



Original article

Carcinoid tumor of cecal appendix: one-year incidence at the Santa Marcelina Hospital[☆]



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ABSTRACT

Introduction: Carcinoid tumors are neuroendocrine malignancies that originate in the neuroectodermal cells of the Amine, Peptide Uptake and Decarboxylation system dispersed in the gastrointestinal mucosa and representing about 80–88% of tumors of cecal appendix. These are tumors usually diagnosed at appendectomies, and it is estimated that from each 100 appendectomies yearly performed, at least one case is a neuroendocrine tumor.

Objectives: To report the experience of an University Teaching Hospital in health and reference at the east side of São Paulo and great São Paulo in cases of these rare appendicular tumors, with emphasis on the importance of these descriptions, as probably are rare those surgeons in particular who will acquire extensive wisdom in these cases.

Method: Retrospective analysis of 237 patients who underwent appendectomy from September 2010 to September 2012 in the Hospital Santa Marcelina-SP. We evaluated data on age, gender, initial clinical presentation and surgical findings of patients undergoing appendectomy with subsequent anatomic and immunopathological diagnosis of carcinoid tumor of cecal appendix.

Results: The presence of a carcinoid tumor of the appendix was observed in 5 patients, which corresponds to 2.1% of all appendectomies performed. Regarding gender, 4 patients (80%) were female and the average age was 34.2 years, with a range from 17 to 68 years. In all patients the initial hypothesis for surgery indication was acute appendicitis, with an intraoperative finding of necroperforated phase acute appendicitis in 3 patients (60%).

[☆] Study conducted at the Coloproctology Medical Residency Program, Department of General Surgery, Hospital Santa Marcelina, São Paulo, SP, Brazil.

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Conclusion: The therapeutical conduct after the diagnosis of carcinoid tumors of the appendix must be based on the data provided by pathological and immunohistochemical studies, besides the judicious judgment of the attending physician.

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Tumor Carcinoide de Apêndice Cecal: incidência em um ano no Hospital Santa Marcelina

R E S U M O

Palavras-chave:

Apendicite aguda
Tumor carcinoide de apêndice
Conduta
Seguimento

Introdução: Os tumores carcinoides são neoplasias malignas neuroendócrinas que se originam em células neuroectodérmicas do sistema APUD (*Amine, Peptide Uptake and Decarboxylation*), dispersas na mucosa gastrointestinal e que representam cerca de 80–88% das neoplasias do apêndice cecal. São tumores diagnosticados geralmente durante apendicectomias e estima-se que de cada 100 apendicectomias realizadas por ano, ao menos um caso será TNE.

Objetivos: Objetiva-se nesse artigo relatar experiência de Hospital Universitário e de Ensino (HUE) em saúde e referência na zona leste de São Paulo e grande São Paulo em casos desses raros tumores apendiculares, com ênfase na importância dessas descrições, já que provavelmente raros cirurgiões em particular irão adquirir uma extensa sapiência nesses casos.

Método: Análise retrospectiva de 237 pacientes submetidos à apendicectomia no período de setembro de 2010 a setembro de 2012 no Hospital Santa Marcelina-SP. Foram avaliados os dados referentes a idade, sexo, quadro clínico inicial, achados operatórios dos pacientes submetidos à apendicectomia com posterior diagnóstico anatomopatológico e imunopatológico de tumor carcinoide de apêndice.

Resultados: Verificou-se a presença de tumor carcinoide de apêndice em 5 pacientes, o que corresponde a 2,1% das apendicectomias realizadas. Com relação ao gênero, 4 pacientes (80%) eram mulheres e a média de idade foi de 34,2 anos, com variação de 17 a 68 anos. Em todos os pacientes a hipótese inicial para indicação de cirurgia fora de apendicite aguda, com achado intra-operatório de apendicite aguda em fase necroperfurada em 3 pacientes (60%).

Conclusão: A conduta após o diagnóstico de tumores carcinoides de apêndice cecal deve ser alicerçada nos dados fornecidos por exames anatomopatológicos e imunoistoquímicos, além do julgamento criterioso do médico assistente.

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Introduction

Recognized since the late nineteenth century and receiving the designation “karzinoid” only in 1917 by Oberndorfer,^{1,2} carcinoid tumors are neuroendocrine malignancies that originate in neuroectodermal cells of the APUD (*Amine, Peptide Uptake and Decarboxylation*) system, dispersed in the gastrointestinal mucosa and representing about 80–88% of tumors of the appendix.^{3,4}

The appendix is the second most frequent site of onset of neuroendocrine tumors (NET) throughout the digestive tract, with a frequency of 25–30%,⁵ after tumors of the small intestine.^{6,7} Usually these tumors are diagnosed during appendectomies, and it is estimated that at each 100 appendectomies performed yearly, at least one case is NET.⁸ Others, like Fernando et al., demonstrate an incidence of 0.3–0.7% of the histopathological findings in appendectomies.⁹

