

Comparison of carcinoid tumors with the other tumors of appendix

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Abstract

Aim: Carcinoid tumor is the most frequent primary tumor of the appendix which may reach up to 60% of all appendiceal neoplasms. We aimed to evaluate the incidental appendiceal carcinoid tumors following acute appendicitis analyzing the demographics, clinical, laboratory, pathological features and follow-up results of the patients.

Material and Methods: We evaluated the patients retrospectively who had been operated for acute appendicitis between January 2006 and May 2018.

Results: We found 29 patients with carcinoid tumor among 7122 cases (0.4%) between 2006-2018. Median size of tumors was found to be 7.5 mm (Min: 0.8, max: 20 mm). While appendectomy was sufficient for 27 of the patients, right hemicolectomy was performed for 2 cases. When laboratory values were analysed the neutrophil / WBC ratio was significantly higher and lymphocyte count in the study group was significantly lower than control group ($p < 0.05$). The neutrophil / lymphocyte ratio was significantly higher than control group ($p < 0.05$).

Conclusion: Evaluation of laboratory values at admission, histopathological examination of appendiceal specimens, early diagnosis of cancer and performing the appropriate treatment are required for the survival of patients.

Keywords: Carcinoids; appendiceal mass; neuroendocrine tumors.

INTRODUCTION

Acute appendicitis is the most common causes of acute abdomen and appendectomy is the most frequently performed emergency procedure in surgical practice worldwide. Although the highest incidence is seen in children and younger population, acute appendicitis can be seen in all ages of both genders. The main underlying pathology is the obstruction of the appendiceal lumen which may be due to lymphoid hyperplasia, parasitic infections (1-3), food residues and although relatively rare; malignant (4-8) or benign (4,5,9,10) tumors.

Malignant and inflammatory masses of appendix are encountered incidentally in 2%-6% of all appendectomies (11,12). Appendiceal masses usually do not show any clinical manifestations preoperatively rather than symptoms of acute appendicitis. They are diagnosed peroperatively or postoperative period following pathological evaluation. Approximately in 2-10% of the cases, inflammation causes abscess or phlegmon

development (13,14).

Appendiceal tumors can be classified as benign or malignant, which include primary adenocarcinomas, mucinous cystadenocarcinomas, mucoceles, lymphomas, goblet cell carcinoids and carcinoids (9,15,16). Carcinoid tumor has the highest incidence of primary malignant tumors of the appendix that consist of the 60% of all appendiceal tumors (8).

The aim of this study was to evaluate the demographic, clinical, laboratory, pathological features and follow-up results of the patients that incidental appendiceal carcinoid tumors following acute appendicitis..

MATERIAL and METHODS

We evaluated the patients retrospectively who had been operated for acute appendicitis between January 2006 and May 2018. None of the patients had been suspected for malignancy in pre-operative period. Among those patients, we found the cases that had been diagnosed

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as appendiceal carcinoid tumor following pathological examination. The control group was consisted of patients with other appendix malignancies, e.g: Low grade mucinous neoplasia in 32 patients, mucinous adenocarcinoma in 3 patients, serrated adenoma in 20 patients, mucocoele in 2 and polyp in 2 patients. We evaluated the cases, for histopathological findings, follow-up, survival and compared our results with review of the literature. Due to the retrospective design of the study, we did not have an ethical committee approval.

Written informed consent was obtained from all patients included in this study. The authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects."

