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Original Article

Pathology Section

Clinicopathologic Study of Appendix Specimens- A Two Year Retrospective Study at a Tertiary Care Center

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ABSTRACT

Introduction: Acute appendicitis is the most common abdominal emergency and has remained an on going diagnostic challenge. Histopathologic studies are the gold standard for final diagnosis.

Aim: To study the histopathological features of appendix and utility of Ultrasonography (USG) in diagnosis of appendicitis.

Materials and Methods: A two-year retrospective study from 1st January 2016 to 31st December 2017 of 472 appendectomy cases. Demography, clinical findings, radiologic and laboratory studies, histopathology findings were analysed.

Results: Among the 472 appendectomy cases 283 (59.95%) were males and 189 (40.04%) were female patients. Most of the patients presented in the 3rd decade. Mean age was 29.25± 15.09 years (median age-26). Most common histopathological finding was Acute Appendicitis with Perforation comprising of 187 cases (39.61%) followed by acute appendicitis comprising of 117 cases (24.78%). Unusual findings were tubercular appendicitis. Most common neoplasm was Low Grade Mucinous Neoplasm (LAMN) four cases (0.84%) followed by carcinoid three (0.63%) and goblet cell carcinoid one (0.21%). USG and histopathologic correlation was significant only when USG was combined with clinical and laboratory findings.

Conclusion: Histopathological examination of appendix is necessary for confirmation of type of inflammation. In addition vigilant grossing should be done to detect parasitic infestations, appendicolith, diverticuli, tubercular appendicitis and neoplasms of appendix. USG should be correlated with clinical and laboratory findings to diagnose appendicitis.

Keywords: Appendiceal neoplasms, Appendicitis, Goblet cell carcinoid, Low grade mucinous neoplasm

INTRODUCTION

The appendix, a vestigial organ in humans, is attached to caecum. Appendicitis is one of the common causes of acute abdomen and emergency surgery resulting in significant morbidity and mortality [1].

Acute appendicitis presents with pain in the right iliac fossa, fever, vomiting, tenderness, guarding and rigidity with rebound tenderness. These patients commonly have leukocytosis and absolute neutrophilia. Early appendectomy relieves all symptoms. Misdiagnosis often leads to removal of un-inflamed appendix. The thought that prevailed in 20th century was that the immediate complication i.e., perforation of appendix is avoided by early surgical removal resulting in rise of negative appendix rates to more than 20% [2]. Diagnostic laparoscopy combined with Alvarado score is one such step taken to reduce it [3]. There is rise in use of Ultrasonography (USG), Computed Tomography (CT), Magnetic Resonance Imaging (MRI) to reduce negative appendectomy rates [4].

All appendices removed not always have inflammatory changes alone. Some may harbor neoplasms with grave prognosis such as adenocarcinoma [5], Low Grade Mucinous Neoplasm (LAMN) [6], neuroendocrine tumours [7], non-Hodgkin lymphoma [8] or may be the site of metastasis [9,10]. There are very few studies in India highlighting the importance of proper grossing methods in diagnosis of appendix specimens and the importance of combining the clinical findings, laboratory parameters with USG instead of considering USG features alone in diagnosis of appendicitis. Proper histopathologic evaluation is most important in appendix disease management. Hence, a retrospective study was attempted to find the sensitivity and specificity of USG in identifying diseased appendix, to study the histopathologic features of lesions of appendix in patients presenting with clinical features indicative of appendicitis. The study also discusses about rare appendicular lesions encountered.

MATERIALS AND METHODS

The present study was a retrospective, cross-sectional study of two-year duration from January 2016 to December 2017 conducted in Shri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Dharwad, Karnataka, India.

