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RESEARCH ARTICLE

Diverticular Disease of the Vermiform Appendix - Is it a Distinctive Clinico-Pathological Entity?

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Abstract:

Background:

Diverticular disease of the appendix [DDOA] is a rare occurrence. Although acquired in nature, its impact on the disease process of appendicitis is not well-defined. The purpose of the current study is to include a comprehensive clinico-pathological definition of the disease through a retrospective single-center cohort analysis with a prospective pathological re-evaluation.

Methods:

A retrospective analysis of post-appendectomy patients over a period of 16 years [2000-2015] was carried out. Patients with DDOA were identified and compared to a control group of patients with acute appendicitis. Histology was re-evaluated prospectively by a senior pathologist. Primary measures of the outcome included clinical and surgical differences. Pathological macroscopic differences between the two groups and a comprehensive description of the DDOA itself were performed.

Results:

6846 post appendectomy patients were operated on during the study period, and 127 [1.9%] were diagnosed with DDOA. The DDOA group showed significantly higher age, longer duration of complaints, and a different clinical presentation. Operative time was significantly longer in the study group and had higher rates of severe postoperative complications such as postoperative bleeding, need for ICU recovery, and need for postoperative mechanical ventilation. All diverticula were pseudo-diverticula and were significantly shorter and wider. Multivariate analysis showed that age, length, and width of the appendix were independently associated with DDOA.

Conclusion:

The results of this study suggest that DDOA is an independent clinical entity, showing differences in etiology, clinical presentation, and postoperative outcome. Prospective studies are needed to assess whether the preoperative diagnosis is feasible and will change conventional surgical management.

Keywords: Diverticula, Appendix, Diverticulitis, Pathology, DDOA, Etiology.

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1. BACKGROUND

Diverticular disease of the appendix [DDOA] is a rare occurrence, first described by Kelynack in his book entitled "A Contribution to the Pathology of the Vermiform Appendix" [1]. During autopsies, this pathology is encountered in 0.2-1.4% of the cases [2]. In appendectomy specimens, it is encountered in 2.1% of the cases [3]. Congenital DDOA, though, is extremely rare [0.0014%] [2].

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Although DDOA is an acquired pathology, its impact on the disease process of the appendix is seldomly discussed. This fact is not necessarily because of its low incidence but rather because of the low impact it has on the diagnosis and the surgical treatment of the appendicular disease. Therefore most DDOA is diagnosed postoperatively.

Over the years, the clinico-pathological description of DDOA was described only in case reports or small case series [4 - 22].

The current study evaluates the incidence, clinical, diagnostic, and pathological process of this rare entity and aims to compare this pathology to a random cohort of patients

diagnosed with acute appendicitis. This may be used as a definite source of information and may add to the body of knowledge regarding this uncommon diverticular disease.

2. MATERIALS AND METHODS

Charts of all patients undergoing appendectomy from January 2000 through December 2015 were retrospectively examined. Patients with post appendectomy pathological diagnosis of DDOA were identified and further scrutinized. Data collected included demographic, clinical, and operative parameters. Pathology slides of all patients were re-evaluated by a senior pathologist. Slides were evaluated for morphometrics, location of the diverticula [tip *vs*. non-tip of the appendix], type of diverticula [false *vs*. true diverticula], and source of inflammation [appendix *vs*. diverticula].

A group of 140 consecutive contemporary patients with acute appendicitis was elected as a control group. Three patients were excluded from the study; one patient for missing data and two that were not evaluated in our institution. All parameters were compared in a univariate and multivariate fashion to find significant differences or associations between the two groups of patients.

Patients of all age groups were included in the study with no exclusion criteria in the two cohorts of patients.

2.1. Statistical Analysis

Continuous parametric variables were analyzed using the Student's t-test. The Mann-Whitney U test was used to analyze non-parametric variables. Chi-square test was applied to analyze the association between frequencies in a univariate fashion. Multivariate analysis was performed using a stepwise logistic regression model, and a likelihood ratio test was applied to identify positive associations with the primary and secondary measure of outcome. JMP Pro for Mac [Version 14.0.0] was used to analyze the data. $P < 0.05$ [2-sided] was considered statistically significant.

