Primary malignant neoplasms of the cecal appendix: unusual findings in acute appendicitis

Julia Carolina Barbosa Garcia[1], Fernanda Marcante Carlotto[2], Nathalia Beck Corrêa[2], Marcos Dal Vesco Neto[3], Josiane Borges Stolfo[4], Lucas Duda Schmitz[5], Juarez Antonio Dal Vesco[2,5], Jorge Roberto Marcante Carlotto[1,2,5]

1 Universidade Federal da Fronteira Sul. Passo Fundo, RS, Brasil.

2 Universidade de Passo Fundo. Passo Fundo, RS, Brasil.

3 Hospital de Clínicas de Porto Alegre. Porto Alegre, RS, Brasil.

4 Instituto de Patologia de Passo Fundo. Passo Fundo, RS, Brasil.

5 Hospital de Clínicas de Passo Fundo. Passo Fundo, RS, Brasil.

Corresponding author:
Fernanda Marcante Carlotto
fmcarlotto@gmail.com
Universidade de Passo Fundo
Rua Fagundes dos Reis, 466, apto 403
99010-070, Passo Fundo, RS, Brasil.

ABSTRACT

Introduction: To evaluate the prevalence of appendix neoplasia correlating with patient profile, histological types and frequency.

Methods: Data collection was performed in the Pathology Department of a General Hospital, with the objective of identifying patients diagnosed with malignant cecal appendix tumors by histopathologic study of specimens from acute appendicitis.

Results: The prevalence of malignant primary epithelial neoplasia of the appendix was 1%. Fifty percent of the cases were neuroendocrine tumors, 35% were mucinous, and 15% were adenocarcinomas. The mean age at diagnosis was 41.3 (SD, 20.4) years (range16-81), with a women/men ratio of 3:1.

Discussion: Appendiceal neoplasms are rare and should be suspected manly in women over 40 years of age with suggestive symptoms of acute appendicitis. The size, location, extent, margins and presence of mucin are essential findings for the treatment of these patients.

Keywords: *Appendix; Appendiceal neoplasms; Appendectomy; Surgical Pathology; Pseudomyxoma*

INTRODUCTION

Appendectomy is the most commonly performed surgical procedure, due to an estimated risk lifetime risk of acute appendicitis of 7%[1]. Appendicitis is secondary to obstruction of the lumen of the cecal appendix, resulting in mucosal ischemia and bacterial invasion. The most common etiology is obstruction by fecalith[2], however other events can result in or resemble acute appendicitis[3], such as malignant tumors, and therefore a histopathologic study is relevant and mandatory.

The cecal appendix removed from patients with suspected acute appendicitis may appear macroscopically normal, but the histopathological analysis can demonstrate severe underlying diseases that may affect treatment and patient outcome[4]. Unusual diseases were suspected only in 4.7 % of the macroscopic analyses performed by surgeons and pathologists in a study by Alemayehu et al.[2] including 3,602 patients.

Malignant neoplasms are confirmed by pathologic analysis in less than 3% of all appendectomies due to acute appendicitis[5]. This condition is incidentally recognized during abdominal surgery or by pathologic examination of the resected specimens[5]. Cancer of the appendix can cause appendicitis and organ rupture, which is commonly the first sign of the disease. The incidence of malignancies in the appendix is about 0.12 in 1,000,000 per year[6]. Recently, some studies showed an increased incidence of malignant appendiceal tumors, ranging from 5.9% to 12%[7], probably due to prior imaging detection[8].

The incidence of malignant neoplasms in the cecal appendix is higher (10%-29%) in patients whose presentation is a mass described as inflammation or abscess[7]. If a suspected mass is found in the appendix, an intraoperative frozen section should be required, if available[9].

