



A Novel Chronic Enteropathy Associated with *SLCO2A1* Gene Mutation: Enterography Findings in a Multicenter Korean Registry

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Objective: Chronic enteropathy associated with *SLCO2A1* gene (CEAS) is a recently recognized disease. We aimed to evaluate the enterographic findings of CEAS.

Materials and Methods: Altogether, 14 patients with CEAS were confirmed based on known *SLCO2A1* mutations. They were registered in a multicenter Korean registry between July 2018 and July 2021. Nine of the patients (37.2 ± 13 years; all female) who underwent surgery-naïve-state computed tomography enterography (CTE) or magnetic resonance enterography (MRE) were identified. Two experienced radiologists reviewed 25 and 2 sets of CTE and MRE examinations, respectively, regarding the small bowel findings.

Results: In initial evaluation, eight patients showed a total of 37 areas with mural abnormalities in the ileum on CTE, including 1–4 segments in six and > 10 segments in two patients. One patient showed unremarkable CTE. The involved segments were 10–85 mm (median, 20 mm) in length, 3–14 mm (median, 7 mm) in mural thickness, circumferential in 86.5% (32/37), and showed stratified enhancement in the enteric and portal phases in 91.9% (34/37) and 81.8% (9/11), respectively. Perienteric infiltration and prominent vasa recta were noted in 2.7% (1/37) and 13.5% (5/37), respectively. Bowel strictures were identified in six patients (66.7%), with a maximum upstream diameter of 31–48 mm. Two patients underwent surgery for strictures immediately after the initial enterography. Follow-up CTE and MRE in the remaining patients showed minimal-to-mild changes in the extent and thickness of the mural involvement for 17–138 months (median, 47.5 months) after initial enterography. Two patients required surgery for bowel stricture at 19 and 38 months of follow-up, respectively.

Conclusion: CEAS of the small bowel typically manifested on enterography in varying numbers and lengths of abnormal ileal segments that showed circumferential mural thickening with layered enhancement without perienteric abnormalities. The lesions caused bowel strictures that required surgery in some patients.

Keywords: Chronic enteropathy associated with *SLCO2A1* gene; Inflammatory bowel disease; Crohn's disease; Radiology; Enterography; Chronic intestinal ulcer

INTRODUCTION

Chronic enteropathy associated with *SLCO2A1* gene (CEAS) is a recently recognized, rare, chronic enteropathy

characterized by multiple ulcerations and strictures in the small bowel. It is caused by loss-of-function mutations in the *SLCO2A1* gene [1-5]. Since the first report from Japan in 2015 [1], only a few dozen cases have been reported

Received: September 12, 2022 **Revised:** January 19, 2023 **Accepted:** January 19, 2023

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worldwide. These cases were mostly from northeast Asia [2-7]. CEAS usually affects adolescents or middle-aged females and presents with abdominal pain associated with anemia and hypoalbuminemia [2-5]. It predominantly involves the small bowel and often excludes the colorectal region [3,5,7]. Studies on CEAS have focused on describing its clinical characteristics, including laboratory findings, genetic findings, and relationships with other diseases [2-5], with no published studies on the radiological findings/diagnosis of the disease. CEAS is frequently misdiagnosed as Crohn's disease because of overlaps in clinical manifestations and unfamiliarity with CEAS owing to its novelty and rarity [1,3]. However, since it is intractable to medications for Crohn's disease, recognizing the possibility of CEAS and recommending early diagnostic genetic testing are critical to avoid unmatched treatments [2,4,8].

Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are the primary radiological modalities used to evaluate patients with suspected chronic inflammatory conditions in the bowel [9,10]. The role of CTE and MRE is even more important in patients with suspected small-bowel strictures, as small-bowel endoscopy is difficult to perform in such patients. Considering the disease characteristics of CEAS (i.e., a novel, rare, chronic inflammatory condition associated with strictures that predominantly involve the small bowel) and the role of radiological enterography in evaluating the small bowel, studying enterographic findings of CEAS becomes clinically and timely relevant. Knowledge of the enterographic findings of CEAS may help avoid delayed or incorrect diagnosis by suggesting the possibility of CEAS and the need for genetic testing to confirm CEAS. To the best of our knowledge, no study has investigated the enterographic findings of CEAS. Therefore, we aim to evaluate the enterographic findings of CEAS of the small bowel in a small cohort of patients from a multicenter Korean registry.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board of Asan Medical Center (2022-0802). The requirement for informed patient consent was waived.

