominal pain. Histologically, 6 carcinoid lesions were demonstrated at the apex, 2 at midportion and one at the base of the appendix. The carcinoid tumors in this series ranged 4-19 mm in diameter (median 9.5 mm). Concomitant suppurative appendicitis was identified in 3 cases, although no patient was found to have a perforated appendix. Histopathology of one patient (17 years, 19 mm tumor at the appendicular base) revealed inadequate resection margins which required a right hemicolectomy 3 weeks after the first operation. All patients remained disease-free after a median follow up duration of 7 years (range, 4-10 years). Patient's follow up was arranged with yearly evaluation of urinary 5-hydroxyindoleacetic acid (5-HIAA) and abdominal ultrasonography.

Discussion. Carcinoid tumors of the appendix account for one third to one half of all the appendiceal tumors^{12,13} and occur in women twice as often as in men¹⁴ with a reported mean age of 42 years.² Seventy to ninety percent of all appendiceal carcinoids are 1 cm in diameter, 4-25% are 1-2 cm, and few are 2 cm.¹⁵ The calculated risk of metastasis from tumors 1 cm is zero while a definite increase of risk occurs with tumor size 2

Table 1 - Case presentations of patients with carcinoid tumors of the appendix (N=9).

| Patient's number | Age (years) | Gender | Surgical procedure | Tumor localization | Tumor Size (mm) | Concomitant appendicitis | Second surgery |
|------------------|-------------|--------|--------------------|--------------------|-----------------|--------------------------|----------------|
| 1 | 23 | Male | OA | Apex | 7 | Yes | No |
| 2 | 19 | Male | OA | Apex | 12 | Yes | No |
| 3 | 37 | Male | OA | Midportion | 5 | No | No |
| 4 | 26 | Female | LA | Apex | 8 | No | No |
| 5 | 51 | Female | OA | Apex | 16 | No | No |
| 6 | 17 | Female | LA | Base | 19 | Yes | RH* |
| 7 | 44 | Female | OA | Midportion | 8 | No | No |
| 8 | 20 | Male | OA | Apex | 4 | No | No |
| 9 | 32 | Female | LA | Apex | 9 | No | No |

OA - open appendectomy, LA - laparoscopic appendectomy, *right hemicolectomy.

cm, the rate of metastasis ranging from 20%¹⁶ to almost 85%.¹⁷ The mean diameter of tumor in this study was 9.5 mm and all the patients presented with a localized disease. The presence of carcinoid syndrome signifies malignant potential and is usually associated with metastatic disease.¹⁸ Carcinoid of the appendix is typically undiagnosed preoperatively,¹⁹ an observation consistent with the results of our series where none of the appendiceal carcinoids could be detected before surgery.

Twenty-four hours urinary 5-HIAA, a degraded product of serotonin is the most widely employed test in the endocrine work up of carcinoid tumors. However, it lacks accuracy as its levels may be elevated in tropical sprue, Celiac and Whipple's disease, as well as by the ingestion of serotonin rich foods.²⁰ On the other hand, urinary serotonin and platelet serotonin, indicators of serotonin overproduction, provide confirmatory evidence in the evaluation of potential carcinoid tumors.²¹ Nobels et al²² reported that the specificity of Chromogranin A, a glycoprotein secreted by endocrine tumors, approaches 100% and make its measurement extremely useful in the early detection of recurrences and follow up. Abdominal ultrasonography is helpful to identify liver metastasis while computerized tomography scan of the abdomen can outline the classic soft-tissue stranding in the mesenteric fat due to intense desmoplastic reaction.²³ Other radiological methods used to localize the carcinoids include somatostatin receptor scintigraphy, and ¹³¹I radio labeled metaiodobenzylguanidine (¹³¹I-MIBG). In view of the indolent course of the appendiceal carcinoids, the aforementioned laboratory and radiological work up rarely yields positive results.

Surgery for the carcinoids of the appendix is usually curative, giving a favorable 5-year survival rate of 90-100%.²⁴ Most authors advocate simple appendectomy for tumors 1 cm and a right hemicolectomy if the tumor size exceeds 2 cm.²⁵⁻²⁶ If the tumor dimensions range 1-2 cm, most patients are adequately treated with simple appendectomy, but for those with transmural invasion or mesenteric expansion, an extended surgery (ileocecal resection or right hemicolectomy) is mandatory.^{12,27} This approach is justifiable due to a profound risk of lymph node metastasis of such larger lesions.²⁸ In the present study, 3 out of 9 patients underwent LA with no peri operative morbidity. Guller et al⁹ documented that the patients with LA had outright benefits over those with OA in terms of mean hospital stay, rate of routine discharge, in-hospital mortality and overall complications. Likewise, recently published reports advocate LA as a feasible and effective surgical modality.³⁰⁻³² For the disseminated disease, many investigators^{33,34} demonstrated a success rate of 50-67% by using various agents including indium-labeled octreotide,

¹³¹I-MIBG, Interferons, and chemotherapy with 5-fluorouracil and streptozotocin.

Histologically, a striking feature of the carcinoid tumors is the intense desmoplasia which may lead to vascular occlusion secondary to anatomic distortion caused by the surrounding tissue reaction.³⁴ The tumor is composed of uniform cells with rare mitotic figures. Two types of silver staining, argyrophilic and argentaffin, are commonly used to identify neuroendocrine cells. Classically the foregut and hindgut carcinoids are argyrophilic, and midgut serotonin secreting midgut lesions are argentaffin.³⁵ One patient (26-year-old female, tumor at appendiceal apex) in our study was identified to have goblet cell carcinoid of the appendix; a variant of carcinoid tumors with aggressive natural history, significant malignant potential and controversial surgical management: appendectomy versus right hemicolectomy.³⁶ Our patient underwent appendectomy and remained symptom-free during her most recent follow up.

To conclude, carcinoid tumor of the appendix is a unique pathological entity which is almost always diagnosed after surgery. The lesions are best treated with simple appendectomy while the need for additional surgical resection is determined by the size and histological features of the tumor. Although appendiceal carcinoids have an excellent overall prognosis, the patients should be followed up with yearly 5-HIAA urinary assays and abdominal ultrasonography.

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