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Research Article

Can Conservative Management of Simple Acute Appendicitis Miss a Diagnosis of Appendiceal Neoplasms? A Histological Evaluation of 686 Appendectomies of Simple Appendicitis

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ABSTRACT

Background: Acute appendicitis is one of the most common surgical disease with an estimated lifetime risk of about 6-8%. Non-operative management of appendicitis is gaining popularity worldwide. Appendiceal tumors are rare and confirmed by histopathological examination in 0.5-2.5% of all appendectomies. The risk of missing an appendiceal tumor with a non-operative treatment is not well established. The aim of this study was to assess the incidence of appendiceal neoplasm in patients presented with simple non-perforated appendicitis. **Materials and Methods:** A retrospective study of all patients, that underwent an appendectomy from January 2018 to June 2020 in a single academic center. The histopathological reports were reviewed for appendiceal tumor. The patients' and disease characteristics were recorded. Final analysis included only patients with simple acute appendicitis. **Results:** 686 patients that underwent an emergent appendectomy for a simple acute appendicitis, nine patients (1.41%) were found to have an appendiceal neoplasm on final pathology. The preoperative imaging study did not reveal any suspicious findings for appendiceal neoplasm. Neoplasms revealed by histopathological examination include three neuroendocrine tumor (NET), four low-grade mucinous neoplasm and two adenocarcinomas. The mean age for appendiceal NET was 25.33 ± 4.72, for mucinous neoplasm 48.75 ± 29.22 and 62 ± 12.72 for adenocarcinoma. Logistic regression demonstrated a significant difference in appendiceal diameter and white blood cell count between the neoplasm and acute appendicitis group. **Conclusion:** Although appendiceal neoplasm following an appendectomy for simple acute appendicitis is not common, it is a concern that need to be addressed. Despite the wide use of imaging study for the diagnosis, it does not provide diagnostic indication for the existence of an appendiceal neoplasm in our cases. The risk of an appendiceal neoplasm, albeit low, should be taken into consideration in the management of adult patients with acute appendicitis before a decision to embark on a non-operative therapy.

1. Introduction

Acute appendicitis is one of the most common surgical disease with an estimated lifetime risk of about 6-8% [1]. Appendectomy for acute appendicitis is the most common emergency intra-abdominal operation performed by general surgeons, and approximately 300,000 appendectomies are performed annually in the USA alone [2]. Traditionally, acute appendicitis classified to simple or complicated by the preoperative assessment as described by Bhangu *et al.* at 2015 [3].

Historically, more than 50% of appendiceal neoplasm are diagnosed after emergent appendectomy. Commonly, it is mistaken for acute inflammatory appendicitis since growing tumor obstructs the appendiceal orifice or lumen leading to the abnormal imaging study that mimicking acute appendicitis [3]. In some cases, it may be also an incidental finding along with appendicitis [3]. Appendiceal neoplasm are rare and confirmed by histopathological examination in 0.5-2.5% of all appendectomies [4-6]. Recently, a non-operative approach for acute appendicitis has gained popularity. The dogma of conservative management has been tested by a lot of studies like the CODA trial (Comparison of Drugs versus Appendectomy), which found that early

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outcomes of medical management of appendicitis, with or without appendicolith, was non-inferior to surgery [7]. During the current COVID19 pandemic, non-operative management become more common at some centers around the globe with reasonable outcomes [8]. At 2020, during the COVID19 pandemic peak, the conservative approach has been adopted and relevant guideline has been published by the American College of Surgeons [9]. This changing paradigm in treating acute appendicitis rises a concern about the risk of missed diagnosis of appendiceal tumors with potential late consequences. The correlation between complicated appendicitis and appendiceal neoplasm is already well established by several recent studies. At 2021 Hayes *et al.* shown an 11% rate of appendiceal neoplasm in patients 30 years and older [10], similar results has been published Peltrini *et al.* The aim of this study was to assess the incidence of appendiceal neoplasm in non-tumor-suspected appendectomies for acute simple appendicitis that might have been suitable for non-operative management.

2. Materials and Methods

This is a retrospective study that analyzed 686 appendectomies for acute simple appendicitis at adults, who underwent appendectomy from January 2018 to June 2020 at a single academic center. Inclusion criteria were patients age 18 years and older that were diagnosed with acute simple appendicitis and underwent a same admission appendectomy. Appendicitis diagnosis was confirmed by an ultrasound (US) scan or a CT scan. Exclusion criteria include patients under 18 years old, other diagnosis than acute appendicitis or neoplasm of the appendix, complicated appendicitis as defined by a peri-appendicular abscess, appendix involved by other non-primary appendiceal malignancy and missing relevant data. Patients' data, such as demographics, comorbidities, preoperative findings (blood results, imaging type, appendix diameter etc.), intraoperative findings and postoperative course were collected and assessed. All the histopathological reports were reviewed for appendiceal neoplasm.

Statistical analysis was performed by SPSS software version 25.0 package and included univariable, multivariable logistic regression and Kruksal-Walis test for a-parametric variables. For all tests , a p-value of less than 0.05 was considered significant.

