Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2021.76646.2236 Volume 30, Issue 2, March 2024
Manuscript ID ZUMJ-2105-2236 (R3)
DOI 10.21608/ZUMJ.2021.76646.2236

ORIGINAL ARTICLE

Unusual Incidental Pathological Findings of the Appendix Histopathological and Immunohistochemical Study

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submit Date 2021-05-19
Revise Date 2021-06-17
Accept Date 2021-07-07

ABSTRACT

Background: Acute appendicitis is one of the most common surgical emergencies. Incidental appendiceal findings without any prior clinical or radiological diagnosis are still challenging. Histopathological diagnosis can help in avoiding further complications for patient safety.

Methods: A retrospective study of 504 resected appendices done in Al Emadi Hospital Doha, Qatar, during the four years from January 2016 to December 2019 and diagnosed as appendicitis underwent pathological examination that revealed confirm appendicitis in 471 (93.5%) cases while 33 (6.5%) of cases showed unusual pathological findings that did not detect either clinically or radiologically.

Results: Out of 504 specimens of the appendix, appendicitis accounted for 93.5% with peak occurrence at the age group of 20 to 40 years and female predominance. Suppurative appendicitis (47.8%) was the most common findings. It was found an incidental finding in 33 (6.5%) cases, 21 (4.1%) cases were appendicitis obliterans, three (0.6%) cases were a well-differentiated neuroendocrine tumor, three (0.6%) cases were low grade appendiceal mucinous neoplasm, three (0.6%) cases were diverticulosis, two (0.4%) cases were granuloma of the appendix, and one (0.2%) case was diagnosed as eosinophilic appendicitis.

Conclusions: Routine histopathoogical examination of appendectomy specimens are of value to discover unusual pathologies that require further postoperative management. Gross examination alone is not a good indicator of an unexpected finding.

Keywords: Appendicitis; Appendicectomy; Incidental neuroendocrinal tumor; Incidental mucinous neoplasm; Unusual histopathological findings.

INTRODUCTION

Acute appendicitis is considered one of the most common general surgical emergencies. About 7% of individuals in the western countries will suffer from an episode of acute appendicitis while the incidence of acute appendicitis in Asian and African countries is lower which may be attributed to their dietary habits of high fiber diet that decrease the viscosity of faeces, decrease bowel transit time, and discourage the formation of fecalith, which predispose to lumen obstructions [1].

Various causes for acute appendicitis have been identified, but lumen obstruction is considered the most critical factor that has triggered the inflammatory process. Although fecalith and lymphoid hyperplasia are the main causative factors of lumen obstruction, unusual factors can cause the same effect, including enterobiasis, amebiasis, taeniasis [2], mucocele [3], eosinophilic granuloma [4], tuberculosis, actinomycosis, adenovirus, other granulomatous diseases [5], neurogenic appendicopathy [6], diverticulitis [7], and different appendiceal neoplasms, such as carcinoid tumor, gastrointestinal stromal tumor, adenoma, neurofibroma, mucinous neoplasm, adenocarcinoma, and lymphoma [8]. Opponents of screening argue that not sending the specimens is justified by the rarity of aberrant findings, the low clinical significance, and the significant costs of specimen processing [9]. Also, unusual incidental findings found in a small percentage of appendectomies, but still have a major consequence and selective histopathology for appendiceal specimens might induce the risk of missing significant pathological findings, which may have an impact on patient management [10].

The most common primary neoplasm affecting the appendix is a neuroendocrinal tumor (carcinoid tumor), comprising 25% to 40% of all appendix's malignancies. The overall incidence of carcinoid after the appendectomy is low, 0.3% to 0.9% [11]. Appendicular mucinous neoplasms are rare, and a complex, diverse group of epithelial neoplasms causing cystic dilation of the appendicular lumen with an incidence of 0.2%–0.3% of appendectomy specimens. An appendiceal mucinous neoplasm refers to a tumor-associated with neoplastic adenomatous growth (adenoma or adenocarcinoma), that if rupture can result in the dreaded complication of pseudomyxoma peritonei (PMP) [12]. Histological examinations of appendix specimens are routinely done at our institution; we need to correlate the histopathological findings with the clinical diagnosis of appendicitis and discover incidental findings that may change the postoperative management plan. Routine pathological examination of appendectomy specimens is of value for recognizing unusual pathologies that require further management.