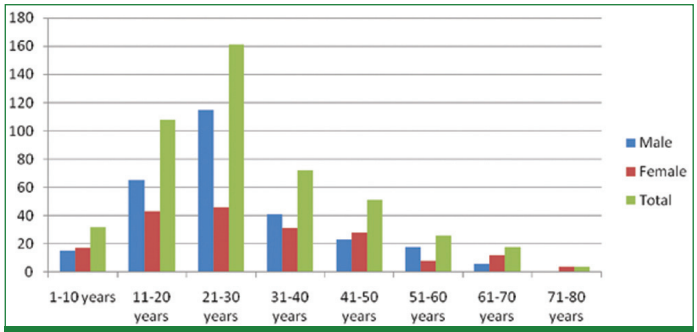
The study included the patients who underwent appendectomy for having clinical features of appendicitis. Appendectomies done additionally along with another abdominal surgery without presenting with clinical features of appendicitis were excluded from the study. The slides and blocks were retrieved from histopathology based on pathology registry and section were re-examined. The patient's clinical history, laboratory parameters, radiologic reports, operative notes, follow-up were recorded.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences Software (Version 21.0; SPSS, Inc, Chicago, IL). Patient data for each demographic or histopathologic characteristic were summarized as Mean±standard deviation. Incidence of a characteristic within a particular group was calculated as percentage of the entire study population. Fisher's-exact test was performed and a p-value of <0.05 was considered statistically significant.

RESULTS

A total of 472 specimens of appendix which satisfied the inclusion and exclusion criteria were studied. Out of which 460 (97.5%) of the patients underwent emergency appendectomy and 12 (2.5%) underwent interval appendectomy for the clinical diagnosis of acute appendicitis. There were 283 (59.95%) males and 189 (40.04%) female patients, with Male: Female ratio of 1.5:1. Most patients in both genders were in 3rd decade [Table/Fig-1]. The youngest patient



[Table/Fig-1]: The bar chart depiction of decade wise patient distribution with respect age and sex shows most patients in third decade.

was three-year-old male and oldest 78-year-old female. Mean age was 29.25±15.09 years (Median age- 26 years).

Patients presented with multiple symptoms and the most common symptoms were right iliac fossa pain 465 (98.52%) followed by vomiting 240 (50.8%) and fever 148 patients (31.35%). Other symptoms were constipation (5.28%), loose stools (4.86%). dysuria (3.175), nausea (2.95%) and anorexia (2.32%).

Only 130 patients (27.5%) presented within the first 24 hours with mean duration of presentation being 7.47±15.2 days (Median-3 days).

The leukocyte count of above 11,000/mm^3 and absolute neutrophil count (>7000/mm^3) were found to be supportive of acute appendicitis and perforated appendix. Leukocytosis was seen in 233/472 (49.36%) patients whereas 52.75% (249/472) had neutrophilia (Differential count with >75% neutrophils) and eosinophilia was seen in 68/472 (14.40%).

USG findings were available in 367 cases. Whenever, USG suggested appendicular pathology (inflammation, mucocele and neoplasm), it correlated with histopathological findings in 269 cases with a sensitivity of 79.9%, specificity of 31.03%. Positive Predictive Value (PPV) was 93.08 % and Negative Predictive Value (NPV) was 11.54%. Fisher's-exact test showed a p-value of 0.179 and hence was not statistically significant [Table/Fig-2].

However, when the USG was combined with clinical findings (right iliac fossa pain, vomiting, fever and tenderness) and laboratory findings (leukocytosis >11,000/mm3, neutrophilia >75%) the Fisher's-exact test showed a p-value of 0.00028 (i.e., <0.05) hence highly significant [Table/Fig-3].

CT and histopathologic correlation was available in 83 patients and correlation with abnormal appendix was 100%. Negative appendectomy was found in 7 cases (1.48%).

The most common histopathologic diagnosis was acute appendicitis with perforation (39.61%) (M: F- 1.37:1) followed by acute appendicitis (24.78%) (M: F- 3:1) [Table/Fig-4].

Eosinophilic appendicitis accounted for 28 cases (5.93%) and showed transmural and mucosal eosinophilic infiltrate with pericellular oedema around eosinophils. However, only 12/28 (42.8%) cases of eosinophilic appendicitis were associated with eosinophilia. There were four cases of xanthogranulomatous appendicitis and only one case of tubercular appendicitis [Table/Fig-5].

