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Exploration of the Infectious Causes in the Histopathological Section of Appendicectomy Specimens

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Acute appendicitis is one of the most common surgical emergencies and may present with a wide variety of clinical manifestations. Appendectomy via open laparotomy through a limited right lower quadrant incision or via laparoscopy, is the standard treatment for acute appendicitis. To identify the common infectious organisms which cause acute appendicitis in appendicectomy specimens in Taif population. And to detect the rate of negative appendicectomy in examined specimens A retrospective study was conducted in King Abdulaziz Specialized Hospital (KAASH), Taif during the period from January to April 2022, one hundred appendicectomy specimens were examined grossly to detect macroscopic pathological changes and microscopically. Clinical data such as age, sex and complete blood count results were collected from the hospital medical records.A total of one hundred appendectomy cases included in the study, their age range from 6 to 85 years and mean age ± stander deviation (SD) is 26.4±14.9. 40(74%) cases were male and 14(26%) were female. Complete blood count showed increased WBCs number (leucocytosis) in all cases, mean count ± SD is 14.01±4.71. The gross (macroscopic) examination of appendectomy specimens showed criteria of acute simple appendicitis in 50(50%) of cases, pus in appendicular lumen (suppurative appendicitis) in 32(32%) of cases, gangrenous appendicular wall (gangrenous appendicitis) in 9(9%) of cases. The fibrous obliteration detected in 5(5%) of cases and acute perforated specimens detected in 4(4%). The microscopic examination showed dense neutrophilic infiltration in 70(70%) of cases that indicates acute bacterial infection of appendicitis, lymphocytes in 50(50%) that indicates viral and chronic cause for inflammation, eosinophiles in 46(46%) that indicates parasitic or immunological causes, monocytes in 11(11%) and basophiles in 7(7%) both indicate chronic causes. The lymphoid hyperplasia detected in 27(27%) of cases indicating viral causes, finally parasitic egg (Enterobius *vermicularis*) detected in 2(2%) and negative appendectomy in 5% of cases. The infectious causes of appendicitis constitute the majority of cases with prevalence of bacterial infection among other microorganisms. Identification of the common infectious organism causing appendicitis help planning for preventive measures and early and proper diagnosis of appendicitis help to reduce the surgical intervention.

Keywords: Appendicitis, Appendectomy, Histopathology, Infectious Diseases, Parasites.

INTRODUCTION

Appendix is a true diverticulum arising from the posteromedial cecal border, is located in close proximity to the ileocecal valve. The base of the appendix can be reliably located near the convergence of the taeniae coli at the tip of the cecum. The term vermiform is Latin for worm like and ascribes to its long [1].

Acute appendicitis is one of the most common surgical emergencies and may present with a wide variety of clinical manifestations [2]. In rare circumstances, appendicitis can cause life-threatening complications e.g., septic shock. Appendicitis is typically caused by luminal obstruction, and this may be due to lymphoid hyperplasia and appendicolith, resulting in the invasion of the appendix wall by the gut flora. The increased intraluminal pressure may lead to venous congestion, arterial insufficiency, ischemia, necrosis and ultimately perforation. In cases of perforated appendicitis, spillage of

infected and fecal matter into the peritoneal cavity may lead to peritonitis and life-threatening infection [3].

The most common age range for appendicitis is between 5 and 45, with a mean age of 28. The prevalence rate is about 233 per 100,000 individuals. Acute appendicitis is slightly more common in men than in women, with lifetime prevalence rate of 8.6% for men and 6.7 % for women. In the United States, over 300,000 hospital visits for appendicitis-related conditions occur annually [4]. According to a recent global study, the prevalence of acute appendicitis has risen in some newly industrialized countries in Asia, South America, and the Middle East in the 21st century [5]. Since 2000, Asian, Latin American, and Middle Eastern countries have had higher rates of appendicitis than many Western countries [6].

