Original Article

Background factors of idiopathic peptic ulcers and optimal treatment methods: a multicenter retrospective Japanese study

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This study investigated the trends in idiopathic peptic ulcers, examined the characteristics of refractory idiopathic peptic ulcer, and identified the optimal treatment. The characteristics of 309 patients with idiopathic peptic ulcer were examined. We allocated idiopathic peptic ulcers that did not heal after 8 weeks' treatment (6 weeks for duodenal ulcers) to the refractory group and those that healed within this period to the healed group. The typical risk factors for idiopathic peptic ulcer (atherosclerosis-related underlying disease or liver cirrhosis complications) were absent in 46.6% of patients. Absence of gastric mucosal atrophy (refractory group: 51.4%, healed group: 28.4%; $p = 0.016$), and gastric fundic gland polyps (refractory group: 17.6%, healed group: 5.9%; $p = 0.045$) were significantly more common in the refractory group compared to the healed group. A history of *H. pylori* eradication (refractory group: 85.3%, healed group: 66.0%; $p = 0.016$), previous *H. pylori* infection (i.e., gastric mucosal atrophy or history of *H. pylori* eradication) (refractory group: 48.5%, healed group: 80.0%; $p = 0.001$), and potassium-competitive acid blocker treatment (refractory group: 28.6%, healed group, 64.1%; $p = 0.001$) were significantly more frequent in the healed group compared to the refractory group. Thus, acid hypersecretion may be a major factor underlying the refractoriness of idiopathic peptic ulcer.

***Key Words*: duodenal ulcers, idiopathic ulcers, gastric ulcers, potassium-competitive acid blockers, refractoriness**

Helicobacter pylori (*H. pylori*) infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin constitute the two major causes of peptic ulcers.[1,2] The proportion of idiopathic peptic ulcers (IPUs) that is not caused by *H. pylori* or NSAIDs has increased in recent years.[3–5] IPU is characterized by greater complications than simple *H. pylori*-positive ulcers,[3,6–11] and a higher frequency of concomitant atherosclerosis-causing diseases, such as hypertension, diabetes, and hyperlipidemia,[4,12] which are associated with serious complications, including liver cirrhosis, sepsis, and malignancy.[13–15] Smoking decreases prostaglandin levels and reduces the barrier function of the gastric mucosa, but some studies have indicated that smoking is not associated with IPU, leading to a lack of consensus about the role of smoking in IPU.[16–19] IPU is also problematic from the clinical perspective since it is more refractory and has a higher recurrence rate than simple *H. pylori*-positive ulcers.[3,20] Some studies, albeit relatively small in scale, have postulated that the pathogenesis of IPU may be based on acid hypersecretion, hypergastrinemia, increased gastric excretion, genetic predisposition, smoking, and weak mucosal defense

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mechanisms,[21–24] while the precise pathogenesis and risk factors for IPU remain unclear. Proton pump inhibitors (PPIs) or potassium-competitive acid blockers (PCABs) are the principal therapeutic agents for IPU;[3,5,20] the latter have stronger acid secretion inhibitory effects than the former, although no study has compared their efficacy for the treatment of IPU. Therefore, we aimed to accumulate a large sample population of IPU, clarify the pathogenesis of IPU and the factors responsible for refractoriness, and propose the optimal treatment method.

Materials and Methods

This study was approved by the Research Ethics Committee of Osaka Medical and Pharmaceutical University Review (Approval No. 2856). Informed consent was obtained using the opt-out protocol for retrospective research (patients were included unless they expressed their desire to be excluded from the study), and information about the conduct of the research was disclosed. This study recruited patients with IPU who visited Osaka Medical and Pharmaceutical University Hospital and 24 partner institutions between October 1, 2014, and September 30, 2019. We collected data on background factors (age, sex, height, weight, smoking habits, alcohol consumption, comorbidities, and history of *H. pylori* eradication), endoscopic findings (ulcer characteristics, degree of atrophic gastritis, presence of fundic gland polyps, and reflux esophagitis), symptoms, blood test results, and treatment details.

The inclusion criteria for this study were as follows: (1) patients diagnosed with active stage or healing stage gastric or duodenal ulcers using esophagogastroduodenoscopy (EGD), including those with ulcer diameters of 5 mm or less; (2) patients confirmed to be negative for *H. pylori* by one or more of the following methods, viz. serum antibody titer (<10 U/ml was deemed negative), rapid urease test, urea breath test, or stool antigen.