3. Results

This study including 686 patients who presented with acute simple appendicitis and underwent appendectomy at the index hospitalization. Nine (1.41%) patients had appendiceal neoplasm. Demographic characteristics present at (Table 1). The mean age for the acute inflammation group is 36.18 ± 16.92 and 43.89 ± 23.85 for neoplasm group without significant difference. Other characteristics as gender, BMI, ASA classification, appendiceal diameter at imaging and c-reactive protein revealed non-significant differences. The only characteristic that found to be significant is white blood count that was lower and within the normal range at the neoplasm group (9.88 ± 2.75 vs. 12.78 ± 4.28, p-value 0.044).

Table 1. Comparison between appendicitis and neoplasm regarding to background characteristics, disease characteristics.

	Appendicitis N=629 (98.6%)	**Neoplasm N= 9 (1.3%)**	**P value**
Age (mean ± SD)	36.18 ± 16.92 Range= 18-89	43.89 ±23.85 Range= 18-85	0.362
BMI	25.19 ± 4.56 Range= 15-41	25.16 ± 4.75 Range= 20-31	0.987
Gender [N (%)]			0.507
M	323 (51.4)	6 (66.7)	
F	306 (48.6)	3 (33.3)	
Comorbidities general	154 (24.5%)	2 (22.2%)	1.000
ASA score			0.920
1	304 (48.6)	5 (55.6)	
2	284 (45.4)	3 (33.3)	
3	34 (5.4)	1 (11.1)	
4	1 (0.2)	0 (0.0)	
5	2 (0.3)	0 (0.0)	
WBC	12.78 ± 4.28 Range= 3-31	9.88 ± 2.75 Range= 6-14	**0.044**
CRP	2.71 ± 4.18 Range= 0-36	4.88 ± 5.30 Range= 0-15	0.125
Appendix diameter	10.50 ± 2.64 Range= 5-22	13.50 ± 7.13 Range= 9-30	0.274
LOS (length of stay)	1.81 ± 4.22 Range= 0-83.31	1.57 ± 0.99 Range- 0-3.2	0.864
Post- op. complications (no/yes)	10 (1.6)	0 (0.0)	1.000
Clavian dindo			0.997

0	619 (98.4)	9 (100)	
1	2 (0.3)	0 (0.0)	
2	3 (0.5)	0 (0.0)	
3	3 (0.5)	0 (0.0)	
4	2 (0.3)	0 (0.0)	
30 d readmission	41 (6.5)	1 (11.1)	0.460

Table 2. Univariable regression of association between specific risk factors and pathology type.

	OR	**CI**	**P value**
Age	1.022	0.98- 1.057	0.187
BMI	0.999	0.837- 1.19	0.987
Gender	0.528	0.131- 2.129	0.369
comorbidities	0.881	0.18- 4.28	0.876
WBC	0.831	0.69- 0.996	**0.045**
CRP	1.074	0.997- 1.18	0.141
Appendix diameter	1.240	1.064- 1.44	**0.006**
LOS	0.970	0.672- 1.401	0.872
30 d readmission	1.79	0.21- 14.68	0.58

There was no difference at perioperative parameters as length of stay, post-operative complications by clavian-dindo classification and 30 days readmission rate. Univariable logistic regression analysis for association between specific risk factors and appendiceal neoplasm revealed two significant parameters. The first is white blood count (OR 0.831, CI 0.69- 0.996, P value 0.045) and the second is appendiceal diameter (OR 1.240, CI 1.064- 1.44, P value 0.006). Our axiom of age related appendiceal neoplasm has been tested by trying to adjust the significant risk factors - white blood count and appendiceal diameter, by age (Table 3). The multivariable logistic regression analysis revealed that appendiceal diameter is the only significant risk factor of neoplasm (OR 1.214, CI, 1.035- 1.423, P value 0.017) within all the parameters that who've been tested. Neoplasm types included three patients with neuroendocrine tumors (NET), four patients with low-grade mucinous neoplasms and two patients with adenocarcinoma of the appendix (Table 4).

Table 3. Multivariable regression of association between significant risk factors and pathology - adjusted for age.

	OR	**CI**	**P value**
WBC	0.840	0.701- 1.007	0.060
Appendix diameter	1.214	1.035- 1.423	**0.017**

Table 4. Abnormal pathology findings in the appendectomy specimens.

Neoplasm Pathology	**Number**
Neuroendocrine Tumor/Carcinoid	3
Appendiceal mucinous neoplasm	4
Adenocarcinoma	2
Total	9

Statistical comparison of demographic and perioperative characteristics for type of neoplasm - neuroendocrine tumor, low-grade mucinous neoplasms and adenocarcinoma, didn't lead to any significant insight (Table 5).

Table 5. Comparison between tumor types regarding background characteristics.

