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Status of Appendiceal Neoplasms in Acute Appendicitis Cases

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ABSTRACT

Introduction: Appendiceal neoplasms (AN) are exceedingly rare and mostly diagnosed incidentally during appendectomy due to non-specific clinical manifestations. Our study focused on assessing the clinical and postoperative histopathological features of ANs to differentiate them from acute appendicitis (AA) diagnosis in order to prevent complications and metastasis in aggressive malignancies.

Methods: In this retrospective study, we analyzed 2,906 patients who underwent a appendectomy. We compared the demographic characteristics, imaging, and preoperative laboratory findings and postoperative histopathology results between the groups with AN and AA.

Results: The prevalence of AN was found to be 2.82% (n=82). We observed a significant difference in age between patients diagnosed with AN and those with AA, with patients being notably older. The rate of perforation and diverticula was also increased in patients with neoplasms. Low-grade mucinous adenoma (39.02%) was the most common neoplasm, followed by precancerous serrated adenoma (28.04%) and carcinoid tumor (21.95%), respectively. Moreover, the mean diameter of carcinoid tumors was 6.32±4.69 mm and 2 patients with >20 mm lesion diameter underwent right hemicolectomy. Carcinoid tumors were mostly located at the tip of the appendix. In addition, no lymphovascular invasion or distant metastasis was observed in any of the patients.

Conclusion: Primary ANs are exceedingly rare and easily overlooked, the increased incidence of major complications such as perforation should be taken into consideration with AA-like clinical presentation in AN patients. Thus, preoperative laboratory and especially radiological outcomes should be carefully evaluated.

Keywords: Appendiceal neoplasms, acute appendicitis, carcinoid tumor, low grade mucinous neoplasm

Introduction

Appendiceal neoplasms (AN) represent about 0.9 to 1.4% of all AN (1). Due to unevaluated postoperative lesions, the rate of actual appendix mass is estimated to be up to 5% (2). AN represent a broad heterogeneous group classified as epithelial and non-epithelial (3). Mucinous neoplasms that are histologically classified as low or high grade are the most common (85%) malignancy of all epithelial ANs, while neuroendocrine tumors comprise the majority of non-epithelial tumors with increased incidence recently (4,5).

The clinical presentation of ANs is usually non-specific with typical or atypical acute appendicitis (AA)-like symptoms even hormonally active carcinoid neoplasms (3). Thus, the absence of pathognomonic findings mostly results in delayed diagnosis or incidental diagnosis during appendicectomy (5). ANs are rarely aggressive tumors and their prognosis depends on stage, histological type. Although nodal involvement and distant metastases are less frequently documented during diagnosis, appendiceal adenocarcinoma is significantly associated with lower 5-year survival rates (1). Therefore, appropriate surgical resection is still the standard suggested curative option for ANs without distant metastasis (6). However, in some instances, further surgery such as right hemicolectomy may be required, particularly in neuroendocrine neoplasms with potentially malignant larger lesions (7).

Although the majority of ANs are associated with better overall prognosis, various tumors exhibit higher perforation risks, malignant potential with possible regional and distant metastases. Accurate and prompt diagnosis and effective management of surgical approach are crucial in patients with ANs (1,5). Therefore, our objective was to assess the clinical and postoperative histopathological features of ANs that differ from the diagnosis of AA to prevent complications associated with aggressive malignancies.

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Methods

Conducted at the Department of Surgery in University of Health Sciences Turkey, İstanbul Training and Research Hospital, this study took place from January 2016 to December 2021. The study protocol received approval from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 2847, date: 04.06.2021), and informed consent was obtained from all participating patients. A total of 2,906 patients who underwent appendectomy were retrospectively evaluated in this study. We compared the demographic characteristics, imaging, and preoperative laboratory findings of the patients as well as the postoperative histopathology results (both from laparoscopic and open appendectomy procedures) between the groups with AN and AA.

Patients in this study exhibited symptoms such as appetite loss, nausea, and vomiting. The surgeon assessed the clinical and physical manifestations of AA, with at least one clinical finding indicating a likelihood of AA. These clinical findings included right lower abdominal pain, percussion, and rebound tenderness, and localized and diffuse rigidity of the abdominal wall. A definitive diagnosis was established through histopathological evaluation.