3. RESULTS

During the study period [16 years], 6846 appendectomies were performed [428 per year]. Pathology assessment revealed 127 [1.9%] patients with DDOA with an increasing incidence over the years from 0.76% at the beginning of the study to 3.3% at its end.

The mean age of the DDOA group was 48±18.6 years, and 54.3% [n-69] were males. The most common complaint at presentation was abdominal pain in 96.8% [n-123], followed by nausea in 33% [n-42], and emesis in 13.4% [n-17]. Table **1** depicts the demographic and clinical differences between the two groups. Laboratory results showed a significant increase in the absolute number of leukocytes in the no DDOA group [$14.1x10^3 \pm 4.5x10^3$ *vs*. $12.43x10^3 \pm 4.3x10^3$ cells per ml^3, $p<0.001$] [Normal values 4.3 – 10.8 $x10^3$ cells per ml^3] with significant left deviation in the percentage of neutrophils [73.7%±11 *vs*. 76.8%±9.7, p-0.02]. Creatinine [0.9±0.3 *vs*. 0.7±0.3 mg/dl, $p<0.001$] and blood urea nitrogen [BUN] levels [14±7.7 *vs*. 11.2±4.1 mmol/l, $p<0.001$] were increased significantly in the DDOA group. This could suggest a smoldering disease versus a more acute one in the non-DDOA group.

The diagnosis was performed by trans-abdominal ultrasound in 40.5% [n-51] of the cases *vs*. 48.5% [n-66], with no significant difference between the two groups. On the other hand, Computerized Tomography [CT] scan was used significantly more in the DDOA group [73.2% *vs*. 57%, $p<0.001$]. This may reflect on the fact that peri-appendicular abscess was diagnosed in 11.8% [n-15] of the patients in the DDOA group and in only 2.1% [n-3] of the controls [p-0.001].

Surgical approach preference did not differ among the group study [Laparoscopy, 59.8% *vs*. 56.9, p-0.9]. Operative time was significantly longer in the DDOA group [51.1±23.2 *vs*. 39.1±22.1, $p<0.001$] with higher rates of drain placement [16.3% *vs*. 5.3%, $p<0.001$]. All patients presenting with a peri-appendicular abscess had an interval appendectomy performed.

Postoperative complications were generally minor in the control group [wound infection and postoperative intra-peritoneal abscesses]; however, in the DDOA group, major complications such as bleeding, pulmonary embolism, and an actual need for postoperative intensive care unit admission and postoperative mechanical ventilation (Table **2**) were noticed. Rates of re-admissions to the hospital showed no significant difference between the two groups.

Table 1. Demographic and clinical differences between patients with DDOA and the controls.

Clinical Variables	DDOA n-127	No DDOA n-137	Univariate P Value
Age	48.5±18.6	27.2±18.2	**<0.001**
Gender [male] [%]	69 [21.1]	57 [17.7]	0.63
Length of complaints [days] [median]	2 [1 - 14]	1 [1 - 14]	**<0.001**
Clinical presentation			
Abdominal pain [%]	123 [96.8]	137 [100]	**0.036**
Nausea [%]	42 [33]	67 [48.9]	**0.009**
Vomit [%]	17 [13.4]	49 [35.7]	**<0.001**
Diarrhea [%]	11 [8.7]	18 [13.1]	0.18
Constipation [%]	3 [2.4]	2 [1.4]	0.1
Fever [%]	28 [22.1]	39 [28.5]	0.23

Table 2. Clinical differences between diverticular disease of the appendix and simple appendicitis.

Diverticular Disease of the Appendix	Simple Appendicitis
Longer duration of complaints	Shorter duration of complaints
Older age group	Younger age group
Absence or lower incidence of GIT symptoms	Consistent GIT* symptoms *e.g.* nausea, anorexia, emesis
High incidence of peri-appendicular abscesses	-
Longer operative time	-
Similar rate of simple complications	-
Higher rate of life threatening complications	-
*GIT – Gastrointestinal tract	

The pathology reports and slides were re-evaluated by a senior pathologist. The morphometrics for the length and width of the appendix were taken from the macroscopic evaluation of the appendix in the pathology report. The appendix was significantly shorter [6.2±1.6cm *vs*. 7.5±2.1cm, p<0.001] and wider [1.2±0.4cm *vs*. 0.95±0.6cm, p<0.001] in the DDOA group. The diverticulum was present in the tip of the appendix in 74.8% [n-95].