The occlusion of the appendiceal orifice is thought to be the cause of appendicitis [4]. Despite the fact that obstruction is most commonly caused by lymphoid hyperplasia as a result of inflammatory bowel illness or infections, fecal stasis, and fecaliths, it is also been attributed on a variety of uncommon reasons such as bacteria (Yersinia species, Adenovirus, Cytomegalovirus, Actinomycosis, Mycobacteria species, Histoplasma species), Parasites (e. g., Schistosomes species, Entamoeba histolytica), Pin- worms 'Enterobius vermicularis' , Ascariasis, serositis, Eosinophilic infiltration, foreign bodies, tuberculosis, carcinoid, mucocele, Endometriosis, Intussusception [7].

Bacterial overgrowth develops in the obstructed appendix, with aerobic bacteria predominating early in the course and mixed aerobes and anaerobes after. Escherichia coli, Peptostreptococcus, Bacteroides, and Pseudomonas are among the most common bacteria. [4].

Parasitic infection of the appendix is rare. However, parasitic agents as *Schistosoma spp.*, *Taenia spp.*, *Ascaris lumbricoides* and Enterobius *vermicularis* have been reported as a cause [8].

A rise in white blood cells occurs with a left shift and is shown by laboratory data at presentation [9]. In 80% of cases of acute appendicitis there is a rise in the number of white blood cells (WBC) greater than 10,000 per mm^3 [10]. There is also a 70% increase in the number of WBC for patients with right lower quadrant pain [11]. High WBC are therefore of little predictive importance. WBC serial measurements (over 4 to 8 hours) likely in suspected cases to increase privacy, when the number of WBC in acute appendicitis increases (except in cases of perforation, in which it may initially fall) [12].

Measurement of C-reactive protein (CRP) is most likely to be elevated in appendicitis if symptoms are present for more than 12 h. First described in 1986, the Alvarado scoring is the most reported scoring system for appendicitis. However, this score alone is not accurate enough to diagnose or rule out appendicitis [9].

Computed tomography (CT) is an excellent diagnostic option for all other patients, is recommended if the results of patients with acute abdominal pain are not optimal, uncertain, or normal. A threshold diameter of 6 mm has been used to diagnose appendicitis. The normal circumference of the appendix size for an adult patient is 3-10 mm. Therefore, it is more accurate to use the threshold size of 9 mm for the diagnosis of appendicitis. Doppler US tests usually show an increase in vascular distribution in and around the acutely inflamed appendix. This test serves as an additional sign of appendicitis [9].

Diagnosing acute appendicitis is a challenging task because many clinicians rely on the signs and symptoms presented by the patient. In case of elusive diagnosis, close observation, laboratory tests, and imaging can be helpful. However, the accurate diagnosis of acute right iliac fossa pain remains a challenging clinical problem as the differential diagnosis of pain in this region is not straight-forward. To overcome morbidity and mortality of perforation before surgery, a negative appendicectomy is somewhat acceptable traditionally. However, in recent years, many have considered this unacceptable since the surgical procedure itself could be a potential cause of morbidity and mortality. Although appendicectomy has markedly reduced the morbidity, it has led to an increase in diagnostic error rate. The rate of negative appendicectomy remains high, varying between 15%–30% globally. Negative appendicectomy rates can be reduced with an accurate and prompt diagnosis [13].

Surgery has been the most widely used treatment since surgeons began appendectomy in the 19th century. Appendectomy is one of the most frequently performed surgical interventions in the world [14]. Current evidence shows that laparoscopic appendectomy (LA) is the most effective surgical treatment compared to open appendectomy (OA). The most common postoperative complications such as wound infections, intra-abdominal abscesses, and intestinal obstructions [15].

There is, however, a lack of studies and data about the common types of causative infectious agents for appendicitis in Taif population. The present study plan to determine the common infectious agent to provide early treatment and avoid appendicectomy. As well as to help in planning for preventive methods.

MATERIALS AND METHODS

Retrospective study was taken place during the period from January 2022 to April 2022. in King Abdulaziz Specialized Hospital (KAASH). The study included 100 patients of different age group and both sex, the patients were selected according to inclusion and exclusion criteria.

Inclusion criteria: all patients who have appendicectomy and diagnosed clinically to have Acute appendicitis.

