

Histopathological Evaluation of Lesions of Appendix - A Cross Sectional Study

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ABSTRACT

BACKGROUND

Appendix is considered as a vestigial organ in medical history. But recent studies reveal its importance in immunological function. Appendectomy is one of the most common surgeries performed and acute appendicitis being the most frequent pathology noted. Various less common pathologies like parasitic infestation, granuloma, diverticulum, neoplasms are also described. In our institute, we have seen an increased rate of acute appendicitis and a relative increase in neoplastic conditions. The purpose of this study was histopathological evaluation of lesions of appendix over a period of five years and its association with demographic data.

METHODS

This cross-sectional study included all specimens received in the department of pathology with primary pathology in appendix. Appendix removed as a part of other surgical procedures were excluded. Relevant clinical data, gross findings and histopathological diagnoses were retrieved from pathology records and computer databases and statistical analysis was done using Statistical Package for Social Sciences (SPSS 16.0).

RESULTS

Out of the 576 cases, 485 (84 %) patients showed findings consistent with acute appendicitis on histopathological examination. Perforation rate was 4.86 % and was higher in male patients. Other pathologies include chronic appendicitis in 58 cases (10.06 %), eosinophilic appendicitis in one case (0.17 %), appendix with lymphoid hyperplasia in 14 cases (2.43 %), periappendicitis in 4 cases (0.69 %), fibrous obliteration of appendix in 2 cases (0.34 %), granulomatous appendicitis in 4 cases (0.69 %), appendix with lymphoid hyperplasia in 14 cases (2.43 %), diverticulitis in one case (0.17 %), tubular adenoma with low grade dysplasia in one case (0.17 %), neuroendocrine tumour in one case (0.17 %) and mucinous neoplasms in 5 cases (0.86 %).

CONCLUSIONS

The study supports routine histological examination of all the appendectomy specimens to avoid missing of any clinically important condition which has significant impact on treatment and prognosis. Also noted an increased number of mucinous neoplasms suggesting the importance of future studies in this field.

KEYWORDS

Appendix, Acute Appendicitis, Chronic Appendicitis, Mucinous Neoplasms of Appendix, Diverticulitis

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DOI: 10.18410/jebmh/2021/580

How to Cite This Article:

*Punnoose AP, Joseph E, Joseph D, et al.
Histopathological evaluation of lesions of
appendix - a cross sectional study. J Evid
Based Med Healthc 2021;8(34):3187-
3192. DOI: 10.18410/jebmh/2021/580*

*Submission 30-06-2021,
Peer Review 10-07-2021,
Acceptance 03-08-2021,
Published 23-08-2021.*

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BACKGROUND

The human appendix has been regarded as a rudimentary part of the intestine in medical history. However, in recent years, several studies have thrown light on its immunological importance. Appendix acts as a 'safe house' for the commensal gut flora and these studies have hypothesized that commensal bacteria can be reintroduced from the appendix in case of disease.^{1,2,3,4} Acute appendicitis is the most common pathology described in appendix and this is the most common surgical emergency worldwide.⁵ Despite of advances in technology and imaging modalities, there is dilemma in the clinical diagnosis of acute appendicitis. Histopathological examination remains the gold standard method for the confirmation of the appendicitis.

Many aetiologies have been identified for appendicitis. All these aetiologies result in luminal obstruction, rise in intraluminal pressure, venous outflow obstruction and ischemia. Ischemia weakens the epithelial integrity and increases the organ's risk of bacterial invasion. Fecaliths and lymphoid hyperplasia are described as the most common causative factors of luminal obstruction. Other less frequent factors associated with this condition include enterobiasis,⁶ endometriosis,^{6,7,8} tuberculosis,⁶ amoebiasis,⁶ actinomycosis,⁶ adenovirus,⁵ granulomatous diseases,^{6,7,9} eosinophilic granuloma,¹⁰ neurogenic appendicopathy,¹¹ foreign body melanosis,⁵ neurofibroma,⁵ diverticulitis,⁶ taeniasis,⁶ appendiceal neoplasms such as neuroendocrine tumour,^{6,12} gastrointestinal stromal tumour,⁶ hyperplastic polyp,⁶ adenoma,⁶ adenocarcinoma,⁶ mucinous neoplasms,⁶ lymphoma,⁶ and leukemia.⁶ Primary and secondary neoplasms of the appendix are rare tumours found in approximately 1 % of appendectomy specimens.¹³ A few recent studies reported an increased incidence of primary appendiceal neoplasms.^{14,15}