The exclusion criteria were as follows: (1) patients administered oral, intravenous, or topical NSAIDs more than once a week; (2) patients with indeterminate results after *H. pylori* eradication; (3) patients using steroid medication; (4) patients with a history of esophageal, gastric, or duodenal surgery; (5) ulcers associated with malignant diseases (including metastatic tumors and lymphomas), and (6) presence of ulcers after endoscopic treatment.

The degree of gastric mucosal atrophy was evaluated using the Kimura–Takemoto classification.

Part 1. Characteristics of IPU. First, we analyzed the characteristics of IPU of the study participants.

Part 2. Investigation of the factors causing refractoriness in IPU. In the second part of the study, we examined the factors responsible for the recalcitrance of IPU. According to the presence or absence of healing, participants with IPUs were allocated to the refractory group or healed group for the purpose of comparison. The refractory group was defined as patients with residual active stage or healing stage ulcers in the gastric mucosa on EGD after 8 weeks of treatment and in the duodenal mucosa after 6 weeks of treatment. The healed group was defined as patients who had confirmed scar stage ulcers during the corresponding period. Patients who were administered non-standard IPU treatment other than PPI or PCAB, such as histamine-2 receptor antagonist (H2RA) and unspecified treatment, were excluded from the analysis.

Statistical analysis. In Table 1 and 2, the background continuous variables are expressed as the median (interquartile range, IQR) and categorical variables as numbers (*n*) (%) rounded to the third decimal place. Continuous variables were analyzed using the Kruskal–Wallis test, and categorical variables using the *chi*-square test. Multivariate logistic regression analysis was employed to identify independent predictors (or risk factors) of refractory IPU, adjusting for factors considered highly influential based on our clinical experience. Odds ratios (OR) and 95% confidence intervals (CIs) were estimated where appropriate. Missing values in the multivariate logistic regression analysis were imputed using the multiple assignment method, and missing values were omitted from the denominator. *P* values <0.05 were considered statistically significant. All analyses were performed using R ver. 4.1.2.

Results

Part 1. Characteristics of IPU. Of the total 309 patients with IPU included in this study, 187 (60.5%) were confirmed to be negative for *H. pylori* by serum antibody, 20 (6.4%) by rapid urease test, 38 (11.9%) by the urea breath test, 37 (11.9%) by two or more methods, and 27 (8.7%) by other methods.

The study population included 109 men (35.3%) and the median age was 69.0 years. Table 1 provides the participants' background information, including lifestyle, limitations in the activities of daily living, underlying medical conditions, medications, and symptoms at the time of ulcer detection as well as the endoscopic characteristics of patients with IPU and the primary therapeutic agents used during the first two months. The results of the blood tests are provided in Supplemental Table 1*.

Part 2. Investigation of the factors responsible for refractory IPU. A total of 127 patients with IPU were included in the analysis [median age: 69.0 years; gastric ulcers, $n = 102$ (80.3%); duodenal ulcers, $n = 24$ (18.9%); and both gastric and duodenal ulcers, $n = 1$ (0.8%)], after excluding 179 patients without endoscopic follow-up and 2 patients who were treated with H2RA or unknown therapy.

Thirty-five (27.6%) patients were assigned to the refractory group and 92 (72.4%) to the healed group (Fig. 1). Scarring was achieved in 72.4% of IPUs after 8 weeks of treatment (6 weeks for duodenal ulcers). The healing rate for PCAB and regular-dose PPI therapy was 85.5% and 56.8%, respectively. Univariate analysis showed that the proportion of absence of gastric mucosal atrophy (Kimura–Takemoto classification C-0) (refractory group: 51.4%, healed group: 28.4%; $p = 0.016$), and presence of fundus gland polyps (refractory group: 17.6%, healed group: 5.9%; $p = 0.045$) was significantly higher in the refractory group. The proportion of patients with hypertension (refractory group: 22.9%, healed group: 47.8%; $p = 0.011$), history of *H. pylori* eradication (refractory group: 14.7%, healed group: 44.0%; $p = 0.016$), patients thought to have previous *H. pylori* infection (defined as gastric mucosal atrophy or history of *H. pylori* eradication) (refractory group: 48.5%, healed group: 80.0%; $p = 0.001$), and PCAB treatment (refractory group: 28.6%, healed group, 64.1%; $p = 0.001$) was significantly more common in the healed group. The body mass index (BMI) also differed significantly between the two groups (refractory group: 20.7, healed group: 22.0; $p = 0.042$) (Table 2). Multivariate analysis adjusted for BMI showed that previous *H. pylori* infection [OR 0.143 (95% CI: 0.042–0.482), $p = 0.002$] and treatment with PCAB [OR 0.122 (95% CI: 0.038–0.389), $p = 0.001$] were independent factors associated with healing of IPU (Table 3).