Venous blood samples from the patients were collected for cell blood count analysis. The hematological parameters were assessed using a hematology analyser (Cell-Dyne 3700, Abbott, Abbott Park, IL, USA). Additionally, serum samples were obtained for biochemical analysis which was conducted through electro-chemiluminescence immunoassay on the Beckman Coulter Unicel DXI 800 analyzer.

Statistical Analysis

The data analysis was conducted using SPSS software for Windows (v21.0; IBM, Armonk, NY, USA). Descriptive statistics, including mean, standard deviations, medians, interquartile range, frequency distributions, and percentages, were employed to summarize both individual and aggregate data. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. For variables that did not follow a normal distribution, the Mann-Whitney and Kruskal-Wallis tests were employed to compare between groups. The evaluation of categorical variables was performed using the chi-square test. P-values below 0.05 were considered statistically significant.

Results

Out of the 2,906 patients included in this study, 1830 (63.00%) were male and 1076 (37.00%) were female, resulting in a male-to-female ratio of 1.70. The median age of all patients was 32.00 years. In our study sample, the overall prevalence of AN was 2.82% (n=82). There was no significant difference observed between genders within the groups. However, patients with AN were notably older than those diagnosed with AA. Additionally, AA patients had significantly higher rates of perforation and diverticulosis, as shown in Table 1.

Upon analyzing the laboratory findings, it was observed that the white blood cell count and neutrophil values were significantly higher in the AA group (p-values: 0.001, 0.005, respectively). Furthermore, patients with AN had significantly elevated mean platelet volume (MPV) compared with the AA group (p-value: 0.001) (Table 2).

The overall incidence of perforated appendicitis in the entire patient cohort was determined to be 6.4% (n=188). Specifically, within the AA group, the incidence of perforated appendicitis was found to be 6.3% (n=178). However, among patients with AN, the perforation rate increased to 13.8% (n=10), indicating a statistically significant difference (p-value: 0.032). Furthermore, the prevalence of appendiceal

Table 1. Comparison of age and gender between groups

		Appendicitis (n=2,824)	Neoplasia (n=82)	p-value
Age (median - IQR)		32.00-15.00	43.00-31.00	0.001
Gender	Female (n, %)	1,040 (36.8%)	36 (43.9%)	0.191
	Male (n, %)	1,784 (63.2%)	46 (56.1%)	
Diverticula	No (n, %)	2,763 (97.8%)	73 (89%)	0.001
	Yes (n, %)	61 (2.2%)	9 (11%)	
Perforation	No (n, %)	2,646 (93.6%)	72 (84.1%)	0.032
	Yes (n, %)	178 (6.3%)	10 (13.8%)	

IQR: Interquartile range

Table 2. Comparison of laboratory outcomes between the AA and groups

Laboratory results	Appendicitis (n=2,824)	Neoplasia (n=82)	p-value
WBC ($x10^9$/L), (median - IQR)	14.00-5.45	12.00-6.00	0.001
Neutrophil ($x10^9$/L), (median - IQR)	10.98-5.45	9.20-5.37	0.005
Lymphocyte ($x10^9$/L), (median - IQR)	1.80-1.18	1.80-1.20	0.105
Neutrophil/lymphocyte, (median - IQR)	5.90-6.03	5.28-5.56	0.462
Platelet ($x10^9$/L), (median - IQR)	247.00-84.00	248.00-87.00	0.754
MPV (fL), (median - IQR)	8.30-1.50	8.90-1.70	0.001
Bilirubin (mg/dL) (median - IQR)	0.60-0.20	0.65-0.30	0.174

AA: Acute appendicitis, IQR: Interquartile range

Table 3. The distribution of neoplasms

Neoplasia types	According to the number of total samples	According to the number of neoplasia samples
Mesothelial cysts (n, %)	1 (0.03%)	1 (1.21%)
Low-grade mucinous neoplasm (n, %)	32 (1.10%)	32 (39.02%)
Hyperplastic polio (n, %)	3 (0.09%)	3 (3.63%)
Intramucosal carcinoma (n, %)	1 (0.03%)	1 (1.21%)
Carcinoid tumor (n, %)	18 (0.61%)	18 (21.95%)
Mucosal (n, %)	2 (0.06%)	2 (2.42%)
Over adenocarcinoma inflitration (n, %)	1 (0.03%)	1 (1.21%)
Mucinous adenocarcinoma (n, %)	1 (0.03%)	1 (1.21%)
Sessile serrated adenoma (n, %)	23 (0.79%)	23 (28.04%)

diverticulosis (AD) was found to be significantly higher in AN patients compared with other groups (p-value: 0.001).