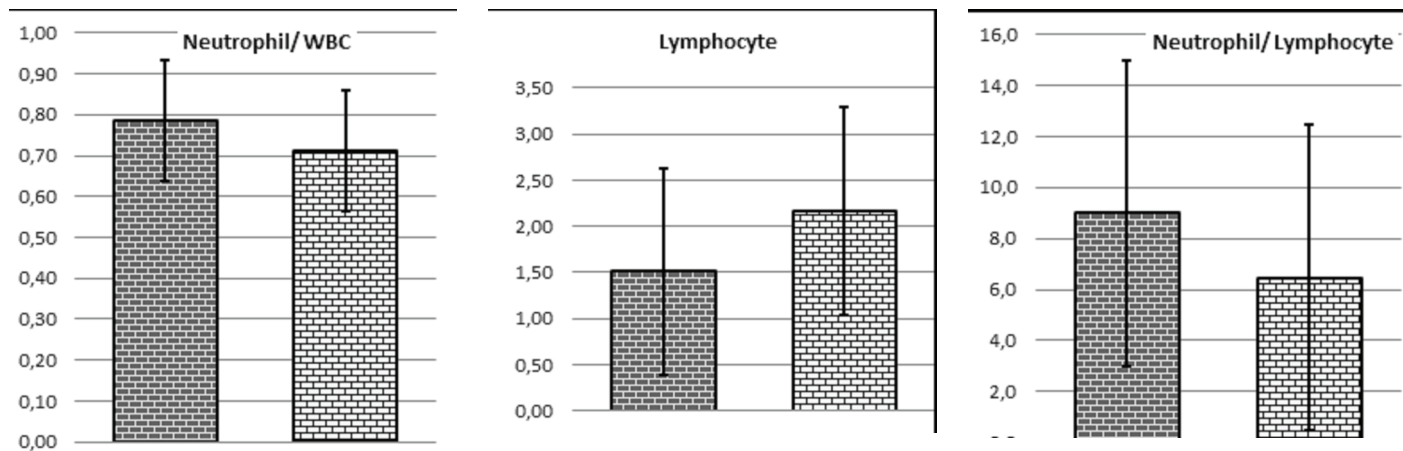
Statistical analysis

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of the variables was measured by the Kolmogorov-Smirnov test. An analysis of quantitative independent values, T test and Mann-Whitney U tests were used. The chi-square test was used to analyze independent qualitative data and Fisher test was used when chi-square test conditions were not met. SPSS 22.0 program was used for statistical analysis.

We found 29 patients with carcinoid tumor among 7122 cases (0.4%) between 2006-2018 years. Thirteen of them were females (44.8%) and 16 were males (55.2%). The median age was found 31 years (Min: 19, max: 68). Median size of tumors was found 7.5 mm (Min: 0.8, max: 20 mm). While appendectomy was sufficient for 27 of the patients, right hemicolectomy was performed for 2 cases. All of the patients with carcinoid tumor were diagnosed with acute appendicitis in pre-operative period. Acute appendicitis was diagnosed with ultrasonography (USG) in four of the patients and contrast enhanced abdominal computerized tomography (CT) was used additionally in four patients. USG was found to be normal in 5 patients. Major symptoms were pain in the right iliac fossa in all patients, nausea and vomiting in 24 (82.7%) and fever in 18 (62%) patients. Direct rebound and tenderness were observed on the Mc Burney point in 27 (93.1%) of the patients. Demographics and clinical findings of patients at admission are shown in table 1. There were not any suspicion of malignancy or plastron like mass at USG and CT in any of the patients at pre-operative period.

The age and sex distribution of the patients were not statistically significant in study and control group ($p > 0.05$). WBC and neutrophil counts did not differ significantly ($p > 0.05$) in both groups, but the neutrophil / WBC ratio was significantly higher in study group ($p < 0.05$). Lymphocyte count was significantly lower in study group ($p < 0.05$). The neutrophil / lymphocyte ratio was significantly higher in study group ($p < 0.05$) (Table 2, figures 1-3).

RESULTS



Figures 1-3. Statistical comparison of laboratory findings (1st column define the study group, 2nd column define the control group)

Age	Number (n)	%
18-30	13	44.8
30-50	11	37.9
50-70	5	17.2
Pain on right iliac fossa	29	100
Rebound & tenderness	27	93.1
Nausea and vomiting	24	82.7
Fever	18	62

Following histopathological confirmation of the diagnosis, staging was performed by CT and serum levels of 24-hour urinary 5-hydroxyindolacetic acid.

