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Enterobius vermicularis Enfeksiyonu Olan Appendektomilerde Bulgular: Kıl Kurdu Apendisit Nedeni Değil

Findings in Appendectomies with Enterobius vermicularis Infection: Pinworm Is Not A Cause of Appendicitis

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ABSTRACT

Objective: To evaluate the histopathological findings in appendectomy materials with *E. vermicularis* infection.
Methods: Appendectomy materials with *E. vermicularis* infection of 24 cases were evaluated for the presence of acute inflammation, congestion, hemorrhage, perforation, lymphoid hyperplasia (LH), necrosis, granuloma, fecalith, obliteration, hyalinization, eosinophilic infiltration and mucosal architectural distortion.
Results: The frequency of *E. vermicularis* among 3222 appendectomies that were scanned for the study was 0.74% (24/3222). Female: male ratio was 1:1 and the median age was 12±9.34 years. The most common findings were LH (100%), and congestion (91.7%) Acute inflammation was found in one third (n=8), with phlegmonous inflammation and/or periappendicitis in 4 of them. The patients with periappendicitis were significantly younger (mean age 4 vs. 14.2 years, p=0.008). Feces was present in the lumen in 79.1% of the patients (fecalith in 25%, soft feces in 29.1% and feces mixed with blood and/or suppuration in 25%). In 6 cases (25%), only *E. vermicularis* was observed in the lumen, with acute appendicitis in 2 of them. Appendiceal lumen was completely obstructed in 12.5% (n=3), while it seemed narrow due to extensive LH in 3 (12.5%) cases. Fibrous obliteration was seen in 4 patients and it was correlated with age and eosinophil count in lamina propria p<0.05.
Conclusion: While *E. vermicularis* infection appears to be an incidental finding in appendectomies rather than being a cause of appendicitis, it probably stimulates LH which may mimic acute appendicitis clinically.
Keywords: Appendix, appendicitis, *Enterobius vermicularis*, eosinophilic infiltration, lymphoid hyperplasia

ÖZ

Amaç: Bu çalışmada, *E. vermicularis* enfeksiyonu ile karşılaşılan apendektomi materyallerinde histopatolojik bulguların değerlendirilmesi amaçlanmıştır.
Yöntemler: *E. vermicularis* enfeksiyonu ile karşılaşılan 24 olgunun apendektomi materyalleri; akut yangı, konjesyon, perforasyon, lenfoid hiperplazi (LH), nekroz, granülom, fekalit, obliterasyon, hyalinizasyon, eozinofil infiltrasyonu ve mukozal arşitektürel düzensizlik varlığı açısından yeniden değerlendirilmiştir.
Bulgular: Çalışma için taranan 3222 apendektomi materyalinde *E. vermicularis* sıklığı %0,74 idi (24/3222). Kadın: erkek oranı 1:1, median yaş 12±9,34 idi. En sık bulgular LH (%100) ve konjesyon (%91,7) idi. Akut yangı olguların sadece 1/3'ünde mevcuttu (n=8); bunların 4'ünde flegmonöz yangı ve/veya periapendisit görüldü. Periapendisit olan olgular daha gençti (ortalama yaş 4 vs. 14.2, p=0,008). Olguların çoğunda (%79,1) lümende feçes saptandı (fekalit %25, yumuşak feçes %29,1 ve kan ve/veya süpürasyonla karışık feçes %25). Altı olguda (%25) lümende yalnızca *E. vermicularis* gözlendi ve bunların yalnızca ikisinde akut apendisit vardı. Apendiks lümeni 3 olguda (%12,5) tamamen tıkalıyken 3 olguda (%12,5) yaygın LH nedeniyle lümen görece dardı. Dört olguda görülen fibröz obliterasyon ile yaş ve lamina propriadaki eozinofil sayısı arasında anlamlı ilişki bulundu (p<0,05).
Sonuç: *E. vermicularis* enfeksiyonu sıklıkla akut apendisit nedeni değildir ve apendektomilerde insidental olarak karşımıza çıkmaktadır. Bununla birlikte; parazitin varlığı klinik olarak akut apendisit tablosunu taklit edebilen LH gelişimine neden olmaktadır.
Anahtar Kelimeler: Appendiks, apendisit, *Enterobius vermicularis*, eozinofil infiltrasyonu, lenfoid hiperplazi