Primary appendix tumors are divided into 3 major groups: epithelial tumors, mesenchymal tumors, and lymphomas[10]. Primary epithelial tumors are subclassified into mucinous tumors, neuroendocrine tumors (NETs), and mixed glandular and endocrine tumors[11]. Adenocarcinomas are in the category of mucinous tumors but are often considered separately due to characteristics that differ from mucinous neoplasms, both related to further disease course and treatment. Since the histologic types of such tumors predict biologic behavior and a tendency towards specific patterns of dissemination, this classification should be histologically determined[8].

NETs are seen in 0.3%-0.9% of appendectomy specimens[12]; mucinous neoplasms of the appendix are present in 0.2%-0.3%[13], and adenocarcinomas in 0.1%-0.22% of all cases of appendicitis[12].

Size, location, extension, and invasion of mesoappendix are important factors in assessing disease recurrence and patient survival rates[7]. The management of such tumors is still controversial and might be related to watchful waiting[8], appendectomy only[8,10], or even right hemicolectomy[3,13], with or without adjuvant chemotherapy[7,13]. Additional procedures such as hysterectomy and bilateral adnexectomy should be considered in selected cases[8].

This study aimed to evaluate the prevalence of cases of appendix neoplasms in a selected medical department during a pre-established period. Furthermore, we aimed to assess the profile of the patient with acute appendicitis and diagnosis of appendix neoplasm, collecting data on age, sex, ethnicity, identifying histologic types and anatomopathological characteristics, and relating them with pre- and postoperative data.

METHODS

This was a cross-sectional study based on the information available in the database of the Pathology Institute of Passo Fundo, state of Rio Grande do Sul. Anatomopathological specimens removed during appendectomies performed at the local Surgical Department of the Hospital de Clínicas de Passo Fundo between 2007 and 2017 were included in this case series. Considering all appendices removed, cases of appendectomy due to trauma and gynecologic surgeries and fragments removed with colorectal tumors were excluded from the analysis. Reports containing descriptions of metastases, invasive implants, and organ involvement by direct extension of tumors to other sites were also excluded from the sample. Of the 1,845 cases, 20 had a diagnosis of neoplasia. Data collection included information on sex, age and ethnicity, histologic findings of the tumor as described in the anatomopathological report (histologic type, grade, length and diameter of the lesion in the major axis, location, tumor extent according to the classification of the American College of Pathology, free margins and presence of peritoneal mucin (extra-appendicular) and pre- and postoperative data of patients (concerns at admission, preoperatively suspicion of neoplasia, surgical procedure performed at first attempt, and need for follow-up). The data were recorded in a previously coded file, double checked in Epidata, version 3.1, and analyzed by Pearson's Chi-square test, using PSPP, version 3. The prevalence of malignant epithelial neoplasia was calculated by dividing the number of cases found by the total of appendectomies.

RESULTS

In the present study, the prevalence of primary malignant epithelial neoplasia of the cecal appendix incidentally diagnosed after surgical procedure for acute appendicitis was 1%. NTEs were seen in 0.5% of patients who underwent appendectomy, mucinous neoplasms of the cecal appendix were present in 0.4% of the specimens, and adenocarcinomas occurred in 0.16% of the appendectomies.

The mean age at diagnosis of malignant epithelial appendix tumor was 41.3 (SD, 20.4) years (range 16-81), with a prevalence of women over men at a ratio of 3 to 1. In the study sample, 94% of patients were white. At admission, 85% of the patients presented signs and symptoms of acute abdomen or acute appendicitis. All patients underwent surgery. In the sample studied, 62.5% were submitted to laparoscopic surgery while 37.5% of the cases underwent open surgery. After anatomopathologic exam of the specimens, 3 cases were not submitted to any further surgical procedure, 2 with low-grade appendiceal mucinous neoplasia (LAMN) and 1 with low-grade neuroendocrine tumor (carcinoid tumor), since those cases were considered cured and discharged from follow-up. The remaining patients were referred to a Coloproctology Department or a Clinical Oncology Department, either for surgical reintervention or follow-up, respectively.