Exclusion criteria: patients who does not have any data in hospital records.

Appendicular specimens from patients diagnosed clinically to have acute appendicitis and removed surgically and sent to histopathology laboratory in 10% formalin. Multiple tissue bits were taken from different regions, tip, base and

appendicular wall, routinely processed in an automatic tissue processor, and then were embedded in paraffin wax. Three to five serial sections of four-micron thickness were cut on rotatory microtome and were analyzed microscopically for signs of inflammation and evidence of any causative infectious agents after staining with Hematoxylin and Eosin stain.

Relevant important clinical data for each patient from the hospital files in histopathology lab and medical records were collected retrospectively including Patient age, sex, complete blood count (CBC). Statistical analysis of data was done using SPSS version 20 (IBM© Corp., Armonk, NY, USA). Categorical variables are presented as counts and percentages, Continuous numerical data are presented as mean and standard deviation, p-values < 0.05 are considered statistically significant.

Permission to conduct the study were taken from the research committee in Collage of Applied Medical Sciences - Taif University and from the ethics committee of the king Abdul-Aziz Specialized Hospital.

RESULTS

A total of ***100*** appendectomy cases included in the study, their age range from 6 to 85 years and mean age ± stander deviation (SD) is 26.4±14.9. Regarding sex, 74(74%) cases were male and 26(26%).

Complete blood count of the patients showed increased WBCs number (leukocytosis) in all cases, mean count ± SD is 14.01±4.71, the differential count showed neutrophiles (neutrophilia) mean count ± SD is 10.12 ±4.56, lymphocytes (normal) mean count ± SD is 2.13±1.13, Monocytes (monocytosis) mean count ± SD is 1.03±0.58 eosinophils (eosinophilia) mean count ± SD is 0.87±0.25 as shown in table 1.

The gross (macroscopic) examination of appendectomy specimens showed criteria of acute simple appendicitis in 50% of cases, pus in appendicular lumen (suppurative appendicitis) in 32% of cases, gangrenous appendicular wall (gangrenous appendicitis) in 9% of cases. The fibrous obliteration detected in 5% of cases and finally acute perforated specimens detected in 4% as shown in figure 1.

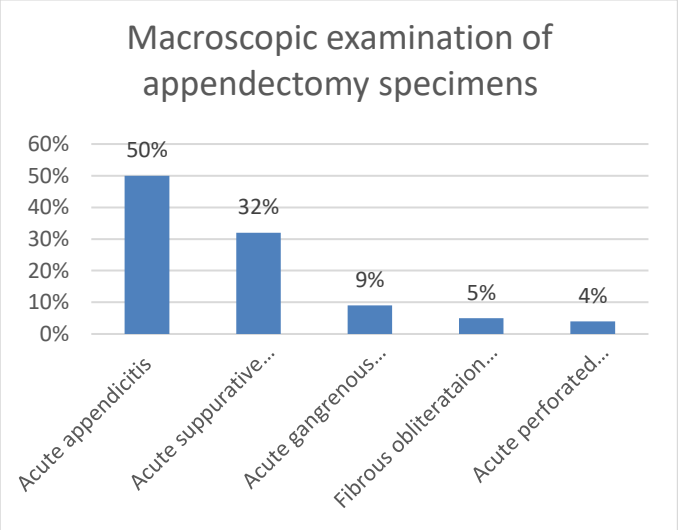

Figure1: Macroscopic examination finding of appendectomy specimens

The microscopic examination of stained sections from appendectomy specimens showed dense neutrophilic infiltration in all layers of the appendicular wall specially lamina propria and submucosa in 70% of cases that indicates acute bacterial infection of appendicitis, lymphocytes in 50% that indicates viral and chronic cause for inflammation, eosinophiles in 46% that indicates parasitic or immunological causes, monocytes in 11% and basophiles in 7% both indicate chronic causes. The lymphoid hyperplasia detected in 27% of cases indicating viral causes, parasitic egg of *Enterobius vermicularis* detected in 2% of examined cases and 5% negative appendectomy in examined specimens as shown in figure 2.