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Türkiye PARAZİTOLOJİ Dergisi

INTRODUCTION

Appendicitis usually presents with abdominal pain, nausea and loss of appetite and is characterized by the inflammation of the appendiceal wall, albeit in a relatively broad spectrum, changing from mild inflammation to gangrenous inflammation. It is still an important cause of emergency abdominal surgery, although some cases might be self-limiting or respond to antibiotics alone (1). While the incidence of appendectomy has been decreased and the incidence of appendicitis has been stabilized in the Western countries, the incidence of appendicitis or appendectomy is still high in newly industrialized countries in Asia, the Middle East, and Southern America (2). Appendicitis may occur due to several etiologic factors, including parasitic infections. *Enterobius vermicularis* (*E. vermicularis*), a nematode, also known as "pinworm" affects more than 200 million people worldwide (3). Children are more commonly infected by *E. vermicularis* but adults may also be infected. Pinworms are found in 0.6% to 13% of appendectomies (4), but the casual relationship between *E. vermicularis* and acute appendicitis remains controversial. Some authors have suggested that the pinworm invades the mucosa after the removal of appendix to escape hypoxia (5), but appendiceal mucosal invasion by the parasite associated with ulceration and inflammation has also been reported (4).

In this study, we aimed to evaluate the histopathological findings in *E. vermicularis* infected appendectomies and to reveal whether there is any causal relationship between *E. vermicularis* infection and acute appendicitis.

METHODS

The study protocol was approved by Institutional Ethics Committee. A total of 3.222 appendectomies that were evaluated in our department in a seven-year period (between January 2010 and January 2017) were retrospectively scanned using the hospital information system to identify the cases with *E. vermicularis* infection and hematoxylin-eosin stained slides of 24 appendectomies with *E. vermicularis* infection were re-examined for the presence of acute inflammation, congestion, hemorrhage, perforation, lymphoid hyperplasia (LH; lymphoid follicles forming germinal centers), necrosis, granuloma, obliteration, hyalinization, tip involution/obliteration and mucosal architectural distortion. Luminal content was noted. The localization of the parasite was also noted as in the tip, corpus and/or proximal edge. The number of the eosinophils per one high-power field (HPF) in lamina propria was counted. Clinical data was recruited from patient records.

Statistical Analysis

Statistical analysis was performed using the software SPSS version 24.0 (*SPSS Inc. Chicago, IL*). Descriptive analyses were used and variables were compared using nonparametric tests since the sample size was small and showed non-normal distribution (χ^2 to compare between frequencies and Kruskal Wallis test to compare means between more than 2 groups). $P<0.05$ was considered significant.

RESULTS

Clinicopathologic findings are summarized in Table 1. The frequency of *E. vermicularis* among 3222 appendectomies that were scanned for the study was 0.74%. Female: male ratio was 1:1 and the median age was 12±9.34 (interquartile range: 3-40 years old). All cases underwent appendectomy due to suspicion of acute appendicitis, with abdominal pain (58.3%) and nausea (50%) being the most common symptoms.

The appendix had been entirely submitted for histopathologic evaluation in 5 cases and the mean number of the pieces submitted per case was 3.73 (2-7 pieces) in the remaining 19 patients. The largest diameter of the appendix ranged between 5 to 10 mm (mean: 5.75 mm). The most common findings were LH (n=24, 100%), which was seen in all cases, (Figure 1A, B and 2A, B) and congestion (n=22, 91.7%) (Figure 2A). *E. vermicularis* was seen in corpus in 18 cases (75%), followed by the tip (n=5, 20.8%) and involving both tip and corpus in only one patient (4.2%). The localization and/or number of the parasites was not associated with histopathological features ($p>0.05$).

Feces was present in the lumen in more than half of the patients (n=18, 79.1%), as fecalith in 6 (25%) (Figure 3A), soft feces in 7 (29.1%) and admixed with blood and/or suppuration in 5 (20.8%) (Figure 2B). In 6 cases (25%), only *E. vermicularis* was observed in the lumen. Appendiceal lumen was completely obstructed in 3 patients (12.5%), while the lumen seemed to be narrower due to extensive lymphoid hyperplasia in another 3 cases (12.5%).