Study Patients

Between July 2018 and July 2021, 14 confirmed patients with CEAS based on known *SLCO2A1* mutations through genetic testing were registered in a multicenter Korean

registry [4]. The 14 CEAS patients were identified through genetic testing of 46 patients with unexplained chronic multiple ulcerations in the small bowel, as per previous reports [4]. Of them, five patients without available enterography images obtained before abdominal surgery were excluded (Supplementary Table 1). Nine patients (mean age \pm standard deviation, 37.2 ± 13 years; all female) were included in the image analysis of this study. Only surgery-naïve-state images were analyzed to exclude any effects of surgery on the bowel findings.

Demographic and clinical data of the patients, including age, sex, initial clinical impression, entire disease distribution, patient course after diagnosis, bowel surgery records, and pathological results, were collected separately from the image analysis.

CTE and MRE Acquisition

Nine patients were recruited from a single institution. Therefore, the enterography method was homogeneous. Both CTE and MRE were performed after oral administration of 1200 mL of polyethylene glycol. For CTE, enteric-phase images with or without portal-phase images were obtained after intravenous injection of contrast media (100–150 mL of 320 mg/mL) at a rate of 3 mL/s using 32- to 128-detector row scanners (SOMATOM Series; Siemens). The scan parameters were as follows: beam pitch, 1; gantry rotation time, 0.5 seconds; field of view to fit; 100 or 120 kVp; and automated tube current modulation (CARE Dose 4D; Siemens) with quality reference mAs set at 200. Both axial and coronal images were obtained with 3-mm thickness at 3-mm intervals.

MRE was performed using a 3-T imager (Ingenia; Philips Healthcare). The imaging protocol included coronal T2-weighted half-Fourier sequences with and without fat suppression; axial T2-weighted half-Fourier sequence with fat suppression; coronal free-breathing diffusion-weighted imaging (DWI) with *b* factors of 0 and 900 s/mm² and apparent diffusion coefficient (ADC) map; coronal dynamic T1-weighted spoiled gradient-echo sequences with fat suppression (precontrast and enteric and portal phases after intravenous administration of 0.2 mL/kg of gadoterate meglumine at a rate of 2 mL/s); and axial delayed contrast-enhanced T1-weighted spoiled gradient-echo sequence with fat suppression. Further details can be found in previous studies [11,12].

CTE and MRE Analysis

In total, 25 sets of CTE (9 initial and 16 follow-

up) examinations and two sets of MRE as follow-up examinations, all of which were obtained in a surgery-naïve state, were analyzed. Two board-certified gastrointestinal radiologists (with > 10 and 5 years of experience in CTE and MRE of inflammatory bowel diseases, respectively) reviewed the images in consensus. We used consensus reading, given the study's purpose of describing the imaging findings as precisely as possible, instead of reporting the reader performance. Images were first reviewed after blinding all information except for the diagnosis of CEAS and reexamined later with the knowledge of endoscopic results.

For the initial enterography, we assessed various findings in the small bowel, perienteric area, and mesentery (Table 1). For a patient with > 10 abnormal small bowel areas (i.e., an "area" indicates a contiguous bowel segment with mural abnormalities without an intervening normal wall) identified on CTE/MRE, the 10 areas with the most prominent abnormalities were analyzed. Regarding the location, the proximal 2/5 and distal 3/5 of the small bowel, except the duodenum, were considered as the jejunum and ileum, respectively. Although CEAS is a different disease, we followed the recent consensus for enterography interpretation of small bowel Crohn's disease [10,13] for itemizing and categorizing the enterography findings to enable a comparison of our study results with those in the literature about other chronic inflammatory bowel diseases such as Crohn's disease. The length of each bowel involvement was rounded to the nearest 5 mm, considering the inevitable errors in measuring nonstraight structures. The mural thickness was measured at the thickest location in each abnormal bowel segment and rounded off to the closest millimeter. The maximum small bowel diameter and the presence or absence of small bowel stricture in each patient were recorded. The maximum small bowel diameter indicates the largest bowel diameter of the entire small bowel, and small bowel stricture was defined as a diameter \geq 3 cm in the bowel upstream of narrowing. However, we avoided counting the strictures because a bowel stricture precludes precise evaluation of downstream bowel strictures if present. All follow-up surgery-naïve enterography images were reviewed in the same manner, and changes compared to the initial enterography were recorded.

