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Infiltration of Appendix with eosinophils in Acute Appendicitis: A Prospective Study

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Background: Acute eosinophilic appendicitis is an uncommon inflammatory condition of appendix. Histological hallmark of entity is eosinophilic in rather than neutrophilic, of the muscularis propria with accompanying edema, separating muscle. Present study aimed to study etiology and prevalence of eosinophilic appendicitis. **Material and Methods**: Tissue specimens were included from appendectomy procedure done either as an elective or emergency procedure in surgical department of hospital. A total of 125 cases were studied for one year. The related clinical history and the patients' data were obtained from the surgical department of the hospital. The tissue samples of the studied cases were processed in the department of pathology. For light microscopy, one slide from each block was stained with H&E to arrive at a diagnosis. **Results**: In 125 cases of appendectomies were studied, out of which 73 patients (59%) of the appendectomies were performed as an emergency procedure, and 52 cases (41%) were done as an elective procedure. Out of 125 cases, 118 cases (95%) of the appendectomy specimens showed congested. They dilated blood vessels on the external surface. One hundred twenty-one cases (97%) of appendectomy were sent along with a mesoappendix which also showed signs of congestion. The primary cause of appendectomies performed was for acute appendicitis 72 cases (58%), followed by periappendicitis 17 cases (13.2%).In the cases of acute appendicitis and periappendicitis, also a male predominance was seen, which was 72 cases(57.6%) and 9 cases (55%). **Conclusion**: The etiology of appendicitis is multifactorial: obstruction, diet and infection. Inflammation triggered by type 1 hypersensitivity allergic response is a recently described etiology. Acute eosinophilic appendicitis shares similar morphological features as acute appendicitis with a male predominance.

Keywords: Acute Eosinophilic Appendicitis, Appendectomies, Neutrophils

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Introduction

Appendicitis is the most common reason for acute abdominal pain. In Western countries, the risk for individuals to develop acute appendicitis is 7% during their lifetimes. The etiology of acute appendicitis is unknown, but it is probably multifactorial; luminal obstruction, diet and family factors are responsible. Acute eosinophilic appendicitis (AEA) is a rare clinical entity that is characterized clinically by acute abdominal pain and a grossly inflamed appendix with few or absence of neutrophils in the muscle layer microscopically [1,2].

Acute eosinophilic appendicitis is an uncommon ammatory condition of the appendix. It is a rare condition of unknown etiology, having vague and unexplained symptoms. The clinical presentation is similar to acute appendicitis, and the grossly appendix shows an inflamed appendix. The histological hallmark of the entity is eosinophilic in rather than neutrophilic, of the muscularis propria with accompanying edema, separating muscle[3,4].In a more recent paper, the appendix was found to have evolved at least 32 times (and perhaps as many as 38 times) and been lost no more than six times (3). This suggests that the caecal appendix has a selective advantage in many situations and argues strongly against its vestigial nature [5]. These complex evolutionary histories of the appendix, along with significant heterogeneity in its evolutionary rate in various taxa, suggest that it is a recurrent trait. Keeping the above points in mind, the present study aimed to study the etiology and prevalence of eosinophilic appendicitis.

Materials & Methods

The present is the prospective study done in the department of pathology in the medical college associated with a hospital. The tissue specimens were included from the appendectomy procedure done either as an elective or emergency procedure in the surgical department of the hospital. The ethical committee of the college institute was informed about the study, and the ethical clearance certificate was obtained from them before the start of the study. A total of 125 cases were studied for one year. The related clinical history and the

Patients' data were obtained from the surgical department of the hospital. The tissue samples of the studied cases were processed in the department of pathology.

Inclusion Criteria:

01. All specimens of acute appendicectomy cases were studied.
02. Suspected cases of worm manifestation due to gastroenteritis were also included.

Exclusion Criteria:

01. Gangrenous appendicectomy cases were excluded.
02. Appendiceal tumors were excluded.

Fixation For Light Microscopy

All specimens obtained were fixed in buffered neutral formalin for a period of 12-24 hrs. The specimens fixed in 10% formalin were collected along with the demographic data. The gross examinations of the specimens were studied. The length and the point of maximum circumference of the thickness of the appendix were noted. Areas of perforation and gangrenous change were analyzed. After formalin fixation, three cross-sections were taken representing the base, middle and tip.

