

学位論文（博士）

Diagnostic Utility of Ultrasonography for Duodenal
Ulcers in Pediatric Cases in Japan

（本邦における小児十二指腸潰瘍の超音波検査の診断的
有用性について）

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令和2年10月

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Frontiers in Pediatrics 2020 Jan 20;7:547

(令和2年1月掲載)

〔研究背景〕

上部消化管内視鏡検査 (Esophagogastroduodenoscopy ; EGD) は十二指腸潰瘍 (Duodenal ulcer ; DU) の確定診断に必要な検査であるが、専門的なスキルが必要であり、鎮静下で検査を行うため侵襲が高いことなどが問題点として挙げられる。超音波検査は広く普及した検査の一つで、低侵襲で、簡便な点で小児患者に導入しやすい検査である。腸重積症における target sign に代表されるように腹部超音波検査が消化器疾患の診断に用いられている。本邦成人例を対象とした研究で、十二指腸壁の肥厚が DU の診断に有用な所見として報告されているが、小児例の超音波所見に関する報告はない。十二指腸腫瘍でも同様な所見が認められることから、成人例での有用性は高くないと考えられている。一方で、小児期の十二指腸腫瘍の発生は極めてまれであり、十二指腸壁肥厚は DU の特異的所見となると考えた。本邦での小児 DU の超音波所見を確立することで、初診時の疾患鑑別に有用であると考えた。また、治療前後での超音波所見の比較により治療反応性や再燃の評価も可能であると考えた。本研究を通して、超音波検査を組み込んだ新たな DU の管理を検討する。

〔要旨〕

本研究では小児 DU 患者の内視鏡検査前に行った腹部超音波検査所見を後方視的に検討し、診断的有用性のある所見を決定した。また、治療前後での所見の変化、安定期に定期的な超音波所見の確認を行い、治療反応性や再発時の所見についても検討を行った。本研究は単施設で受診した小児 DU 患者 (16 歳未満) 5 名を対象とした。男 3 名、女 2 名で年齢の中央値は 12.5 歳であった。腹痛は全例で認め、初診時に血液検査、腹部超音波検査を行った。DU を疑う超音波所見は肥厚した十二指腸壁および肥厚した壁に接する高輝度な線状帯 (Hypertrophic wall of the duodenal bulb with a hyperechoic lumen: HH sign) と定義した。肥厚の基準は既報告を参考に 5mm 以上とした。

5 名中 4 名が HH sign 陽性で、1 名は十二指腸に連続する腫瘤様所見を認めた。1 名のみ HH sign に加え、広範囲に腹水を認め、CT 検査で穿孔性 DU と診断した。穿孔した 1 名は先に治療を行って状態を安定させた後に EGD を行い、他 4 名は治療開始前に EGD を行った。HH sign 陽性であった 4 名は十二指腸球部前壁に、陰性例では球部後壁側に潰瘍形成を認めた。全例、プロトンポンプ阻害薬で治療を開始し、HH sign の変化を確認した。

全例で治療介入による HH sign の消失を認めた。また、全例で *Helicobacter pylori* 感染を確認し、除菌療法を潰瘍治療後に行った。再発を認めた 2 名で、HH sign が再度出現し、治療により消失したことを確認した。

HH sign 陽性であった 4 名は十二指腸球部前壁に潰瘍が出現し、HH sign 陰性の 1 名は十二指腸球部後壁に潰瘍を認めた。本邦の成人 DU の超音波検査所見をまとめた報告から、後壁に存在する潰瘍は超音波検査で描出が困難であることがわかっている。潰瘍の位置により超音波検査所見が異なる可能性は十分に考えられた。

5 名中 3 名で内視鏡検査前に CT 検査を行った。穿孔例を含めた 2 名で DU を指摘でき、1 例は異常を認めなかった。非穿孔性 DU に限れば、潰瘍を指摘できたのは 1 例のみであった。非穿孔性胃・十二指腸潰瘍と CT 検査の診断的有用性に関して、CT 検査の感度は低く、胃潰瘍に比べ DU は診断が困難であったと報告されている。超音波検査では潰瘍周囲の free air や穿孔部位を通過する消化管ガスの描出、腹水の貯留は穿孔関連所見として検討されている。自験例では超音波検査において腹水の存在から潰瘍の穿孔を疑い、確認のため CT 検査を行った。放射線被曝も考慮すると、小児例においては診断目的の CT 検査の適用は慎重に検討する必要がある。