The pathology slides were reassessed for the type of the diverticula and the source of inflammation. Interestingly enough, all the diverticula were false, and wall layers included the mucosa and submucosa and did not include the muscular layers or the adventitia. The source of inflammation was the diverticula alone in 44.1% of the cases, and both appendix and diverticula were involved in 38.6%. 4.7% of the cases showed diverticula in a normal appendix with no inflammation.

Fig. (**1**) shows a transverse slice of the appendix with all the layers intact [A] and a diverticulum in the body [B] and in the tip of appendix [C]. Fig. (**2**) shows acute inflammation in an appendicular diverticula [Hematoxylin and eosin, left panel 2x, right panel 20x].

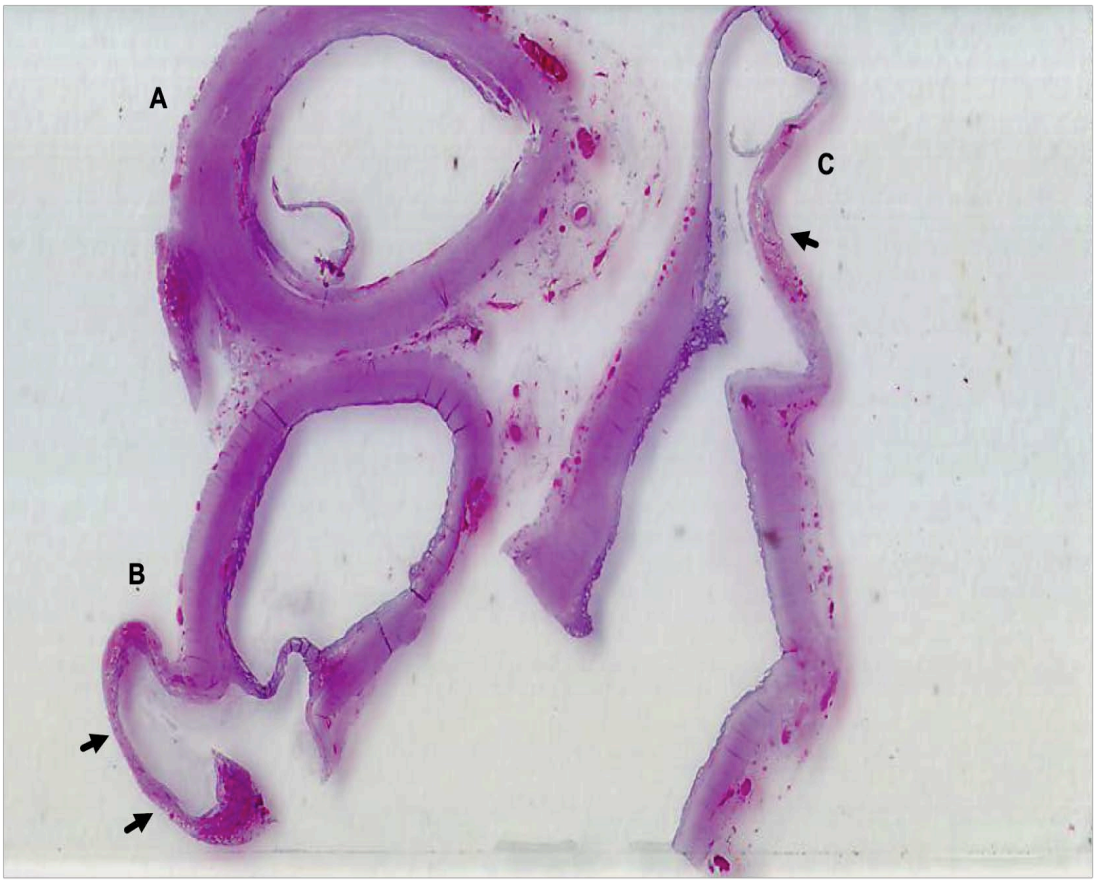

Fig. (1). Pathological microscopic evaluation. Transverse slice of an appendix showing the intact layers of the appendix [A] compare to the same appendix that had a diverticula in the body of the appendix [B] and one in the tip [C].

