

World Journal of *Gastroenterology*

World J Gastroenterol 2018 July 28; 24(28): 3055-3200



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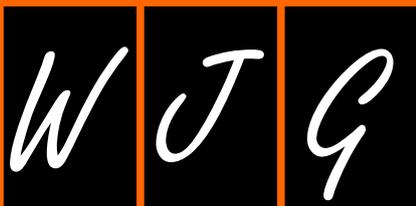
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World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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Pleasanton, CA 94588, USA
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PUBLICATION DATE
July 28, 2018

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Genetic analysis is helpful for the diagnosis of small bowel ulceration

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Supported by the Practical Research Project for Rare/Intractable Diseases from Japan Agency for Medical Research and Development (AMED), No. 15ek0109053h0002; and the Japan Society for the Promotion of Science (JSPS) KAKENHI, No. 25460953.

Conflict-of-interest statement: None declared.

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Manuscript source: Unsolicited manuscript

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Received: May 17, 2018

Peer-review started: May 18, 2018

First decision: June 4, 2018

Revised: June 7, 2018

Accepted: June 22, 2018

Article in press: June 22, 2018

Published online: July 28, 2018

Abstract

The widespread use of capsule endoscopy and balloon-assisted endoscopy has provided easy access for detailed mucosal assessment of the small intestine. However, the diagnosis of rare small bowel diseases, such as cryptogenic multifocal ulcerous stenosing enteritis (CMUSE), remains difficult because clinical and morphological features of these diseases are obscure even for gastroenterologists. In an issue of this journal in 2017, Hwang *et al* reviewed and summarized clinical and radiographic features of 20 patients with an established diagnosis of CMUSE. Recently, recessive mutations in the *PLA2G4A* and *SLCO2A1* genes have been shown to cause small intestinal diseases. The small bowel ulcers in each disease mimic those in the other and furthermore those found in nonsteroidal anti-inflammatory drug-induced enteropathy. These recent and novel findings suggest that a clinical diagnosis exclusively based on the characteristics of small bowel lesions is possibly imprecise. Genetic analyses seem to be inevitable for the diagnosis of rare small bowel disorders such as CMUSE.

Key words: Cryptogenic multifocal ulcerous stenosing enteritis; Chronic nonspecific multiple ulcers of the small intestine; Chronic enteropathy associated with *SLCO2A1* gene; Crohn's disease

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Core tip: The purpose of this letter to the editor is to

comment on the differential diagnosis of small intestinal ulcers. Mutations in *PLA2G4A* and *SLCO2A1*, encoding proteins involved in the production and degradation of prostaglandins, cause rare gastrointestinal diseases with multiple small intestinal ulcers. In addition to conventional gastrointestinal examinations, genetic analyses are helpful in distinguishing these diseases.

Umeno J, Matsumoto T, Hirano A, Fuyuno Y, Esaki M. Genetic analysis is helpful for the diagnosis of small bowel ulceration. *World J Gastroenterol* 2018; 24(28): 3198-3200 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i28/3198.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i28.3198>

TO THE EDITOR

We read with interest the article titled "Cryptogenic multifocal ulcerous stenosing enteritis: Radiologic features and clinical behavior" by Hwang *et al.*^[1]. This group reviewed the medical records of 36 patients suspected of having cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) from seven hospitals in South Korea and finally diagnosed 20 patients as CMUSE. They performed a detailed investigation of clinical and radiographic features of the patients and claimed that radiologic features of CMUSE are multiple short strictures and/or shallow ulcers of the small intestine without significant bowel obstruction. They also stated that these radiologic features might be helpful in differentiating CMUSE from other inflammatory bowel diseases, especially Crohn's disease (CD).

Hwang *et al.*^[1] diagnosed CMUSE based on the published criteria^[2,3]: (1) Unexplained small bowel strictures; (2) superficial ulcer in the mucosa and submucosa; (3) chronic or relapsing ulcerative stenosis and abdominal pain; (4) no signs of systemic inflammation; and (5) persistent and occult blood loss from the gastrointestinal tract except during bowel rest or the postoperative period. We agree with the diagnosis of the patients as non-CD, but we have a major concern about the diagnosis of CMUSE. First, they did not mention the history of nonsteroidal anti-inflammatory drug (NSAID) use, and the possibility of NSAID-induced enteropathy could not be excluded. Second, they did not distinguish CMUSE from chronic nonspecific multiple ulcers of the small intestine (CNSU). Recently, CMUSE has been found to be an autosomal recessive inherited disease caused by mutations in the *PLA2G4A* gene^[4,5]. Because the *PLA2G4A* gene encodes cytoplasmic phospholipase A2- α (cPLA2 α), which catalyzes the release of arachidonic acid from membrane phospholipids, CMUSE patients exhibit reduced production of prostaglandins and thromboxane A2, resulting in multiple ulcers of the small intestine and platelet dysfunction. We also identified that loss-of-function mutations in the *SLCO2A1* gene encoding a prostaglandin transporter cause CNSU and established a new disease entity as "chronic enteropathy associated

with *SLCO2A1* gene" (CEAS)^[6]. Thus, additional genetic analysis is helpful in diagnosing CMUSE and CEAS. Given that the endoscopic and radiographic features of CMUSE, CEAS, and NSAID-induced enteropathy are quite similar^[7], updated information on genetic tests and history of NSAID use is necessary to confirm the diagnosis. An accurate diagnosis also aids in further understanding the patient's clinical and radiographic features.

We have reported a nationwide survey with genetic analysis in Japanese patients with CEAS^[8]. We believe that the prevalence rate of CEAS is increased compared with CMUSE because some pathogenic mutations of the *SLCO2A1* gene are observed in the general population according to the dbSNP database^[9] (e.g., the mutation allele frequency of rs765249238, c.940+1G>A is 0.00003295). By contrast, identified mutations of the *PLA2G4A* gene such as rs121434634 and rs121434635 are not observed in the general population. Therefore, it is possible that some patients in the study by Hwang *et al.*^[1] harbor recessive *SLCO2A1* gene mutations. The *SLCO2A1* gene encodes a prostaglandin transporter that mediates the uptake and clearance of prostaglandins. The *SLCO2A1* gene is also known as a cause of primary hypertrophic osteoarthropathy (PHO), which affects the skin and bones, presenting as digital clubbing, periostosis, acroosteolysis, painful joint enlargement, and thickened skin^[10]. We previously reported that 30% of CEAS patients have at least one clinical feature of PHO as an extra-intestinal manifestation^[8]. Data regarding the prevalence of these extra-intestinal manifestations among the patients are of particular interest. We are also eager to obtain this information for the patients in the study by Hwang *et al.*^[1].

In conclusion, additional genetic analysis should be helpful for the differential diagnosis of CMUSE and CEAS.

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P- Reviewer: Akarsu M, Chen CH, huang LY, Langner C, Ogata Y, Yamamoto S

S- Editor: Gong ZM **L- Editor:** A **E- Editor:** Yin SY





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ISSN 1007-9327