In terms of the relationship between degree of atrophy and refractoriness by gastric ulcer site, ulcers with lesser gastric mucosal atrophy were significantly more common in the L region than in the U or M region, and ulcers with advanced mucosal atrophy were significantly more common in the U or M region than in the L region ($p = 0.005$). Moreover, in the refractory group, the ulcers were significantly more likely to be located in the L region than in the U or M region, whereas in the healed group, ulcers were significantly more likely to be located in the U or M region than in the L region ($p = 0.047$) (Table 4). A case of refractory IPU in the L region without atrophic gastritis and another case of healed IPU in the M region with advanced

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Table 1. Background information of patients with idiopathic ulcers (*n* = 309)

Variables		Overall *n* = 309 (%)
Patient characteristics		
Men (%)		109 (35.3)
Age (years), median [IQR]		69.00 [58.00, 77.00]
Height (cm), median [IQR]		161.20 [154.00, 167.05]
Weight (kg), median [IQR]		57.60 [48.50, 65.30]
BMI, median [IQR]		21.71 [19.65, 24.49]
Habits		
Smoking (%)	Never/Current/Former	152 (54.7)/66 (23.7)/60 (21.6)
Alcohol (%)	No drinking/Regular drinking/ Opportunistic drinking	137 (49.2)/117 (42.0)/24 (8.6)
ADL (%)	Active/Bedridden/Other	271 (94.4)/4 (1.4)/12 (4.2)
Comorbidity		
Hypertension (%)		128 (41.4)
Diabetes mellitus (%)		57 (18.4)
Dyslipidemia (%)		54 (17.5)
Chronic kidney disease (%)		12 (3.9)
Dialysis (%)		11 (3.6)
Ischemic heart disease (%)		6 (1.9)
Liver cirrhosis (%)		19 (6.1)
Child–Pugh classification	A/B/C/Unknown	7 (36.8)/5 (26.3)/3 (15.7)/4 (21.0)
Collagen disease (%)		2 (0.6)
Stroke (%)		7 (2.2)
Cancer (%)		19 (6.1)
Concomitant drug		
Antithrombotic drug (%)	Thienopyridine series/Warfarin/DOAC	6 (1.9)/15 (4.9)/13 (4.2)
Antipsychotic drug (%)		11 (3.5)
Bisphosphonate (%)		2 (0.6)
Symptoms at the time of ulcer diagnosis	No symptoms/Hematemesis/Bleeding/ Abdominal pain/Other	91 (29.6)/38 (12.3)/88 (28.6)/51 (16.6)/39 (12.7)
Endoscopic features		
Gastric/Duodenal (%)	GU/DU/GDU	229 (74.1)/71 (23.0)/9 (2.9)
Number of ulcers (%)	Single/Multiple	190 (64.2)/106 (35.8)
Ulcer diameter (mm), median [IQR]		10.00 [6.00, 15.00]
Ulcer location		
Gastric (%)		229 (74.1)
U or M/L (%)		111 (46.2)/129 (53.8)
Duodenal (%)		71 (23.0)
Bulb/Post bulb (%)		62 (77.5)/18 (22.5)
Both gastric and duodenal (%)		9 (2.9)
U or M/L/Bulb/Post bulb		2 (22.2)/7 (77.8)/3 (33.3)/1 (11.1)
Stage (%)	A1/A2/H1/H2	134 (43.6)/94 (30.6)/52 (17.0)/27 (8.8)
Forrest's classification (%)	Ia/Ib/II/III	14 (4.6)/33 (10.8)/48 (15.7)/210 (68.9)
Gastric atrophy (Kimura–Takemoto classification) (%)	C-0/C-1/C-2/C-3/O-1/O-2/O-3	112 (36.2)/31 (10.0)/35 (11.3)/33 (10.7)/ 36 (11.7)/31 (10.0)/31 (10.0)
Gastric polyp (%)		30 (10.0)
RE (Los Angeles classification) (%)	Grade N/M/A/B/C/D	159 (68.5)/41 (17.6)/21 (9.1)/6 (2.6)/3 (1.3)/2 (0.8)
Helicobacter pylori eradication (%)		70 (24.1)
H. pylori infection (%)	Uninfected/Previous infection	97 (32.9)/198 (67.1)
Treatment drug		
Acid secretion inhibitor (%)	H2RA/PPI/PCAB	6 (2.0)/159 (53.3)/133 (44.6)
Concomitant use of cytoprotective agents (%)		51 (16.5)