DU の確定診断に EGD は必須であり、出血部位の緊急止血や粘膜組織生検など臨床的に有益な検査である。好酸球性胃腸炎やクローン病などの鑑別すべき消化管疾患の否定、緊急的止血が必要な場合は EGD が必須であるため、初期診断時には超音波検査は補助的な位置づけになる。

しかし、DU 患者の 5% は治療抵抗性を示し、初回治療から 6 か月以内に再発する例が 20% になることがわかっている。自験例では治療により消失していた HH sign が再発時に出現し、再度治療により改善したことを確認した。一般的に治療効果の確認、特に治癒確認のために EGD を行うことはほとんどない。HH sign の変化を系時的に観察することで治療経過の確認や再発の評価をベッドサイドで評価できると考えられる。

超音波検査は検者のスキルに依存することが問題点である。また、消化管ガスや皮下脂肪貯留はアーチファクトの原因となり、鮮明な画像が得にくい状況も考えられる。また、本研究の対象例は少数であり、単施設での実施である。HH sign の診断的有用性についてさらなる検討を行うために、症例の蓄積や多施設共同研究が必要と考える。

本研究を通して、HH sign は小児 DU 患者の診断所見として有用で、特に治療効果判定や再発時の評価に非常に役に立つ可能性が示唆された。放射線被曝もなく、低侵襲のため、反復して施行可能であることなど超音波検査の利点も再確認できた。今後、症例の蓄積により HH sign の有用性について引き続き検討を行っていく予定である。



Diagnostic Utility of Ultrasonography for Duodenal Ulcers in Pediatric Cases in Japan

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OPEN ACCESS

Edited by:

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Gastroenterologia, Centro Hospitalar
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Specialty section:

This article was submitted to
Pediatric Gastroenterology,
Hepatology and Nutrition,
a section of the journal
Frontiers in Pediatrics

Received: 23 August 2019

Accepted: 13 December 2019

Published: 20 January 2020

Citation:

Sakata Y, Yasudo H, Uchida M,
Saito M, Azuma Y and Hasegawa S
(2020) Diagnostic Utility of
Ultrasonography for Duodenal Ulcers
in Pediatric Cases in Japan.
Front. Pediatr. 7:547.
doi: 10.3389/fped.2019.00547

Objective: To evaluate the diagnostic utility of wall hypertrophy of the duodenal bulb with a hyperechoic lumen, designated as the “HH sign,” using ultrasound sonography (US) in pediatric duodenal ulcer (DU) patients.

Study design: We performed a US for five pediatric subjects diagnosed with DU by upper gastroscopy to determine the presence of the potentially diagnostic HH sign. The sonographic images were analyzed before and after DU treatment. Computed tomography was performed in three cases and fecal occult blood test (FOBT) in all five cases.

Results: Upper gastroscopy confirmed DU in all patients. While the HH sign was observed using US in four cases, with the DU located in the anterior bulb, the FOBT was positive in only one case. In these four cases, the HH sign diminished in response to treatment, as visualized by US. This was observed for both the initial as well as recurrent episodes. A mass-like region was observed in only one case, with the ulcer located in the proximity of the inferior duodenal wall.

Conclusion: The HH sign is useful for the follow-up of DU, and US may be a suitable modality for the follow-up. We believe that this diagnostic marker can aid in following up a greater number of DU cases.

Keywords: upper gastroscopy, *Helicobacter pylori*, fecal occult blood test, computed tomography, antiulcer drug, HH sign, pediatric duodenal ulcer, ultrasound sonography

INTRODUCTION

Duodenal ulcer (DU), a major peptic ulcer, is defined as a disorder of mucosal defects in the duodenum. DU patients exhibit gastrointestinal symptoms such as abdominal pain, discomfort, nausea, and an episode of melena. *Helicobacter pylori* (*H. pylori*) infection is a major cause of DU and the eradication of *H. pylori* is essential to prevent the development of DU (1). In the duodenal bulb, anterior ulcers are common, with Kang et al. reporting that recurrent DUs were more likely to occur in the anterior region (2). While antiulcer drugs are the first choice of therapy, surgical and endoscopic therapies are additionally adopted in perforated or bleeding DU cases (3, 4). Although relatively common in adults, DU is rare in pediatric cases.

An upper gastroscopy is needed for diagnosis. However, it requires professional skills. Most patients undergo additional screening tests such as the fecal occult blood test (FOBT), X-ray, and/or

TABLE 1 | Clinical features of patients.

