

# FREQUENCY DETERMINATION OF NEGATIVE APPENDECTOMY AND UNUSUAL FINDINGS OF ACUTE APPENDICITIS: A RETROSPECTIVE STUDY

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## ABSTRACT

**Objective:** To find out the frequency and implications of unusual histopathological findings in appendectomy specimens from patients with suspected acute appendicitis and to ascertain the rate of negative appendectomy in multiple health care institutes of Pakistan.

**Material & Methods:** The epidemiological and pathological data of all the patients who were operated for the initial diagnosis of acute appendicitis between January 2015 and December 2015 was retrospectively evaluated. Histologically the cases were sub classified under four categories; acute appendicitis, lymphoid hyperplasia, unusual histopathological findings and negative appendectomy. The patient's age, clinical history, sex, operative reports, histopathological reports were assessed.

**Results:** Total 1093 samples were collected during the study period, of which 755 were males and 338 females. Their age range was from 2 to 80 years. Amongst all the collected samples, 572 patients were operated because of acute appendicitis and 342 due to lymphoid hyperplasia. The appendectomy due to unusual histopathological findings was carried out in 55 patients and the most common cause was fibrous obliteration that accounted for 56 % (31/55). Negative appendectomy rate was found to be 10.8 % (119/1093).

**Conclusion:** Definite diagnosis of appendicitis and many unusual diseases is only possible histologically irrespective of the macroscopic appearance of appendectomy specimens and clinical presentation. Advancements in the diagnostic and imaging techniques have not significantly reduced the rates of negative appendectomy. Clinical assessment outweighs other diagnostic modalities in the management of patients with suspected acute appendicitis.

**Key Words:** Appendicitis, Appendectomy specimens, Histopathology, Unusual findings, Appendiceal malignancy, Negative appendectomy.

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## INTRODUCTION

Acute appendicitis is the most common acute abdominal emergency requiring surgery. Worldwide most common surgical procedure performed is appendectomy [1]. It is evident that 10 to 19 years old have the highest incidence accounting for 0.233 % of the population. Men are at a higher risk who have a lifetime incidence of 8.6 % while women have an incidence of 6.7 % [2].

The lifetime incidence of acute appendicitis is estimated to be 7.0 % overall. Male/ female lifetime risk of appendectomy is 12 % versus 23 %

respectively [3].

The incidence of acute appendicitis roughly parallels that of lymphoid development. In second and third decades of life the chances of appendicitis are the greatest. Acute appendicitis histologically is an acute neutrophilic inflammation of the muscularis propria which can spill over to other parts of the organ and outside. Multiple causes have been described for this condition but obstruction of lumen is considered the most important because it starts the inflammatory process [4]. Luminal obstruction is mainly caused by lymphoid hyperplasia and other less frequent etiologies include intestinal parasites, endometriosis, lymphomas, tuberculosis, stromal tumors, carcinoid tumors, eosinophilic granulomas, adenomas, mucoceles, dysplastic changes and adenocarcinomas [5]. Though advancements in diagnostic modalities have improved the diagnosis of

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appendectomy yet negative appendectomies rate is high. Negative appendectomies poses a significant challenge due to the unnecessary risks to both patients and institutions in terms of complications and cost. According to one regional data the rate of negative appendectomy and unusual findings in acute appendectomy are 6 % and 7 % respectively [6]. In another local study it was found to be much higher (18 %) [7].

The aim of this study was to find the frequency of unusual pathologic findings in appendectomy specimens of patients who had underwent surgery to treat acute appendicitis. Another objective was to determine the incidence of negative appendectomies.

## MATERIAL AND METHODS

The data of all the patients who underwent appendectomy at the Combined Military Hospitals of Pakistan between January 2015 and December 2015 was retrieved from Armed Forces Institute of Pathology record system and retrospectively analyzed.