BMI, body mass index; IQR, interquartile range; ADL, activities of daily living; DOAC, direct oral anticoagulant; GU, gastric ulcer; DU, duodenal ulcer; GDU, gastroduodenal ulcer; RE, reflux esophagitis; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker.

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Table 2. Univariate analysis of the refractory and healed groups: background factors

Variables	Level	Healed group $n = 92$	Refractory group $n = 35$	p value
Patient characteristics				
Age (years), median [IQR]		69.50 [60.00, 78.25]	69.00 [57.00, 75.00]	0.195
Height (cm), median [IQR]		161.00 [154.75, 166.40]	158.50 [152.07, 163.85]	0.23
Weight (kg), median [IQR]		57.50 [48.88, 66.75]	51.80 [44.75, 60.65]	0.029
BMI, median [IQR]		22.03 [19.89, 24.71]	20.76 [18.81, 22.55]	0.042
Comorbidity				
Hypertension (%)		44 (47.8)	8 (22.9)	0.011
Diabetes mellitus (%)		17 (18.5)	4 (11.4)	0.339
Dyslipidemia (%)		15 (16.3)	4 (11.4)	0.491
Chronic kidney disease (%)		3 (3.3)	0 (0.0)	0.28
Dialysis (%)		2 (2.2)	0 (0.0)	0.374
Ischemic heart disease (%)		3 (3.3)	0 (0.0)	0.28
Liver cirrhosis (%)		1 (1.1)	3 (8.6)	0.032
Collagen disease (%)		0 (0.0)	1 (2.9)	0.104
Stroke (%)		4 (4.3)	0 (0.0)	0.21
Cancer (%)		3 (3.3)	4 (11.4)	0.072
Concomitant drug				
Antithrombotic drug (%)	Thienopyridine series	1 (2.9)	2 (2.2)	0.409
	Warfarin	1 (2.9)	7 (7.7)	
	DOAC	1 (2.9)	1 (1.1)	
Antipsychotic drug (%)		0 (0.0)	2 (2.2)	0.379
Bisphosphonates (%)		0 (0.0)	1 (1.1)	0.536
Gastric/Duodenal (%)	GU	74 (80.4)	28 (80.0)	0.814
	DU	17 (18.5)	7 (20.0)	
	GDU	1 (1.1)	0 (0.0)	
Number of ulcers (%)	Single ulcer	54 (60.7)	18 (52.9)	0.436
	Multiple ulcers	35 (39.3)	16 (47.1)	
Ulcer diameter (mm), median [IQR]		10.00 [7.50, 15.00]	12.50 [10.00, 20.00]	0.066
Location of ulcers (Gastric) (%)	U or M region	50 (54.2)	10 (28.4)	0.047
	L region	36 (39.1)	19 (54.2)	
Location of ulcers (Duodenal) (%)	Bulb	15 (16.3)	7 (20.0)	0.25
	Post bulb	5 (5.4)	1 (2.8)	0.478
Stage (%)	A1	44 (47.8)	11 (31.4)	0.337
	A2	32 (34.8)	15 (42.9)	
	H1	14 (15.2)	7 (20.0)	
	H2	2 (2.2)	2 (5.7)	
Gastric atrophy (Kimura–Takemoto classification) (%)	C-0	25 (28.4)	18 (51.4)	0.016
	C-1-O-3	63 (71.6)	17 (48.6)	
Gastric polyp (%)		5 (5.9)	6 (17.6)	0.045
RE (Los Angeles classification Grade A and above)		6 (11.5)	3 (13.6)	0.801
Helicobacter pylori infection (%)	Uninfected	18 (20.0)	17 (51.5)	0.001
	Previous infection	72 (80.0)	16 (48.5)	
H. pylori eradication (%)		29 (33.3)	5 (14.7)	0.04
Treatment drug				
Acid-secretion inhibitor (%)	PPI	33 (35.9)	25 (71.4)	0.001
	PCAB	59 (64.1)	10 (28.6)	
Cytoprotective drug (%)		12 (13.0)	8 (22.9)	0.175

BMI, body mass index; IQR, interquartile range; DOAC, direct oral anticoagulant; GU, gastric ulcer; DU, duodenal ulcer; GDU, gastroduodenal ulcer; RE, reflux esophagitis; PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker.

atrophic gastritis are presented in Fig. 2 and 3, respectively, showing the ulcers (Fig. 2A and 3A) and background mucosa (Fig. 2B and 3B).