Additional MRE-specific findings, including the signal intensities of the involved bowel segment on T2-weighted images and DWI/ADC, were also evaluated. Restricted diffusion was defined as high signal intensity on high *b*-value DWI images ($b = 900$ s/mm²) with a low value on the

corresponding ADC maps [11,12].

RESULTS

Findings of CEAS at Initial Surgery-Naïve Enterography

All nine patients underwent CTE as the initial enterography. The CTE was unremarkable in one patient. The CTE data revealed 37 small bowel areas with mural abnormalities in the ileum in eight other patients at the blinded reading, including 1–4 segments in six patients and > 10 segments in two patients (Table 1). After re-examining the images with the knowledge of endoscopic results, we identified an additional area of involvement in the duodenum in one patient. This duodenal lesion showed a similar but less prominent appearance compared with the ileal lesions (Table 1).

The per-lesion and per-patient details of enterographic abnormalities are provided in Table 1. The ileal lesions were 10–85 mm (median, 20 mm) in length, 3–14 mm (median, 7 mm) in mural thickness, predominantly circumferential (86.5%, 32/37), and mostly showed stratified enhancement with a hyperenhancing inner layer and less-enhancing outer layer both in enteric (91.9%, 34/37) and portal (81.8%, 9/11) phases. Perienteric infiltration and prominent vasa recta were not observed in most lesions. Small bowel strictures were identified in six patients (66.7%, 6/9), with a maximum upstream bowel diameter of 31–48 mm. None of the patients had penetrating complications, mesenteric venous thromboocclusion, or necrotic lymphadenopathy. The exemplary cases are shown in Figures 1 and 2.

Follow-Up

Two patients underwent surgery for bowel strictures immediately after initial enterography (patients 2 and 5). One patient with an unremarkable CTE did not undergo enterographic follow-up. Therefore, the remaining six patients underwent surgery-naïve-state follow-up enterography examinations, including a total of 16 CTE and two MRE examinations obtained during 17–138 months (median, 47.5 months) after the initial enterography. Of the six patients, four (66.7%) showed a slight increase in the thickness of the involved bowel walls from 3–14 mm (median, 7 mm) to 5–14 mm (median, 8 mm), 17–130 months later (Fig. 1). One patient (16.7%) had new bowel involvement while the initial bowel involvement remained stable, 138 months later. Another patient (16.7%) showed a slight improvement in the mural thickness at the initial involvement, 18 months later. Two of the six

Table 1. Characteristics of Study Patients and Their Enterography Findings in the Small Bowel