The approximate incidence of this neoplasm is 2–3 cases per million, with a preference for females of 2–4:1,¹⁰ but with no race predilection. The peak incidence is between 15 and 19 years in women and 20–24 years in men.¹⁰

The preoperative diagnosis of a malignant neoplasm of the appendix is rarely performed because of its nonspecific clinical picture, often compatible with an acute appendicitis.¹¹

As for treatment, considering that the diagnosis is usually established by the pathologist during the postoperative period, it is up to the surgeon the task, sometimes hard, to determine, through the pathology report (basically analyzing tumor size and its location in the appendix, the patient’s age and presence of metastases), if the patient will be treated with a second surgical intervention, this time of a more aggressive type, in the form of right hemicolectomy.

This study aims to relate the experience of an University Teaching Hospital (HTH) in health and reference on the east

side of São Paulo and greater São Paulo in those rare cases of appendicular tumors, with emphasis on the importance of these descriptions, considering that probably few surgeons in particular will acquire an extensive experience in these cases.

Patients and methods

This is a retrospective analysis of 237 patients who underwent appendectomy from September 2010 to September 2012 in the Hospital Santa Marcelina-SP.

Data for age, gender, baseline clinical picture, surgical findings of patients undergoing appendectomy, with subsequent anatomical and immunopathological diagnosis of carcinoid tumor of the appendix were evaluated. In this search, we studied data on macroscopic location of the tumor and its size, as well as its histopathologic features. Regarding immunohistochemistry, we analyzed positive tumor markers and Ki67 index.

Next, additional tests were performed in order to achieve a better tumor staging and for the approach to be adopted, with subsequent follow-up and clinical outcome analysis.

Results

During the study period between September 2010 and September 2012, 237 appendectomies were performed at the department of general surgery, Hospital Santa Marcelina, São Paulo. Of this total, carcinoid tumor of the appendix was diagnosed in 5 patients, which corresponds to 2.1% of all appendectomies performed (Fig. 1).

It is worth noting that all patients were referred to the coloproctology outpatient clinic, and one of these patients came from an external service.

As to the gender, 4 patients (80%) were female and the average age was 34.2 years, with a range of 17-68 years. In all patients the initial hypothesis for indication of surgery had been acute appendicitis, with an intraoperative finding of necroperforated-stage acute appendicitis in 3 patients (60%)

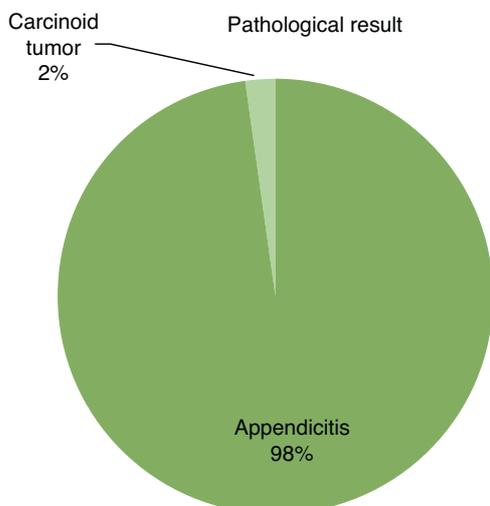


Fig. 1 – Percentage of carcinoid tumors by pathological diagnosis after appendectomy.

Table 1 – Age, localization data, tumor size and immunohistochemistry of the carcinoid tumor and cecal appendix operations.

Name	Age	Size	Location	Ki67
AFFS	17 years	7 mm	Basal	No data available
NF	50 years	1 mm	Basal	Inconclusive
LEA	17 years	9 mm	Extremity	1%
TRLM	19 years	7 mm	Basal	<1%
SAD	68 years	6 mm	Extremity	<1%

and phlegmonous-stage acute appendicitis in two patients (40%).

Table 1 shows data regarding pathological and immunohistochemistry examinations.

A conduct of right hemicolectomy was adopted in two patients and watchful waiting for the other three; the surgical choices were due to the fact that, in the first patient, a massive mesoappendix invasion was observed; and in the second patient, the immunohistochemistry report was inconclusive for defining tumor histogenesis.

Discussion

Carcinoid tumors are neoplasms of the diffuse neuroendocrine cell system with genetic involvement in its etiology, with possible deletion of the gene PLCβ3 and consequent uncontrolled growth of neuroendocrine cells, distortion of the apoptosis process and development of neoplasms.^{12,13}

The five cases of carcinoid tumor of the appendix described in this study present an incidence of 2.1% of the total of 237 appendectomies performed in the period of two years at the Hospital Santa Marcelina, coincident with the incidence described in the literature.¹¹

Importantly, malignant neoplasms of the appendix, regardless of histological type, are presented most of the time with a clinical picture highly suggestive of acute appendicitis (about 68%), probably due to the obstruction of the appendiceal lumen by the neoplastic injury, causing an overlapping infection.^{14,15} In none of the cases here reported a preoperative suspicion of cancer of the appendix was raised; and in all reports the initial hypothesis was acute appendicitis, although in one patient (NF) the medical history with its evolution time of five days did not match the physical examination. The definitive diagnosis of neoplasia and its histologic type are confirmed only by histological and immunopathological studies of the surgical specimen.