METHODS

A retrospective study of 504 patients underwent appendectomy for a clinical presentation consistent with acute appendicitis in Al Emadi Hospital Doha, Qatar, during the four years from January 2016 to December 2019. Written informed consent was obtained from all participants. This study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the Institutional Ethical Committee. The study includes all emergency appendectomies and interval appendectomies performed on clinically suspected appendicitis after radiological confirmation of appendicitis. In all cases, 491 (98%) were laparoscopically removed and only 10 (2%) had open surgery. All specimens were formally fixed and were sent for histopathological examination. All specimens underwent macroscopic examination followed by cutting with consideration of surgical margins and processed to paraffin blocks followed by hematoxylin and eosin stain (H&E stain) and then microscope examination for confirming or excluding the diagnosis of appendicitis. For unusual incidental findings, neuroendocrinal tumor, and mucinous neoplasm, additional ancillary studies were performed. For neuroendocrinal tumor immunostaining was performed with adequate control for synaptophysin, chromogranin, CK AE1/3, and KI67 immunostaining. For mucinous neoplasm immunostaining of SATB2, CDX2, CK20, CK7, and TTF-1 were performed in addition to PAS stain for mucous.

***Statistical analysis*:**

The data were checked, coded, entered, and analyzed by using SPSS software (IBM SPSS Statistics Version 24; SPSS Inc., Chicago, Illinois, USA) and the results were expressed in percentage.

RESULTS

The clinicopathological characteristics of the study groups: The current study was conducted on 504 cases diagnosed clinically as appendicitis and underwent either laparoscopic or open appendectomy. Most patients (61.1%) were in the age group 20-40 years with age mean + SD (age range) 29.6±11 (4-60 years). 245 (48.6%) were male and 259 (51.4%) were female. Most of the patients (93.65%) were complaining of abdominal pain. The most frequent pathological findings were suppurative appendicitis (47.8%) (fig.1A), followed by acute appendicitis (39.9%). Chronic appendicitis (fig.1B), gangrenous appendicitis, and perforated appendicitis have an incidence of (2.8%, 2.2%, and 0.8 respectively). Incidental findings were noticed in 33 (6.5%) cases (Table 1).

The clinicopathological characteristics of patients with unusual (incidental) histopathological findings: Unusual histopathologic findings were found in 33 cases (6.5%). Most of the patients were between 20-40 years with an age mean ± SD (range, years) was: 34±10 (10-54 years). Females were 57.6%, and males were 42.4 %. Most of the patients were complaining of abdominal pain (97%) only one (3%) patient presented with the hernial sac. Regarding the incidental histopathological diagnosis, 21 (4.1%) cases were fibrous obliteration (FO), three (0.6%) cases were well-differentiated neuroendocrine tumor (NET), three (0.6%) cases were low grade appendiceal mucinous neoplasm (LAMN), three (0.6%) cases were diverticulosis of the appendix, two (0.4%) cases were granuloma of the appendix, and one (0.2%) case was diagnosed as acute eosinophilic appendicitis (AEA) (table 1).

Fibrous obliteration of the appendix was incidentally found in 21 cases. All patients were complaining of abdominal pain. Grossly, obliteration of the appendiceal lumen was noticed and microscopically the occlusive proliferation is predominantly neurogenic (fig.1E). None of the three patients with an initial diagnosis of acute appendicitis, but with a histologic diagnosis of the neuroendocrine tumor had exhibited symptoms of carcinoid syndrome or been preoperatively diagnosed with an appendicular tumor. Two out of three histologically detected tumors were in the distal appendix both less than 1 cm (range, 3–7 mm), the third one was in a proximal location at the surgical margin was (3 x 5 mm in maximum dimensions). The tumor consisted of small uniform round cells arranged in small nests separated by

thin connective tissue stroma with no serosal invasion (Fig.2A). Immunostaining was done for confirmation with adequate control for synaptophysin, chromogranin, CK AE1/3, and KI67 and immunostaining results revealed diffuse positivity for CKAE1/3 (fig.2B), and synaptophysin (fig.2C), a focal positive for chromogranin (fig.2D) and Ki67 (fig.2E) revealed low proliferation index (1%) (Table 3). In the two patients who underwent the appendectomy and a tumor less than 1 cm localized in the distal part (tip), no reintervention was performed. The patients have remained free from the tumor in the subsequent two years of follow-up. The case with proximal localization underwent right hemicolectomy and was free for any tumor foci.