S. No	Histopathological changes	Total (%)	Male	Female
Normal Histology				
1	Normal	7 (1.48%)	4 (57.15%)	3 (42.85%)
Anatomic abnormalities				
2	Diverticulum	22 (4.66%)	12 (54.54%)	10 (45.45%)
3	Fibrous obliteration	9 (1.90%)	3 (33.33%)	6 (66.66%)
Inflammatory appendix disorders				
4	Acute Appendicitis with Perforation	187 (39.61%)	108 (57.75%)	79 (42.25%)
5	Acute appendicitis	117 (24.78%)	88 (75.21%)	29 (24.79%)
6	Gangrene	6 (1.27%)	4 (66.66%)	2 (33.33%)
7	Periappendicitis	5 (1.05%)	3 (0.6%)	2 (0.4%)
8	Chronic appendicitis	27 (5.71%)	13 (48.15%)	14 (51.85%)
9	Resolving appendicitis	20 (4.23%)	13 (65%)	7 (35%)
10	Eosinophilic appendicitis	28 (5.93%)	14 (50%)	14 (50%)
11	Xanthogranulomatous appendicitis	4 (0.84%)	2 (50%)	2 (50%)
12	Tubercular appendicitis	1 (0.21%)	0	1 (100%)
Infectious causes of acute and chronic appendicitis				
13	*Enterobius vermicularis*	5 (1.05%)	2 (0.4%)	3 (0.6%)
Miscellaneous non neoplastic disorders				
14	Mucocele	10 (2.11%)	5 (50%)	5 (50%)
15	Lymphoid hyperplasia	14 (2.96%)	6 (42.85%)	8 (57.15%)
16	Foreign body giant cell reaction	1 (0.21%)	1 (100%)	0
17	Mesothelial cyst of appendix	1(0.21%)	1 (100%)	0
Neoplastic				
18	LAMN	4 (0.84%)	2 (50%)	2 (50%)
19	Carcinoid	3 (0.63%)	2 (66.66%)	1 (33.33%)
20	Goblet cell carcinoid	1 (0.21%)	0	1 (100%)

[Table/Fig-4]: Distribution of various lesions in specimens of appendix based on incidence and sex.

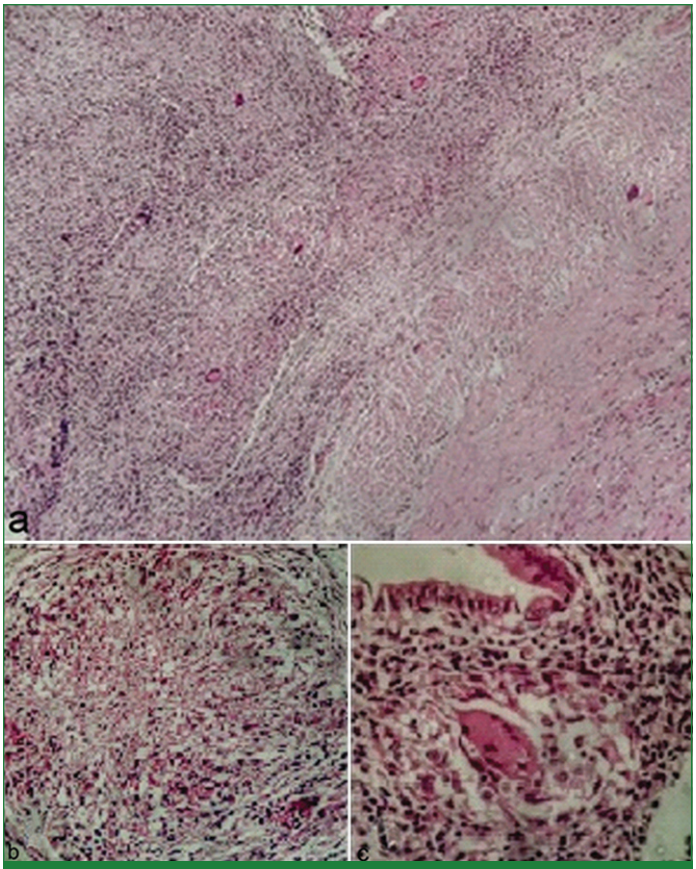
Foreign body giant cell reaction with central calcified area was noted in appendix of a 37-year-old male patient. He had no past history of abdominal surgery. The foreign bodies are not uncommon in appendicitis [Table/Fig-6] [11]. We encountered eight (1.7%) patients with neoplastic appendicular pathology. LAMN [Table/Fig-4] found to be most common neoplasm among all with four cases (0.84%) followed by carcinoid three cases (0.63%) [Table/Fig-4] and one case of goblet cell carcinoid (0.21%) was seen. LAMN accounted for 50% of all appendiceal neoplasms in our study. Microscopy showed long villous processes lined by atypical mucinous epithelium with mucin