Technique Of Processing:

01. Dehydration-3 changes of graded alcohol and two changes of acetone.
02. Clearing-by chloroform.
03. Paraffin impregnation-2 changes at 60 ^{o}C.
04. Embedded in paraffin wax, labelled and blocks were made after trimming excess paraffin.
05. Sections were cut at a microtome setting of 4 microns.
06. The sections were mounted on a slide using a skinny layer of glycerol egg albumin as an adhesive.

For light microscopy, one slide from each block was stained with H&E to arrive at a diagnosis.

Results of staining were assessed as follows:

Nuclei- blue to black

Cytoplasm and other substances- pink.

In cases diagnosed with Eosinophilic appendicitis,

The entire appendix was sectioned to exclude areas of neutrophil infiltration. Also, stool examination was done to rule out worm infestation.

Statistical analysis

The clinical and morphological variables were compared between the groups by Chi-square test for qualitative variables, and Student's T-test was done for quantitative variables.

Results

The study comprised of 125 cases of appendectomies performed in Medical College. In 125patients of appendectomies were studied, 73 patients (59%) of the appendectomies were performed as an emergency procedure, and 52 cases (41%) were done as an elective procedure.

A gross examination of the appendectomy specimens was done. Out of 125 cases, 118 cases (95%) of the appendectomy specimens showed congested. They dilated blood vessels on the external surface; 121patients (97%) of appendectomy were sent along with a mesoappendix that showed signs of congestion. One case of Enterobius vermicularis infestation of the appendix was sent along with the worm. One appendectomy case showed perforation on the external surface.

On cut surface, 95 cases (76%) of the appendectomy specimens had fecolith. Fifty-three patients (43%) of the appendectomy specimens showed thickened walls, and only 1case (0.8%) of the appendectomy had complete wall obliteration. The demographic data of the specimens were analyzed. The majority of the appendectomies were done in males. 85 (68%) of the appendectomies were performed in males, and 40 (32%) were females.

Table 1: Gender wise distribution of study participants

Gender	Number	Percentage
Male	85	68
Female	40	32
Total	125	100

Appendectomies were done in patients whose ages varied from 0-70 years, and a significant population of the patients belonged

To the age group of 10-20 years, followed by the age group of 20-30 years. In the age group of 10-20 years, the male gender was most commonly affected than the female population. The number of appendectomies performed was less in the younger and older age groups.

The primary cause of appendectomies performed was for acute appendicitis, 72 cases followed by periappendicitis 17 cases. In the cases of acute appendicitis and periappendicitis, also a male predominance was seen, which was 72 cases and 9 cases.

The other lesion for which appendectomies were done in decreasing frequency are as follows: hypertrophied lymphoid follicles 15 cases, acute eosinophilic appendicitis 7 cases, suppurative appendicitis 6 cases, focal gangrenous appendicitis 2 cases, xanthogranulomatous appendicitis 2 cases, worm infestation 1 case and perforated appendices 1 case and appendicular abscess 1 cases.

Female predominance was seen in cases of hypertrophied lymphoid follicles in ten patients, whereas male predominance was seen in all other lesions.

Appendectomies were also associated with other diseases like adenocarcinoma of the intestine, peritonitis, tuberculosis and cholecystitis. Out of 125 cases of appendectomies studied, seven patients were diagnosed with acute eosinophilic appendicitis. The entire specimen of the appendix was processed in these cases to rule out foci of neutrophilic infiltration. Neutrophils were less than 5 per 10 high power fields in these cases. Stool examination was also done following the diagnosis of eosinophilic appendicitis to rule out worm infestation in the gastrointestinal tract. Stool examination revealed normal gastrointestinal flora in 6 cases, and in one case, stool examination could not be performed as patients were non-compliant.

In the cases of eosinophilic appendicitis, the most common age group involved was 10-20 years. Eosinophilic appendicitis also showed a male predominance. One case of eosinophilic appendicitis was associated with eosinophilic enteritis presented with peritonitis.