Two patients with LAMN complaining of abdominal pain and were not suspected clinically or radiologically. One case was complaining of a hernia sac. Surgery revealed peritoneal lesion diagnosed histologically as pseudomyxoma peritonei (fig.3B) of appendiceal origin. Growth examination of the appendix revealed dilated lumen with mucoid material and localized wall thickening was noticed mainly at the distal part. Microscopic examination revealed well-preserved epithelium with papillary villous structure showing low-grade atypia represents the mucosal adenomatous component (fig.3A) that is followed by immunostaining of SATB2, CDX2, CK20, CK7, and TTF-1. Immunostaining results revealed SATB2 (fig.3C), CDX2 (fig.3D), CK20 (fig.3E) positive for tumor cells and CK7 and TTF-1 were negative. For mucoid material PAS stain, was done and shows positive staining (fig.3F) (table 3).

Evaluation of the medical histories of the two patients with granulomatous inflammation (fig.1C) revealed no history of tuberculosis or Crohn's disease. The two patients with appendiceal diverticulosis were not diagnosed clinically or radiologically. The single patient with acute eosinophilic appendicitis has no history of allergy (fig.1D).

Table (1): The general characteristics of the studied groups

General characteristics	**The studied biopsies No = 504**	
	No	**%**
Age mean + SD (age range) 29.6±11 (4-60 years) **Age categories:**		
< 20 years	120	**23.8%**
20 – 40 years	308	**61.1%**
> 40 years	76	**15.1%**
Gender		
Male	245	**48.6%**
Female	259	**51.4%**
Patients complaint		
Abdominal pain	472	**93.65%**
Vomiting and fever	31	**6.15%**
Hernia sac	1	**0.2%**
Usual pathological finding 471 (93.5%)		
Suppurative appendicitis	241	**47.8%**
Acute appendicitis	201	**39.9%**
Chronic appendicitis	14	**2.8%**
Gangrenous appendicitis	11	**2.2%**
Perforated appendicitis	4	**0.8%**
Incidental pathological finding 33 (6.5%)		
Fibrous obliteration	21	**4.1%**
Nonendocrine tumor	3	**0.6%**
Low grade appendiceal mucinous neoplasm	3	**0.6%**
Diverticulosis of the appendix	3	**0.6%**
Granulomatous appendicitis	2	**0.4%**
Acute eosinophilic appendicitis	1	**0.2%**

Table (2): The clinicopathologic characteristics of cases with incidental pathological findings.

	Incidental Pathologic Findings						Total No = 33 (100%)
	FO 21 (63.6%)	NET 3 (9.1%)	LAMN 3 (9.1%)	DA 3 (9.1%)	GA 2 (6.1%)	AEA 1 (3%)	
Age categories	**Age mean ± SD (age range): 34±10 (10-54 years)**						
< 20 years	3(14.3%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (12.1%)
20 – 40 years	14 (66.7%)	1 (33.3%)	1 (33%)	1 (33.3%)	2 (100%)	1 (100%)	20 (60.6%)
> 40 years	4 (19%)	1 (33.3%)	2 (67%)	2 (66.7%)	0 (0%)	0 (0%)	9 (27.3%)
Gender							
Male	8 (38%)	1 (33.3%)	2 (67%)	2 (66.7%)	1 (50%)	0 (0%)	14 (42.4%)
Female	13 (62%)	2 (66.7%)	1 (33%)	1 (33.3%)	1 (50%)	1 (100%)	19 (57.6%)
Complaint							
Abdominal pain	21 (100%)	3 (100%)	2 (67%)	3 (100%)	2 (100%)	1 (100%)	32 (97%)
Hernia sac	0 (0%)	0 (0%)	1 (33%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)

FO Fibrous obliteration, NET neuroendocrinal tumor, LAMN low grade appendiceal mucinous neoplasm, DA diverticulosis of the appendix, GA granuloma of the appendix, AEA Acute eosinophilic appendicitis.

Table (3): Ancillary studies for cases with NET and LAMN diagnosis.

Ancillary study	**Synaptophysin**	**Chromogranin**	**AE1/3**	**KI67**	**-**	**-**
NET	Diffuse +	Focal +	Diffuse +	Low Index	-	-
Ancillary study	**SATB2**	**CDX2**	**CK20**	**CK7**	**TTF-1**	**PAS stain**
LAMN	+	+	+	-	-	+

NET neuroendocrinal tumor, LAMN low grade appendiceal mucinous neoplasm.