	Histopathology positive for appendicular lesions	Histopathology negative for appendicitis	Total	p-value
USG (Positive for appendicitis)	269	20	289	0.179 (Statistically not significant since p-value >0.05)
USG (Negative for appendicitis)	69	9	78	
Total	338	29	367	

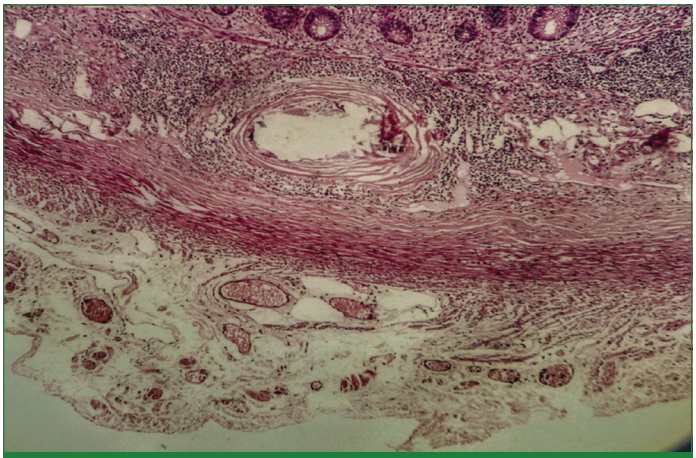
[Table/Fig-2]: Fisher's-exact test using 2X2 contingency table for appendicitis diagnosed by ultrasonography versus histopathology.

	Histopathology positive for appendicular lesions	Histopathology negative for appendicitis	Total	p-value
USG Positive for appendicitis + Clinical & Laboratory findings of appendicitis	307	20	327	0.00028 (Statistically significant since p-value <0.05)
USG Negative for appendicitis + Clinical & Laboratory findings appendicitis	31	9	40	
Total	338	29	367	

[Table/Fig-3]: Fisher's-exact test using 2x2 contingency table for appendicitis diagnosed by ultrasonography, Clinical and laboratory findings versus histopathology.



[Table/Fig-5]: Tubercular appendicitis. Epithelioid cell granulomas noted in all layers (a) (10x, H & E). Caseous necrosis in epithelioid cell granuloma (b) (10x, H & E). Epithelioid cell granuloma in lamina propria with Langhan's type giant cell. (c) (10x, H & E).



