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Comparison of Clinical Characteristics According to the Existence of Secondary Appendicitis in Pediatric Acute Enterocolitis: A Single Center Study

So Yoon Choi [1,2]

[1]Department of Pediatrics, Kosin University College of Medicine, Kosin University Gospel Hospital, Busan, Korea
[2]Department of Pediatrics, Inje University College of Medicine, Haeundae Paik Hospital, Busan, Korea

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Correspondence to
So Yoon Choi
Kosin University College of Medicine, Kosin University Gospel Hospital, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea.
E-mail: dimplech@naver.com

ORCID iDs
So Yoon Choi
https://orcid.org/0000-0002-7389-7678

Conflict of Interest
The author have no financial conflicts of interest.

ABSTRACT

Purpose: In patients with acute enterocolitis, radiologic findings are sometimes accompanied by secondary inflammation of the appendix. The purpose of this study was to evaluate the clinical features of acute enterocolitis with secondary inflammation of the appendix.
Methods: Medical records from patients who underwent abdominal ultrasonography or computed tomography (CT) among those admitted for acute enterocolitis were retrospectively reviewed. Clinical features were compared by distinguishing patients with inflammation of the appendix from those without, based on their symptoms and laboratory findings.
Results: Of the 165 patients, 12 (7.3%) had secondary inflammation of the appendix on ultrasonography and/or CT. Patients with secondary inflammation of the appendix were significantly older than those without (11.7 vs. 6.1 years, p=0.011) and more frequently had fever (83.3% vs. 49.0%, p=0.033), and high values of C-reactive protein (CRP) (5.38 vs. 0.32 mg/dL, p<0.001). The proportion of bacterial pathogens was higher in patients with secondary inflammation of the appendix (60% vs. 15.1%, p=0.004).
Conclusion: Patients with acute enterocolitis accompanied by secondary appendicitis more commonly have fever, higher CRP levels, higher bacterial pathogen detection rates, and longer hospital stays. Treatment equivalent to that of bacterial infection is required for patients with secondary appendicitis, and that their symptoms should be closely and continuously monitored and followed-up.

Keywords: Enterocolitis; Appendicitis; Child

INTRODUCTION

Acute enterocolitis, a disease characterized by inflammation of the small and large intestines. Most cases are diagnosed through history assessment and physical examination without special testing needed. Most patients improve with symptomatic treatment, including fluid resuscitation and supplemental nutrition. However, if a patient shows severe or prolonged clinical symptoms, or the site of pain is the right lower quadrant, or if there are signs of peritoneal irritation, it is necessary to differentiate it from others conditions such as acute appendicitis, mesenteric lymphadenitis, appendiceal diverticulitis, and chronic inflammatory

bowel disease; this is usually done using radiologic testing [1-3]. Radiologic tests (abdominal computed tomography [CT] or abdominal ultrasound [US]) sometimes reveal secondary appendicitis in addition to inflammation in the small and large intestines. Secondary appendicitis refers to inflammation of the appendix resulting from lesions in colonic or periappendiceal sites. Secondary appendicitis is classified as intrinsic or extrinsic, where intrinsic appendicitis is caused by an inflammation of the cecum or large intestine connected to the appendix (e.g., ischemic colitis, infectious colitis, pseudomembranous colitis), and extrinsic appendicitis is caused by inflammation resulting from a spread of lesion in the surrounding organs, such as the gallbladder, liver, bladder, ovaries, kidney, or terminal ileum (e.g., Crohn's disease, cystitis, cholecystitis, sigmoid diverticulosis) [4,5].

Although acute enterocolitis is relatively common in children, the clinical features and prognosis of acute enterocolitis according to the presence of secondary appendicitis have rarely been reported [5,6]. Whether the two disease entities should be classified into a single category or should be considered independent categories with distinct treatment approaches remains controversial. Therefore, in the present study, we compared the clinical features and courses of acute enterocolitis according to the presence of secondary appendicitis.