Inclusion criteria for selection include receipt of appendectomy to treat an initial diagnosis of acute appendicitis. Exclusion criteria was receipt of incidental appendectomy during other surgical procedures. On the basis of histopathology, the specimens were classified as either positive for acute appendicitis features or negative. Positive specimens revealed fecaliths or worms, fibrosis, appendiceal neuroma, granulomatous inflammation, foreign body reaction, mucocele, endometriosis, cystadenoma, or appendiceal tumors. Whereas, negative specimens were microscopically normal with no evidence of inflammation [5].

## RESULTS

Total 1093 patients met the inclusion criteria, including 755 (69 %) males and 338 (31 %) females. The mean age was 26.9067 + 13.02. Whereas the age range was 2-80 years. Majority of the patients i.e. 54.2% were between 21 and 40 years.

The histopathological characteristics of 1093 patients are summarized in Table-1. Histopathologic findings indicated that 969/1093 (88.65 %) samples were positive for acute appendicitis. Among these 342 (35.2%) were positive for lymphoid hyperplasia. Unusual pathology was found in 55 (5.7 %) specimens. However, 119 of the specimens showed no pathology. Therefore, negative appendicitis rate in our study was calculated to be 10.8 %.

**Table-1: Etiopathological characteristics of 1093 patients with acute appendicitis**

<b>Patients' characteristics Results</b>	
Patients (n)	1093
Sex [n (%)]	
Male	755 (30.9)
Female	338 (69.1)
<b>Age [mean+ SD (range)]</b>	
Overall	26.9067+13.02 (2-80)
Female	25.4024 + 12.64(5-74)
Male	27.5801+ 13.736(2-80)
<b>Distribution of patients according to age range [n (%)]</b>	
0–20 y	355 (32.5)
21–40 y	593 (54.2)
41–60 y	129 (11.8)
61–80 y	16 (1.5)
<b>Distribution of patients according to histopathological findings</b>	
Positive appendectomy [n (%)]	969 (88.65)
Negative appendectomy [n (%)]	119 (10.8)
<b>Positive appendectomy [n (%)]</b>	<b>969 (100)</b>
Acute appendicitis	572 (59.1)
Lymphoid hyperplasia	342 (35.2)
Unusual histopathological findings	55 (5.7)
<b>Negative appendectomy [n (%)]</b>	<b>119 (100)</b>
Male	84(70.6)
Female	35 (29.4)
<b>Age distribution of patients with negative appendectomy [n (%)]</b>	
1 - 20 y	38 (31.9)
21 - 40 y	66 (55.5)
41 - 60 y	15 (12.6)

Unusual histopathological findings were detected in 55 (5.7 %) of the total patients who underwent appendectomy. The clinic pathologic characteristics of these patients are summarized in Table-2.

**Table-2: Clinicopathological features of 55 patients with unusual histopathological findings**

<u>Sex [n (%)]</u>	
Male	35 (63.6)
Female	20 (36.4)
<u>Histopathological findings [n (%)]</u>	
Fibrous obliteration	31 (56.3)
Carcinoid tumor	1 (1.8)
Enterobius vermicularis	5 (9.1)
Granulomatous inflammation	4 (7.27)
Endometriosis	3 (5.45)
Mucocele	5 (9.1)
Eosinophilic infiltration	2 (3.6)
Taenia Saginata	1 (1.8)
Appendicular diverticulitis	3 (5.45)

**Table-3: Comparison of current study with international studies.**

S. No	No of cases (n)	Mean Age (years)	Negative appendectomy rate (%)	Reference
1	1255	34	6%	[28] (Turkey)
2	853	38	9.2%	[29] (Saudi)
3	168	39	18.45%	[30] Pak
4	1093	26	9.2%	Current study