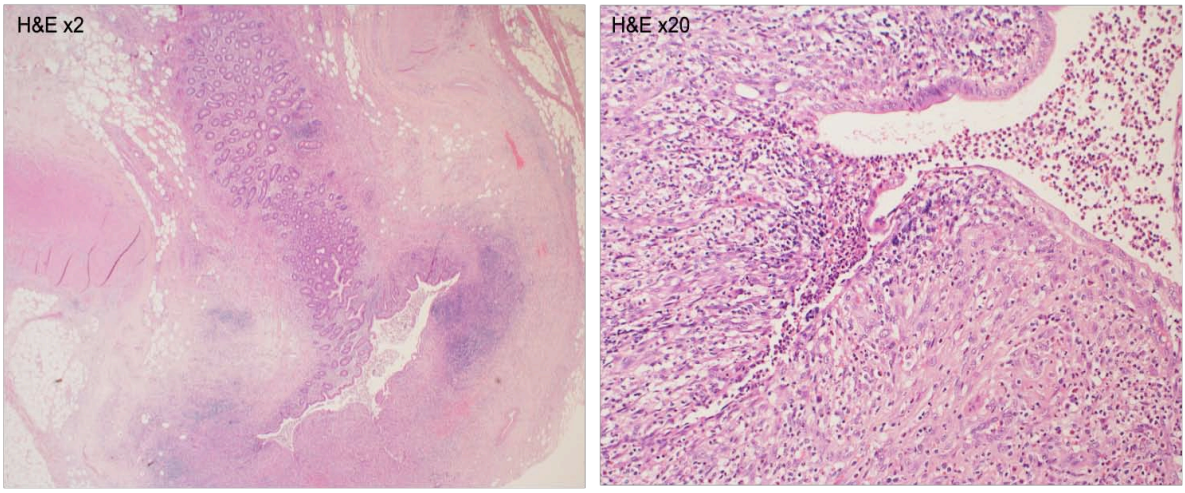

Fig. (2). Acute inflammation within an appendicular diverticula [Hematoxylin and eosin, left panel 2x, right panel 20x].

Table 3. Rates of postoperative complications in both groups showing higher rates of major complications in DDOA group.

Complications	DDOA n-127	No DDOA n-137	Univariate P Value
Wound infection [%]	6 [4.8]	3 [2.3]	0.3
Abscess [%]	6 [4.8]	7 [5.3]	0.9
Bleeding [%]	4 [3.3]	0 [0]	**0.04**
Post op Mechanical ventilation [%]	4 [3.3]	0 [0]	**0.04**
Need for ICU [%]	5 [4]	0 [0]	**0.02**
Pulmonary Embolism [%]	1 [0.8]	0 [0]	0.5
Re-Admissions [%]	6 [4.8]	10 [7.5]	0.4
ICU-intensive care unit			

A multivariate analysis using a stepwise logistic regression model and a likelihood ratio test was applied to identify positive associations with DDOA. Length [$p<0.001$] and width of the appendix [$p=0.04$] along with age [$p<0.001$] were independently associated with the presence of diverticula.

Table **3** summarizes the clinical differences between diverticular disease of the appendix and simple appendicitis.

4. DISCUSSION

Diverticula of the gastrointestinal tract are defined as a herniation of the mucosa and submucosa through *locus minoris resistentiae* of the intestinal wall. The formation of diverticula in the appendix was studied at the beginning of the 1900s. Stout, in 1923, theorized that the appendiceal mucosa herniates through the site of penetrating vessels or on the site of a previous perforation. Some other contributing factors such as muscular contraction and obstruction of the base of the appendix were also considered [23]. Gramse A E *et al*. further evaluated the inflammatory theory and concluded that a sequence of events caused by inflammation is at the base of the diverticulum formation [24]. Wilson postulated that a] passive distention alone could not be the sole cause of diverticula formation, b] a significant constriction and obliteration of the base of the appendix, on the other hand, is possibly the main cause, and c] muscular hypertrophy combined with stenosis may also have a role. Wilson excluded the inflammatory theory at this point mostly because there was not enough data to support it at the time [25]. Since the 1950s, physicians overlooked this disease, and further etiological studies were not published in the English literature. The current study does not investigate the etiology of the diverticula formation, but we observed that appendices with the diverticular disease were significantly shorter and wider than the controls, and our multivariate analysis shows that these are independently associated with the presence of diverticula. This might reflect on some of the pressure theories postulated by Wilson *et al*.