Half of the sample studied was composed of individuals with NETs. In these patients, the mean age at diagnosis was 25.5 (SD, 6.8) years (range 16-37). The women/men ratio was 4:1. All cases, according to immunohistochemical staining, were well differentiated and of low-degree (carcinoid tumor). All of them were located at the apex of the organ. The mean size 10 mm (SD, 3.7 mm), ranging from

4 to 17 mm on the largest axis). Fifty-six per cent of them were smaller than 10 mm and 44% were 1 to 2 cm (p = 0.06). In this sample, 33% of tumors invaded the mucosa muscle layer, in 1 case there was serosa invasion, and in the remaining 44% of cases, invasion reached the mesoappendix. None of the cases had residual tumors.

Of the 3 cases of adenocarcinoma present in the sample, the mean age at diagnosis was 58.66 (SD, 16.93) years, (range 40-81). All cases occurred in women. Only one histologic report referred to the site of the lesion in the apex. In 2 reports that had the measure of the lesion, sizes were 1.8 cm and 3.5 cm, in both cases the tumor invaded the appendix muscle wall. In all 3 cases, margins were considered free of residual tumor invasion after appendectomy.

Considering the cases of mucinous neoplasia, the mean age at diagnosis was 56.57 (SD,14.98) years (range 26-72). The women/men ratio was 4:3 (Table 1). There was only 1 case of high-grade appendiceal mucinous neoplasia (HAMN), where extra-appendicular mucin was found in the anatomopathologic analysis of the specimen. This case recurred with metastasis to the ovaries. The other 6 cases were HAMN. Of these, only 1 was positive for the presence of extra-appendicular mucin and later developed pseudomyxoma peritonei (PMP).

Table 1: Characteristics of patients with malignant cecal appendix neoplasm in a general hospital, Passo Fundo, RS, 2007-2017 (n = 20).

Variables	Neuroendocrine tumor (NET) (n = 10)	Mucinous neoplasm (n = 7)	Adenocarcinoma (n = 3)	p
Age at diagnosis (years)				0.38
Rate (SD)	25.5 (6.8)	56.6 (15)	58.7 (16.9)	
Reach	16-37	26-72	40-81	
Sex (%)				0.31
Men	20	42.9	0	
Women	80	57.1	100	

SD: standard deviation.

DISSCUSSION

In the present study, the prevalence of malignant epithelial neoplasms incidentally diagnosed in the specimens removed due to acute appendicitis was 1.1%. Another Brazilian study with a similar purpose found a value of 0.8% of cases of malignant cecal appendiceal neoplasms incidentally found in the appendectomies performed between 1994 and 1997 in a regional hospital[14].

NETs accounted for 50% of the cases of neoplasms in the sample studied, 35% of the tumors were mucinous neoplasms and 15% were diagnosed as adenocarcinomas. There was no diagnosis of mixed adenoneuroendocrine tumor. In an analysis of 24,697 patients submitted to appendectomy, of which 171 cases were neoplasms[15], 53% were carcinoid tumors (NET well differentiated and low grade), 35% were mucinous lesions, 9% were diagnosed as primary adenocarcinoma, and the remaining sample was composed of non-epithelial tumors. Another study[3] found a prevalence of 87% of well-differentiated and low-grade neuroendocrine tumors, corroborating the higher prevalence of NETs in the remaining sample.

The mean ± SD age (range) of patients with malignant epithelial appendiceal neoplasms in a study of 1621 patients in a health service with similar population was 49.1 (SD, 16.7) years (21-74) and the ratio between women and men was 7:4[5].

In this study, the mean ± SD age was 41.35 (SD, 20.43) years (range 16-81), with 75% of the sample being women and 25% men (women/men ratio of 3:1). However, there are studies showing a slight prevalence of men (59%) over women, although the sample profile was comparable, including age ranging from 19 to 84 years[1].