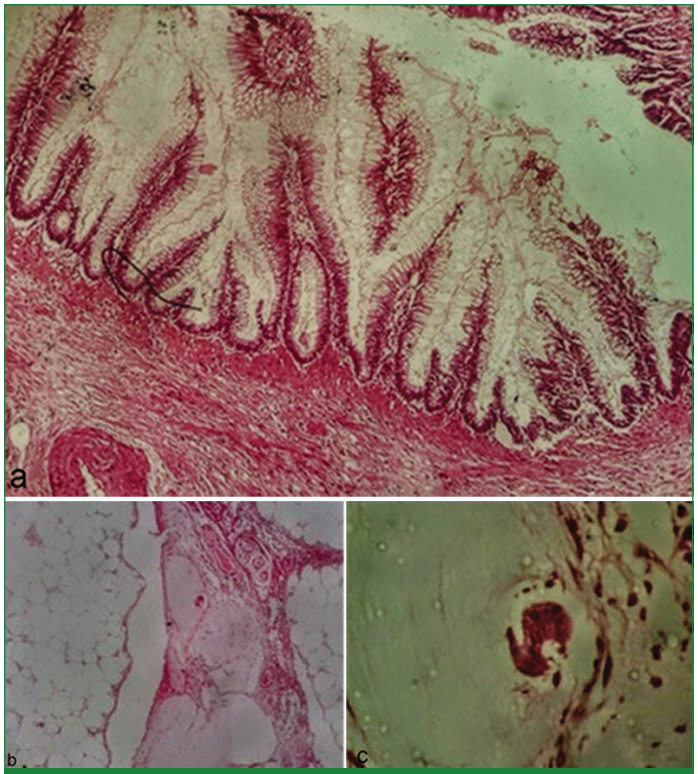
[Table/Fig-6]: Foreign body granuloma in submucosa with giant cells and calcification (10x, H & E).

pools and exhibiting pushing invasion. One case had peritoneal cavity with numerous gelatinous globules of mucin which microscopically showed strips of mucinous epithelium [Table/Fig-7].

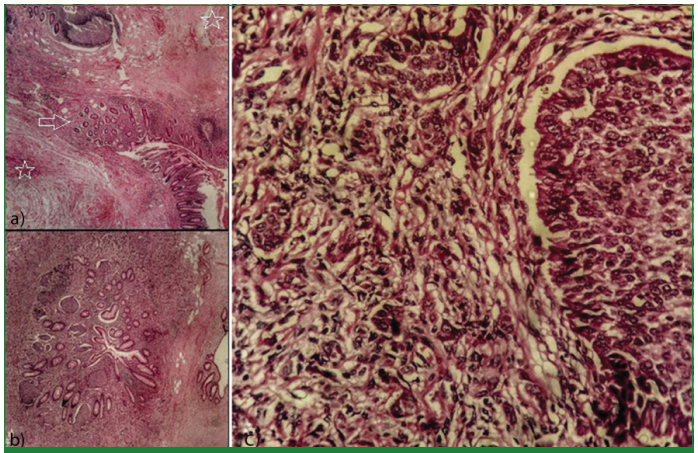
Carcinoid (well differentiated neuroendocrine tumour) accounted for 37.5% of all appendicular neoplasms in our study and microscopically showed homogenous population of small polygonal cells arranged in nested and trabecular patterns. One of the case also showed a diverticulum associated with carcinoid [Table/Fig-8].

Goblet cell carcinoid showed tumour nests and acini infiltrating submucosa and muscularis propria. Most of the neoplastic cells took on a goblet cell or signet- ring-like morphology with a small compressed nucleus and abundant intracytoplasmic mucin. On immunohistochemistry, tumour cells were reactive for synaptophysin, chromogranin and Carcino-Embryonic Antigen (CEA) [Table/Fig-9].

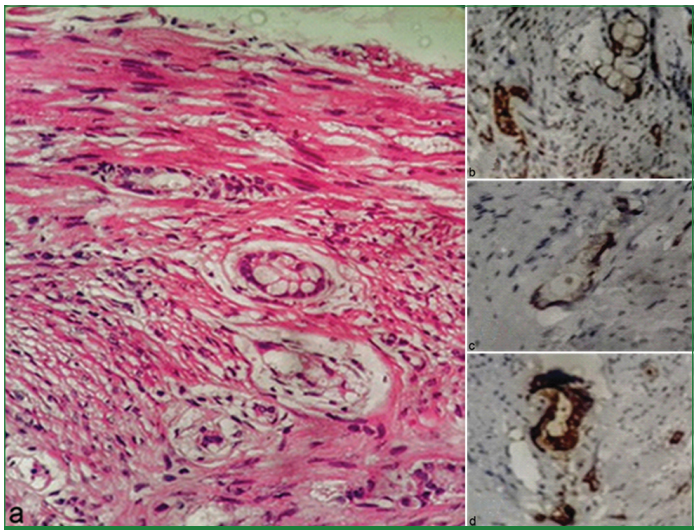
Perforation (39.61%) was the most common complication. The other major complication noted in our study was stump appendicitis.