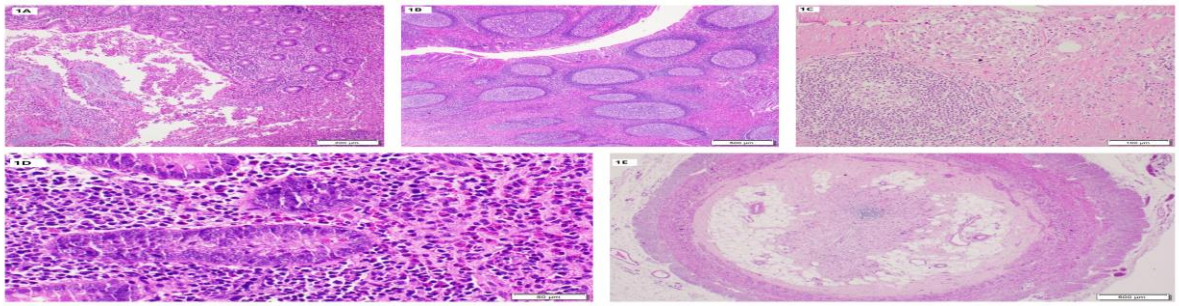

Figure 1: (A) Suppurative appendicitis showing heavy transmural neutrophilic infiltration (H&E x100), (B) Chronic appendicitis showing reactive lymphoid follicles (H&E x40), (C) Granulomatous appendicitis showing epithelioid histiocytes surround by lymphocytes (H&E x200), (D) Acute eosinophilic appendicitis showing heavy eosinophilic infiltration (H&E x400), (E) Fibrous obliteration showing obliteration of the lumen by proliferating spindle cells, fat cells and chronic inflammatory cells with loss of mucosal lining and lymphoid follicles (H&E x40)

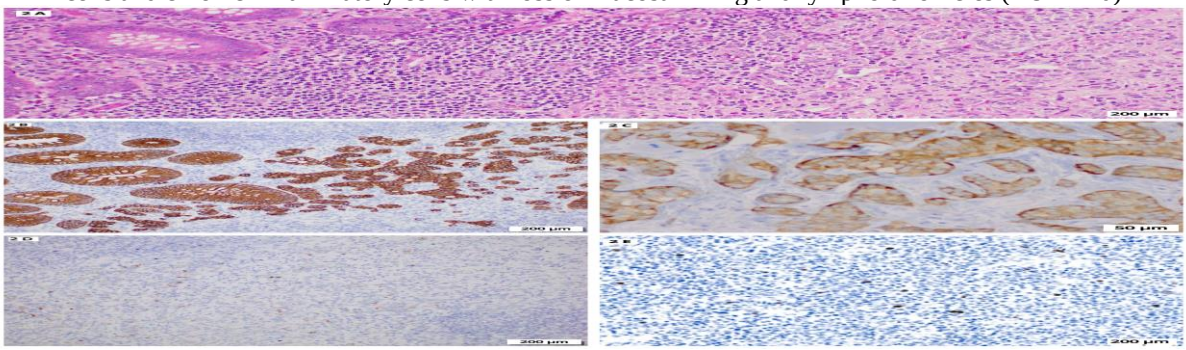

Figure 2: (A) Well-differentiated neuroendocrinal tumor showing infiltration by uniform cells of organoid growth pattern with minimal pleomorphism and diffusely scattered chromatin (H&E x100), (B) Well-differentiated neuroendocrinal tumor showing diffuse positivity for CK AE1/3 (IHC x100), (C) Well-differentiated neuroendocrinal tumor showing diffuse positivity for synaptophysin (IHC x400), (D) Well-differentiated neuroendocrinal tumor showing focal positivity

for chromogranin (IHC x100), (E) Well-differentiated neuroendocrinal tumor showing Ki67 low proliferation index (IHC x100).