## DISCUSSION

A combination of various modalities including clinical history, examination and lab findings are usually enough to reach an accurate diagnosis of acute appendicitis without the need of further imaging [6,14]. Different clinical scoring systems usually combine all the modalities in a systemic pattern that ensure more reproducibility and compliance along with better management but they cannot rule out the possibility of appendicitis definitively. Nonetheless, differential diagnosis of acute appendicitis can be reached in most patients with abdominal ultrasonography (USG), computed tomography (CT) or diagnostic laparoscopy. Though USG is a rapid and accessible modality for the diagnosis of doubtful cases of appendicitis but CT scan has emerged as the most reliable, quick and diagnostically accurate tool in patients whose diagnosis is doubtful by other methods. Moreover, it is operator-independent and relatively easy to perform and provides images that are easy to comprehend. CT is also very helpful in finding the definite underlying etiology of appendicular diseases [8,15, 16].

Therefore, exact diagnosis of acute appendicitis requires a combination of patient's history, laboratory investigations, imaging techniques along with the surgeon's clinical assessment. In spite of all technological advancement, the reported rates of histology proven negative cases following appendectomy have ranged between 9.2 % and 35 % [4,12,13]. Intriguingly, the rates are particularly high for women during child bearing years [7,12,13]. The rate of negative appendectomy found in the current study (9.2 %) is comparable to that in the existing collective literature.

The pathological process of appendicitis follows other inflammatory diseases. Initial inflammation results in localized ischemia that further leads to perforation, abscess formation. Obliteration of lumen is the single most important event in the pathogenesis of acute appendicitis. The frequency of fibrous obliteration was observed to be about 30 %. In simplified form it is a spindle cell proliferation that replaces the lumen of the appendix. Appendiceal

neuroma is a synonymous diagnostic terminology. The pathogenesis is largely unknown. The main process is inflammation that leads to proliferation of neuroendocrine cells. Differential diagnosis between appendiceal neuroma and acute appendicitis relies on the patients clinical history, symptoms, laboratory and physical examination findings. However, majority of patients found to have neuroma are found incidentally, with the histopathological finding of obliterating fibrosis in asymptomatic patients [9,17, 18]. In infants most prevalent cause of acute appendicitis is also the lymphoid hyperplasia, however in older age groups fecalith is the leading cause. In the current study apart from these common factors several other unusual factors were also found to be associated with acute appendicitis.

Carcinoid is the most common malignant tumors of appendix vermiformis [10,19]. On gross examination it is usually circumscribed with yellowish cut surface and has a hard consistency. In a reported series this entity makes up for 51 % of the malignant tumors of the appendix [11,20]. The overall frequency of this entity varies from 0.02 to 2.27 % of all appendiceal pathologies. It is not usually diagnosed clinically and is usually found incidentally on histopathology [3-12]. In majority of the cases carcinoid measuring less than 2 cm are found at the tip of the appendix. Most cases have a benign clinical course and they rarely metastasize. Risk of metastasis varies with the size of the tumor. If the size is less than 1 cm it rarely metastasize and can be managed by simple appendectomy. However, increased tumor size (>2 cm) can metastasize with frequency of metastasis ranging from 80 to 90 % and is managed by right hemicolectomy [3, 21]. The frequency of carcinoid in our study was 0.1 % (1/969).

The *Enterobius vermicularis* infection also called pinworms is very common worldwide. The incidence of appendix infested by pin worm ranges between 0.6 % and 3.8 % [22]. Furthermore, the rate of inflammation in infected appendices varies from 13-37 % [23]. The rate of pinworms in our study was recorded to be 0.5 % (5/969).

Appendicular granulomas may be found in a patient clinical presenting as acute appendicitis. The incidence of granulomatous appendix as reported in western literature ranges from 0.14-0.3 % and its incidence in underdeveloped countries varies from 1.3-2.3 % [24]. Multiple factors causing granulomas include *Mycobacterium tuberculosis*, *Yersinia*, *Schistosoma* along with other noninfectious etiologies such as sarcoidosis and Crohn's disease [25].

Frequency of granulomas caused by Crohn's disease in patients of acute appendicitis is only 5 to 10 %. In our study the rate of granulomatous appendicitis was very low i.e. 0.4 %. Moreover, tuberculosis is the leading cause of granulomatous inflammation in this region as confirmed by gene expert analysis for confirmation of T.B.