Discussion

This is the first study that enrolled a nationwide sample of more than 300 patients with IPU in Japan to investigate the possible causative factors and identify the optimal treatment for

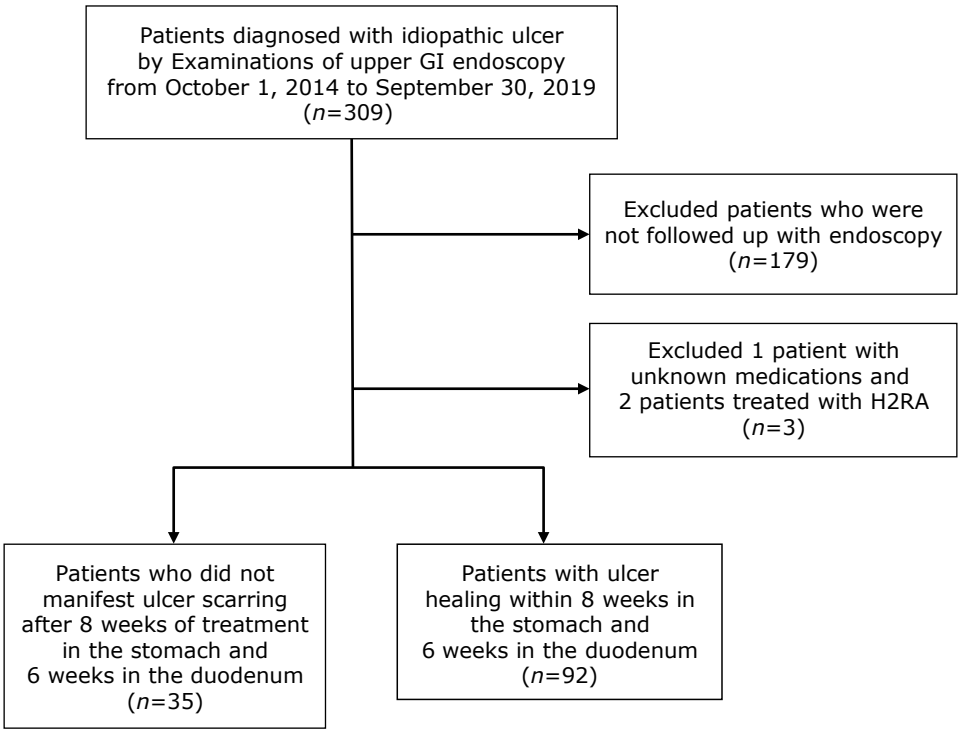

Fig. 1. Study design.

Table 3. Multivariate analysis of patients with refractory and healed idiopathic peptic ulcers

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Previous *Helicobacter pylori* infection	0.21 (0.09–0.51)	0.001	0.143 (0.042–0.482)	0.002
Treatment with PCAB	0.25 (0.10–0.58)	0.001	0.122 (0.038–0.389)	0.001

OR, odds ratio; CI, confidence interval; PCAB, potassium-competitive acid blocker.

Table 4. Relationship between the degree of atrophy and refractoriness by gastric ulcer site

	L region *n* = 136	U/M region *n* = 113	*p* value
Gastric atrophy (Kimura–Takemoto classification)			
C-0 (%)	50 (37.6)	27 (26.7)	0.005
C-1–C-3 (%)	47 (35.3)	26 (25.7)	
O-1–O-3 (%)	36 (27.1)	48 (47.5)	
Refractoriness			
Healed group (%)	37 (63.8)	39 (81.2)	0.047
Refractory group (%)	21 (36.2)	9 (18.8)	

IPU. In our large dataset of patients with IPU, approximately 53.4% (56.7% of gastric ulcers, 57.7% of duodenal ulcers, and 44.4% of both gastric and duodenal ulcers) of patients had at least one of the following risk factors: hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, ischemic heart disease, and complications of liver cirrhosis. These results indicate that nearly half of the patients with IPU (almost 47%) did not have any previously reported risk factors. IPU in these patients may have been caused by stress or other easily masked risk factors.