[Table/Fig-7]: Low grade mucinous neoplasm of appendix with pushing invasion (a) (10x, H & E). The patient also had pseudomyxoma peritonei (b) (10x, H & E) with floating tumour cells in mucin pool. (c) (40x, H & E)



[Table/Fig-8]: Diverticulum (arrow) of appendix through muscular propria (star) (a) (4x, H & E). The patient also had well differentiated neuroendocrine tumour (carcinoid). Note diverticulum on right side (b) (4x, H & E).Tumour cells in both organoid and infiltrative pattern (c) (40x, H & E).



[Table/Fig-9]: Conventional type goblet cell carcinoid of appendix in glandular pattern invading muscular propria (a) (40x, H & E). Cells are positive for Chromogranin (b). Synaptophysin (c) and Carcino-Embryonic Antigen (CEA) (d)

DISCUSSION

Acute appendicitis is a one of the most common condition which requires emergency operative solution. It presents with sudden onset of symptoms of pain in lower abdomen later localizing to Mc Burney's point, nausea, vomiting and fever. The signs include tenderness, rebound tenderness (Rovsing's sign). The localized peritonitis can be detected by guarding and rigidity. Acute symptoms if tolerated may further lead to formation of appendicular mass, a protective phenomenon by viscera and omentum to localize the peritonitis. If left untreated, it may lead to perforation of appendix, pus collection in peritoneal cavity, generalized peritonitis and septicaemia.

Appendectomy specimens must be grossed thoroughly, documenting every abnormality present externally and on cut surface. The lesions can be very tiny and sometimes even less than a microscopic field. It is better if bisected tip of the appendix is entirely submitted for processing. The base of the appendix should be inked for recognition. Cross sectional bits should be submitted from every centimeter including the perforation sites and nodules. The luminal material should not be emptied while submitting. Shorter appendix must be submitted entirely for processing. These practices may reduce the negative appendectomy rates. Histologic examination of un-submitted portions of appendix may be considered before designating negative appendectomy.

Histopathology of appendectomy specimens is always necessary to ensure appropriate management and rule out further dreaded conditions as tuberculosis and malignant neoplasms which also present in similar way as acute appendicitis.

Appendectomy was carried out more commonly in 3rd decade followed by second decade, in both male and female sexes. This pattern of age distribution is common [6,12-14] but some studies showed peak age falling in second decade followed by third decade [8,15].

Modalities used in enforcing clinical diagnosis of acute appendicitis are USG, CT, MRI and barium enema. In our study USG was available in 367 cases; however USG and histopathologic agreement was seen only in 269 cases with a sensitivity of 79.9%, Specificity of 31.03%. PPV was 93.08% and NPV was 11.54%. In a review study by Pinto F et al., on the utility of USG in appendicitis showed an overall sensitivity of USG in adult and adolescent patients was 86%, specificity 81%, the PPV of graded compression USG was 84% (range from 46% to 95%), and the NPV of graded compression USG was 85% (range from 60% to 97) [16]. While the range of reported accuracy (82% to 96%) for USG in children has been acceptable, the sensitivity (44% to 100%) and the specificity (47% to 99%) varied considerably. Several factors might be taken into account as the causes of these variations. First, because USG is an operator-dependent technique, with a steep learning curve, difficulties to scan populations of fertile age females may be related to the broad and frequent overlap of the symptoms for acute abdominal conditions. In addition, variability in the appendiceal location, non-visualization of appendix is well-known cause for clinical misdiagnosis. In view of low accuracy, USG should be combined with clinical findings and laboratory findings of leukocytosis and neutrophilia to improve accuracy.

In our study, the CT examination proved to be most useful in diagnosing acute appendicitis or suspecting appendicular pathology as cause of abdominal pain in 100% of cases comprising 83 patients. Routine use of CT in diagnosing is not advisable in clear cut clinical presentation and to avoid exposure to ionizing radiation. It was also not found to be improving the negative appendectomy rates [17].