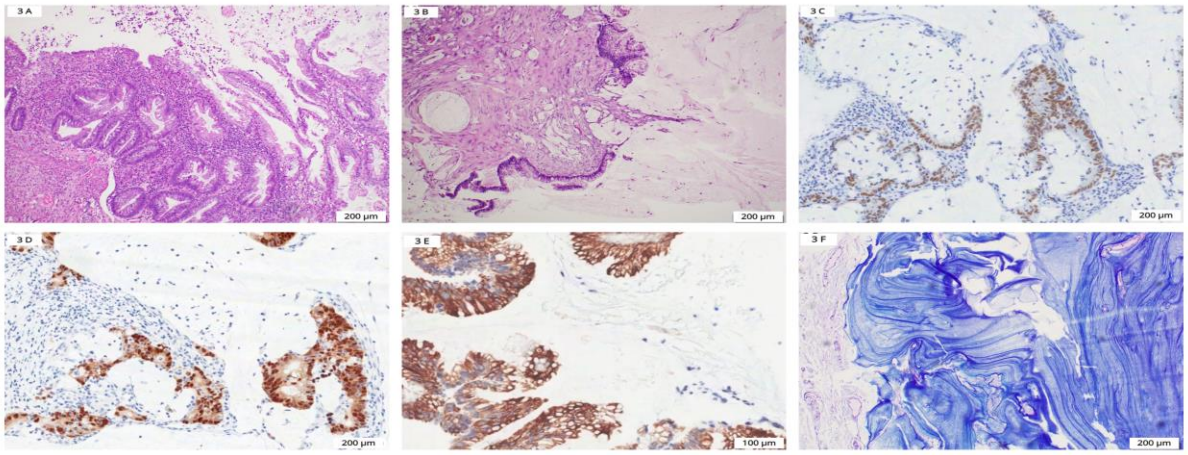

Figure 3: (A) Low grade appendiceal mucinous neoplasm revealed well-preserved epithelium focally shows papillary villous structure with low-grade nuclear atypia (H&E x100), (B) Pseudomyxoma peritonei, LAMN with paucicellular mucinous spread to the peritoneal surfaces (H&E x100), (C) LAMN positive for SATB2 (IHC x100), (D) LAMN positive for CDX2 (IHC x100), (E) LAMN positive for CK20 (IHC x200), (F) Mucinous material PAS-positive (PAS stain x100).

DISCUSSION

Acute appendicitis is defined as the presence of transmural inflammation or pus in the appendicular lumen; it is the most common surgical emergency in the world [13]. Acute appendicitis can occur at any age; especially at younger ages between 10 to 20 years [14]. In our serious, the most frequent pathological finding was suppurative appendicitis and acute appendicitis, followed by complicated acute appendicitis including gangrenous appendicitis and perforation; suppuration, gangrene, and perforation usually indicating a delay in seeking medical advice [15]. Chronic appendicitis is a rare clinical diagnosis that represents a diagnostic dilemma for the clinician as most of the patients present with atypical symptoms. It comprises 1.5% of all cases with a history of acute appendicitis [16]. It could be due to partial and transient obstruction of the appendicular lumen. Furthermore, it is usually diagnosed after the pathological examination [17]. Pathologically, chronic appendicitis can show florid reactive follicular hyperplasia, transmural chronic inflammation with lymphoid aggregates, foci of xanthomatous inflammation, granulomatous reaction, or fibrosis [16]. The present study includes 14 (2.8%) cases of chronic appendicitis.

Incidental pathological findings are those lesions in surgical specimens of the appendix, removed for suspected acute appendicitis or with colectomy specimens [18]. Pathological analysis is the standard method for the confirmation of appendicitis and exclusion of other lesions that may affect the post-operative management plane [15]. Fibrous obliteration is thought to be a part of the aging process. Repeated, subclinical inflammation is probably the trigger for this lesion; it can mimic appendicitis. It begins in the distal portion of the appendix and extends proximally, resulting in the loss of the normal appendiceal mucosa and Peyer patches, and finally replaces the mucosa and submucosa with fibrous tissue. Distal fibrous occlusion may be secondary to hyperplasia of neuroendocrine cells that possibly and eventually result in neuroendocrinal tumors [19]. This condition is uncommon to the clinicians, and radiologists and its imaging findings are rarely seen [20]. The current study included 21 (4.1%) cases of fibrous obliteration, all of them presented with acute abdominal pain. Thirteen appendectomy specimens showed obliteration at the tip while the remaining 8 showed obliteration of the entire lumens. The diagnosis of fibrous obliteration was achieved by microscopic examination, which revealed replacement of the lumen by proliferating spindle cells, nerve bundles, and adipose tissue with chronic inflammatory cells infiltrate. This was in accordance with Yilmaz *et al*., who found that 3.7% of cases show fibrous obliteration [21]. In a study conducted by Dincel *et al*., fibrous obliteration was reported in 16 (27.1%) cases and appendiceal neuroma in 3 (5%) cases [22]. Complete excision of the appendix is the treatment of choice and close patient follow up is recommended [23].