Case no.	Age* (year)	Sex	Symptom	Recurrent episodes	On admission				Findings of CT
					WBC (/ μ L)	Hb (g/dL)	CRP (g/dL)	Occult blood test	
1	14	F	Abdominal pain	None	11970	14,5	0,56	Negative	Perforated DU
2	13	M	Upper abdominal pain	Two	7420	8,6	1,25	Negative	Non-perforated DU
3	12	F	Upper abdominal pain	Four	7370	13,0	0,17	Negative	Not done
4	11	M	Upper abdominal pain	None	6400	13,8	<0,02	Negative	Not done
5	13	M	Upper abdominal pain Dizziness	None	8500	9,2	<0,02	Positive	Unremarkable

*Age at diagnosis; F, female; M, male; CT, computed tomography; WBC, white blood cells; Hb, hemoglobin; CRP, C-reactive protein; DU, duodenal ulcer.

computed tomography (CT); however, the latter two are associated with radiation exposure risks. It is reported that the FOBT is not useful for diagnosing DU (5).

Due to improvements in ultrasonic equipment, high resolution images can be obtained; therefore, several studies have used ultrasound sonography (US) to report the diagnostic utility of the hypertrophic wall of the duodenal bulb with its central echoic line in adult DU cases (6, 7). However, pediatric cases have received little attention (8). In this study, using US, we aimed to evaluate the hypertrophic wall of the duodenal bulb with a hyperechoic lumen (hereafter designated as the “HH sign”) as a potential diagnostic marker for DU in five pediatric patients.

METHODS

Patients

Our study was a single center, retrospective case series. The subjects were five patients: three men and two women, aged between 11 and 14 years (mean age: 12.5 years), who were presented to the Tokuyama Central Hospital (Yamaguchi, Japan) between 2007 and 2017. Clinical features of these patients are shown in **Table 1**. This study was conducted in accordance with the recommendations of Institutional Review Board of Tokuyama Central Hospital. The protocol was approved by the Institutional Review Board of Tokuyama Central Hospital (K346-20190807). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Diagnostic Procedures

The US equipment used in this study included the Xario SSA-650A and Aplio400 from Canon Medical Systems Corporation (Tochigi, Japan), with convex (3.5, 6 MHz) and linear (8, 10 MHz) transducers. The liver, gallbladder, kidneys, pancreas, spleen, the gastrointestinal tract (gastroduodenal region, small intestine, colon, and rectum), and the aorta with its branches (such as the celiac and superior mesenteric arteries) were evaluated by US. CT was performed in three patients, and the FOBT was performed in all patients. DU was confirmed by upper gastroscopy in all cases. All patients underwent a proper treatment for DU, including the administration of proton pump inhibitors. *H. pylori* infection was confirmed in all cases. An antibiotic agent was administered to the patient with perforated

DU, and an eradication therapy for *H. pylori* was adopted in all patients.

Diagnostic Criteria

The duodenum was identified in the epigastric or right hypochondriac region. A normal image of the duodenal bulb shows three layers: the hyperechoic inner and outer layers and a hypoechoic middle layer (**Supplementary Figure 1**). The HH sign was determined to be the sonographic criterion of a DU, consisting of duodenal wall hypertrophy with thickness ≥ 5 mm, along with the central hyperechoic line.

RESULTS

Case 1

A 14-year-old girl was admitted to our hospital with sudden abdominal pain. Diffuse tenderness with abdominal guarding was observed on admission. The body height (BH) and body weight (BW) were 157 centimeters (cm) and 49.0 kilograms (kg) on admission, respectively. A blood test revealed slightly elevated counts of white blood cells (WBC: $12.0 \times 10^9/L$) and C reactive protein (CRP: 0.56 mg/dL, reference range: ≤ 0.3 mg/dL), and the FOBT was negative (**Table 1**). We performed an abdominal sonography, which revealed peritoneal fluid accumulation and the HH sign in the duodenal bulb (**Figure 1A**). CT revealed edematous changes and wall defects in the duodenal bulb, which indicated a perforated DU. An antiulcer drug and antibiotic agent were administered, with concomitant fasting. Eight days after admission, we performed an endoscopy and identified ulceration in the duodenal bulb, on the basis of which, the patient was diagnosed with DU.