The diagnosis of DDOA is mostly postoperative but some authors reported preoperative sonographic [26, 27] or computerized tomographic diagnosis [28].

These published findings were all incidental, and thus far, there is no recommendation to look specifically for the diverticula on the preoperative imaging, probably because as for now, this will not change the treatment plan of these patients. In our study, we found that CT was used significantly more in the DDOA group. This is explained by the longer duration of complaints, older age of the patients, and the higher rates of peri-appendicular abscesses.

Our study suggests DDOA related appendicitis presents with a different clinical course than classic appendicitis. We showed that the study group has a significantly longer duration of complaints. This may suggest a more flaming and long clinical course than the controls. We believe that the relatively

high rates of peri-appendicular abscesses [11.8%] compared to the controls support this theory as well.

Several randomized control trials reviewed the possibility of antibiotic treatment instead of appendectomy in patients with simple appendicitis [29 - 33]. The relatively high recurrence rate, high rates of peritonitis after the failure of non-operative management, and the need for strict follow-up still dictate the choice of appendectomy in many of the surgical departments around the world. Open or laparoscopic appendectomy is considered a straightforward operation with a very low complication rate and a reasonable learning curve. This study shows that surgery in the DDOA group was significantly longer [51.1±23.2 *vs*. 39.1±22.1 minutes, $p<0.001$]. This fact and the high rates of close suction drain placement [16.3% *vs*. 5.3%, $p<0.001$] could be used as a surrogate for the complexity of the intervention mostly due to what seems to be a long-standing disease with intense inflammation and peritonitis. This is further reverberated by the high rates of major postoperative complications as described in Table **2**.

Primary neoplasms of the appendix are identified in 0.5% of all post-appendectomy specimens; carcinoid tumors representing >50% of all these neoplasms [34, 35]. Some authors associated the presence of DDOA with neoplasms of the appendix. Lamps *et al*. described a 25% association with mucinous neoplasms of the appendix [36, 37]. Others associated it with different neoplasms, including well-differentiated neuroendocrine tumors [carcinoid], tubular adenomas, and appendiceal adenocarcinoma [38 - 40]. The association of these neoplasms with DDOA in these small case series was significant; therefore, these authors considered DDOA as a marker for regional neoplasms.

In our study, 47 patients [n-6846, 0.7%] were identified with neoplasms of the appendix, of which 31 [0.45%] were carcinoid tumors. The remaining had either mucinous cystadenoma or carcinoma of the appendix. Three patients [2.4%] presented with concomitant DDOA and carcinoid tumor of the appendix, and no such concomitance was observed for the mucinous neoplasms. This is indeed 5 times higher than the rate of carcinoid tumors in the general population, but it is not close to the 25-43.6% reported in the past. We believe that specimens identified with DDOA should be thoroughly examined for concomitant tumors. However, there is no room to recommend a colonoscopy or any other imaging technique such as Somatostatin scan or 68 gadolinium DOTATATE PET/CT scan in these unique cohorts of patients if no other indication exists.

Our study is limited by its retrospective nature. It is possible that the incidence of DDOA is higher than described as pathologists claim that it is often overlooked in the macroscopic evaluation of the inflamed specimen and is not in the pathology report protocol of appendices.

CONCLUSION

Although the treatment plan for this cohort of patients is not different from acute appendicitis, its long clinical course, high rates of peri-appendicular abscesses, and relatively complicated surgery require more attention. The current study summarizes the knowledge regarding this seemingly rare entity and may prove to be a definitive source of information.

AUTHORS' CONTRIBUTIONS

OBI: Study conception and design, analysis of the data, drafting of the manuscript.

NAQ: Data collection.

YZ: Pathology review and critical review of the manuscript

YK: Critical review of the manuscript

All authors read and approved the article in its current form

LIST OF ABBREVIATIONS

DDOA	=	Diverticular Disease of the Appendix
ICU	=	Intensive Care Unit

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the institutional review board of the Rambam Health Care Campus in Haifa, Israel.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was waived by the IRB committee due to the retrospective nature and the lack of clinical impact on the patients involved in the study.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analysed during the current study are available from the corresponding author [O.B.I] on reasonable request.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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