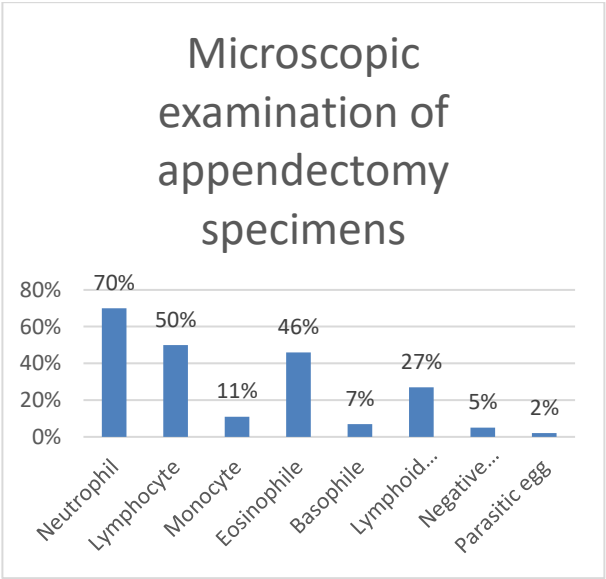

Figure 2: Microscopic examination finding of appendectomy specimens

Table 1: Total white blood cells (WBC) and differential mean count and SD

Type of cell	WBC (4.5-11K/ µl)	Neutrophils (2.5-7 K/µl)	Lymphocytes (1-4.8 K/µl)	Monocytes (0.2-0.8 K/µl)	Eosinophiles (0.03-0.3 K/µl)
Mean count (K/µl)	14.01	10.12	2.13	1.03	0.87
Stander deviations (SD)	4.71	4.56	1.13	0.58	0.25