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
<i>Demographic and clinical findings</i>									
Age at diagnosis, yr	39	45	48	44	19	21	52	51	16
Sex	F	F	F	F	F	F	F	F	F
Initial clinical impression	CD	CD	CD	CD	CD	CD	CD	Tuberculosis	CD
Entire disease distribution	Jejunum, ileum	Ileum	Stomach, duodenum, ileum, colon	Stomach, duodenum, ileum	Ileum	Ileum	Ileum	Jejunum, ileum	Ileum
<i>Initial surgery-naïve enterography findings</i>									
Imaging modality	CTE	CTE	CTE	CTE	CTE	CTE	CTE	CTE	CTE
Blinded reading—per-lesion findings*									
Number of abnormal segments	> 10	3	1	4	> 10	4	3	2	0
Location	Ileum	Ileum	Ileum	Ileum	Ileum	Ileum	Ileum	Ileum	Ileum
Length ¹ , mm	17.5 (10–30)	35 (25–60)	85	22.5 (10–40)	17.5 (10–50)	25 (15–35)	45 (20–85)	27.5 (25–30)	
Mural thickness ¹ , mm	7.5 (3–11)	11 (8–12)	11	6 (5–6)	6.5 (3–9)	6 (4–14)	8 (7–8)	13.5 (13–14)	
Mural thickness category (3–5 mm, > 5–9 mm, ≥ 10 mm)	3, 5, 2	0, 1, 2	0, 0, 1	1, 3, 0	3, 7, 0	2, 1, 1	0, 3, 0	0, 0, 2	
Involvement (CIRC:non-CIRC)	9:1	2:1	1:0	4:0	9:1	2:2	3:0	2:0	
Enhancement (stratified:homogeneous)									
In enteric phase	9:1	3:0	1:0	4:0	9:1	3:1	3:0	2:0	
In portal phase	N/A	3:0	1:0	N/A	N/A	2:2	3:0	N/A	
Perienteric infiltration (present:absent)	0:10	1:2	0:1	0:4	0:10	0:4	0:3	0:2	
Prominent vasa recta (present:absent)	0:10	2:1	1:0	0:4	0:10	0:4	1:2	1:1	
<i>Blinded reading—per-patient findings</i>									
Maximum small bowel diameter, mm	48	36	31	29	35	31	21	34	20
Small bowel stricture (diameter ≥ 3 cm)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Penetrating complications	No	No	No	No	No	No	No	No	No
Venous thrombo-occlusion	No	No	No	No	No	No	No	No	No
Necrotic mesenteric lymphadenopathy	No	No	No	No	No	No	No	No	No
Reexamination with the knowledge of endoscopic results	No additional visible involvement	No additional visible involvement	A duodenal involvement	No additional visible involvement	No additional visible involvement	No additional visible involvement	No additional visible involvement	No additional visible involvement	No additional visible involvement
<i>Follow-up surgery-naïve enterography findings</i>									
Number of follow-up enterography	2	0	5	2	0	1	6	2	0
Imaging modality	CTE	CTE	CTE	CTE	MRE	CTE and MRE	CTE	CTE	
Time from the initial to the last follow-up enterography, month	38	138	138	57	17	130	18	18	
Finding at the last follow-up enterography									
Number of abnormal segments	> 10 (unchanged)	6 (increased)	4 (unchanged)	4 (unchanged)	4 (unchanged)	3 (unchanged)	2 (unchanged)	2 (unchanged)	
Mural thickness ¹ , mm	9.5 (5–11)	8 (6–11)	8 (5–8)	6.5 (6–14)	8 (7–12)	8 (8–8)	8 (8–8)	8 (8–8)	
Maximum small bowel diameter, mm	48	35	26	31	28	28	38	38	

*In cases of > 10 abnormal small bowel areas, the 10 areas with the most prominent abnormalities were analyzed and included in the results. ¹Data are presented as medians and ranges in parentheses. CD = Crohn's disease, CIRC = circumferential, CTE = computed tomography enterography, MRE = magnetic resonance enterography, N/A = not available, F = female