Histopathological features of tumors are shown in table III. Right hemicolectomy was performed in 2 patients because of the presence of lymphovascular invasion. All of the patients have been followed-up without recurrence or any complications (min:60, max: 120 months). All patients were discharged uneventfully. There were two (6.9%) cases with complications of wound infection at postoperative period.

Table 2. Statistical comparison of demographics and laboratory findings of both groups

	Study group		Control group		p
	Med.±SD/ n-%	Median	Med.±SD/ n-%	Median	
Age	35.7±14.1	310	37.4±13.7	35.0	0.394 ^m
Gender	M 16 55.2%		43 72.9%		0.097 ^{x2}
	F 13 44.8%		16 27.1%		
WBC	12.5±4.0	12.0	12.5±3.5	12.6	0.797 ^m
Neu	10.0±3.7	10.0	9.2±3.4	12.6	0.387 ^m
Neu / WBC	0.79±0.09	0.81	0.71±0.15	0.75	0.016 ^m
Lymph	1.51±0.68	1.60	2.16±1.12	2.20	0.001 ^m
Neu / lymph	9.01±5.85	7.25	6.45±7.11	4.54	0.002 ^m
Plt	228.9±51.1	222.0	245.5±57.0	250.0	0.187 ^t
MPV	8.5±1.0	8.7	8.4±1.3	8.5	0.820 ^t
Billirubin	0.85±0.37	0.7	0.81±0.49	0.60	0.302 ^m

^m Mann-whitney U test, ^t t test, ^{x2} Chi-square test, M: Male, F:Female, Neu: neutrophil, Lymph: lymphocyte, Plt: platelet

Table 3. Tumor size (mm), localization, treatment, pathology

Mitosis	None	21	72.4%
	1-5/HPF	8	27.6%
Localization	Distal	24	82.7%
	Middle	3	10.3%
	Proximal	2	7%
Differentiation	Well dif.NET grade 1	28	96.6%
	Well dif.NET grade 2	1	3.4%
Lymphovascular invasion	-	27	93.1%
	+	2	6.89%
Perineural invasion	-	25	86.3%
	+	4	13.7%
Chromogranin	-	8	27.6%
	+	21	72.4%
Synaptophysin	-	7	24.1%
	+	22	75.9%
CD 56	-	19	65.5%
	+	10	34.5%
Tumor size			
Parietal spread	0.8-20 mm	29	100%
	1mm-5 mm		
Ki-67 Proliferation index	1%	21	72.4%
	2%	5	17.2%
	3%	2	6.8%
	5-10%	1	3.4%

DISCUSSION

cute appendicitis is the most common surgical emergency, resulting from the luminal obstruction and inflammatory process which may be due to hyperplasia of lymphoid tissue, fecaliths and although it is relatively rare, tumors of appendix. Although it is very common, typical

presentations are only encountered in half of the patients and pre-operative diagnosis may be a challenge in some of the cases, even for experienced surgeons in spite of latest radiological advances.

Although most of the appendiceal masses are benign, diverticula, mucocele, carcinoma, lymphoma, endometriosis and carcinoid may be encountered and require complex resections or specific procedures such as ileocecal resection or right hemicolectomy. Because of the fact that appendiceal masses usually cause non specific symptoms such as abdominal pain; USG or CT have gain importance in means of accurate diagnosis and treatment strategy. In our study, we aimed to determine whether there was a correlation in carcinoid tumor cases in means of laboratory values.

Median age in our patients was found to be 31 which was consistent with the literature. The diagnosis of appendiceal diseases by USG has been reported as 72% (17). In our study, 24 out of 29 cases were diagnosed as acute appendicitis by USG (82.7%) in pre-operative period.