Case 2

A 13-year-old boy was presented to our hospital with upper abdominal pain lasting for 3 months. The BH and BW were 151.5 cm and 40.4 kg on admission, respectively. A blood test revealed anemia (hemoglobin 8.6 g/dL) with a slight elevation of CRP level (1.25 mg/dL), and the FOBT was negative (**Table 1**). An abdominal US scan revealed the presence of the HH sign (**Figure 1B**) and the absence of free air and ascites that usually indicate a perforated DU. CT revealed wall hyperplasia in the duodenal bulb, consistent with a DU. An endoscopy revealed a microhemorrhage in the anteriorly located DU. Five days after the initiation of the antiulcer drug, we performed a US and found that the HH sign had diminished (data not shown). He experienced two recurrent episodes, and in both, the HH sign,

Abbreviations: HH sign, hypertrophic wall of duodenal bulb with a hyperechoic lumen.

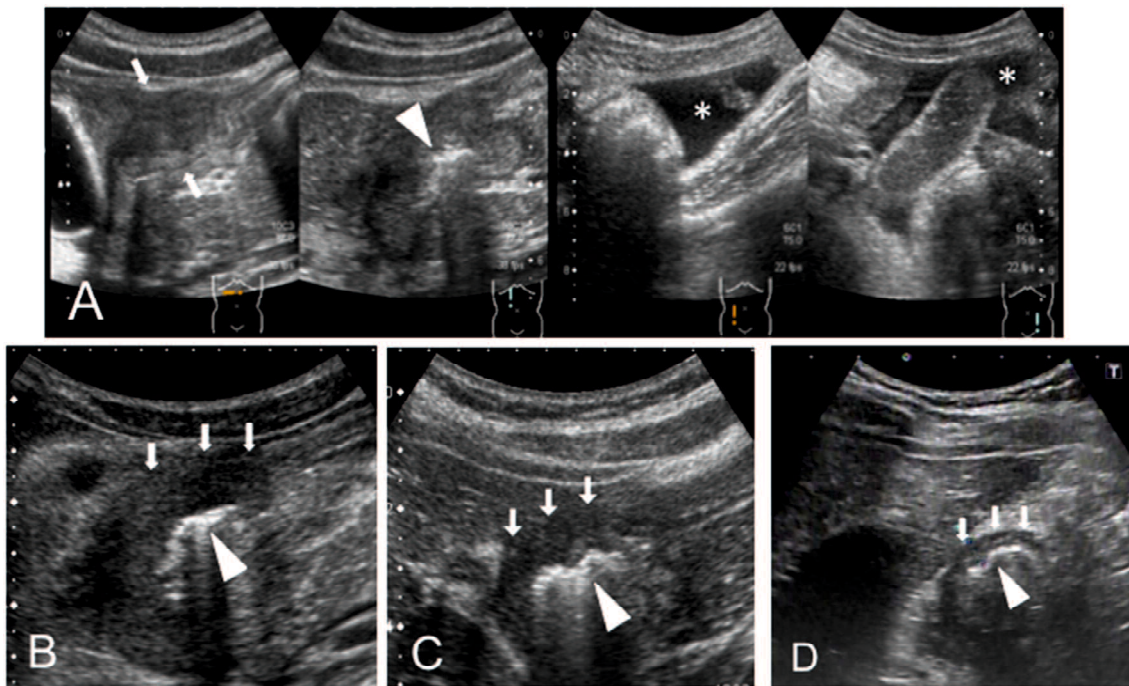


FIGURE 1 | (A) Case 1, **(B)** Case 2, **(C)** Case 3, and **(D)** Case 4. The HH sign—extensive hyperplasia of the duodenal wall (white arrows) and the hyperechoic inner layer (white head-arrow)—was observed. The peritoneal fluid (*) is identified in case 1.