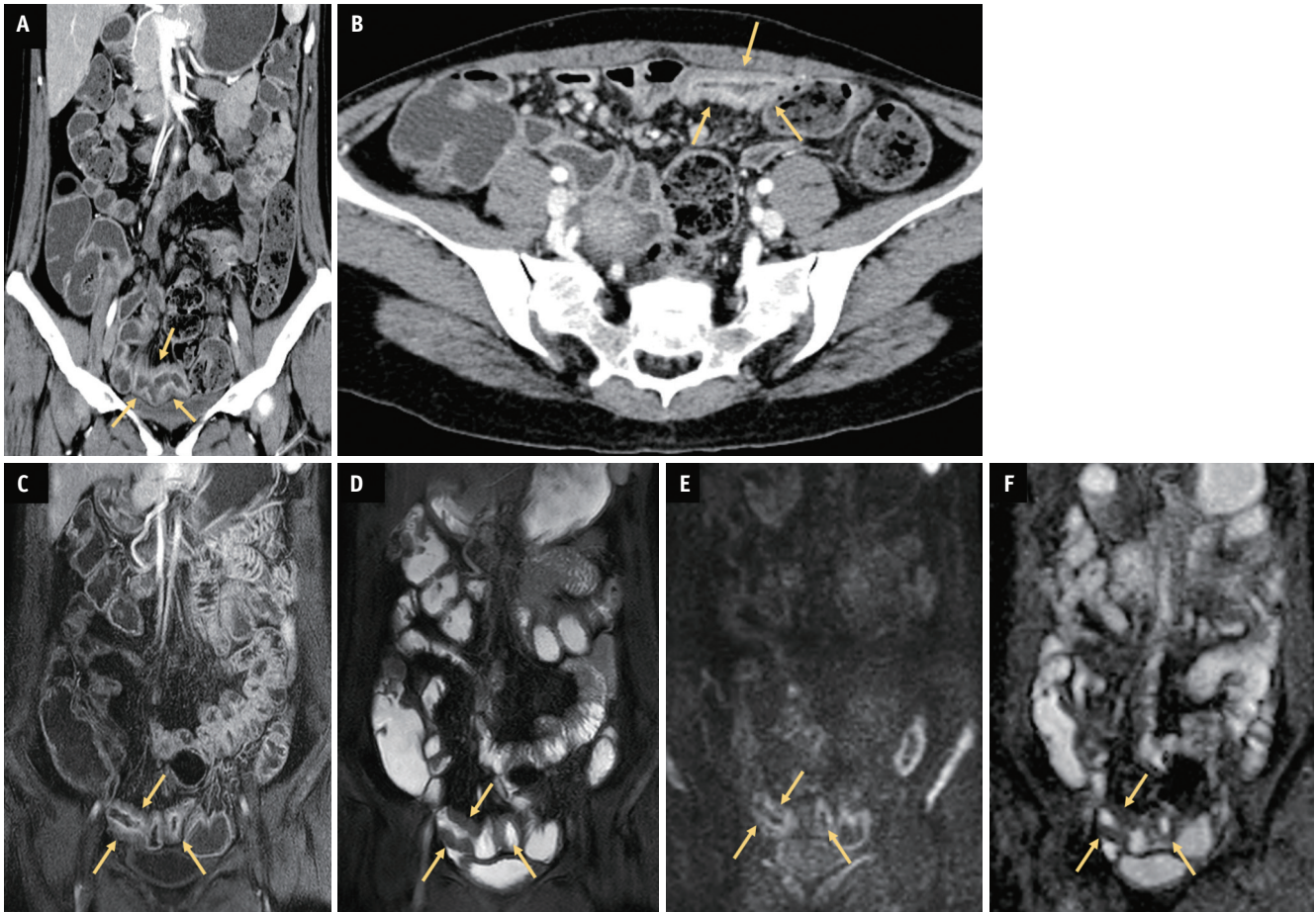


Fig. 1. A 52-year-old (at initial diagnosis) female with chronic enteropathy associated with *SLC02A1* gene (CEAS) who was initially evaluated with computed tomography enterography (CTE) and then followed with magnetic resonance enterography (MRE). CTE images (**A**, enteric phase; **B**, portal phase) show an ileal segment involved with CEAS (arrows) which demonstrates circumferential wall thickening with stratified enhancement in the distal ileum. On a follow-up MRE (**C**, enteric-phase contrast-enhanced T1; **D**, fat-saturated T2; **E**, diffusion-weighted imaging; **F**, apparent diffusion coefficient map) at 130 months from the CTE, the lesion (arrows) shows similar findings, except for a slight increase in mural thickness. The involved bowel wall shows a slightly increased signal on T2 and mild restricted diffusion.

patients (patients 1 and 8) required bowel surgery due to strictures, 19 and 38 months after the initial enterography, respectively.

Two patients underwent a surgery-naïve-state MRE. Five abnormal small bowel segments were identified in the two patients. All bowel lesions showed slightly increased mural signal on the T2-weighted sequence, stratified enhancement with a hyperenhancing inner layer in both the enteric and portal phases, and mild restricted diffusion (Fig. 1).

Pathological Findings

Pathological examination of the four patients undergoing surgery revealed segmental strictures with ulcers. There were intervening normal-looking skipped areas. Stricture bands were arranged in circumferential and diagonal directions. Fistula, inter-loop adhesion, and fat creeping were not

observed. Microscopically, the ulcers were characterized by two patterns: 1) active ulcers with trapezoid submucosal fibrosis and mild chronic transmural inflammation that was confined to adjacent short bowel segments and 2) inactive ulcer scar with luminal web-like elevated submucosal fibrosis (Fig. 2).