Negative appendectomy (normal appendix on histopathology) was found in 7 cases (1.48%) in our study which is comparable to 11 cases (2.7% cases) by Patel MM et al., [18]

Appendicular diverticulum may be congenital (having muscular propria in the wall) or acquired. The later is more common and occur due to increased luminal pressure leading to herniation of mucosa at the site of penetrating artery and lack muscular propria [19]. The acquired diverticula can become infected and perforated. Uncomplicated diverticuli can be asymptomatic or produce symptoms of acute appendicitis. In present study, acquired diverticuli with/without inflammation and without perforation were seen as sole abnormality in 22 (4.66%) appendectomies. Al-Brahim N et al., reported 14 acquired diverticuli in 9 years study [20]. No congenital diverticulum was seen.

Fibrous obliteration of appendicular lumen (neuroma) was observed in 1.90% cases. Patients were between 3-6th decade of age with male to female ratio of 1:2. The sections showed neural hyperplasia in collagenous and myxoid background. It is hypothesized to be due to prior inflammatory event. Although this abnormality is said to be usually incidental [19] all the patients in our study had pain as the common symptom. In the WHO classification it is considered as neoplasm [21].

Acute appendicitis with perforation, acute appendicitis and gangrene appendix was seen in 187 (39.61%), 117 (24.78%) and 6 (1.27%) cases respectively which was comparable to a study by Kulkarni MP et al., who found 92 (21.20%), 102 (23.40%) and 03 (0.68%) respectively [Table/Fig-10] [8].

S. No	Histopathological changes	Total (N=472)	Kulkarni MP et al., (N=436)
Normal Histology			
1	Normal	7 (1.48%)	-
Anatomic abnormalities			
2	Diverticulum	22 (4.66%)	-
3	Fibrous obliteration	9 (1.90%)	15 (3.4%)
Inflammatory appendix disorders			
4	Acute appendicitis with perforation	187 (39.61%)	92 (21.20%)
5	Acute appendicitis	117 (24.78%)	102 (23.40%)
6	Gangrene	6 (1.27%)	03 (0.68%)
7	Periappendicitis	5 (1.05%)	1 (0.22%)
8	Chronic appendicitis	27 (5.71%)	205 (47.02%)
9	Resolving appendicitis	20 (4.23%)	-
10	Eosinophilic appendicitis	28 (5.93%)	-
11	Xanthogranulomatous appendicitis	4 (0.84%)	01 (0.22%)
12	Tubercular appendicitis	1 (0.21%)	-
Infectious causes of Acute and chronic appendicitis			
13	*Enterobius vermicularis*	5 (1.05%)	14 (3.3%)
Miscellaneous Non-Neoplastic appendix disorders			
14	Mucocele	10 (2.11%)	-
15	Lymphoid hyperplasia	14 (2.96%)	-
16	Foreign body giant cell reaction	1 (0.21%)	-
17	Mesothelial cyst of appendix	1 (0.21%)	-
Neoplastic			
18	LAMN	4 (0.84%)	-
19	Carcinoid	3 (0.63%)	1 (0.22%)
20	Goblet cell carcinoid	1 (0.21%)	-
21	Adenoma	-	1 (0.22%)
22	Non-Hodgkin lymphoma	-	1 (0.22%)

[Table/Fig-10]: Comparison of present study with the study by Kulkarni MP et al., for histopathologic diagnoses.

Periappendicitis was seen in 2 female and 3 male patients. One 29-year-old female patient had history of endometriosis and associated left tubo-ovarian mass at the time of appendectomy. Other female had LSCS 10 days before the appendectomy wherein an ignored

right dermoid cyst was noted at the time of appendectomy. Appendectomy alone might be incomplete management if cause of periappendicitis is not identified [19]. Kulkarni MP et al., found only one case (0.22%) of periappendicitis [8].