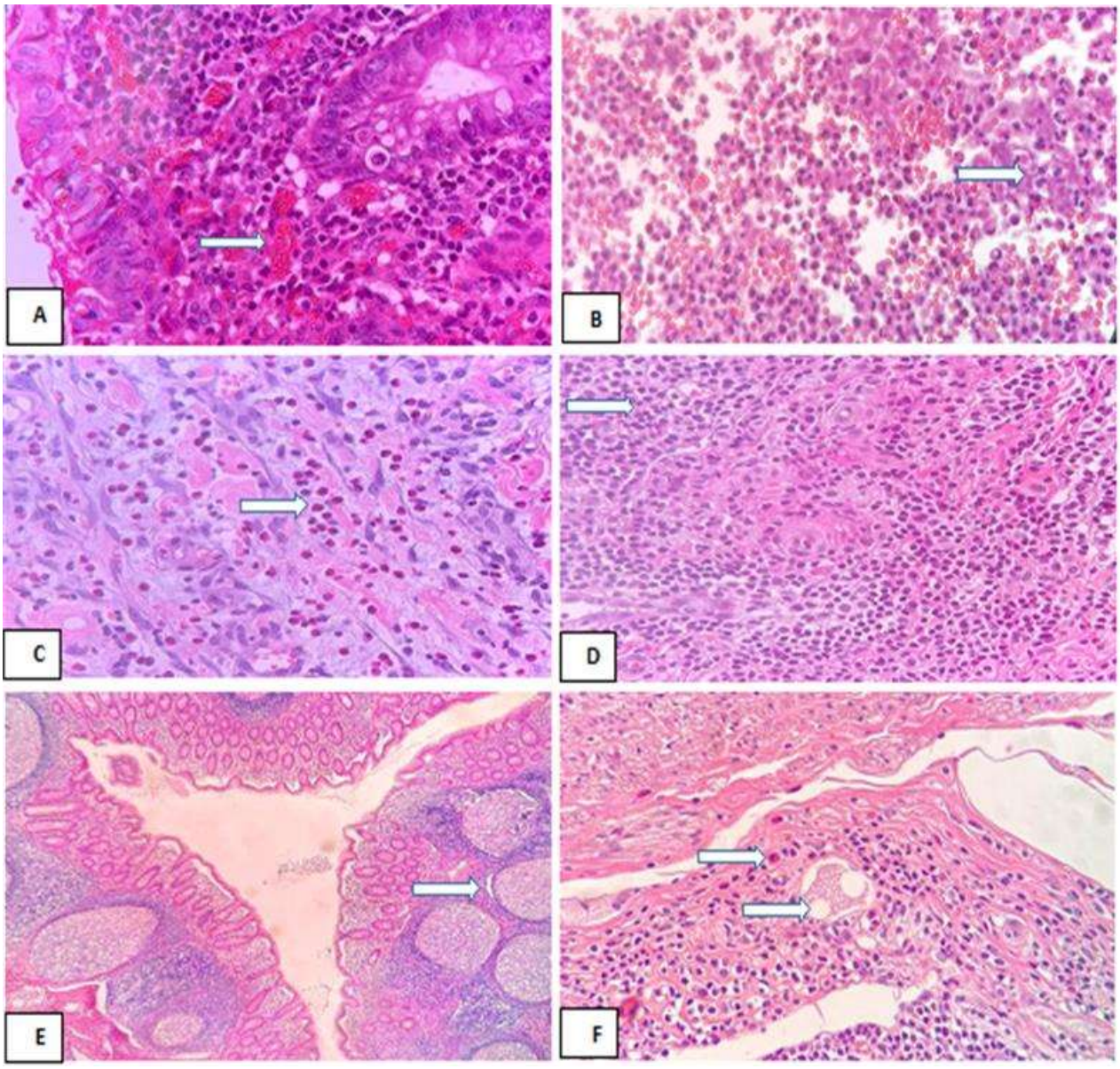

Figure 3: (A-F) (Photomicrograph of 5 microns thick H & E-stained paraffin section). The examined microscopic sections from different appendicular specimens showing dilated congested capillaries, edema and dense neutrophilic inflammatory infiltrate (A&B). Eosinophilic infiltration (C). Mixed chronic inflammatory infiltrates (lymphocytes, monocytes and basophiles) (D). Lymphoid hyperplasia with germinal center (E). Parasitic egg of Enterobius *vermicularis* in the submucosa (F).

DISCUSSION

Appendectomy via open laparotomy through a limited right lower quadrant incision or via laparoscopy, is the standard treatment for acute appendicitis. Compared with open laparotomy, laparoscopic appendectomy resulted in a lower incidence of wound infection, fewer complications, but a longer operation time [16].

In the current study it was found that there was an increase in the percentage of males who have had an appendectomy procedure in Taif city with 74%, While the percentage of females who had an appendectomy was 26%. In a previous study, in Hail region of Saudi Arabia done by Alosayfir et al., [14] showed that the percentage of males who had an appendectomy was 67.7%, and the percentage of females was 32.3% this more or less go with our result. In another study, in Aseer Region of Saudi Arabia done by Alahmari et al., [17] appendectomy results showed that to be 52.9% for males and 47.1% for females the difference between our study and previous studies may be due to sample size and difference in geographic region. In another study done in Jagdalpur of India by Dhruv et al., [18] showed that appendectomy results are opposite to our results where the percentage of males was 39.4% and 60.6% for females, the results may differ from our results due to environmental factors, the lifestyle, and the nature of food and drinking water of each country.

In this study as showed in table 1, it was found that there was an increase in WBCs number (leukocytosis) in all cases, mean count (k/µl) ± SD is 14.01±4.71. In study done by Nassir et al., [19], in King Abdulaziz Hospital & Oncology Center in Jeddah, showed that there was elevated in WBC 16.3(12.3-24.2) and another study done by Althoubaity, [20] in university hospital in western region of Saudi Arabia show a similar results , WBCs 12.09 ± 5.10 (3.80-28.40), as regard other study outside Saudi Arabia done by Wu et al., [21] in Huizhou Hospital of Sun Yat-Sun University, Huizhou, Guangdong Province in China, show a similar result too, WBCs 12.6 ±2.2. In our study the differential count the result showed neutrophils (neutrophilia) mean count ± SD is 10.12 ±4.56, lymphocytes (normal) mean count ± SD is 2.13±1.13, in another study done by Peksöz and Bayar [22], in Turkey WBC mean count ± SD is (x103/µl) 13.12 ± 4.06 , neutrophiles (x103/µl) 9.90± 4.01 , lymphocytes (x103/µl) 2.19 ±0.92, this study go more or less with our results as appendicitis is usually accompanied by inflammation and increase in total white blood cells counts.