MATERIALS AND METHODS

Patients and study design

Medical records of pediatric patients aged 18 years or younger who received inpatient treatment for acute enterocolitis at the Inje University Haeundae Paik Hospital between June 2017 and June 2019 were retrospectively analyzed.

Among the patients presenting with inflamed small and large intestines upon radiologic testing (abdominal US or abdominal CT), those with normal appendix were classified as the control group, and those with inflamed appendix were classified as the study group. We collected the following patient information: sex, age at diagnosis, blood tests (white blood cell, C-reactive protein [CRP], erythrocyte sedimentation rate, albumin, hemoglobin, amylase, lipase, aspartate aminotransferase, and alanine aminotransferase), stool tests (using stool polymerase chain reaction [PCR]), length of hospital stay, duration of nil per oral status, use of antibiotics, complications (e.g., acute kidney injury and hemolytic uremic syndrome), and surgery.

The sensitivity and specificity of appendicitis diagnosis were 100% and 68%, respectively, using a maximal outer diameter (MOD) cutoff of 6 mm and 94% and 88%, respectively, using a cutoff value of 7 mm [7]. The MOD of the appendix was measured in the transverse plane, where the distance from one outer wall to the opposite outer wall of 6 mm or less was considered normal, and a MOD of 7 mm or higher was considered appendicitis. When the MOD was between 6 mm and 7 mm, color Doppler imaging was performed, and appendicitis was diagnosed based on findings indicating hyperemia [8]. We also measured bowel wall thickness: a thickness of 2 mm or higher was considered thickening. Appendiceal wall thickness was defined as the distance from the inner mucosal layer to the serosal layer, where a distance of 3 mm or higher considered appendicitis [9,10].

Stool samples were tested for five viruses (group A rotavirus, enteric adenovirus, norovirus GI/GII, and astrovirus) and ten bacteria (*Salmonella* spp., *Shigella* spp., *Vibrio* spp., *Campylobacter* spp.,

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Clostridium difficile toxin B, *Clostridium perfringens*, *Yersinia enterocolitica*, *Aeromonas* spp., *Escherichia coli* O157:H7, and verocytotoxin-producing *E. coli*) using Seeplex Diarrhea ACE detection kits (Seegene, Seoul, Korea), which utilize multiplex PCR. Positive samples were analyzed.

Statistical analysis

The data were expressed as frequency with percentage for categorical variables and median with range for continuous variables. Differences in study participants' characteristics were compared across subgroups using the chi-square test or Fisher's exact test for categorical variables and the independent *t*-test or Mann-Whitney's U-test for continuous variables as appropriate. To check for normal distribution, we used the Shapiro–Wilk test. All statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 24.0 (IBM Co., Armonk, NY, USA), and *p*-values less than 0.05 were considered statistically significant.

Ethics statement

This study was approved by the Institutional Review Board of Haeundae Paik Hospital and was conducted in accordance with the Declaration of Helsinki (Approval No. 2019-10-068-001). As a retrospective medical record study, informed consent was waived from the patient.

RESULTS

Age and sex distribution

Of the 642 patients admitted to the pediatric ward at Inje University Haeundae Paik Hospital between June 2017 and June 2019 for acute enterocolitis, 165 patients underwent radiologic testing, particularly abdominal US or abdominal CT, after excluding neonates and patients with underlying diseases. One hundred twenty-six (76.4%) underwent abdominal US, and 39 (23.6%) underwent abdominal CT. Twelve of these patients (7.2%) had secondary appendicitis, with a male-to-female sex ratio of 3:1 (nine boys, three girls). Ages ranged from 6–17 years. The mean age of patients with secondary appendicitis was 141 months, which was higher than that of the non-secondary appendicitis group (p=0.011), suggesting that appendicitis was more common in older children (**Table 1**).

Presenting symptoms

The major symptoms upon hospital visit were abdominal pain and fever among patients with secondary appendicitis, while diarrhea was the most common symptom among those without secondary appendicitis (**Table 2**). The percentage of patients with fever was significantly greater among those with secondary appendicitis (p=0.033).