Moreover, the pathologic diagnosis of acute inflammation, detection of unusual findings such as incidental tumours, granuloma, parasites in appendix which have significant impact on treatment and outcome highlight the importance of the pathologic analysis of every single resected appendix.

Aim of this study was histopathological evaluation of lesions of appendix over a period of five years in our institute and its association with demographic data. Relevant clinical data, gross findings and histopathological diagnoses were retrieved from pathology records and computer databases.

METHODS

The present cross-sectional study was conducted in the Department of Pathology, Believers Church Medical College, Thiruvalla, Kerala, India. It included all specimens with primary pathology in appendix received for 5 years from 1st January 2016 to 31st December 2020. Appendix removed as a part of other surgical procedures such as intestinal resection for ischemic bowel disease and right hemicolectomy specimens for colonic malignancies were excluded. Statistical analysis was done using SPSS 16.0.

RESULTS

A total of 576 cases with suspected primary pathology in appendix were received in the histopathology department during the period of 5 years from January 2016 to December 2020. 571 cases were appendectomy specimens and 5 cases were right hemicolectomy. The mean age of the study population was 25.35 years (age ranges from 9 years to 79 years). Among them, 338 (58.7 %) cases were males and 238 (41.3 %) cases were females with male to female ratio being 1.42. Appendix specimens constituted approximately 2.5 % to 3 % of all specimens received in the department of pathology every year. Due to the Covid 19 outbreak, there was a decline in the number of cases in 2020. The distribution of histopathological diagnoses with sex characteristic is shown in Table 1.

Diagnostic Categories	Female	Male	Total
Acute appendicitis	143	211	354
Acute appendicitis with periappendicitis	26	50	76
Acute suppurative appendicitis	7	15	22
Acute appendicitis with perforation	12	16	28
Acute gangrenous appendicitis	3	2	5
Acute eosinophilic appendicitis	0	1	1
Appendix with lymphoid hyperplasia	8	6	14
Chronic appendicitis	27	31	58
Periappendicitis	2	2	4
Granulomatous appendicitis	2	2	4
Fibrous obliteration of appendix	2	0	2
Diverticulitis	0	1	1
Adenoma	1	0	1
Neuroendocrine tumour	1	0	1
Mucinous neoplasms	4	1	5
Total	238	338	576

Table 1. Sex Wise Distribution of Histopathological Diagnoses

Acute appendicitis (including acute appendicitis with or without periappendicitis, perforation, gangrenous and suppurative appendicitis) constitutes 84 % (485 cases) of specimens (294 cases were males and 191 cases were females). Most common age group with acute appendicitis was 11 - 20 years with 60 % of cases in age group between 11 - 30 years. Acute appendicitis with perforation was observed in 4.86 % (28 cases) of specimens. It was observed to be more common in males than in females with 68 % of the cases were less than 40 years of age.

Acute eosinophilic appendicitis with transmural and mucosal eosinophilic infiltrate was observed in a single case (0.17 %) of a 24-year-old male patient. Appendix with lymphoid hyperplasia was observed in 2.43 % (14 cases) of specimens. Majority of these cases were females, and it was observed more in patients with less than 20 years of age. Chronic appendicitis was observed in 10.06 % (58 cases) of cases. Periappendicitis was observed in 0.69 % (4 cases) of specimens. Fibrous obliteration of appendix was observed in 0.34 % (2 cases) of specimens.

