

Factors Affecting Depth of Gastric Ulcers

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[purpose] We investigated the differences in background factors, clinical features, and gastric function tests among gastric ulcers of various depths.

[Patients and Methods] The subjects were 68 patients (male 64, female 4) who were diagnosed as having a gastric ulcer at the angulus. The ulcers were classified according to depth based on the following: UL2 (shallow) ulceration to the submucosa; UL3 (intermediate), to the muscularis propria; and UL4 (deep excavation), beyond the muscularis propria. The depth of each ulcer was determined by endoscopic ultrasonography and/or ordinary endoscopic findings. We assessed clinical features, age, gender, smoking habit, alcohol consumption, ulcer history, presence of *H. pylori*, gastric acid secretion, gastric emptying, serum gastrin level, healing rate, and recurrence rate.

[Results] Patients with UL4-type ulcers had a higher rate of recurrence and a significantly higher incidence of *H. pylori* infection. Patients with hyperacidity and currently smoking or consuming alcohol were significantly more likely to have UL4-type ulcers than of UL2 or 3 ulcers. Furthermore, a close relationship was recognized between recurrence, intractability and deeply excavated ulcers. Ulcer depth was not correlated significantly with any of the following factors: 1) patient's profile; including gender and hemorrhagic symptoms; 2) gastric function; including gastric emptying and serum gastrin levels.

[Conclusions] Smoking, alcohol consumption, recurrence of ulcers, hyperacidity and *H. pylori* infections are important factors associated with deep ulcers.

Key words : Depth of gastric ulcers, Background factors, Clinical features, Gastric function, *H. pylori* infection

INTRODUCTION

Many factors involved in the development of gastric ulcers have been reported. However, factors that contribute to ulcer depth have not been clarified. In this study, differences in background factors, clinical features and gastric physiological functions were examined with respect to gastric ulcer depth.

PATIENTS AND METHODS

This study included patients with gastric ulcers of the angulus who were admitted to the Tokai University Hospital. Patients with serious complications were excluded. The depth of the ulcer was classified according to Murakami *et al.* [11]; UL2 represented ulceration to the submucosa, UL3 to the muscularis propria, UL4 beyond the muscularis propria. Lesions in which endoscopy

revealed a deeply excavated ulcer with roundwall-like swellings were considered UL4 ulcers in the angulus [13], as were lesions in which endoscopic ultrasonography revealed rupture of the muscularis propria [19]. Ulcers that did not show the findings described above were regarded as UL2 or 3. The following items were compared. Background factors included age, gender, rate of habitual smoking, rate of alcohol drinking and incidence of initial or recurrent ulcers. Clinical features included the presence or absence of hemorrhagic symptoms, frequency of endoscopic hemostasis, mean hemoglobin (Hb) values, blood transfusions, endoscopic healing rates 8 weeks after start of treatment (with H₂ receptor antagonist therapy), incidence of *Helicobacter Pylori* (*H. pylori*) infection and recurrence rate. The incidence of *H. pylori* infection was

Table 1 Correlation between background factors and depth of gastric ulceration

	UL4 (n=35)	UL2 or 3 (n=33)	significance
Age (years)*	57.6±2.4	50.2±2.2	p<0.05
Sex			
Male	33	31	N. S.**
Female	2	2	
Smoking habit			
<20 cigarettes/day	6	15	p<0.05
≥20 cigarettes/day	29	18	
Alcohol drinking			
daily (+)	14	9	p<0.05
daily (-)	21	24	
History			
ulcer (-)	8	15	p<0.05
ulcer (+)	27	18	

* mean ± S. E.

** N. S.=not significant

determined by histological examination and culture using biopsy specimens collected by endoscopy. Patients with a positive result on at least one test were regarded as positive for *H. pylori*. Endoscopy was performed every week after admission. After healing of the ulcer, endoscopy was performed at 6 and 12 months. Endoscopy was also performed in addition to the scheduled times in the event symptoms developed. Endoscopic detection of a white coat at the base of the ulcer was regarded as being indicative of recurrence. As gastric function tests, basal acid output (BAO), tetragastrin (4 µg/kg)-stimulated maximal acid output (MAO), peak acid output (PAO), and one hour volume output (OVO) were examined to monitor gastric acid secretion. The acetaminophen method⁴⁾ was used to assess gastric emptying, and serum gastrin levels were determined by radioimmunoassay. The integrated gastrin response (IGR) was tested at the same time as gastric emptying, and was expressed as the amount released during 60 minutes after a test meal [17]. Patients on omeprazole and lansoprazole, proton pump inhibitors, were excluded from these experiments, and all drugs were stopped 48 hours before testing. Significance of differences was tested using either the chi square test or unpaired T-test.