Acute inflammation was found in one third (n=8), with phlegmonous inflammation and/or periappendicitis in 4 of them (Figure 3B). Acute inflammation was not associated with age, however, the patients with periappendicitis were significantly younger than the patients without periappendicitis (mean 4 vs. 14.20, p=0.008). The presence of acute inflammation was

Table 1. Clinicopathologic characteristics

The frequency of *E. vermicularis*	0.74% (n=24 in 3222 appendectomies)
Female: male ratio	1:1 (12 females and 12 males)
Age range Mean age Median age	3-40 years old 13.83±9.34 12±9.34
The largest diameter of the appendix	Range 5-10 mm (mean: 5.75 mm)
Lymphoid hyperplasia	100% (n=24)
Congestion	91.7% (n=22)
Acute appendicitis	33.3% (n=8)
Hemorrhage	45.8%
The location of the parasite Corpus Corpus and tip Tip	 75% 20.8% 4.2%
The status of the appendiceal lumen Obstructed Narrow due to lymphoid hyperplasia Open	 12.5% (n=3) 12.5% (n=3) 75% (n=18)
Luminal content Fecalith Soft feces Feces admixed with blood and/or suppuration Only *E. vermicularis*	 25% (n=6) 29.1% (n=7) 25% (n=6) 25% (n=6)

associated with the presence of hemorrhage and periappendicitis (p=0.043 and p=0.002, respectively). No significant association was found between acute inflammation and other parameters. Mucosal parasite invasion was noted in only one patient (4.2%) (Figure 3C). Mucosal architecture was slightly distorted in 3 cases (12.5%) due to hemorrhage, LH and necrosis (Figure 3D). Almost half of the cases (n=11, 45.8%) had hemorrhage in the appendiceal wall, with necrosis present in only 1 case. No granuloma, hyalinization or perforation was detected.

The number of the eosinophils per 1 HPF in lamina propria ranged between 6 and 138 (median: 28±27.41). The mean number of the eosinophils was significantly higher in patients that were older than 18 years old (mean 18.80 vs. 10.84, p=0.025). The eosinophil count also tended to increase by age but the difference was not statistically significant (p>0.05). We found a significant association between the eosinophil count and the presence of tip involution/obliteration (mean 19.50 vs. 11.10, p=0.03). While tip was fibrotic in 4 patients at ages 16, 21, 23, and 37, the presence of tip involution/obliteration was found to be associated with age as well (mean age 20.88 vs. 10.83, p=0.009). No significant association was found between the number of the eosinophils/HPF and luminal content, although higher eosinophil counts were observed in cases with feces in the lumen (mean 13.12 vs. 11.77, p=0.64). No significant association was found between the number of the eosinophils/HPF and other parameters.

DISCUSSION

The frequency of *E. vermicularis* (0.74%) in the study group is consistent with the literature (4). We observed lymphoid hyperplasia in all cases as lymphoid hyperplasia of the appendix is another disputed entity. Excessive lymphoid hyperplasia of the appendix was suggested as the cause of recurrent appendiceal symptoms in children and to be classified as a separate entity among the diseases of the appendix in 1924 by Smith (6). Three decades later, Nathans and colleagues reported lymphoid hyperplasia as a frequent precursor of acute appendicitis (7). In 1976, Jona and colleagues described acute and chronic forms of lymphoid hyperplasia of the bowel and they concluded that an infectious process precipitated the acute lymphoid hyperplasia and that it usually manifested as acute appendicitis (8). For the last two decades, the lymphoid follicles are considered as a part of functional appendix histology based on its important role in the intestinal immune system (9). However, the extent of the lymphoid hyperplasia is still not well-delineated in healthy individuals. Lymphoid hyperplasia has been reported as a major finding without acute appendicitis in a recent study focusing on *E. vermicularis*-appendicitis association (10), similar to our findings. Also, da Silva and colleagues have suggested an association between *E. vermicularis* and lymphoid hyperplasia (11). We detected acute inflammation in only one third of the patients, but the presence of abdominal pain, nausea and leukocytosis in almost all patients with available clinical data suggests that lymphoid hyperplasia causes a clinical entity resembling acute appendicitis, which may not be distinguished from appendicitis even radiologically (12), and along with congestion, which is the second most common finding in the present study, it may be representing an exaggerated response of the intestinal immune system. On the other hand, some authors have suggested that *E. vermicularis* may cause an abdominal pain, mimicking appendicitis (13,14).

