Detection of multiple intramucosal signet-ring cell carcinomas by white-light endoscopy and magnifying endoscopy with narrow-band imaging in a hereditary diffuse gastric cancer patient with a \textit{CDH1} germline mutation

Ken Namikawa, MD,1 Hiroshi Kawachi, MD, PhD,2 Yuta Tsugeno, MD,2 Takeshi Nakajima, MD, PhD,3 Junko Fujisaki, MD, PhD1

Hereditary diffuse gastric cancer (HDGC) is an autosomal-dominant syndrome, accounting for approximately 1% of gastric cancers. The germline pathogenic variant of \textit{CDH1}, encoding for the tumor-suppressor protein E-cadherin, is implicated in the genetic pathogenesis of HDGC.1,2 Patients with a pathogenic variant of \textit{CDH1} are recommended to undergo a prophylactic gastrectomy owing to a high cumulative risk of diffuse-type gastric cancer over the age of 80 years: 70% for men and 56% for women.3,4 Thus, it is important to identify this hereditary cancer syndrome to provide an appropriate treatment.

For some patients with the pathogenic variant of that gene who decline to undergo prophylactic gastrectomy, histologic assessment of the presence of microscopic foci of intramucosal signet-ring cell carcinoma (SRCC) and its precursor lesions (which are characteristic of early HDGC)5,6 could be a helpful factor during the decision-making process. Owing to the difficulty of detecting the tiny SRCC foci endoscopically, collecting at least 30 random endoscopic biopsy specimens is recommended in the Cambridge protocol.7 In contrast, some studies have reported that targeted biopsies or a combination of targeted and random biopsies might increase diagnostic accuracy.8,9 However, the usefulness of that approach is controversial.10 To improve the diagnostic performance for early HDGC
lesions, it is essential to describe the characteristic endoscopic features of those tumors.

In this video report, we detected multiple SRCC foci in preoperative EGD for endoscopic submucosal dissection, which led to the successful diagnosis of HDGC with a CDH1 mutation. We introduce a video (Video 1, available online at www.giejournal.org) showing multiple lesions of early HDGC in white-light imaging, narrow-band imaging (NBI), and magnifying endoscopy with NBI.

ETHICS

This study was conducted according to the Helsinki Declaration of the World Medical Association and was approved by the Institutional Review Board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (approval number 2020–1158).

CASE REPORT

A 34-year-old man with a family history of gastric cancer underwent EGD in another hospital to assess the cause of discomfort in his throat. There, he was histologically diagnosed with an early diffuse-type gastric cancer (DGC). He was referred to our institution for further investigation by EGD. He was intended to undergo endoscopic submucosal dissection for DGC, which was suspected to be a sporadic cancer. He had no history of Helicobacter pylori infection or eradication therapy.

EGD in our institution revealed 6 more pale lesions under white-light imaging with slightly irregular microvessels and/or microsurface structures under magnifying endoscopy with NBI, suggesting cancerous lesions (Figs. 1 to 4; Video 1, available online at www.VideoGIE.org). We conducted a targeted biopsy for 4 highly suspicious lesions, and SRCC foci were detected histologically in 2 of 4 lesions (Figs. 3 to 5). Considering the clinical and endoscopic findings, genetic counseling and germline CDH1 genetic testing were performed for this patient, which revealed the presence of the CDH1 pathogenic variant (c.603del, p.Val202Leufs*13).

The patient underwent total gastrectomy with lymph node dissection. Histopathologic analysis of the entire resected specimen, which had been cut into 400 blocks,

Figure 3. A, White-light imaging revealed a flat and slightly pale lesion at the greater curvature of the gastric antrum, located distal side of the main lesion (Fig. 1). B, The pale mucosa was visualized more clearly as a whitish lesion under narrow-band imaging.

Figure 4. Magnifying endoscopy with narrow-band imaging of the area in the yellow square frame in Figure 3A and B (marginal area of distal side of the lesion) revealed unclear surface structures and irregular microvessels (arrow).
revealed the presence of 42 intramucosal SRCCs without any component of poorly differentiated adenocarcinoma, including 26 intramucosal invasive carcinomas (pT1a) and 16 foci of a noninvasive signet-ring cell carcinoma (pTis) (Fig. 6). No lymph node metastasis was found. The final pathologic staging of the tumor was pT1aN0M0.

**ACKNOWLEDGMENTS**

The authors thank Dr Shoichi Yoshimizu (Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Japanese Foundation for Cancer Research) and Soya Nunobe (Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Japanese Foundation for Cancer Research) for advice on this article.

**DISCLOSURE**

All authors disclosed no financial relationships.

**REFERENCES**

1. Guilford P, Hopkins J, Harraway J, et al. E-cadherin germline mutations in familial gastric cancer. Nature 1998;392:402-5.
2. Oliveira C, Pinheiro H, Figueiredo J, et al. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. Lancet Oncol 2015;16:e60-70.
3. Hansford S, Kaurah P, Li-Chang H, et al. Hereditary diffuse gastric cancer syndrome. JAMA Oncol 2015;1:23-32.
4. Van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet 2015;52:361-74.
5. Charlton A, Blair V, Shaw D, et al. Hereditary diffuse gastric cancer: predominance of multiple foci of signet ring cell carcinoma in distal stomach and transitional zone. Gut 2004;53:814-20.
6. Tsugeno Y, Nakano K, Nakajima T, et al. Histopathologic analysis of signet-ring cell carcinoma in situ in patients with hereditary diffuse gastric cancer. Am J Surg Pathol 2020;44:1204-12.
7. Fitzgerald RC, Hardwick R, Huntsman D, et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. J Med Genet 2010;47:436-44.

8. Shaw D, Blair V, Framp A, et al. Chromoendoscopic surveillance in hereditary diffuse gastric cancer: an alternative to prophylactic gastrectomy? Gut 2005;54:461-8.

9. Mi EZ, Mi EZ, di Pietro M, et al. Comparative study of endoscopic surveillance in hereditary diffuse gastric cancer according to CDH1 mutation status. Gastrointest Endosc 2018;87: 408-18.

10. Huneburg R, Marwitz T, van Heteren P, et al. Chromoendoscopy in combination with random biopsies does not improve detection of gastric cancer foci in CDH1 mutation positive patients. Endosc Int Open 2016;4:E1305-10.

Read Articles in Press Online Today!
Visit www.videogie.org

VideoGIE posts in-press articles online in advance of their appearance in a monthly edition of the journal. These articles are available on the VideoGIE website by clicking on the “Articles in Press” tab. Articles in Press represent the final edited text of articles that are accepted for publication but not yet scheduled to appear in a specific issue. They are considered officially published as of the date of Web publication, which means readers can access the information and authors can cite the research months prior to its availability in an issue. To cite Articles in Press, include the journal title, year, and the article’s Digital Object Identifier (DOI), located in the article footnote. Visit the website today to stay current on the latest research in the field of gastrointestinal endoscopy.