Light microscopic findings:

Acute appendicitis cases revealed transmural neutrophilic infiltration, with areas of necrosis .68cases of acute appendicitis cases showed mucosal ulceration. All patients showed subserosal vessel congestion and modest infiltration of neutrophils into all the wall layers, especially the muscularis propria. Sixty-nine cases of cases showed vegetable matter within the lumen of the appendix microscopically.

Periappendicitis: Periappendicitis also showed neutrophilic infiltration in the submucosa. The neutrophilic infiltration was more severe in the serosal layer. Mesoappendix also showed neutrophilic infiltration with congested blood vessels. Seven cases of the periappendictis cases also showed mucosal ulceration. Congested and dilated blood vessels were also in most of the cases of periappendicitis. 2 cases of periappendicitis showed thrombosed blood vessels in the muscularis propria, serosa and the mesoappendix.

Hypertrophied lymphoid follicles: 15 cases of cases were diagnosed of hypertrophied lymphoid follicles in which 6 cases of the appendices also showed mild to moderate fibrosis in the muscularis propria and the serosa. Seven patients showed vegetable matter within the appendicular lumen.

Suppurative appendicitis: Six cases of the appendectomy specimens were diagnosed with suppurative appendicitis. These cases showed focal mucosal ulcerations, extensive neutrophilic infiltration, and edema and congested blood vessels. Five cases of acute suppurative appendicitis showed focal abscess formation. Few ill-formed granulomas were also seen in 3patients.

Focal gangrenous appendicitis:2 cases of gangrenous appendicitis were studied in 125 appendectomies. The gangrenous change was mainly identified at the tip of the appendix. One appendix showed gangrenous difference at the base of the appendix, which was a case of acute intestinal peritonitis. Areas of hemorrhagic necrosis, edema, fibrinopurulent exudate, extensive neutrophilic infiltration, thrombosed and congested blood vessels were also seen in these cases.

Xanthogranulomatous appendicitis:

Three cases of the appendectomy specimens were diagnosed as xanthogranulomatous appendicitis. These cases showed well-formed granulomas with foreign body giant cells. All these three cases also showed mucosal ulceration and neutrophilic infiltration.

Worm infestation:2 cases of appendicitis were diagnosed as due to worm infestation. One case of Ascaris lumbricoides was identified, and one case of Enterobius vermicularis was identified. These appendices also showed focal eosinophilic infiltration. The mucosa and submucosa showed neutrophilic infiltration. One patient also offered a few ill-formed granulomas.

Perforated appendices: One case (0.8%) of the appendectomy specimens were diagnosed with a perforated appendix. These appendices showed extensive neutrophilic and plasma cell infiltration into the serosal layers. One case showed vast areas of hemorrhage and necrosis.

Eosinophilic appendicitis: Out of 124 cases received, 7 cases of patients were diagnosed with eosinophilic appendicitis. These cases showed eosinophil infiltration of the muscularis propria, along with a few areas which showed edemaseparating the muscle fibres. Six cases of eosinophilic appendices showed normal mucosa with no ulceration. All the cases studied had a thin muscle layer. A varying degree of oedema was noted in these cases infiltrating into the muscular layer. About 5 cases of Eosinophilic appendicitis also showed lymphoid hyperplasia.

Discussion

The present study was carried out on 125 appendectomy cases. The specimens were examined for analyzingetiology of appendicitis, with particular emphasis given to eosinophilic appendicitis. The entire appendix was processed in cases of eosinophilic appendicitis.

The incidence of appendicitis is 1 in 400 people or 0.25%. Buttler C et al. [5] studied in 1981 that 74% of the cases operated for appendectomies were on an emergency basis. In our study, we studied that 70% of our appendectomies were operated on an emergency basis. Acute appendicitis was the most common histopathological diagnosis in most studies; this was also seen in our research.

Al Mulhim et al. [6]studied that the percentage of the perforated appendix was 26.6% and 14%, which was much higher than the present study. We had received only 0.8 % of the perforated appendix. This could be because of early surgical intervention in cases suspected of acute appendicitis.