RESULTS

1. Background factors related to depth of gastric ulcer (Table 1)

In UL4 patients, the mean age was 57.6 years, and was higher than in UL2 or 3 patients (50.2 years). Concerning gender, the proportion of males was markedly higher than females in both groups. There was no significant difference between the two groups. Concerning habitual smoking, the percentage of UL4 patients who smoked 20 cigarettes/day or more was significantly higher than that of UL2 or 3 patients. With regard to alcohol drinking, patients were divided into 2 groups, the one group consumed alcohol daily, the other group did not. The percentage of UL4 patients drinking alcohol daily was higher than that of UL2 or 3 patients. Furthermore, when the incidence of initial or recurrent ulcers was evaluated by endoscopy, it was found that the incidence of recurrent ulcers was higher in UL4 than in UL2 or 3 patients.

2. Clinical features related to depth of gastric ulcer (Table 2)

There was no difference between the incidence of hemorrhagic symptoms such as hematemesis and/or melena, and the frequency of endoscopic hemostasis in UL4 and UL2 or 3 patients. Furthermore, neither

Table 2 Correlation between clinical features and the depth of gastric ulceration

	UL4 (n=35)	UL2 or 3 (n=33)	significance
Hemorrhagic symptoms (+)	19/35 (54%)	21/33 (64%)	N. S.*
Endoscopic hemostasis (+)	23/35 (66%)	26/33 (79%)	N. S.
Hb values (M±S. E.)	10.9±0.5 (g/dl)	10.1±0.6 (g/dl)	N. S.
Blood transfusion (+)	7/35 (20%)	4/33 (12%)	N. S.
Endoscopic healing rate (8 weeks)	14/35 (40%)	28/33 (85%)	p<0.01
Recurrence rate	15/35 (43%)	3/33 (9%)	p<0.01
Incidence of <i>H. pylori</i> infection	34/35 (97%)	26/33 (79%)	p<0.01

* N. S.=not significant

Table 3 Correlation between gastric physiological functions and the depth of gastric ulceration

	UL4 (n=35)	UL2 or 3 (n=33)	significance
BAO (mEq/h)	2.7±0.4 *	1.4±0.3	p<0.02
MAO (mEq/h)	14.4±1.5	10.3±1.1	p<0.05
PAO (mEq/h)	18.1±1.5	13.2±1.6	p<0.05
OVO (ml/h)	173.5±11.2	135.6±13.7	p<0.05
Gastric emptying (μ g/ml)	7.1±0.5	7.5±0.5	N. S.**
FGL (pg/ml)	81.7±9.3	89.8±8.1	N. S.
IGR (min ng/ml)	4.1±0.6	4.3±0.5	N. S.

BAO : basal acid output, MAO : maximal acid output
 PAO : peak acid output, OVO : one hour volume output
 FGL : fasting gastrin levels, IGR : integrated gastrin response

* Mean ± S. E.

** N. S.=not significant

the mean Hb. values nor rates of blood transfusion differed between the two groups.

Eight weeks after start of treatment with H₂ blockers, endoscopic healing rates were 40% (14/35) for UL4 patients and 85% (28/33) for UL2 or 3 patients, a significant difference. The recurrence rate one year after treatment with a half dose of H₂ block-

ers was examined. Recurrence rates were 43% (15/35) for UL4 patients and 9% (3/33) for UL2 or 3 patients, also significantly different. Incidence of *H. pylori* infection was 79% (26/33) for UL2 or 3 patients and 97% (34/35) for UL4 patients. This difference is also significant.

3. Gastric physiological functions related to depth of gastric ulcer (Table 3)

Gastric physiological functions were measured after healing. Concerning gastric acid secretion, the BAO in UL4 patients was 2.7 mEq/h, and was higher than that in UL2 or 3 patients (1.4 mEq/h). In UL4 patients, the MAO was 14.4 mEq/h, higher than in UL2 or 3 patients (10.3 mEq/h). In UL4 patients, the PAO was 18.1 mEq/h, significantly higher than in UL2 or 3 patients (13.2 mEq/h). The OVO in UL4 patients was 173.5 ml/h, and was higher than in UL2 or 3 patients (135.6 ml/h). In UL4 patients, gastric emptying was slightly delayed compared to UL2 or 3 patients. There were no significant differences in FGL or IGR between the two groups.