Appendiceal neoplasms are rare tumors and represent about 1% of appendectomy specimens. The most common tumors of the appendix are epithelial neoplasms and neuroendocrine tumors [24]. The most frequent initial manifestation of appendiceal tumors is acute appendicitis, seen in 30%–50% of patients and more commonly in NETs than in epithelial neoplasms [25].

Appendiceal NETs are commonly diagnosed incidentally, and their diagnosis is often established by histopathology after the routine appendectomy [11,26]. Benign NETs more commonly affect females and those in the early twenties. Whilst malignant tumors have an increased incidence at an age of 50 years [27]. Poorly differentiated NETs are Grade 3 if they are>20% on the Ki-67 index and/or more than 20 mitoses/10HPF and are referred to as neuroendocrine carcinomas, whereas well-differentiated neoplasms are termed NETs or "carcinoids". Appendiceal NETs uncommonly involve regional lymph nodes and do not commonly metastasize to the liver. They are mostly located at the tip [27]. The current study included three (0.6%) cases of WNETs, they were an incidental pathological finding in patients with manifestations of acute appendicitis. Two cases were female, and one was male. On gross examination of appendectomy specimens, well-circumscribed yellowish, firm nodules, with a size of (< 1 cm) in diameter were observed to cause luminal narrowing. Two masses were located at the tip while one was detected in the base very close to the surgical margin. The tumors showed the classic microscopic features of well-differentiated NETs, the organoid growth pattern of uniform cells with minimal pleomorphism, and rare mitotic activity. Cells displayed a moderate amount of eosinophilic cytoplasm and diffusely scattered chromatin. The histopathologic diagnosis was proved after IHC studies, tumor cells were diffusely positive for synaptophysin, AE1/3, and focally positive for chromogranin with a low Ki67 index. Previous studies reported percentages of NETs GI from 0.02 to 0.9% [18,22]. Both tumor sizes and the presence of metastases are important for patient prognoses. Tumors smaller than two cm with no metastases have five-year survival rates close to 100%, but if the tumor size is between one and two 2 cm with lymph node metastases or tumors are larger than two cm, the five-year survival rates become about 78%. When the tumor has metastasized to any organ, regardless of tumor size, the five-year survival rate falls to 32% [28]. For patient management, tumors that are smaller than two 2 cm, appendectomy is considered to be the definitive management no need for subsequent follow-up. But if a hemicolectomy has been performed for tumor between one and two cm or tumors larger than two cm, follow-up using abdominal computed tomography with double contrast, and blood tests for tumor markers such as chromogranin must be carried out every year to determine the presence of metastasis or any symptoms suggestive of carcinoid syndrome. For patients whose tumor has metastasized distally, follow-up examinations are indicated every 6 months [29].

Appendiceal mucinous neoplasms represent rare lesions with an incidence of <1% of appendectomies [30]. LAMN confined to the appendiceal lumen do not show definitive malignant features, they can proliferate outside the appendix in a malignant fashion and result in the development of pseudomyxoma peritonei (PMP). PMP is a diffuse accumulation of gelatinous material in the abdomen and pelvis with or without neoplastic cells. Most cases of PMP arise from the appendix and comprise local spread into the peritoneal cavity [31]. About 20% of patients with a mucinous neoplasm of the appendix develop PMP. 94% of cases of PMP develop from a mucinous tumor of the appendix [32]. Our series included 3 (0.6%) cases of LAMN which were incidentally discovered, two patients were complaining of abdominal pain suspected of acute appendicitis, and one case presented with a hernia sac. Two cases were male, and one was female. Grossly, the appendices of the three cases were dilated and filled with mucin and localize wall thickening was noticed. On microscopic examination, the appendix showed villous epithelial proliferation with low-grade atypia that lack features of invasion, which is confirmed by an immunohistochemical study that demonstrate positive staining for SATB2, CDX2, CK20, and negative staining for CK7, and TTF-1. The mucinous material was PAS-positive. Several published studies have reported mucinous neoplasms as the most common primary appendiceal tumors [12,18]. Surgical management of LAMN with peritoneal mucin spillage is still controversial. Acellular or cellular mucin is of significant value for the patient's prognosis. For early lesions with localized cellular mucin spillage the use of cytoreductive surgery is advocated and if treated by the appendectomy or right hemicolectomy alone likelihood of progression to extensive intra-abdominal disease is high [33]. Three, five, seven, and ten-year overall survival rates for LAMN with extra appendiceal spread are 100%, 86%, 60%, and 45%, respectively. It is not recommended to give adjuvant chemotherapy for LAMN and should only be considered in case of lymphovascular or lymph node involvement or of mixed-type histology [34].