Table 1. Age and sex distribution

Variable	With secondary appendicitis (n=12)			Without secondary appendicitis (n=153)			*p*-value
Sex (male)	9 (75.0)			80 (52.3)			0.146*
Age (mo)	141 (82–203)			73 (1–215)			0.011†
Age (yr)	Male	Female	Total	Male	Female	Total	
<12	0 (0.0)	0 (0.0)	0 (0.0)	16 (10.5)	9 (5.9)	25 (16.3)	
13–72	0 (0.0)	0 (0.0)	0 (0.0)	27 (17.6)	24 (15.7)	51 (33.3)	
73–144	3 (25.0)	3 (25.0)	6 (50.0)	20 (13.1)	19 (12.4)	39 (25.5)	
>145	6 (50.0)	0 (0.0)	6 (50.0)	17 (11.1)	21 (13.7)	38 (24.8)	
Total	9 (75.0)	3 (25.0)	12 (100.0)	80 (52.3)	73 (47.7)	153 (100)	

Values are presented as number (%), median (range).
Shapiro–Wilk's test was employed for test of normality assumption.
*p-values were derived from the Chi-square test. †p-values were derived from the Mann–Whitney's U-test.

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Table 2. Comparison of presenting symptoms between two groups

Presenting symptoms	With secondary appendicitis (n=12)	Without secondary appendicitis (n=153)	*p*-value
Abdominal pain	10 (83.3)	90 (58.8)	0.128*
Diarrhea	8 (66.7)	109 (71.2)	0.747*
Vomiting	4 (33.3)	88 (57.5)	0.135†
Fever	10 (83.3)	75 (49.0)	0.033†
Hematochezia	1 (8.3)	18 (11.8)	1.000*

Values are presented as number (%).
*p-values were derived from the Fisher's exact test. †p-values were derived from the Chi-square test.

Table 3. Comparison of blood tests results between two groups

Blood tests	With secondary appendicitis (n=12)	Without secondary appendicitis (n=153)	*p*-value
White blood cell count (/mm^3)	10,790 (4,670–20,950)	8,750 (2,930–24,470)	0.088†
Hemoglobin (g/dL)	13.4 (11.8–15.4)	12.9 (8.2–18.6)	0.583†
Platelet (/mm^3)	240.5 (170–287)	288 (96–727)	0.002†
Erythrocyte sedimentation rate (mm/h)	35 (7–60)	14 (2–70)	0.102†
C-reactive protein (mg/dL)	5.38 (0.05–20.99)	0.32 (0.01–22.07)	0.001†
Albumin (g/dL)	4.25 (3.3–4.6)	4.4 (3.1–5.8)	0.306*
Aspartate aminotransferase (U/L)	27.5 (21–140)	32 (12–266)	0.915†
Alanine aminotransferase (U/L)	16 (12–251)	17 (6–195)	0.782†
Amylase (U/L)	54 (26–273)	49 (4–159)	0.503†
Lipase (U/L)	18 (14–53)	18 (8–110)	0.622†

Values are presented as mean (range).
Shapiro–Wilk's test was employed for test of normality assumption.
*p-values were derived from an independent t-test. †p-values were derived from the Mann–Whitney's U-test.

Blood tests

Platelet counts were significantly lower among those in the secondary appendicitis group than in those in the non-secondary appendicitis group (p=0.002) (**Table 3**). CRP levels were significantly higher among those in the secondary appendicitis group than in those in the non-secondary appendicitis group (p<0.001).

Stool multiplex PCR tests

Three cases of non-typhoidal *Salmonella*, two cases of *Campylobacter* spp., and one case of *Clostridium perfringens* were detected in stool samples from patients with secondary appendicitis (**Table 4**). The detection rate of patients positive for *Salmonella* spp. was significantly higher among patients with secondary appendicitis (p=0.005). The detection rate of bacterial pathogens such as *Salmonella* and *Campylobacter* were significantly greater among patients with secondary appendicitis. While, viral pathogens such as norovirus, rotavirus, and enteric adenovirus were detected only in patients without secondary appendicitis.