DISCUSSION

As observed, CEAS of the small bowel typically manifested on enterography with varying numbers (1 to > 10) of 10–85-mm-long abnormal segments in the ileum. Generally, there was circumferential mural thickening with layered enhancement that was unaccompanied by perienteric abnormalities. They also caused bowel strictures, necessitating surgery either initially or later during follow-

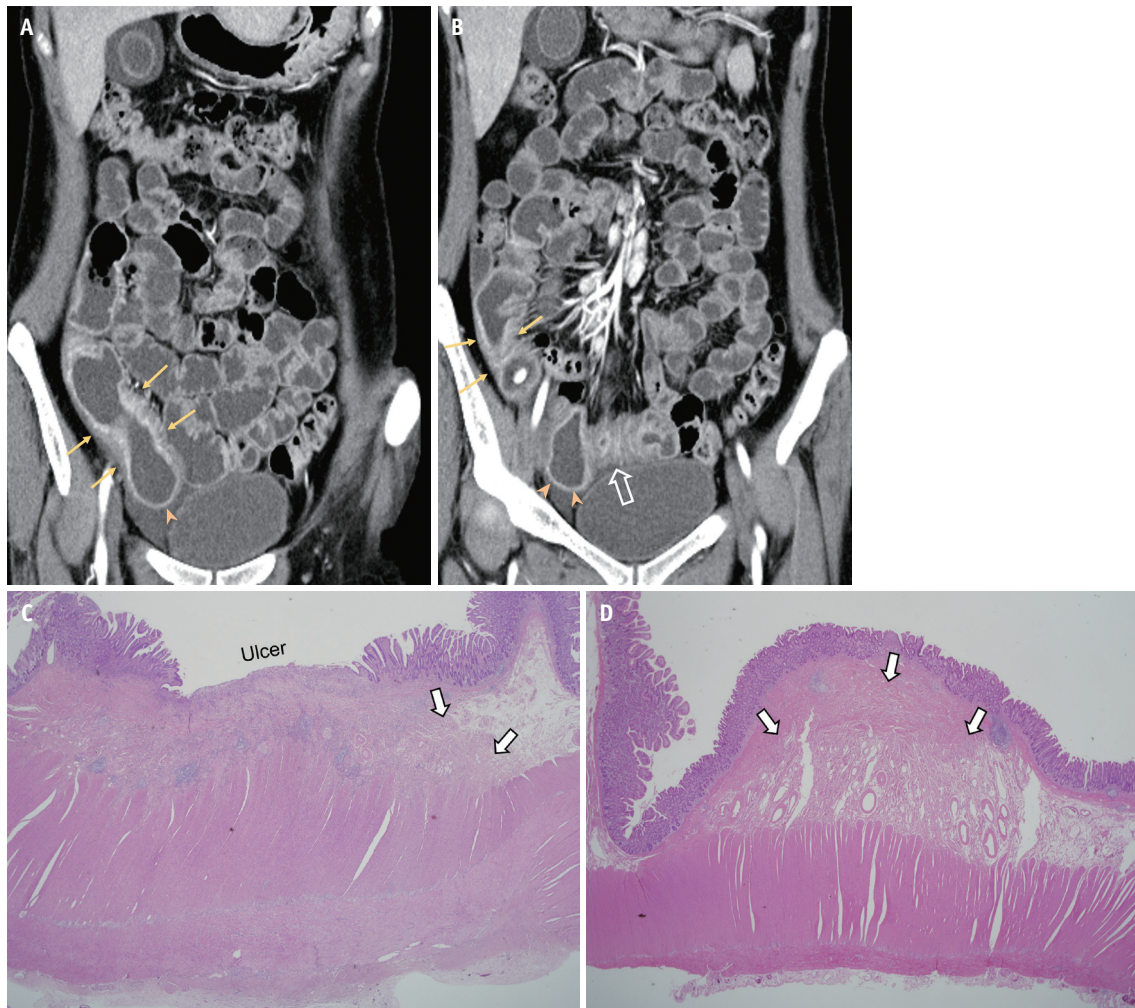


Fig. 2. A 45-year-old (at initial diagnosis) female who underwent surgery for ileal stricture caused by chronic enteropathy associated with *SLC02A1* gene (CEAS). **A, B:** Computed tomography enterography (CTE) images in the enteric phase obtained at initial presentation (**A and B**) show ileal segments involved with CEAS (arrows), manifesting mostly as circumferential wall thickening with stratified enhancement. Stricture in the distal ileal segment (open arrow) caused dilatation of the upstream small bowel (arrowheads). The patient underwent surgery without delay after CTE due to the stricture. **C, D:** Microscopic examination of the surgical specimen reveals an active ulcer with trapezoid or radiating submucosal fibrosis (arrows in **C**) and mild chronic transmural inflammation and a healed ulcer (inactive ulcer scar) showing luminal web-like protruding submucosal fibrosis (arrows in **D**) (hematoxylin and eosin staining, x 12.5).

up in some patients.