Granulomatous appendicitis was noted in 0.69 % (4 cases) of specimens. Of these, one case was a 24-year-old male and microscopy showed granuloma with caseous necrosis. Real time polymerase chain reaction (RT-PCR) for mycobacterium tuberculosis was found to be positive. Another case was a 25-year-old male, appendix revealed microgranuloma without necrosis in muscularis propria, but the endoscopic work up for Crohn's disease and RT PCR for mycobacterium tuberculosis were negative. Rest of the 2 of

the cases showed foreign body granulomatous reaction. Diverticulitis was observed in a single case (0.17 %) who was a 24-year-old male with recurrent history of appendicitis.

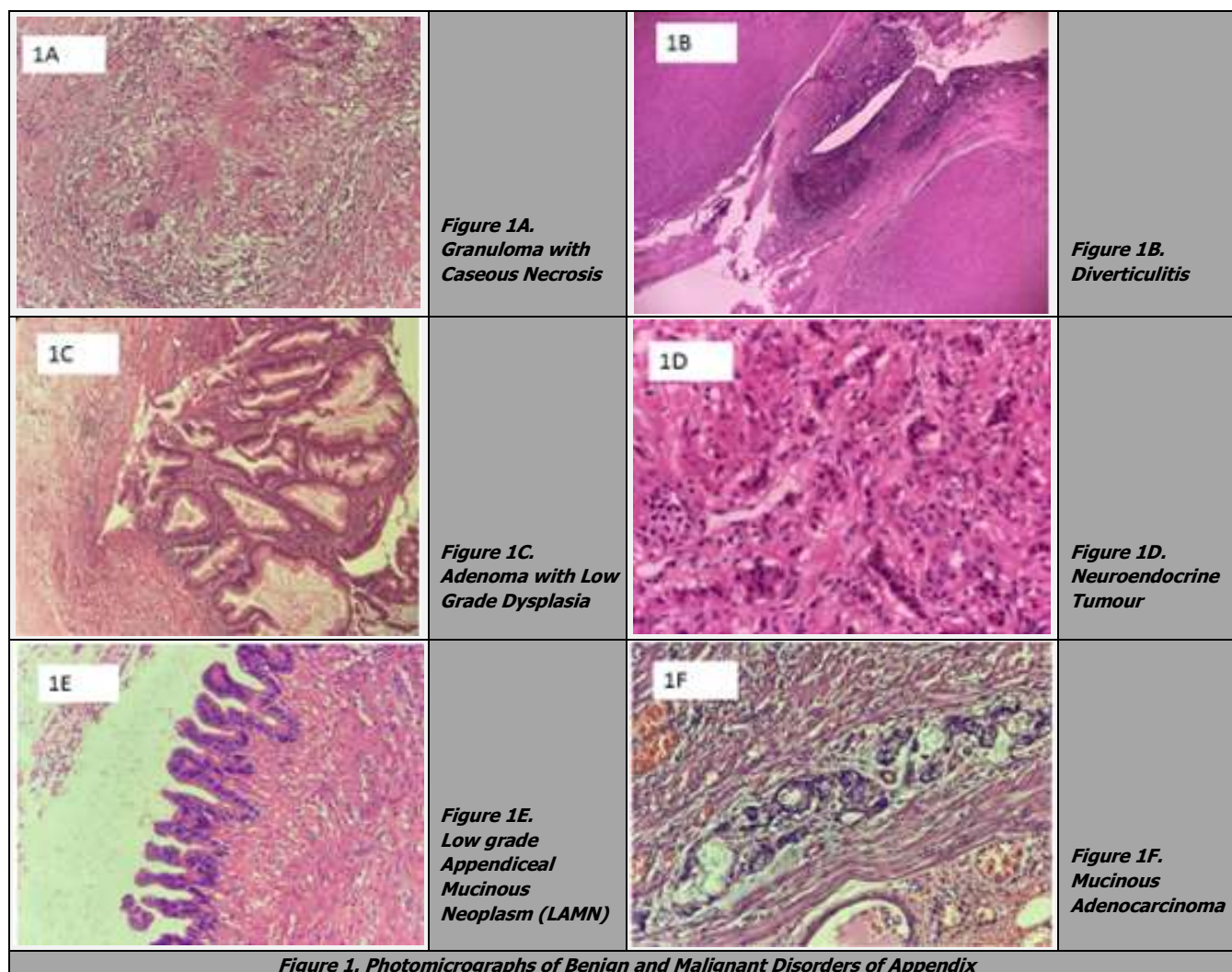
One neuroendocrine tumour (0.17 %) Grade 1 was diagnosed incidentally in a 17-year-old female with clinically suspected appendicitis. The tumour was found at the tip of the appendix measuring 0.2 cm in maximum dimension with no meso-appendiceal or distant metastasis. The patient was kept under close follow up without further surgical intervention. A 72-year-old female with clinically suspected appendicitis showed tubular adenoma with low grade dysplasia (0.17 % of specimens) on histopathology.