Clinical courses

Duration of hospital stay and the time of nil per oral were significantly longer in the secondary appendicitis group (6.5 vs. 4 days, p=0.002) (**Table 5**). The use of antibiotics was significantly higher in the secondary appendicitis group (91.7% vs. 11.1%, p<0.001). The numbers of total radiologic tests were also significantly higher in the secondary appendicitis group (p<0.001). One patient with secondary appendicitis showed perforation on day 2 of admission and underwent emergency appendectomy with cecectomy. All other patients recovered without complications and were discharged.

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Table 4. Comparison of Multiplex Stool PCR results between two groups

Variable	With secondary appendicitis (n=10)	Without secondary appendicitis (n=86)	*p*-value
Pathogen detected by multiplex PCR test	6/10 (60.0)	51/86 (59.3)	0.850
Viral pathogens	0/10 (0.0)	37/86 (43.0)	0.012
Rotavirus	0 (0.0)	10 (6.5)	1.000
Norovirus	0 (0.0)	12 (7.8)	0.603
Astrovirus	0 (0.0)	4 (2.6)	1.000
Enteric adenovirus	0 (0.0)	8 (5.2)	1.000
Sapovirus	0 (0.0)	3 (2.0)	1.000
Bacterial pathogens	6/10 (60.0)	14/86 (16.2)	0.004
Salmonella spp.	3 (25.0)	3 (2.0)	0.005
Shigella spp.	0 (0.0)	0 (0.0)	-
Campylobacter spp.	2 (16.7)	5 (3.3)	0.083
E. coli O157:H7	0 (0.0)	0 (0.0)	-
Clostridium difficile Toxin B	0 (0.0)	5 (3.3)	1.000
Clostridium perfringens	1 (8.3)	0 (0.0)	0.073
Yersinia enterocolitica	0 (0.0)	0 (0.0)	-
Verotoxic *E. coli*	0 (0.0)	0 (0.0)	-
Aeromonas spp.	0 (0.0)	1 (0.7)	1.000

Values are presented as number (%).
PCR: polymerase chain reaction; *E. coli: Escherichia coli*.
p-values were derived from the Fisher's exact test.

Table 5. Comparison of clinical courses between two groups

Variable	With secondary appendicitis (n=12)	Without secondary appendicitis (n=153)	*p*-value
Duration of hospital days	6.5 (4–9)	4 (1–14)	0.002†
Nil per oral period	1 (0–2)	0 (0–1)	0.002†
Use of empirical antibiotics	11/12 (91.7)	34/153 (22.2)	<0.001*
No. of total radiologic tests	2 (1–3)	1 (1–2)	<0.001†
No. of re-examination of radiologic tests	1 (0–2)	0 (0–1)	<0.001†

Values are presented as mean (range) or number (%).
Shapiro-Wilk's test was employed for test of normality assumption.
p-values were derived from Fisher's exact test. †*p*-values were derived from Mann-Whitney's U-test.

DISCUSSION

The clinical significance of appendicitis secondary to acute enterocolitis is largely unknown. This study is the first to investigate the characteristics of pediatric acute enterocolitis with secondary appendicitis compared to patients without secondary appendicitis. The findings will contribute to establishing the direction of clinical treatment.