Carcinoid tumors of gastrointestinal system are most frequently found in appendix, rectum and small intestine in respectively. Carcinoid tumors are encountered with the incidence of 0.3% to 1.4% in patients underwent appendectomy (18,19). The study conducted by Akbulut S et al. they found that 5 patients with carcinoid tumors in 5262 appendectomies (4). In other study, conducted by Ma KW et al. they were detected that carcinoid tumors in 8 out of 17 appendiceal malignancies among total of 1492 appendectomies (9). Similarly, Emre A et al. found 11 cases between 1255 patients (20). Our results were (0.4%) similar to these studies and the literature. Occasionally, appendiceal carcinoids may be encountered in patients who have been operated for other reasons rather than acute appendicitis. O'Hanlan KA et al. found 3 carcinoid tumors in their patients whom they performed incidental appendectomy (257 patients) during total laparoscopic hysterectomy (821 patients) (21).

Clinical symptoms, pathological features and survival rates are related with tumor size, histological subtype and mesoappendiceal involvement. Average tumor size is smaller than 1 cm in almost 95% of the cases (7,8), which is accepted as an advantage for mortality and morbidity rates because the risk of metastasis from tumors of smaller than 1 cm is reported to be nearly zero and these cases may be cured with a simple appendectomy. Tumors larger than 2 cm must be managed with right hemicolectomy because the risk of metastasis is reported to be up to 85% in these patients (5-8,15,22-24). We performed right hemicolectomy in 2 out of 29 carcinoid tumors because of lymphovascular invasion in both. Other indications of right hemicolectomy are tumors localized at the base of the appendix, invasion of lymphatics, serosa or mesoappendix, presence of regional lymph node metastases, mucin production (presence of Goblet cells), cellular pleomorphism with high mitotic index, high levels of Ki-67 expression and childhood tumors (20,25).

Following right hemicolectomy, close follow-up with colonoscopy is recommended for metachronous tumors (26,27).

Appendiceal carcinoids may be found in all ages, but they are more common in females and adult patients (28). These tumors are usually asymptomatic and not suspected until being detected incidentally during laparotomy or laparoscopy for other intraabdominal disorder or diagnosed acute appendicitis. In our study, all of the 29 patients had been operated for acute appendicitis. Although it is not frequently seen, carcinoid tumor related clinical symptoms; such as flushing, facial telangiectasia, asthma, wheezing, diarrhea, which are caused by 5-hydroxytryptamine (serotonin) secreted by tumor cells may be seen in patients especially in the presence of systemic metastasis (29). These symptoms may alert the surgeon in pre-operative period. In our study, we had not encountered such symptoms in the pre-operative anamnesis of patients.

Most of the appendiceal carcinoid tumors are benign nature and as indicated above, smaller than 1 cm. Overall 5-year survival rate is reported to be higher than 90% in these tumors (30), and recurrence was reported up to 2% (31). Location is also an important factor for the type of the operation.

In our study, neutrophil/WBC ratio was significantly higher in carcinoid group when compared to control ($p < 0.05$). Lymphocyte count were significantly lower ($p < 0.05$) and neutrophil/ lymphocyte ratio was significantly higher in study group ($p < 0.05$).

Because of the difficulty in diagnosing the carcinoids of the appendix pre-operatively other than advanced disease, these laboratory values may be helpful in the presence of suspicious radiological findings. Fortunately, 90% of these tumors are located at the tip of the appendix, while 10% are located at the base (32) which necessitate right hemicolectomy. In spite of the fact that appendiceal carcinoids are relatively benign when compared to other malignancies of gastrointestinal system, surgeons and pathologists should be careful about this entity in pre and post-operative periods.

Although relatively rare, it should be kept in mind that tumors obstructing the appendiceal lumen and may be present with the clinical symptoms of acute appendicitis. Careful evaluation of radiological findings in the preoperative period may be life-saving in detecting such malignant lesions. Postoperative histopathological analyses may detect malignant lesions even when appendectomy specimens show normal macroscopic features preoperatively.

CONCLUSION

As a result, careful evaluation of laboratory findings at admission, adequate histopathological examination of appendiceal specimens, early diagnosis of cancer and performing the appropriate treatment are required for the survival of patients.

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