Rate of perforation in young: elderly. A higher percentage of worm infestation was seen in the study of Al Mulhim et al. (109), who studied that 9.6% of the cases for whom appendectomy was performed had worm infestation. In our present study, we saw a lower frequency of cases of worm infestation in cases of acute appendicitis. This could be because of better hygiene and sanitation facilities.

Jonna et al. [7] also had studied two cases in children very similar to eosinophilic appendicitis, presenting clinically as acute appendicitis. They had only transmural eosinophil infiltration. They had also mentioned that they had seen similar cases in the adult population also.

In the cases of acute eosinophil appendicitis, like classic appendicitis, we had seen a male predominance. The majority of the patients with acute eosinophilic appendicitis were 20-30, which is also seen in classic appendicitis. This was also noted by Aravindan et al. [8].

Aravindan et al. [8]. in a study of 120 appendectomies, found that mural eosinophil infiltration is a consistent finding in acute appendicitis. He also described cases similar to what Jona et al. described, in which eosinophils were the sole finding. He suggested that eosinophil infiltrate seen in acute appendicitis is an early event linked to type 1 hypersensitivity. This was in contrast to what was believed earlier- that infiltration of eosinophils is evidence of subacute or chronic inflammation.

The cases of acute eosinophilic appendicitis share clinical and morphological features with classic acute appendicitis in contrast to cases in which surgically removed appendix is of normal histology.

The circumference of the appendix is increased in the acute eosinophilic appendix, which was also studied by Aravindan et al. The absolute eosinophil counts were also higher

In acute suppurative appendicitis and acute eosinophilic appendicitis when compared to normal. Still, they fell below the upper limit of the normal.

In AEA, the appendix was swollen and hyperemic as in acute suppurative appendicitis, but there was an absence of exudate in the cases of AEA [8,9].

Histopathologic features of acute eosinophilic appendicitis include the absence of neutrophils instead of the presence of intense eosinophilic infiltration in muscularis propria and edema separating the muscle fibres (66). All these features were noted in our cases to diagnose acute eosinophilic appendicitis [10].

Occasional neutrophils were noted in the lamina propria, but they did not exceed more than ten cells/ 5 HPF in any of our cases. Eosinophil edema lesion, as described by Aravindan et al., is a distinct lesion seen only in patients having acute symptoms and grossly inflamed appendices. This helped us differentiate the cases of grossly un inflamed appendices in which a variable number of eosinophils can be seen in the muscularis layer. Eosinophils admixed with lymphocytes and unaccompanied by edema can also be seen in cases of resolving appendicitis.

Eosinophil edema lesion was described by Aravindan et al. as a hallmark of acute eosinophilic appendicitis. He also describes this to be seen in acute suppurative appendicitis and in all cases of acute focal appendicitis in areas where neutrophils are sparse or absent. In all our cases of acute eosinophilic appendicitis, we had seen eosinophil edema lesion. We also noted eosinophil edema lesion in a few cases of acute suppurative appendicitis.

Conclusion

The etiology of appendicitis is multifactorial: obstruction, diet and infection. Inflammation triggered by type 1 hypersensitivity allergic response is a recently described etiology. Acute eosinophilic appendicitis shares similar morphological features as acute appendicitis with a male predominance. It is most commonly seen between the age group of 20-30 years of age. Histopathologic features of acute eosinophilic appendicitis include the absence of neutrophils,

The presence of intense eosinophilic infiltration in muscularis propria and edemaseparating the muscle fibres. Neutrophils did not exceed more than ten cells/5 HPF.

Addition of the study to exiting Knowledge

The pathogenesis of appendicitis remains poorly understood. Despite new diagnostic techniques, appendices removed from patients with suspected appendicitis often appear histologically normal on conventional examination. There is increasing evidence of involvement of the enteric nervous system in immune regulation and inflammatory responses in the gastrointestinal system.

Contribution from authors

Dr Swati Patel and **Dr Himanshu Soni** formulated the aims & objectives with study design and helped collect data from the medical record department. **Dr Vishwadeepkesarwani, Dr S.Nandedkar** and **Dr M Purohitcontributed** to preparing the manuscript and Data analysis

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