Endometriosis histologically comprises ectopic endometrium along with hemosiderin laden macrophages outside of the uterine cavity. Intestinal endometriosis occurs in 10 % of the women with endometriosis. Endometriosis in appendix is usually asymptomatic but it can be a source of appendicitis leading to complications like perforation and intussusception. We based our diagnosis on the presence of endometrial glands and stroma in appendix and it occurred at a rate of 0.3 % in patients.

Taeniasis is defined as the presence of helminth in the intestine. The relationship between *Taenia* spp and appendicitis is unclear in literature. The treatment of teniasis is resolved with a single dose of praziquantel so it is not usually found histologically making it a rare entity to be diagnosed with few case reports only [3,26]. Likewise, in the present study only one case was diagnosed with taenia.

Mucocele is defined as accumulation of mucoid material in the lumen resulting in dilation and obstruction leading to appendicitis. The existing literature reports its frequency between 0.2 to 0.7 %. Different types of mucocele include mucinous cystadenocarcinoma, retention cyst, mucosal hyperplasia and mucinouscystadenoma. Mucocele is usually asymptomatic and is usually discovered incidentally. However, the appropriate treatment for cystadenocarcinoma is right hemicolectomy [1,10]. The rate of mucocele in our study was 0.5 % which compares favorably with that of other published studies.

Appendiceal diverticula is a rare entity with reported incidence ranging from 0.004-2.1% [27,28]. The pseudo diverticulum is the pouching of mucosa and sub mucosa in the muscular layer. Four other types of diverticular disease of the appendix includes; acute diverticulitis, acute appendicitis with acute diverticulitis, acute appendicitis with diverticulum and appendix with diverticulum. Pseudo diverticulum is commonly asymptomatic but it can be complicated by perforation and inflammation that cause abdominal pain, mimicking acute appendicitis [27,29]. Endometriosis was found 0.3 % in this study which compares favorably with that of other published

studies. Endometriosis of the appendix may be the first indication of disease also helping to rule out the cause of infertility and providing valuable lifesaving and accurate diagnostic modality [28].

Chronic caseating granulomas in appendix may lead to the finding of highly endemic, treatable but indolent disease like tuberculosis or it may lead to Crohn's disease having a wide variety of vague presentations. Histopathological examination providing vital diagnostic evidence may be lifesaving in such circumstances. Also, infectious diseases like *E. vermicularis*, *T. saginata*, or *Entamoeba histolitica* which often present with vague general symptoms leading to diagnostic confusion may be easily diagnosed and eradicated by single dose of medication. Similarly, diseases having bad prognosis and requiring urgent management like carcinoid or adenocarcinoma (both primary and secondary) may be diagnosed on histopathological examination of unsuspecting appendix specimen but can lead to effective and timely lifesaving surgery. Therefore, even macroscopically normal appendix specimens need to be sent to histopathological examination which at times would prove to be the only reliable diagnostic and lifesaving modality for unsuspecting patient and clinician.

## CONCLUSION

In the current study, we sought to determine incidence of negative appendectomies to identify factors that may reduce the risk of having the normal appendices removed surgically. The currently high rates of negative appendectomy points out a need of continuous research for a better scoring system for the diagnosis of appendicitis and the need to improve the current scoring systems. There is also a case for better integration of history, physical examination, laboratory studies and diagnostic imaging studies to reduce the current rates of negative appendectomy.

## AUTHORS CONTRIBUTION

**Hassan Tariq, Waqas Ranjha & Shahum Khan:** Principal author, data collection, paper writing.

**Hafeez ud Din, Farhan Akhtar & Shoab Nayer Hashmi:** Supervision of the project, Proof reading, literature review.

**Siraj ud Din & Khadijah Abid Khan:** Statistical review, manuscript writing editing.

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