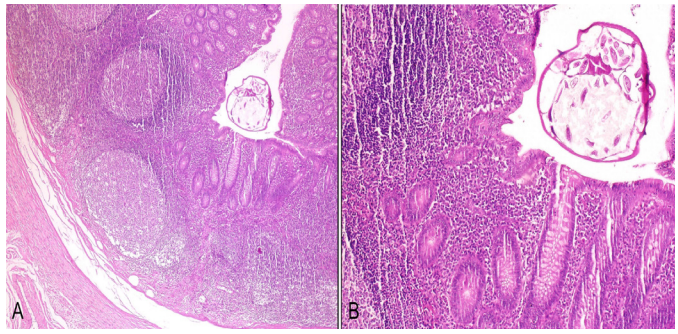

Figure 1. a, b. Lymphoid hyperplasia, the most common finding in our series (100%). In this case, only *E. vermicularis* was present in the lumen, hematoxylin-eosin, x100 and x200

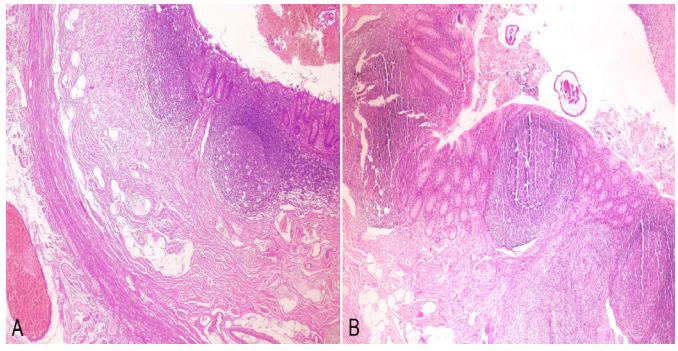

Figure 2. a. The pinworm and blood are seen in the lumen, accompanied by lymphoid hyperplasia and congestion in the appendiceal wall, hematoxylin-eosin, x100, and b. More than one parasite sections are seen in the lumen admixed with suppuration and feces. Lymphoid hyperplasia is also prominent. Hematoxylin-eosin, x200

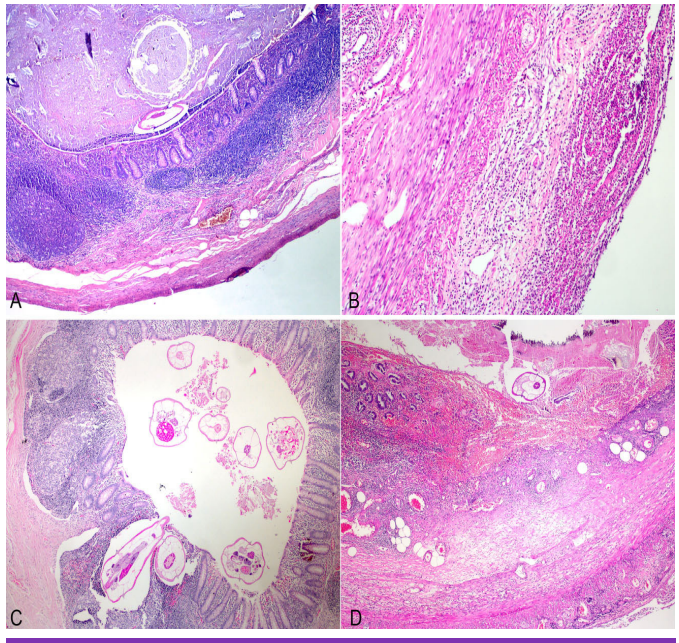

Figure 3. a. Fecalith in the lumen, hematoxylin-eosin, x100, b. Phlegmonous appendicitis and periappendicitis, hematoxylin-eosin, x200, c. Multiple pinworms in appendiceal lumen and mucosal invasion by *E. vermicularis*, hematoxylin-eosin, x40, and d. Mucosal erosion and necrosis, hematoxylin-eosin, x40