A higher proportion of patients in the healed group had gastric mucosal atrophy, history of *H. pylori* eradication, and were considered to have a previous *H. pylori* infection (Table 2) compared to the refractory group. Moreover, a significantly higher proportion of patients in the healed group were treated with PCAB compared to PPI. These findings suggest that acid hypersecretion may play a significant role in the refractoriness of IPU.

The overall healing rate of IPU within 8 weeks (6 weeks in the duodenum) in this study was 72.4% [PCAB, 85.5% (59/69); regular-dose PPI, 56.8% (33/58)]. Kanno *et al.*[20] found that the 12-week healing rate of *H. pylori*-positive ulcers treated with PPI was 95.0% (112/118) and as low as 77.4% (24/31) for IPU,

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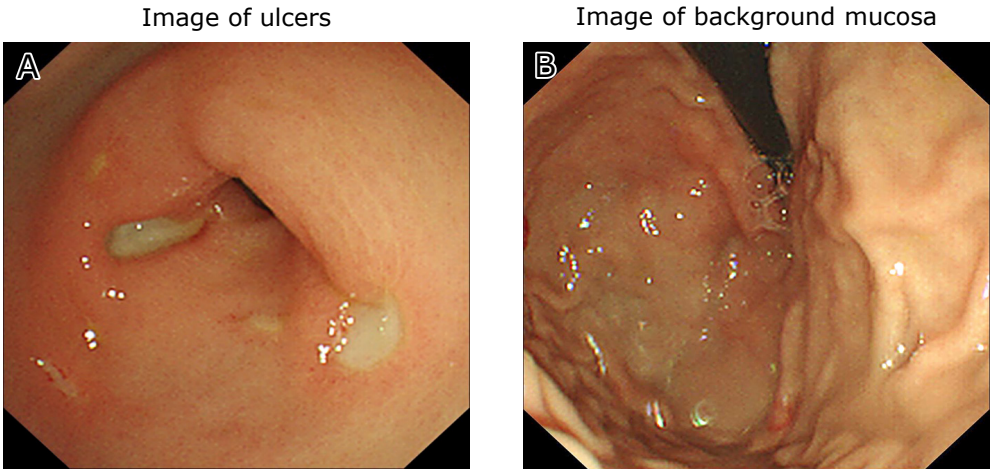

Fig. 2. Refractory ulcer against a background of non-atrophic gastric mucosa. (A) Image of the ulcers. (B) Image of the background mucosa.

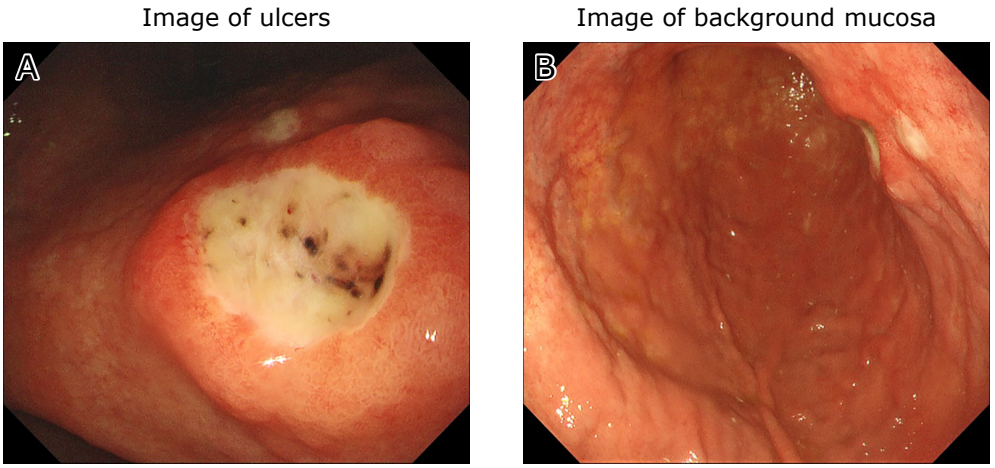

Fig. 3. A case of refractory ulcer against a background of atrophic gastric mucosa. (A) Image of the ulcers. (B) Image of the background mucosa.