Most primary appendicitis occurs as a result of a series of events resulting from a blockage in the lining of the appendix, which in turn cause closed loop obstructions with continued mucus secretion into the appendiceal lining, thereby distending it and continuously increasing the intraluminal pressure [11]. Continuous elevation of intraluminal pressure causes occlusion of the appendiceal veins and damages the mucosal barrier, thereby inducing bacterial entry and progressing inflammation [12]. By contrast, secondary appendicitis refers to periappendicitis or serositis caused by colonic or periappendiceal lesions spreading inflammation to periappendiceal areas, as opposed to a blockage of the appendiceal lumen, and this results from sympathetic mural edema [4]. In the present study, many cases of appendicitis secondary to acute enterocolitis were intrinsic cases caused by acute ileocecitis affecting the ileum and cecum around the appendix. Acute enterocolitis cases in which

the inflammation is confined to the ileum and cecum are called ileocecitis, and most of these cases are caused by infection in these areas by bacteria such as *Yersinia enterocolitica*, *Campylobacter jejuni*, and *Salmonella enteritidis* [13-15]. Acute enterocolitis can be diagnosed based on enlarged ileocecal area and normal appendix [16,17], and some cases may show appendiceal infection as well [18].

In the present study, US was generally the modality chosen, and abdominal CT was performed in the presence of poor acoustic windows, abdominal obesity, and difficulty of ultrasonography. Generally, secondary appendicitis is distinguished from primary appendicitis according to the patterns of cecal wall thickening. Whereas cecal wall thickening is local, asymmetrical, and irregular in primary appendicitis, it is symmetrical, and regular in secondary appendicitis [6,19]. Appendiceal distention can be observed in both cases; however, appendiceal wall thickening and periappendiceal fat deposition are characteristic findings of primary appendicitis. Color Doppler imaging shows increased blood flow in the thickened appendiceal wall in primary appendicitis, while hyperemia of terminal ileum is characteristic of secondary appendicitis [20,21]. Similarly, in this study, in all cases diagnosed as secondary appendicitis, inflammation of the small and large intestine was present, and the symmetrical and regular cecal and appendiceal wall thickening with the absence of blockage in appendiceal lumen were observed.

Most patients showed rapid improvement of symptoms only with symptomatic supportive care for acute enterocolitis. However, patients with secondary appendicitis had significantly more fever and higher CRP levels than those without. These results suggest that patients with secondary appendicitis may have more severe inflammation. Of patients with secondary appendicitis, *Salmonella* spp., *Campylobacter* spp., and *C. perfringens* were detected in the stool samples of five patients, with no viruses detected. These findings suggest that patients with secondary appendicitis may be more likely to have been infected with bacteria, and this should be noted when determining treatment approaches. Moreover, the use of antibiotics was more common among patients with secondary appendicitis. Since the clinical course of secondary appendicitis have been unknown, and secondary ileocecitis can develop along with fat inflammation even in progressed acute appendicitis, empirical antibiotics were preferentially used in patients with secondary appendicitis, in accordance with primary appendicitis.[1] In the present study, one of the patients with secondary appendicitis eventually underwent surgery. The patient had a fever and pain in right lower quadrant a day before the hospital visit. She was initially diagnosed with secondary appendicitis accompanied by ileocecitis by US. However, on the 2nd day of hospitalization, the symptoms worsened, and radiologic test was re-evaluated by CT, and intestinal perforation and peritonitis were observed, and appendectomy with cecectomy were performed. Even if appendicitis secondary to acute enterocolitis had been initially diagnosed, the possibility of ileocecitis secondary to progressed primary appendicitis cannot be excluded. In addition, even if the diagnosis is correct, it may progress severely and cause peritonitis. Therefore, it is important to continuously and closely monitor symptoms and to perform additional radiologic testing as necessary, abdominal CT should be performed in cases in which US findings are unclear.

This study has a few limitations. First, the small sample size limits the generalizability of the clinical presentations. Second, bacterial and viral detection rates using stool PCR were low, at 59.4%. Subsequent studies are required to examine larger sample sizes and to strive to enhance bacterial identification and virus detection using various media in order to illuminate the etiology and clinical course of this disease.

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In conclusion, we found that patients with acute enterocolitis accompanied by secondary appendicitis more commonly had a fever, higher CRP levels, higher bacterial pathogen detection rates, and longer hospital stays. These findings suggest that treatment equivalent to that of bacterial infection is required for patients with secondary appendicitis, and that their symptoms should be closely and continuously monitored and followed-up.

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