Diverticulosis rarely occurs in the appendix with an incidence of about 1%. It can manifest as appendicitis and is usually diagnosed after surgery due to difficulty in visualizing it on imaging [35]. The three (0.6%) cases of appendicular diverticulosis in our study presented clinically as

acute appendicitis and were discovered incidentally. Grossly the appendix has localized area of outer surface irregularity on opening a diverticulum was noticed. Microscopically, there was a mucosal outpouching through the appendiceal wall surrounded by inflammatory cell infiltrate.

Granulomatous appendicitis is a rare lesion, and it can result from many factors, including infections, such as Mycobacterium tuberculosis, parasites, and fungi, or non-infectious factors, like Crohn's disease or sarcoidosis [36]. The definitive diagnosis of granulomatous appendicitis requires long-term follow-up and detailed workup. In most cases, granulomatous appendicitis has been incorrectly diagnosed as Crohn's disease. Idiopathic granulomatous appendicitis is not easily distinguished from early-stage Crohn's disease, which only affects the appendix [5,8]. Crohn's disease of the appendix is infrequent with an incidence of 0.2-0.55%. Grossly, appendiceal Crohn's disease manifests as an enlarged, oedematous appendix with a thickened wall and fibrous adhesions. Classic microscopic features comprise noncaseating granulomas, transmural chronic inflammation, lymphoid aggregates, muscular hypertrophic changes, and the fibrous reaction of the appendiceal wall [37]. The current study included 2 (0.4%) cases of granulomatous appendicitis. One patient was complaining of acute abdominal pain and treated as acute appendicitis, while the other was complaining of chronic abdominal pain. The age was within the range from 20-40 years. The two patients have no preceding or associated bowel symptoms. Grossly, the appendix was swollen with the thickened wall. The histopathologic examination displayed noncaseating granulomas composed of epithelioid cells and lymphocytes, transmural inflammatory infiltration formed of, lymphocytes, and plasma cells, eosinophils, and neutrophils. Stains for acid-fast bacilli were negative. Hence, the histological evaluation was in line with Crohn's disease. Appendiceal Crohn's disease was demonstrated by many studies in appendectomy specimens in patients presented with acute appendicitis [38,39,40]. Acute eosinophilic appendicitis is appendicular inflammation with marked type I hypersensitivity response with eosinophil and edema without supervening infection. Histopathologic features of AEA include the absence of neutrophils, with the presence of marked eosinophilic infiltration in muscularis propria and edema separating muscle fibers [4]. In AEA, factors causing the allergic reaction, particularly parasitic infestations should be kept in mind. Hence, the cure could be possible using anti-parasitic medical therapy [41]. We have one (0.2%) case of AEA presented as acute appendicitis and detected incidentally after pathologic examination of the appendix. The appendix was enlarged, edematous, and inflamed grossly. Microscopically, there was extensive eosinophilic infiltration of the muscle layer and edema without neutrophils. Aravindan *et al*. determined 8 patients of AEA out of 120 patients underwent appendectomies [4].

CONCLUSIONS

The present study showed that histopathological examination of the appendix was very important for patient management undertaken in all cases of acute appendicitis. Early diagnosis of the malignant lesion and initiation of treatment is extremely of benefit for patient survival. Therefore, even with normal macroscopic features, histopathologic analyses may detect an incidental finding that will help to improve the patient's outcome.

Conflict of interest: None

Financial disclosure: None

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To cite:

Omar, A., khalaf, M. Unusual Incidental Pathological Findings of The Appendix Histopathological and Immunohistochemical Study. *Zagazig University Medical Journal*, 2024; (363-371): -. doi: 10.21608/zumj.2021.76646.2236