The gross (macroscopic) examination of appendectomy specimens in our study showed in figure 1, 50% of specimens showed criteria of acute appendicitis (enlarged appendicular specimens with swollen edematous congested wall), in another study done by Alshammari et al., [23] in Hail Region Saudi Arabia done on 129 patients underwent appendectomy show a similar result, the most common cause for the appendectomy was acute appendicitis by (66%) of the cases. a resembling result in a study done by Cariati et al, [24] 86 patients underwent open appendectomy suspected appendicitis have been confirmed by histological examination that 45 of total cases were acute appendicitis representing (52%), in contrast to our study another result in a study done by Alshebromi et al.,[25] at King Fahad Specialist Hospital in Buraidah, Saudi Arabia, showed that among 200 patients, 187 (93.5%) were diagnosed with acute appendicitis by morphologic pathological examination.

Suppurative appendicitis is a later stage of appendicitis which forms when dead bacteria and dead neutrophils admixed with shaded mucosal tissue have accumulated in the lumen of the appendix and cause obstruction of the lymphatic and venous drainage [26], and in our study the result show pus in appendicular lumen (suppurative appendicitis) in 32% of the cases, in a study done by Zhou and Cen [27] during the COVID-19 pandemic in Jiaxing, China, done on 90 patients, patients were diagnosed with suppurative appendicitis were (40%) go more or less with our results, other study with a similar results done by Cariati et al., 2001,[24] on 86 patients underwent open appendectomy 22 (25.5%) of the cases were acute suppurative appendicitis. A study done by Ali et al., [28] King Hamad University Hospital, Bahrain on 340 patients and 28 (8.23%) of the cases has suppurative appendicitis which is less than our results this might be due to environmental factors and personal habits.

Patients with gangrenous non perforated appendicitis have a high risk of developing postsurgical infection. Elisabeth et al., [29] also considered as a complication of acute appendicitis, in our study gangrenous appendicular wall (gangrenous appendicitis) shows in 9% of cases. also, study done by Jat et al.,[30] at a district hospital Arar, Saudi Arabia, out of 480 specimens of the appendix shows acute gangrenous appendicitis 60 (12.5%), study done by Nassir et al, [19] in King Abdulaziz Hospital & oncology center in Jeddah, among 243 patients a 4 (5.19%) show a complicated with gangrene or perforation in the appendix. All these studies in contrast to our results might be due to difference in the number of cases.

Fibrous obliteration of the appendix is considered as a part of the aging process that results in loss of the normal appendiceal mucosa and Peyer patches, which eventually replaces the mucosa and submucosa with fibrotic tissues (Choi et al, 2014)[31]. In our study the fibrous obliteration was detected in 5% of cases. a study done by Alshammari et al.,[23] in Hail Region Saudi Arabia on 129 patients underwent appendectomy show a similar result to our study, 6%of the cases were fibrous obliteration, another study shows nearly equal results to ours done by Alshebromi et al.,[25] the fibrous obliteration was detected in 4.5% of the cases.

Acute perforated is one of the complications of

appendicitis that is associated with increased morbidity and mortality rates [32] infection of the appendix can cause a hole that allows the infection to spread to the rest of the abdomen. This is called a "perforated" or "ruptured" appendicitis. 4% with acute perforated were detected in our study. Prospective clinical study done by Al-Eass [33] in Iraq on 1210 patients with acute appendicitis and perforated appendicitis representing the main type of complicated appendicitis that were observed in 215 (17.76%) patients, most of the patients with perforated appendicitis in Al-Eass were elderly patients, occur much more frequently in elderly patients which may explain the high rate. Another study done by Zhou & Cen [27] in China on 90 patients who presented with appendicitis, (15%) indicated perforated appendicitis. All these studies show a higher rate in the cases than ours due to number of cases and difference in geographic area.