	Adenocarcinoma N=2 (22.2)	**NET N= 3 (33.3)**	**Mucinous N= 4 (44.4)**	**P value**
age	62 ± 12.72 Range- 53- 71	25.33 ± 4.72 Range- 20-29	48.75 ± 29.22 Range- 18-85	0.247
BMI	23.00 ± 4.24 Range= 20-26	24.66 ± 5.03 Range= 20-30	31 (only one value)	0.322
gender				0.060
M	0 (0.0)	3 (100)	3(75.0)	
F	2 (100)	0 (0.0)	1 (25)	
comorbidities	0 (0.0)	0 (0.0)	2 (50)	0.200

WBC	7 ± 1.41 Range= 608	12 ± 2 Range= 10-14	9.75 ± 2.62 Range= 6-12	0.156
CRP	12.50 ± 3.53 Range= 10-15	2.66 ± 2.08 Range= 1-5	2.75 ± 4.27 Range= 0-9	0.108
Appendix diameter	13.5 ± 4.94 Range= 10-17	9.66 ± 0.577 Range= 9-10	17.33 ± 11.01 Range= 10-30	0.209
LOS	1.48 ± 0.079 Range= 1.43-1.54	1.16 ± 0.423 Range- 0.71- 1.55	1.920 ± 1.48 Range= 0- 3.22	0.705

4. Discussion

Non-operative management for acute simple appendicitis has already been investigated well and established for many years in children, toddler and more recently in adults. Although there are reasonable outcomes shown in several major studies, like CODA and APPAC trails [7, 11], conservative treatment carries the risk of missing an appendiceal tumor, mostly in patients with complicated appendecitis [12]. Although the gaining popularity of non-operative management recent years we must take in caution as results of studies like Marmor S *et al.* have reported a 54% increase incidence of appendiceal neoplasm between 2000-2009 [13], an increase that added even more concern regarding the risk of missing an appendiceal tumor with non-operative treatment for what is suspected as an acute appendicitis.

At our study the overall prevalence of appendiceal neoplasm was 1.41%. Our neoplasm incidence is within the accepted literature range for appendiceal neoplasm of 0.7-2.5% [14]. For many years numerous studies established the correlation between complicated appendicitis and risk for neoplasm of the appendix in emergent appendectomy. At 2019, Lietzén E *et al.* were published population-based study with associated tumor risk of 3.2% in complicated appendicitis compared to 0.9% in simple appendicitis [15]. In the same year, similar findings have been reported in a randomized controlled trail by Mällinen J *et al.* that revealed 17% of appendiceal neoplasm in patients underwent interval appendectomy for complicated appendicitis, but most of the patients were older than 40 years old. The trial was prematurely terminated due to ethical concerns [16]. More recently, at 2021, retrospective analysis by Hayes D and colleagues challenge the paradigm of interval appendectomy for complicated appendicitis. 32 out of 402 (9%) patients were diagnosed with appendiceal neoplasm, all of them above 30 years old and the risk increases with increased age. They conclude and recommend to consider interval appendectomy in all patients 30 years and older with complicated appendicitis [10]. Very little attention was given to the rate of possible appendiceal tumors in patients with suspected simple appendicitis as it is considered less likely. Yet, as the use of non-operative treatment gains traction, the concern of missing a tumor should be addressed, especially as these patients may elect to avoid and interval appendectomy later on.

Our study demonstrated a neoplasm incidence of 1.41% for patients with only a simple appendicitis that were operated upon, and without any preoperative clinical or imaging concern for neoplasm. The lack of reliable imaging modality to distinguish between simple appendicitis and an appendiceal tumor should cause a level of uncertainty about further clinical decision. In our study, seven out of nine patients (77.7%) were diagnosed by CT scan and the other two (22.3%) with ultrasonography. Although small sample size, our results support the non-significant trend between increased risk of appendiceal adenocarcinoma and increasing age - the two patients age more than 50 years old.

The presence of neuroendocrine tumor or mucinous neoplasm are more challenging to correlate with age duo non-durable age prevalence. Similar findings about correlation between age and appendiceal neoplasm already been demonstrated by several studies like Furman MJ *et al.* [17] and Wright GP *et al.* [18]. Their studies found that the incidence of neoplasm on interval appendectomy was significant higher for patients 40 years old or older. This study is the first to have shown a similar high prevalence of appendiceal neoplasm within simple appendicitis patients. Most published studies included both simple and complicated appendicitis at their analysis. Our finding in combination with popularity gain of non-operative management raises a major concern about missing crucial histopathological diagnosis and the possibility for further operative intervention or surveillance. Out of the nine patients with appendiceal neoplasm, three (33%) underwent additional laparoscopic right colectomy due to appendiceal adenocarcinomas and one mesoappendix involved by neuroendocrine tumors.

Limitations of our study includes retrospective nature, relatively small group of appendiceal neoplasm, homogenic population, the risk of confounding factors and single-center experience.

5. Conclusion

Despite the wide use of modern imaging studies for the diagnosis of acute appendicitis it's sensitivity for identifying an underline tumor is low. Individual with simple appendicitis is essential to consider the potential of occult malignancy by demography features and especially by WBC count and appendiceal diameter. The risk of an appendiceal neoplasm, albeit low, should be taken into consideration in the management of adult patients with acute simple appendicitis before a decision to embark on a non-operative therapy.

Assistance with the Study

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Conflicts of Interest

None.

Presentation

None.

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