In the current study, the overall prevalence of neoplasm-associated lesions was found to be 2.82% (n=82). Among these lesions, low-grade mucinous neoplasms had the highest frequency, accounting for 39.02% of cases. Precancerous serrated adenoma followed closely with a rate of 28.04%, while carcinoid tumors were identified in 21.95% of cases (Table 3).

The mean tumor diameter was 6.32±4.69 mm (range: 1.0-18.0 mm) in patients who underwent laparoscopic or open appendectomy and were diagnosed incidentally with carcinoid tumors. After histopathological assessment, 2 patients with >20 mm lesion diameter underwent right hemicolectomy. Tumors were located at the tip of the appendix in 15 (83.3%) patients, at the body of the appendix in 2 (11.1%) patients, and the remaining 1 (5.5%) were located in the base of the appendix. The surgical margin was negative in all cases. Ki-67 proliferation was found to be high (≥3%) in 11.1% of cases (n=2), and low (<3%) in 88.9% of cases (n=16) (Table 4). Immunohistochemical evaluation revealed synaptophysin and chromogranin-A positivity in all patients. While perineural invasion was detected in 3 patients (16.6%), no lymphovascular invasion or distant metastasis was observed in any of the patients. A total of 5 patients (27.7%) had subserosa invasion, 6 patients (33.3%) had mesoappendiceal invasion, 4 patients (22.2%) had local invasion into the muscular layer, 1 patient (5.5%) had submucosal invasion, and 1 patient (5.5%) had mucosal invasion.

Table 4. Clinical characteristics of patients with carcinoid tumors

Parameter		Carcinoid tumors (n=18)
Age (mean ± SD)		35.11±14.19
Gender	Female	8 (44.44%)
	Male	10 (55.56%)
Localization	Tip	15 (83.33%)
	Body	2 (11.11%)
	Base	1 (5.55%)
Ki -67 (mean ± SD)	<3%	16 (88.88%)
	>3%	2 (11.12%)
Tumor diameter (mean ± SD)		6.32±4.69

SD: Standard deviation

Discussion

Primary ANs tend to occur more commonly in middle-aged or older patients with the exception of neuroendocrine tumors. Neuroendocrine tumors relatively occur in younger ages than other ANs (1). Tan et al. (6) reported a mean age of 53 years and of the patients 45% were male, 55% were female in their retrospective study with participation of 685 AN patients. Similarly, Kunduz et al. (8) reported significantly greater age (33.24 years vs 44.5 years) in AN patients (n=28) compared to AA patients among 3,554 appendectomies between 2011 and 2017 years. On the other hand, Lamberti et al. (9) documented a median age of 29 years in 339 patients diagnosed with appendiceal neuroendocrine tumors. Consistent with our study findings, it was observed that patients with AN were significantly older than those with AA. Additionally, among AN patients, individuals diagnosed with appendiceal neuroendocrine tumors had an average age of 35.11 years.

Because AA is an inflammatory disease, the severity of AA is associated with increased leukocyte and neutrophil counts as inflammatory markers (10). Furthermore, inflammation can contribute to an upsurge in platelet production, which in turn may lead to variations in platelet volume. As a result, high-grade inflammation characterized by excessive consumption can potentially lead to decreased MPV levels (11). Researchers observed an elevated risk for developing AA in patients with increased leukocyte (12). Likewise, Xharra et al. (13) observed elevated leukocyte and neutrophil counts in AA patients. Additionally, Ceylan et al. (14) reported lower MPV levels in 363 AA patients compared with healthy controls. Consistent with these findings, our study found that the mean leukocyte, neutrophil, and lymphocyte counts in the AN group were statistically lower than those in the AA group. Furthermore, the MPV values measured in the group were statistically higher than those in the AA group.