Chronic appendicitis is not properly defined and controversial. We used this designation when there was fibrous replacement of the appendiceal wall; transmural chronic inflammatory infiltrate was noted [19]. In our study only 27 patients (5.71%) had chronic appendicitis whereas Kulkarni MP et al., found 205 (47.02%) of chronic appendicitis which could be because of the lack of clarity on the definition of chronic appendicitis [Table/Fig-10] [8].

Resolving appendicitis was diagnosed in 20 (4.23%) patients, all had acute symptoms at presentation with average duration of 14.9 days, 7 had previous attacks of appendicitis, one was HIV positive and another one suffered dengue 2 years back; USG report in 16/20 were appendicitis (6), mesenteric lymphadenopathy (5), periappendicitis (1), normal (3), not visualized (1). The appendix in resolving appendicitis showed fibrinous exudate layer on mesothelial surface and subserosal perivascular lymphocytic infiltrate as common histologic feature described similarly in Ciani S et al., and no fibrosis detected [22].

Eosinophilic transmural infiltration with pericellular oedema was first designated as eosinophilic appendicitis by Aravindan K et al., [23]. The neutrophilic inflammation was ruled out in his study by submitting all the tissue. Cause is said to be allergy. Similar histopathologic features were found in our cases.

Mucocele is morphologic description of appendix where it appears dilated due to accumulation of mucin. Mucinous tumours of appendix is one of the cause for mucocele and therefore these terms should not be used synonymously [24]. In our study, mucocele accounted for 2.11% of all specimens of appendix which are much more than the incidence in the range of 0.07% to 0.63% [25].

Foreign body granuloma was found in one case with calcified center. No foreign body was detected. This granulomatous reaction could be due to appendicitis itself. Various foreign bodies have been described in appendix [11].

A mesothelial simple cyst was noted in mesoappendix in 27-year-old male whose appendix had lymphoid hyperplasia. This patient presented with symptoms of acute appendicitis for 2 days. The actual cause of symptoms could be either of them. Mesothelial inclusion cyst is a rare lesion with around 130 cases reported in the literature [26].

LAMN usually manifest in the sixth decade of life with a slight female predilection. Around 15-20% of LAMN's are found incidentally [19]. Appendix may be grossly normal or dilated cystically and may be associated with pseudomyxoma peritonei.

Appendix is a predilection site for neuroendocrine tumours, harboring approximately 19% of all the carcinoids. On the other hand, carcinoids are the most common tumours in the appendix, accounting for 50 –77% of all the neoplasms in the appendix [27].

Appendiceal neuroendocrine neoplasms comprise rare tumours of appendix accounting for 0.16 -2.3 % of appendectomies and are diagnosed incidentally [28]. In a study by Collins DC et al., carcinoid made up 51% of all malignant tumours of appendix and accounted for 0.7% of all appendectomy cases. The present study had 3 cases (0.63%) of carcinoid [29].

Goblet cell carcinoid, coined by Subbuswamy SG et al., is a rare tumour of the appendix [28]. It is now classified as a subtype of carcinoid with displaying dual-differentiation between adenocarcinoma and carcinoid [30].

LIMITATION

In retrospective histopathology-based studies, there are always some limitations in grossing and number of tissue bits submitted for processing. To designate histopathologically a normal appendix, it is necessary to submit entire appendix to see that there are no foci of inflammation, neoplasm or any other appendicular pathology. However, in our institute such a practice was not followed. It is advisable to submit entire specimen in such cases.

CONCLUSION

Histopathological examination of every appendix is necessary for confirmation of type of appendicitis. In addition, extensive grossing should be done to detect parasitic infestations, unusual conditions like tuberculous appendicitis and neoplasms of appendix (carcinoid, goblet cell carcinoid) which are usually incidentally detected. A combination of clinical features (right iliac fossa pain, fever, vomiting and tenderness), laboratory parameters (leukocytosis and neutrophilia) should be combined with ultrasonography to diagnose appendicitis and reduce the rate of negative appendectomy. An early surgical intervention prevents complications like perforation. We recommend a prospective study with standard grossing protocol as discussed above for future studies.

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