There were 5 mucinous neoplasms (0.86 %) of appendix in our study. Pre-operative radiology suspected appendiceal neoplasms in all these five cases. 3 cases were low grade appendiceal mucinous neoplasms (LAMN) and 2 cases were mucinous adenocarcinoma. LAMN on microscopy showed long villous processes lined by atypical mucinous epithelium with mucin and fibrous obliteration of lamina propria. One case of mucinous adenocarcinoma was diagnosed in a 36-year-old female with neoplasm at the tip of appendix and the other mucinous adenocarcinoma observed in a 70-year-

old female. Clinicopathological characteristics of 5 patients with primary appendicular mucinous neoplasms are enlisted in Table 2. Some photomicrographs of specimens of benign and malignant disorders are demonstrated in Figure 1.

Age (y)	Sex	Tumour Size (cm)	Location	Treatment	Diagnosis	Parietal Spread	Follow-up (Month)
53	F	1	Base	Appendicectomy + Right hemicolectomy	LAMN	Mucosa	13
78	F	3	Tip	Appendicectomy + Right hemicolectomy	LAMN	Mucosa	10
44	M	2	Distal half	Appendicectomy + Right hemicolectomy	LAMN	Mucosa	16
36	F	2.5	Tip	Appendicectomy + Right hemicolectomy	Mucinous adenocarcinoma with pseudomyxoma peritonei	Serosa	16
70	F	5	Entire appendix	Appendicectomy + Right hemicolectomy	Mucinous adenocarcinoma	Serosa	6

Table 2. Clinicopathological Characteristics of the Five Patients with Primary Appendicular Mucinous Neoplasms



DISCUSSION

Appendicectomy is a common surgical procedure and histopathological examination is the gold standard for diagnosis of lesions of appendix, it not only confirms the diagnosis but also reveal the pathologies which have significant impact on further patient management. In the western world, acute appendicitis accounts for about 40 % of all surgical emergencies.¹⁶ It is less common in Asian and African subcontinent; however, recent literature review showed that there is an increase in incidence of appendicitis in these countries with adoption of western lifestyle and diets.¹⁷

Appendix constituted 2.5 – 3 % of the total biopsy specimens in our institute from 2015 to 2019. In the present study, 485 (84 %) of the appendicectomy specimens had histological evidence of acute appendicitis which is comparable with other studies (65 - 91 %).¹⁸ As with other studies, the most common age group affected was 11 - 30 years.^{5,17} In our study, 338 (58.7 %) cases were males and 238 (41.3 %) cases were females with a male predominance. M : F ratio was 1.42 which is similar to other studies.^{5,17,19}

The frequency of perforation in the appendix was 4.86 % in our study and was comparable to that reported by Osama Elfaedy et al.²⁰ (5.8 %) and Charfi et al.²¹ (6.4 %). However, several studies^{5,19,22,23} have reported much higher rates between 11 - 22.5 %. By contrast, Shrestha et al.²⁴ and Jat et al.²⁵ have found a low rate of 1.9 % and 2 %, respectively. Most studies have demonstrated that the incidence of appendicular perforation increases with age^{5,19,26} but in the present study the maximum number of cases (57 % cases) with perforation were below 10 years. In general, and within the peak age group, we found a higher incidence of perforated appendicitis in male patients. The exact reason why perforated appendicitis is more common in males is not clear, but similar association has been found in many studies.^{27,28,29} In our opinion, a higher incidence of appendicitis in male patients as documented in most series may explain the increased incidence of perforated appendicitis in the male population.