Malignant cecal appendiceal neoplasms are more prevalent in whites than in other ethnicities[7,13]. In the present study, 94.4% of the sample (n = 18) was white and only 1 individual was from a different ethnicity. In the studied sample, 85% were admitted to the service due to concerns compatible with acute abdomen or acute appendicitis, where appendicitis as the initial manifestation ranged from 30%[8] to 50%[7] of cases incidentally diagnosed in appendectomy specimens, in line with the literature, with values varying according to the histologic type and location. When the tumor was located at the base of the organ, the patient could have signs and symptoms identical to appendicitis as a result of lumen occlusion by the tumor mass[9]. In the study under analysis, all tumors evaluated for location (n = 7) had lesions at the apex of the cecal appendix.

In a study that evaluated the prevalence of NETs in appendectomies[16], 41% of the patients underwent laparoscopic appendectomy while 59% had their appendix removed by open approach. In the present study, 62.5% were submitted to laparoscopic

appendectomy, while 37.5% of cases underwent conventional open surgery.

In another study that evaluated the incidental findings in specimens removed due to acute appendicitis, 61.5% of the patients had their lesions completely resected in the first surgery[4], with no need for surgical reoperation or further treatment. Therefore, in the analysis of this study, discharge rates after regular appendectomy were around 20%, and the remaining patients underwent some type of follow-up, either referred to a clinical oncologist or submitted to the new surgical resection. Nevertheless, all analyzed samples had negative (free) margins.

In the present study, all NETs were low grade and well differentiated (carcinoid tumor) according to an immunohistochemical study. The mean ± SD size of the lesion in the largest diameter was 1.02 cm (SD, 0.37) (range 0.4-1.7 cm) and 44.% deeply invaded the mesoappendix. The prevalence was higher in women, who represented 80% of the sample and the mean age at the time of diagnosis was 25.55 (SD, 6.81) years (range 16-37) years. Similar values were described in the study of Charfi et al.[15], in which the mean tumor size was 1.2 cm with values ranging from 0.1 to 3.5 cm. Some reports presented smaller sizes: means of approximately 0.5 cm with values ranging from 0.1 to 2.0 cm[6,16]. On the other hand, in the study by Emre et al.[3], only 18% of the tumors invaded the periappendicular fat tissue.

Moreover, in the context of this study, patients diagnosed with mucinous and adenocarcinoma were older. Those with mucinous had a mean age of 56.7 (SD, 14.9) and patients with adenocarcinoma, 58.6 (SD, 16.9) years. There was a higher prevalence of women, 57% for mucinous neoplasms and all cases of adenocarcinoma. McCusker et al.[6], studied 1698 cases of malignant neoplasia of the cecal appendix reported to the United States Surveillance, Epidemiology and Final Results Program (SEER) and found a mean age of 60 years at diagnosis of NET for mucosal neoplasms and 62, for adenocarcinoma. The women-to-men ratio was 2.6 in NETs, in mucous neoplasms the ratio was 1.1, and 60% were men in case of adenocarcinomas. Other authors found a higher prevalence of women in mucinous neoplasms[11,17] and, according to the World Health Organization[12], men are more commonly affected than women by adenocarcinomas.

Nutu et al.[17] observed an increased risk of ovarian mucinous tumor in patients diagnosed with mucinous neoplasia and the presence of extraperitoneal pseudomyxoma in 22% of the sample. In this study 33% of the mucinous neoplasms presented extra-appendicular mucin, 1 patient had recurrence of the disease in the ovary and another developed pseudomyxoma peritonei – since several cases with this disease result from mucinous neoplasia[18,19].

CONCLUSION

Although the clinical findings are consistent with the literature due to a similarity of secondary data, the small sample size, and the study design, none of the results were statistically significant. In addition, the various forms of classification, often confusing, contribute to the small sample size of subgroups and an underestimated risk of having an appendiceal tumor diagnosed from appendicitis cases.

REFERENCES

1. Ma KW, Chia NH, Yeung HW, Cheung MT. If not appendicitis, then what else can it be? A retrospective review of 1492 appendectomies. *Hong Kong Med J*. 2010;16(1):12-7.

2. Alemayehu H, Snyder CL, St Peter SD, Ostlie DJ. Incidence and outcomes of unexpected pathology findings after appendectomy. *J Pediatr Surg*. 2014;49(9):1390-3.