E. vermicularis was mostly seen in corpus (75%) and the number of the parasites in the lumen differed between 1 and 14, however, neither location nor number of the parasites was associated with histopathological features. Mucosal parasite invasion was observed in one case without any tissue reaction to the parasite. Although mucosal architecture was slightly distorted in 3 cases (12.5%), it was due to hemorrhage, lymphoid hyperplasia and necrosis; not the parasite itself. Sinniah et al. (5) has attempted to explain the lack of reaction to the parasite's mucosa invasion by claiming that the pinworm migrates into the mucosa after the appendix was excised to escape hypoxia. However, why this phenomenon is observed occasionally remains to be unknown.

E. vermicularis may occasionally be associated with severe inflammation, ulceration and perforation (15). Acute inflammation was found in one third (33.3%) of our cases, with phlegmonous inflammation and/or periappendicitis in 4 of them. Acute inflammation was found to be associated with the presence of hemorrhage and periappendicitis. Periappendicitis is defined as accumulation of inflammatory cells in the serosa and subserosa, usually accompanied by reactive mesothelial cells and a serosal exudate (16) and it may also be caused by other inflammatory processes in the pelvic region. However, the association between acute appendicitis and periappendicitis shows that periappendicitis was the extension of the appendiceal inflammatory reaction into peritoneal surface. Notably, the patients with periappendicitis were significantly younger.

We also counted the number of the eosinophils in the lamina propria. The number of the eosinophils/HPF was not associated with the luminal content. Although eosinophils are considered to have a major role in the defense against helminthic infections (17) and all our cases had *E. vermicularis* infection, the eosinophil count was quite variable, supporting that eosinophilic infiltration is a nonspecific finding in parasitic infections, as previously shown (15).

There was a significant association between the eosinophil count and the presence of tip involution/obliteration. The occurrence of fibrous obliteration of the appendix, a process in which neurogenic tissue is thought to be an essential part of, increases with age (18). It is considered a reactive process, either as a part of ageing or as a consequence of prior attacks of inflammation, with a final phase of fibrosis (18). Eosinophils and mast cells accompany fibroblastic and neural cells in fibrous obliteration, and we think that the increased number of eosinophils in the lamina propria in patients with tip obliteration suggests that eosinophils may play a role in this fibrosing process, considering that eosinophils have been shown to be profibrogenic in *in vitro* studies (17). Although increased numbers of eosinophils and mast cells are detected in acute appendicitis (19,20), the absence of acute inflammation in 3 of 4 patients with tip obliteration supports the possible profibrogenic effect of eosinophils in fibrous obliteration of the appendix.

The presence of lymphoid hyperplasia in all patients while acute inflammation was found in only 8 patients suggest that lymphoid hyperplasia caused the appendicitis-mimicking clinical symptoms in the majority of our cases and we think that lymphoid hyperplasia may be the most common underlying pathology in patients with negative appendectomy. Moreover, we did not find any tissue reaction to the parasite in the case with mucosal invasion of the pinworm and did not observe any significant association between the number and/or localization of the parasite and other histopathological findings, indicating that *E. vermicularis* was most likely a bystander in the appendiceal lumen in our cases. Hence, we conclude that the presence of *E. vermicularis* in appendectomy specimens appears to be incidental rather than being a cause of appendicitis. On the other hand, the presence of *E. vermicularis* probably stimulates the formation of reactive lymphoid follicles, resulting in lymphoid hyperplasia which may mimic acute appendicitis clinically.

* Ethics

Ethics Committee Approval: Study protocol was approved by Adiyaman University Faculty of Medicine Non-interventional Clinical Research Ethics Board (Approval number: 2017/7-4).

Informed Consent: Informed consent of the patients was not obtained due to the retrospective nature of the study and clinical and pathologic data of the patients were de-identified and analyzed anonymously.

Peer-review: Internally peer-reviewed.

* Author Contributions

Concept: B.P., Design: B.P., B.A.K., Data Collection or Processing: B.P., B.A.K., S.İ., S.Ö., M.A., Analysis or Interpretation: B.P., Literature Search: B.P., B.A.K., S.İ., Writing: B.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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