Appendicitis with lymphoid hyperplasia was seen in 8 cases of females and 6 cases of males. This finding was mostly seen in adolescent age group which re-establish the

fact that maximum lymphoid hyperplasia is seen in late childhood/ adolescence.

In our study, 2 males and 2 females showed periappendicitis which is against the findings seen in many other studies in which they reported more incidence of periappendicitis in female patients due to inflammatory diseases related to pelvic organs.

Chronic appendicitis do not present with typical symptoms of acute appendicitis and diagnosis is frequently made following an appendicectomy and based on histopathological findings.³⁰ In our study, the rate of chronic appendicitis was 10.06 % which is comparable to the study conducted by Rehman et al.³¹ which showed chronic appendicitis in 7.9 % of the total of 316 patients. Osama Elfaedy et al.²⁰ Shreshtha et al.²⁴ and Dincel et al.³⁰ have reported lower rates of 5.2 %, 2.6 % and 0.2 %, respectively.

Granulomatous appendicitis is seen in 0.1 % to 2 % of appendicectomy specimens. Causes are usually idiopathic but other causes like Crohn’s disease, Yersinia, foreign body reactions, interval appendicitis, Mycobacterium tuberculosis, pinworm (Enterobius vermicularis), and sarcoidosis are also reported. Present study showed 0.69 % of cases with granulomatous inflammation.

Diverticular disease of the appendix (DDA) is a rare disease characterized by herniation or out pouching of the appendiceal mucosa through the muscular wall which has been reported in 0.2 % to 1.7 % of appendicectomy specimens.^{32,33} Appendiceal diverticula are frequently associated with higher risk of neoplasm especially carcinoid tumours and mucinous neoplasms.³⁴ In the present study, there was a single case of diverticulitis (0.17 %), in a 24 year old male. He presented with recurrent history of abdominal pain and pre-operative imaging showed an appendicular mass with perforation. Histopathological examination revealed diverticulitis and features of acute appendicitis. However, the patient was lost for follow up.

As per the report by National Organisation of Rare Disorders (NORD), neoplasms of the appendix are extremely rare with an estimated incidence of 0.15 - 0.9 per 100,000 people. Appendiceal tumours, found in less than 3 % of all appendectomies, are usually asymptomatic and are usually identified either intraoperatively or during the histopathological examinations.⁶ Well differentiated neuroendocrine tumour of the appendix is the most common type of primary malignant tumour of the appendix.

Author, Year of Publication	Study Population	Acute Appendicitis	Acute Appendicitis with Perforation	Chronic Appendicitis	Granuloma	Parasite	Diverticulum	Adenoma	NET	Non-Neoplastic Mucinous Lesions	Mucinous Neoplasms
Omiyale et al. ³⁵ 2015	238	211 (88.7 %)	nr	nr	1 (0.4 %)	nr	nr	nr	1 (0.4 %)	2 (0.8 %)	Nil
Elfaedy et al. ¹⁹ 2019	4012	3530 (88 %)	204 (5 %)	207 (5.2 %)	1 (0.02 %)	22 (0.54 %)	nr	nr	5 (0.1 %)	09 (0.22 %)	2 (0.04 %)
Yabanoglu H et al. ³³ 2014	1466	1138 (78 %)	nr	nr	1 (0.01 %)	20 (1.4 %)	nr	3 (0.2 %)	7 (0.47 %)	16 (1.1 %)	6 (0.41 %)
Unver N et al. ³⁶ 2018	2047	2013 (98.3 %)	nr	nr	5 (0.24 %)	4 (0.19 %)	nr	nr	6 (0.29 %)	7 (0.34 %)	9 (0.43 %)
Dincel, O et al. ²⁸ 2018	1970	-	-	3	3	13	-	-	8	9	Nil
Charfi S et al. ²⁰ 2014	24697	19,637 (79.5 %)	1239 (6.3 %)	-	46 (0.18 %)	1599 (6.4 %)	nr	nr	90 (0.36 %)	60 (0.24 %)	15 (0.06 %)
Present Study	576	485 (84 %)	28 (4.86)	58 (10.1 %)	4 (0.69 %)	-	1 (0.17 %)	1 (0.17 %)	1 (0.17 %)	Nil	5 (0.86 %)