concluding that IPU may be inadequately treated with regular PPI therapy. Sugawara *et al.*[25] conducted a prospective study (8 weeks for gastric ulcers, 6 weeks for duodenal ulcers) and discovered that the healing rate was significantly lower for IPU (81.2%) compared to 93.5% for simple *H. pylori*-positive ulcers treated with PCAB; the healing rate was even lower (71.4%) among IPU patients without atrophic gastritis and no history of *H. pylori* eradication. However, no previous study has compared the healing rates of IPU treated with PPI and PCAB. Therefore, we compared the healing rates of PCAB and regular-dose PPI in the entire sample of patients with IPU, including patients with previous *H. pylori* infection. The results showed that the healing rate of PCAB-treated IPU was significantly higher (85.5% vs 56.8%), while that of PPI was extremely low. Ten IPU lesions did not heal within 8 weeks (6 weeks for duodenal ulcer) of PCAB treatment, at least 5 of which showed endoscopic ulcer scarring due to continued PCAB therapy. Furthermore, 18 of the 309 patients in this study had active ulcers that were confirmed endoscopically after scarring was achieved, and at least 18 had recurrent ulcers. Scarring of the ulcer was achieved again after resumption of acid-suppressive therapy in 12 of these 18 patients. In light of these facts, PCAB rather than PPI should be used for the initial treatment of IPU, and continuous acid-secretion inhibitors should be considered in some cases to prevent recurrence. Furthermore, in this study, the concomitant use of mucosal defense products did not differ significantly between the refractory and healed groups.

Iijima *et al.*[26] reported that IPU occurred more frequently in the antral region than *H. pylori* ulcers (52% vs 14%), and that 86% of IPUs that were not complicated by atrophic gastritis were found in the antrum or the duodenal bulb. In our study, 53% of gastric ulcers were found in the gastric L region and 77% of duodenal ulcers in the duodenal bulb, consistent with the findings of the previous study. Moreover, a novel finding of the study was the relationship between the degree of gastric mucosal atrophy, gastric ulcer site, and refractoriness: ulcers in the L region showed less atrophy and were more refractory than ulcers in the U or M regions. The location of gastric ulcers has been shown to be correlated with the progression of gastric mucosal atrophy.[27] As gastric mucosal atrophy progresses, the acid-secreting fundus gland mucosa is replaced by non-acid-secreting pyloric mucosa, resulting in decreased gastric acid secretion.[28] The low frequency of refractory cases in the U or M region among the IPUs included in this study may be attributed to the low acid secretion at this site.

A limitation of this study was its retrospective design and only a few cases were followed up endoscopically. In addition, cases of non-*Helicobacter pylori Helicobacters* were not excluded and

the acid secretion capacity was not evaluated by pH monitoring. Moreover, the cases included in this study were not limited to first-episode IPU. Future prospective studies should be designed to overcome these limitations.

In conclusion, approximately 47% of patients with IPU do not have any risk factors, such as hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, ischemic heart disease, or liver cirrhosis. We believe that acid hypersecretion is a major factor responsible for the refractoriness of IPU, and PCAB is a useful initial treatment for IPU, especially for lesions located in the L region, and continued treatment with acid-secretion inhibitors is recommended.

Author Contributions

NN, TTakeuchi: Writing/reviewing/editing of original draft paper, data curation, formal analysis, methodology review, and visualization.

RH, KN, KI, SKoizumi, KK, ME, AN, TTakeda, TTomita, SS, KMizukami, KMurakami, NY, RM, TO, HT, KT, JI, AI, KF, HK, HNishie, YF, KOtani, OH, YM, TU, HH, TF, TT, MN, YN, AH, NS, TI, KOta, SKawaguchi, KH, and HNishikawa: Data collection.

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Abbreviations

BMI	body mass index
CI	confidence interval
EGD	esophagogastroduodenoscopy
H2RA	histamine-2 receptor antagonist
IPU	idiopathic peptic ulcer
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratios
PCAB	potassium-competitive acid blocker
PPI	proton pump inhibitor

Conflict of Interest

No potential conflicts of interest were disclosed.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

Ethical Considerations

This work was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the Research Ethics Committee of Osaka Medical University (approval number: 2856; UMIN test ID: UMIN000040951). Opt-out informed consent protocol was employed for the use of participant data for research purposes. This consent procedure was reviewed and approved by the Research Ethics Committee of Osaka Medical University (approval number: 2856; date of decision: July 8, 2020).

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