The neoplastic tumor cells or mucin production may cause lining and obstruction of the lumen, moreover, lining may lead to herniation into the muscularis propria, and perforation occurs (3). Furthermore, perforation may result with pseudomyxoma peritonei, particularly in mucinous neoplasms (15). Kunduz et al. (8) documented perforation and plastron appendicitis rates of 25% (n=7) and 3.5% (n=1), respectively, in 28 AN patients. Similarly, Tajima et al. (2) reported a perforation rate of 17.6% (n=3) among 17 patients diagnosed with AN. Additionally, Honoré et al. (15) found higher rates of perforated appendicitis (75%) in 25 patients

with mucinous neoplasms, providing further support. Furthermore, there are limited published data regarding the association between AD and neoplastic processes. In Kallenbach et al. (16), a significant association between AN and 43.6% of 39 AD cases were reported among 4,413 appendectomies. Additionally, Marcacuzco et al. (17) identified a neoplastic association in 7.1% of 42 patients diagnosed with AD out of a total of 7,044 appendectomies. In our study, a statistically higher rate of perforation was observed in the group. Furthermore, the incidence of neoplasms associated with AD was found to be 11.0% among the 2906 appendectomies conducted in this study.

The published data indicate that the prevalence of AN diagnosed during surgery ranges from 0.7% to 5% (2). In a retrospective study conducted by Hosseinzadeh et al. (18) involving 4,800 patients between 2010 and 2014, the prevalence of AN was reported as 1.8% (n=86). The researchers observed that carcinoid tumors were the most frequently encountered type of AN in their study (18). Similarly, Tajima et al. (2), in a study involving 803 appendectomy cases, documented an incidence of 2.3% (n=17) for AN. Among these cases, intramucosal neoplasms were found to be the most common type of AN (2). On the other hand, while mucinous carcinoma was the most frequent neoplasm in a study conducted by Tan et al. (6), in another study Kunduz et al. (8) reported neuroendocrine tumors as the most common type of ANs. Moreover, Lietzén et al. (19) reported an overall AN prevalence of 1.24% among 472 AA patients, and researchers highlighted a significantly increased tumor risk in complicated AA. The present study aligns with the reported data, indicating an overall prevalence of 2.8% for AN. Additionally, according to the published data, mucinous neoplasms and carcinoid tumors are the most commonly identified AN. In our study, low-grade mucinous neoplasm was the most frequently determined malignancy, followed by sessile serrated adenoma.

Appendiceal carcinoid tumors are considered a rare etiology of AN, with reported incidences ranging from 0.3% to 0.9% among appendectomy cases. Carcinoid tumors generally emerge in young patients, and the majority of lesions are typically localized at the tip of the appendix (1). Furthermore, it has been observed that an increased tumor size (>2 cm) in carcinoid tumors is linked to a heightened risk of metastasis (18). In't Hof et al. (20) reported a mean age of 32.7 years in patients with carcinoid tumors, and researchers also noted a carcinoid tumor prevalence of 0.47% after 1,485 appendectomies. In addition, a patient with a tumor larger than 2 cm underwent right hemicolectomy (20). It has also been recommended in published data to perform right hemicolectomy in malignant carcinoids lesions larger than 2 cm in diameter (21). Tchana-Sato et al. (22) documented a mean age of 29.2 years in 5 patients with carcinoid tumors after 1,237 appendectomies and lesions were all localized at the tip of appendix. In another study consisting of 50 patients diagnosed with carcinoid tumors between 1994 and 2010 Murray et al. (23) reported a median tumor diameter of 5 mm with all negative margins. Most (76%) of the tumors were determined to be localized at the tip of the appendix in the same study. A researcher also stated that 2 patients underwent right hemicolectomy, and no regional lymph node or distant metastasis was documented (23). Consistent with the data, this study found that patients with carcinoid tumors had a mean tumor diameter of 6.32±4.69 mm, and all cases exhibited negative margins. The lesions were mostly (83.3%) localized at the tip of the appendix. Two patients with >20 mm lesion diameter underwent right hemicolectomy. Additionally, no lymphovascular invasion or distant metastasis was observed in any of our patients.

Study Limitations

Due to the small number of tumoral lesions, rare pathologies were either unobserved or rarely.

Conclusion

Although primary ANs are exceedingly rare, it should be taken into consideration that tumoral obstruction in the appendiceal lumen may present with AA-like clinical presentation. As demonstrated in the present study, due to the increased incidence of major complications such as perforation in patients with ANs, laboratory and radiological findings should be attentively evaluated. Additionally, incidentally detected macroscopic AD, which is also rare and easily overlooked, should be referred to appendectomy due to the increased association of malignant potential. However, appendectomy specimens preperatively manifest normal macroscopic features, adequate histopathological examination is vital for an accurate and early diagnosis of possible neoplasms and appropriate treatment approaches.

Ethics Committee Approval: The study protocol received approval from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 2847, date: 04.06.2021).

Informed Consent: Informed consent was obtained from all participating patients.

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