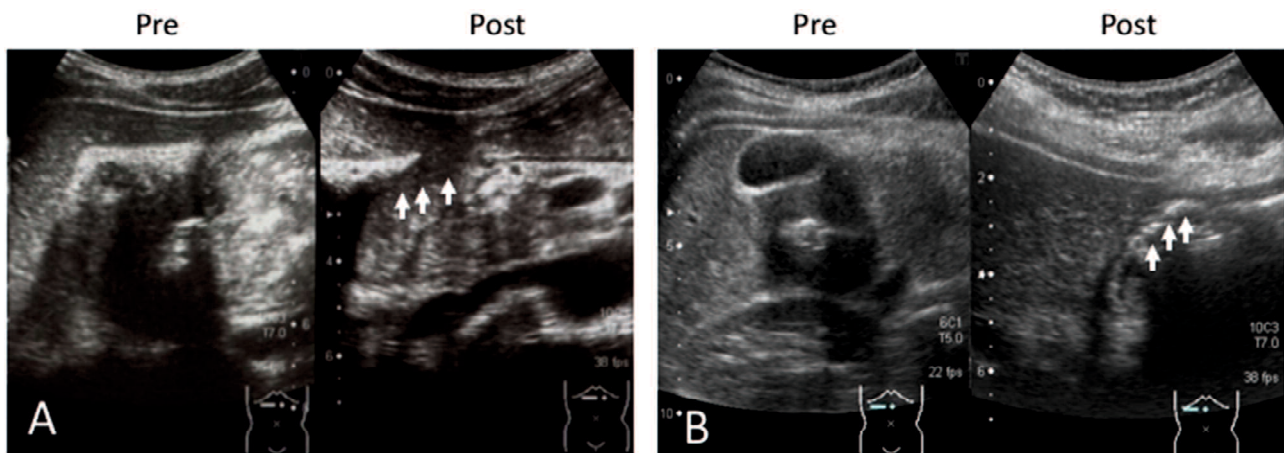


FIGURE 2 | (A) Case 2 and **(B)** Case 3. The sonographic images in the recurrent episode are shown. The hypertrophic wall and echogenic line (HH sign) are shown in “Pre.” The HH sign diminished on treatment with the antiulcer drug (arrows) as shown in “Post.” Pre, pretreatment; Post, post-treatment with antiulcer agent.

which was observed in the symptomatic period, diminished in the post-treatment period (**Figure 2A**).

Case 3

A 12-year-old girl suffering from upper abdominal pain for several months was presented to our hospital. The BH and BW were 150 cm and 39.4 kg on admission, respectively. Her blood tests were normal (WBC $7.4 \times 10^9/L$, hemoglobin 13.0 g/dL, CRP 0.17 mg/dL), and the FOBT was negative (**Table 1**). A US scan revealed the HH sign in the right epigastric region, consistent

with her symptomatic site (**Figure 1C**). An endoscopy revealed DU on the anterior wall of the duodenal bulb. After the first episode, she experienced four recurrent episodes. In each, a pretreatment US scan revealed the HH sign, which disappeared in response to the treatment (**Figure 2B**).

Case 4

An 11-year-old boy was hospitalized for epigastric pain. The BH and BW were 133 cm and 34.6 kg on admission, respectively. The thickness of the duodenal bulb wall was 5.4 mm (which

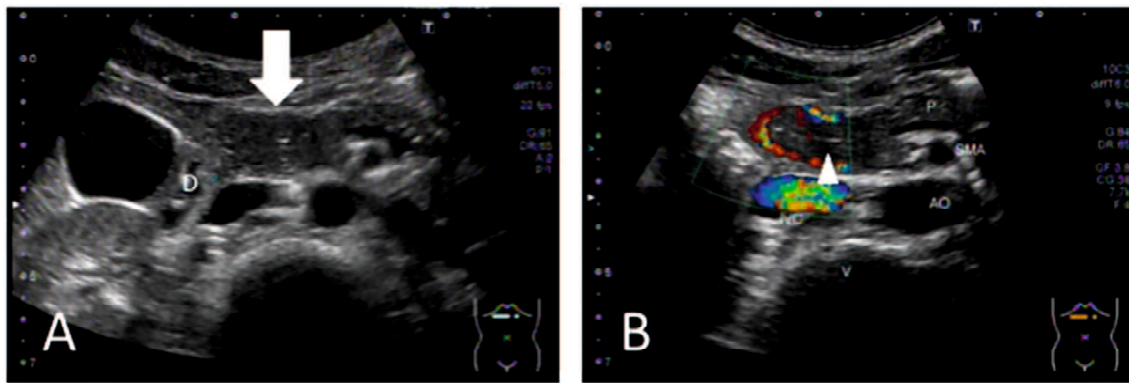


FIGURE 3 | (A) The tumor-like region is identified (white arrow), which is located as part of the DU. **(B)** The blood vessel around the region and the central echogenic line (appearing to be the mucosa) are visualized. D, duodenum; P, pancreas; AO, aorta; IVC, inferior vena cava; SMA; superior mesenteric artery; V, vertebral column.

slightly exceeded the 5 mm limit) and the hyperechoic line was clearly visible, consistent with the HH sign (**Figure 1D**). Blood tests were normal (WBC $6.4 \times 10^9/L$, hemoglobin 13.8 g/dL, CRP <0.02 mg/dL), and the FOBT was negative (**Table 1**). We observed ulceration with highly mucosal edema, and the duodenal lumen was obstructed by the edematous change. The HH sign diminished after the initiation of the antiulcer drug (data not shown).