The ileum was the most common location of CEAS involvement in our study and previous reports [1-4]. The colon was mostly spared in previous studies [3,5,7], although atypical colonic involvement has also been reported [4]. The anatomical distribution may render radiological enterography more important for diagnosing CEAS as the small bowel is difficult to evaluate with endoscopy [14].

As per our study, the enterography findings of CEAS would help raise a suspicion of CEAS and recommend diagnostic genetic testing, as they differ to a certain extent from the findings of other chronic inflammatory conditions of the bowel

in full-blown states. However, otherwise, the enterography findings of CEAS may overlap with those of multiple other chronic inflammatory conditions of the bowel. Therefore, the diagnosis should not be established until genetic testing is conducted.

Crohn's disease is the most relevant differential diagnosis. Nonetheless, "classic" manifestations of Crohn's disease often show asymmetric mural abnormalities with mesenteric dominance, mesenteric shortening with pseudosacculations, penetrating complications, and associated mesenteric findings [13]. These are different from the findings of CEAS. The different imaging features may be attributed to the relatively superficial nature of ulcerations confined to the

mucosa and submucosa in CEAS [2].

Nonsteroidal anti-inflammatory drug (NSAID) enteropathy is another disease associated with shallow ulcerations and strictures in the small bowel, which characteristically involves short segments of the small bowel circumferentially. NSAID enteropathy may differ from CEAS because it affects very short segments of the small bowel and shows minimal hyperenhancement of the involved bowel walls [15].

Ischemic strictures may show features similar to those of CEAS. In a typical case, an ischemic stricture presents as a single long-segmental stricture with concentric wall thickening involving the ileum or watershed zones of the colon [16]. Clinical information, including old age, history of bowel ischemia, and risk factors such as hypertension, diabetes, and cardiac disease, is important for the diagnosis of ischemic stricture.

Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) has imaging and clinical characteristics similar to those of CEAS, except for the female predominance of CEAS [17-19]. Jejunal predominance of CMUSE involvement has been reported in several studies, although recent studies have also reported ileal predominance [18-21]. It seems plausible that inadvertent inclusion of CEAS cases in some of the "CMUSE" studies, as the studies lacked genetic testing for CEAS, may have confounded the lesion locations. In future studies, it would be necessary to determine the similarities and differences between CEAS and CMUSE in terms of imaging and clinical features, as well as the exact relationship between the two entities.

Intestinal tuberculosis may present with concentric wall thickening of the small bowel associated with a stricture. Fixed patulous ileocecal valve and a contracted cecum, necrotic lymphadenopathy, and findings of peritonitis (ascites and infiltration) or pulmonary tuberculosis, when present, can distinguish tuberculosis from CEAS [22].

This study has limitations due to the small study cohort and the lack of enterography in some patients. Nevertheless, the small sample size was due to the novelty and rarity of this disease. With the increasing awareness and knowledge of CEAS, we anticipate a larger registry of patients in the future. This would allow a more in-depth investigation of the disease characteristics, including radiological features.

In conclusion, CEAS of the small bowel typically manifested on enterography in varying numbers and lengths of ileal segments that showed circumferential mural thickening with layered enhancement without perienteric abnormalities. These bowel lesions showed minimal to mild

changes during the imaging follow-up period of 17–138 months. They caused bowel strictures requiring surgery in some patients.

Supplement

The Supplement is available with this article at <https://doi.org/10.3348/kjr.2022.0684>.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article and its supplementary information file.

Conflicts of Interest

Seong Ho Park an Editor-in-Chief of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: all authors. Data curation: Boryeong Jeong. Formal analysis: Boryeong Jeong, Seong Ho Park, Jihun Kim. Investigation: all authors. Methodology: all authors. Project administration: Seong Ho Park. Supervision: Seong Ho Park, Byong Duk Ye. Writing—original draft: Boryeong Jeong. Writing—review & editing: Seong Ho Park, Byong Duk Ye, Jihun Kim, Suk-Kyun Yang.

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Funding Statement

None

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