3. Emre A, Akbulut S, Bozdag Z, Yilmaz M, Kanlioz M, Emre R, et al. Routine histopathologic examination of appendectomy specimens: retrospective analysis of 1255 patients. *Int Surg*. 2013;98(4):354-62.

4. Jones AE, Phillips AW, Jarvis JR, Sargen K. The value of routine histopathological examination of appendicectomy specimens. *BMC Surg*. 2017;7:17.

5. Yilmaz M, Akbulut S, Kutluturk K, Sahin N, Arabaci E, Ara C, et al. Unusual histopathological findings in appendectomy specimens from patients with suspected acute appendicitis. *World J Gastroenterol*. 2013;19(25):4015-22.

6. McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer*. 2002;94(12):3307-12.

7. Teixeira FJR Jr, Couto Netto SD, Akaishi EH, Utiyama EM, Menegozzo CAM, Rocha MC. Acute appendicitis, inflammatory appendiceal mass and the risk of a hidden malignant tumor: a systematic review of the literature. *World J Emerg Surg*. 2017;12:12.

8. Leonards LM, Pahwa A, Patel MK, Petersen J, Nguyen MJ, Jude CM. Neoplasms of the appendix: Pictorial review with clinical and pathologic correlation. *Radiographics*. 2017;37(4):1059-83.

9. Ruoff C, Hanna L, Zhi W, Shahzad G, Gotlieb V, Saif MW. Cancers of the appendix: review of the literatures. *ISRN Oncol*. 2011;2011:728579.

10. Tirumani SH, Fraser-Hill M, Auer R, Shabana W, Walsh C, Lee F, et al. Mucinous neoplasms of the appendix: a current comprehensive clinicopathologic and imaging review. *Cancer Imaging*. 2013;13(1):14-25.

11. Gündoğar Ö, Kımıloğlu E, Komut N, Cin M, Bektaş S, Gönüllü D, İlgün AS, et al. Evaluation of appendiceal mucinous neoplasms with a new classification system and literature review. *Turk J Gastroenterol*. 2018;29(5):532-42.

12. Bosman FT, Carneiro F, Hruban RH, Theise ND, editores. *WHO Classification of Tumours of the Digestive System*. 4th ed. Lyon: IARC Press; 2010. (World Health Organization Classification of Tumours; vol. 3).

13. Shaib WL, Assi R, Shamseddine A, Alese OB, Staley C 3rd, Memis B, et al. Appendiceal mucinous neoplasms: diagnosis and management. *Oncologist*. 2017;22(9):1107-16.

14. Mércio AAP, Weindorfer M, Weber AL, Mano AC. [Primary malignant tumours of the appendix]. *Medicina (Ribeirao Preto)*. 1999;32:193-8. Portuguese.

15. Charfi S, Sellami A, Affes A, Yaïch K, Mzali R, Boudawara TS. Histopathological findings in appendectomy specimens: a study of 24,697 cases. *Int J Colorectal Dis*. 2014;29(8):1009-12.

16. Amr B, Froghi F, Edmond M, Haq K, Thengungal Kochupapy RT. Management and outcomes of appendicular neuroendocrine tumours: Retrospective review with 5-year follow-up. *Eur J Surg Oncol*. 2015;41(9):1243-6.

17. Nutu OA, Marcacuzco AA 5th, Manrique Municio A, Justo Alonso I, Calvo Pulido J, García-Conde M, et al. Mucinous appendiceal neoplasms: Incidence, diagnosis and surgical treatment. *Cir Esp*. 2017;95(6):321-7.

18. Valasek MA, Pai RK. An update on the diagnosis, grading, and staging of appendiceal mucinous neoplasms. *Adv Anat Pathol*. 2018;25(1):38-60.

19. Carr NJ. Updates in Appendix Pathology: The Precarious Cutting Edge. *Surg Pathol Clin*. 2020;13(3):469-84.