Table 3. A Comparison of Present Study with Few Selected Publications

nr- not reported

It represents 60 % of all appendiceal tumours and is discovered in 0.3 % to 2.3 % of the appendicectomy specimens.^{22,30} In the current study, we had a lower rate of appendiceal neuroendocrine tumour (NET) (0.1 %). NET is rarely diagnosed preoperatively, and it is commonly identified as an incidental finding during appendicectomy. For NET, < 1 cm in size, the risk of metastasis is exceedingly low and simple appendicectomy is considered curative. However, NET \geq 2 cm, the risk of metastasis increases up to 85 % and patients usually proceed to right hemicolectomy.^{6,22,30,37}

Appendiceal epithelial neoplasms are observed in 0.2 – 0.3 % of appendicectomy specimens and occur most commonly in between 50 – 70 years of age.³⁸ Radiological detection rate of epithelial neoplasm are high compared to NET because of their larger size and high complication rate. Epithelial neoplasms can be classified into mucinous (70 % of tumours) and non-mucinous (30 % of tumours) based on mucin production.³⁹ We encountered a case of tubular adenoma with low grade dysplasia, which is a rare non mucinous epithelial neoplasm of appendix.

There was significant change over the years in the classification of appendiceal mucinous lesions. The peritoneal surface oncology group international (PSOGI) developed a consensus classification for appendiceal mucinous lesion in 2012 that helped to resolve many confusions in diagnostic terminology.^{40,41} It broadly classifies mucinous lesions as non-neoplastic and neoplastic lesions. Non neoplastic lesions include simple mucocoeles, characterized by degenerative epithelial changes due to obstruction (e.g., fecalith) and distention, without any evidence of mucosal hyperplasia or neoplasia. Neoplastic appendiceal mucinous lesions include serrated polyps of the appendix, mucinous appendiceal neoplasms and mucinous adenocarcinomas of the appendix. Serrated polyp with or without dysplasia, resemble the serrated lesions of the colon but have differing molecular features. Mucinous appendiceal neoplasms are dysplastic mucinous tumours which again can be further classified as low-grade appendiceal mucinous neoplasms (LAMNs) or high-grade appendiceal mucinous neoplasms (HAMNs).

Mucinous adenocarcinomas of the appendix demonstrate frankly infiltrative invasion, features of which include tumour budding (dis-cohesive single cells or clusters of up to five cells) and/or small, irregular glands, typically within a desmoplastic stroma. Appendiceal mucinous neoplasms are present in 0.2 % – 0.3 % of appendicectomy specimens.⁴² Present study showed an increased rate of mucinous neoplasm i.e., 0.8 %. Of these, 60 % of the cases (3 out of 5 cases) were LAMN and 40 % were mucinous adenocarcinoma.

CONCLUSIONS

Pathological examination of appendix is a mandatory test to be done in all appendicectomy specimens. Unusual pathologies revealed on histopathological examination have significant impact on further patient management. The present study highlights it by demonstrating a variety of

diagnostic entities. Present study also reveals a recent significant increase in mucinous neoplasms of appendix.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

We gratefully thank Dr Kripa Susan Thomas, Consultant Pathologist, Tricare diagnostic centre, Thiruvalla, for her assistance in statistical analysis.

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