Consistent with the literature,⁴ in the present study a higher incidence of neuroendocrine tumor (NET) of the appendix was found in females, with 80% of cases (4/5), and with a higher prevalence in young patients, with a mean age of 43.2 years. Large series in the literature indicate that the mean age ranged from 27 to 40 years.¹⁰

With respect to carcinoid tumors of the appendix, the most frequent location is at its extremity in 62-78% of cases; and generally between 70 and 95% of the tumors measure less than 1 cm.^{16,17} More specifically, Roggo et al.¹⁴ report that 80% of their patients' tumors were smaller than 1 cm, 14% between 1 and 2 cm, and 6% larger than 2 cm. In this study, all cases of

Table 2 – Histological grade based on the mitosis number and Ki67 percentage.

Histological grade	Mitosis number	Ki67
Grade I	<2 mitoses/10 fields	<2%
Grade II	2–20 mitoses/10 fields	2–20%
Grade III	>20 mitoses/10 fields	>20%

Table 3 – TNM staging of carcinoid tumor of the appendix.

<i>T-primary tumor</i>	
Tx	A primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤1 cm invading submucosa and muscularis propria
T2	Tumor ≤2 cm invading submucosa, muscularis propria and/or minimal serosal or mesoappendiceal invasion (up to 3 mm)
T3	Tumor >2 cm and/or massive serosal or mesoappendiceal invasion (>3 mm)
T4	Tumor invading peritoneum/other organs
<i>N-regional lymph nodes</i>	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Presence of regional lymph node metastasis
<i>M-Metastasis</i>	
Mx	A distant metastasis cannot be assessed
M0	No distant metastasis
M1	Presence of distant metastasis

Table 4 – Clinical staging.

Clinical stage	T-primary tumor	N-lymph nodes	M-metastasis
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any N	M1

carcinoid tumors measured less than 1 cm, and 40% of them were located at the extremity of the appendix.

Recent consensus established by the European Neuroendocrine Tumor Society (ENETS) proposes a grading system for NETs of the stomach, duodenum and pancreas, based on mitotic count and/or immunohistochemical assessment of Ki67, a proliferation marker (Table 2).¹⁸

Another model widely used for carcinoid tumor of the appendix staging is that also proposed by ENETS in 2007 and presented in Tables 3 and 4.¹⁹

Surgical resection is the most widely established treatment for patients with carcinoid tumor of the appendix. It is known that, for lesions smaller than 1 cm, the appendectomy achieves high cure rates (near 100%). In tumors measuring between 1 and 2 cm and without lymph node involvement, the appendectomy is also indicated. If there is lymph node involvement, it becomes necessary a procedure of right hemicolectomy, although presenting metastases around 3%. In patients with tumors larger than 3 cm, right hemicolectomy

also is the best therapeutic option, but with a high rate of metastases (about 80%).^{20,21} To these indications, we must also add the cases with mesoappendix invasion.²²

Furthermore, some indications for a more aggressive intervention, besides the diameter of the mass, are the extent of the mesoappendix tumor, its location at the base of appendix, subserosal lymphatic invasion, and age of the patient. These criteria for a broader surgery have greater significance when deciding between an appendectomy or a right hemicolectomy in patients with tumors with 1–2 cm.²³

Also with respect to prognosis, It is known that the risk of metastasis in tumors measuring less than 1 cm in diameter is zero; for tumors of 1–2 cm, this risk is 0–11%; and in tumors larger than 2 cm, the risk of metastasis is considerably higher, 30–60%.¹¹

Study conducted by the Abdominal-Pelvic Surgery Service at INCA⁵ evaluated 13 patients operated at, or referenced to, that institution between 1996 and 2008. A predominance of female patients (5.5:1) was noted, with a mean age of 44.7 years. The tumor size ranged from 0.3 to 6 cm, with a median of 2.3 cm; and in two cases the patients have started the disease with a distant lesion. Furthermore, it was shown that, after a mean follow-up of 32 months, 10 patients were alive (77%), one (7.7%) was lost to follow-up, and two (15.3%) died.

Conclusion

The medical conduct after the diagnosis of a carcinoid tumor of the appendix must be based in data provided by pathological and immunohistochemical studies, besides the judicious judgment of the treating physician. In addition (and also because this tumor mainly affects relatively young individuals), we must proceed with the oncological follow-up, despite adopting a conservative approach, since these patients present an increased risk of synchronous or metachronous malignancies in percentages that can reach 29%, particularly in the gastrointestinal tract, breast, cervix and endometrium.

Conflicts of interest

The authors declare no conflicts of interest.

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