In this study as showed in figure 2, Microscopic examination of histopathological specimens found 70% of patients had neutrophil infiltrate that indicates bacterial infection. A large number of appendicitis infections are caused by bacteria. The most common bacteria associated with acute appendicitis were *E. coli*, followed by *K. pneumoniae*, *Streptococcus*, *Enterococcus*, and *P. aeruginosa* [34].

In a previous study, in Iraq done by Faraj et al., [35] showed that neutrophil percentage ranges from 79.1% to 83.68%, the value is close to our study, indicating that bacterial infection is the most common and associated with appendicitis.

In our study also, we found an increase in the percentage of lymphocyte infiltrate with 50%. Lymphocytes mostly target viral infections. In contrast to our study Faraj et al.,[35] showed the percentage of lymphocytes was 16.4%, this may be due to difference in age group.

The percentage of monocytes infiltrate in our study was 11%. Monocytes a type of immune cell that is made in the bone marrow and travels through the blood to tissues in the body where it becomes a macrophage surround and kill microorganisms or a dendritic cell [36].

In another study done in Germany by Nissen et al., [37] showed monocytes percentage was 7.9%, the ratio is less than the results of our study.

Eosinophils help promote inflammation, which plays a beneficial role in isolating and controlling a disease site. But sometimes inflammation may be greater than is necessary, which can lead to troublesome symptoms or even tissue damage. Eosinophils play a key role in the symptoms of asthma and allergies, such as hay fever. Other immune system disorders also can contribute to ongoing chronic inflammation. An increased percentage of eosinophils may be due allergic reaction, parasitic infection [38].

Basophils are one of the several kinds of white blood cells. These blood cells make up less than 1% of all circulating white blood cells and are the least abundant in all mammals. Basophils are a part of the immune system create inside the bone marrow. An increased percentage of basophils may be due to after splenectomy, allergic reaction, and viral infection. A decreased percentage of basophils may be due to acute infection, Cancer, Severe injury [39].

Lymphoid hyperplasia is an increase in the number of lymphoid follicles that are contained in submucosa of the appendix. This most often happens when there is an infection with bacteria, viruses, or other types of germs and is part of the body's reaction to the infection [38].

Parasitic diseases and allergic reactions to medication are among the most common causes of eosinophilia. Increased mural eosinophils were significantly present in acute appendicitis and clinically suspected acute appendicitis but histological normal appendix when compared with control group. Sole presence of increased mural eosinophils might represent acute inflammation. However, cut off value for high eosinophil count could not be established to suggest acute appendicitis [40].

Parasitic infections are among the probable causes in appendicitis and should be kept in mind during differential diagnosis. However, whether every parasitic infection leads to appendiceal inflammatory response is controversial [41].

We found in our study eosinophils infiltrate in the rate of 46%, basophiles in the rate of 7%, lymphoid hyperplasia in the rate of 27%, parasitic eggs (Enterobius *vermicularis*) in 2%. Several studies have found luminal parasites in the appendix associated with or without appendicitis in the range of 0.3 to 3.15%. commonly found parasites include *Enterobius vermicularis* and *Schistosoma species*. In our study only two cases had *Enterobius vermicularis* parasitic infection (2%).

Our study showed 5% prevalence of appendicectomy on normal appendix in contrast to study done by Khairy [42] which showed 9.2% prevalence of normal appendix was removed this may be due to the difference of number of our study group.

CONCLUSION

The infectious causes of appendicitis constitute the majority of cases with prevalence of bacterial infection among other microorganisms. Early and proper diagnosis of appendicitis help to reduce the surgical intervention. Identification of the common infectious organism causing appendicitis help planning for preventive measures.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

HMH, AA, AM, and KAI designed the study, and also wrote the manuscript. BT, ST, NAA, AAA, SAA, EMA, RAR, KA, and AMM, performed data collection and tables deign, AMM, OA, AM, and ASA made data analysis. All authors read and approved the final version.

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