Case 5

A 13-year-old boy was presented to our hospital with complaints of dizziness and upper abdominal pain. On admission, the BH and BW were 153 cm and 38.3 kg, respectively. Blood testing revealed anemia (hemoglobin 9.2 g/dL), and the FOBT was positive (**Table 1**). Since melena was observed on hospitalization, we performed a US, which revealed a mass-like region surrounded by a blood vessel (**Figures 3A,B**) that appeared to be connected to the duodenum. The HH sign was not observed. No remarkable findings were found in the CT image. In the endoscopy, the ulcer was identified at a site between the anterior and posterior bulb. A US performed 20 days after treatment revealed that the mass-like lesion disappeared.

DISCUSSION

Our study aimed to investigate whether the HH sign is a useful US finding for diagnosing pediatric DU cases. This sign was observed in four of the five pediatric DU cases. CT analysis performed in three cases revealed ulceration in two. Although the FOBT was performed in all cases, it was positive only in one. Our findings on US are compatible with previous reports in adult cases that showed that the HH sign was diagnostic for DU (6, 7). In previous reports, the presence of free air and variable amounts of free fluid were significant findings indicating perforated peptic ulcers (9–11). Free air is visualized as a reverberation, having a comet-tail appearance in the ultrasound (9, 10). Fam et al. (11) reported a case of a perforated DU with pneumoperitoneum, where air in the portal and systemic venous systems was confirmed by CT. In our study, in the patient with a perforated DU, there was no

evidence of free air, but a relatively large amount of free fluid was revealed on US.

US, CT, FOBT, and upper gastroscopy are the commonly available screening tests for peptic ulcer, with some studies reporting the diagnostic utility of CT imaging for such ulcers in adult patients (12, 13). In our study, ulceration was observed in two of the three pediatric cases subjected to CT; however, Allen et al. (13) reported that the sensitivity of CT for non-perforated peptic ulcers was low and DUs were hardly identified compared to gastric ulcers. Further, radiation exposure is a matter of concern in children. Regarding acute radiation syndrome, it is reported that hematopoietic disorders are more likely to occur in children than in adults (14). Krille et al. (15) investigated the late effects of exposure to ionizing radiation from CT in a pediatric case, suggesting that this was a risk factor for a secondary cancer.

FOBT is commonly used to assess gastrointestinal diseases with bleeding. However, the Canadian Agency for Drugs and Technologies in Health states that its clinical effectiveness for diagnosis in patients with suspected gastrointestinal bleeding remains unknown (16). Nakama et al. (5) reported that the diagnostic sensitivity of FOBT was low in upper digestive tract diseases. This is in line with our observation, where that it was positive in only one case.

In general, endoscopy is mandatory for confirming DU, provides a local treatment in case of bleeding ulcer, and allows to perform biopsy samples for *H. pylori* diagnosis. Therefore, the interest of US could only be suggested in the patient with isolated epigastric pain showing no bleeding or growth retardation as endoscopy has to be performed irrespective of the US results in the cases with bleeding or other complication. Furthermore, the HH sign observed in recurrent episodes were reversible in case 2 and 3. Approximately 5 percent of DU patients is resistant to antiulcer drug and 20 percent of the patients relapses within 6 months after initial therapy (17, 18). US could be useful in the case of follow-up of DU patients with the recurrence risk because of its non-invasiveness.

The present study has several limitations. First, a US scan is dependent on the clinician's skill. Although a study reported that the sensitivity of US for the diagnosis of peptic ulcers

in older children weighing >30 kg was low (8), in our study, DUs were identified using US in four out of the five pediatric patients weighing >30 kg. Additionally, factors such as bowel gas and obesity could negatively affect the examination. Second, the sample size was very small because pediatric DU patients are very rare and this study was a pilot study conducted in a single center. Further multi-center studies involving different regions are warranted to confirm the diagnostic utility of the HH sign in pediatric DU patients.

In conclusion, we showed that US identified the HH sign in four out of the five pediatric DU patients. The DU was located in the anterior bulb, a common site for these ulcers. Our findings suggest that this sign could be useful for the follow-up of pediatric DU.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Tokuyama Central

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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