DISCUSSION

Lesions in which endoscopy revealed a deeply excavated ulcer with roundwall-like swellings were considered UL4 ulcers in the angulus [13]. In recent years, endoscopic ultrasonography has facilitated confirmation of a complete rupture of the muscularis propria, thereby permitting an accurate diagnosis of UL4 without surgical intervention. It has been reported that UL4 is usually detected in the angulus, a common site of gastric ulcers. Many factors are involved in the etiology of peptic ulcer. However, factors related to ulcer depth and the clinical features of UL4 remain to be clarified.

In this study, clinical features of patients with gastric ulcers in the angulus were correlated with ulcer depth. The mean age of UL4 patients was greater than that of UL2 or 3 patients. This suggests that mucosal defensive factors may be reduced in elderly patients. There are many reports indicating that gastric mucosal blood flow is reduced significantly with increasing age [10]. The relationship between ulcer depth and habits such as cigarette smoking and alcohol consumption was also examined. A high percentage of UL4 patients usually smoked and consumed alcohol. A decrease in mucosa-protecting function due to smoking-related reduction of gastric mucosal blood flow is associated with intractable ulcers, and has been reported as a risk factor for gastric ulcer development [18, 8]. Some studies have found that alcohol increases the risk of a gastric ulcer. However, other studies have

indicated that alcohol promotes healing of an intractable ulcer [16]. This may depend on concentration; high concentrations of ethanol directly damage gastric tissues, while low concentrations protect the stomach against mucosal necrosis. Robert *et al.* [14] reported that mild irritants, given intragastrically, are cytoprotective by stimulating the release of prostaglandin by the stomach. Since the incidence of recurrent ulcers was higher in UL4 patients, it was suggested that histological changes in the previous ulcer site may be a background factor influencing the depth of the recurrent ulcer. In patients with intractable ulcers, endoscopic ultrasonography showed that an irregular hypoechoic area (ulcer echo) around the ulcer remained even after a reduction in the size of the ulcer [12]. It has been speculated that ulcers with marked fibrosis on the serosal side are intractable. A high percentage of UL4 patients may show such findings. Some studies have reported that the duration of disease and the number of recurrences are important background factors in the etiology of intractable ulcers [3]. In the event of recurrence, deep ulcers may be formed, increasing the likelihood of intractability.

Endoscopic healing rates showed that UL4 was more intractable than either UL2 or 3, and that the recurrence rate was significantly higher in UL4 patients. Sakaki *et al.* [15] also reported similar results regarding healing and recurrence in UL4 patients. Intractable UL4 may be associated with a disorder in tissue contraction, an important factor in ulcer healing, related to fibrosis of the tissue surrounding the ulcer and associated with a blood flow disorder as well. However, we did not find any differences in the incidence of hemorrhagic symptoms or mean hemoglobin values between the two groups.

The incidence of *H. pylori* infection, considered a factor in gastric mucosal damage, was significantly higher in UL4 than in UL2 or 3 patients, suggesting that *H. pylori* is an aggressive factor that affects the entire gastric wall. However, *H. pylori* alone on the surface of the mucosal epithelium may not induce the formation of a deep ulcer involving the muscularis propria and serosa. An imbalance between aggressive and defensive factors may be important for ulcer formation. Other evidence that there is a relation-

ship between *H. pylori* and intractable ulcers is that eradication of *H. pylori* results in healing. Some studies have reported that there is no difference in the incidence of *H. pylori* infection between patients with perforating and non-perforating duodenal ulcers [9]. Other studies, however, have reported that the incidence of *H. pylori* infection is lower in perforating cases [6]. Thus, it is still speculative whether a relationship exists between *H. pylori* infection and perforating duodenal ulcers.

In the examination of gastric acid secretion, a factor related to ulcer depth, UL4 patients demonstrated hyperacidity compared to UL2 or 3 patients. This may indicate that ulcer depth is associated with gastric acid secretion. Some studies monitored gastric acid secretion in patients with and without perforating duodenal ulcers, and reported no difference [7]. Other studies, however, indicated that patients with perforating duodenal ulcers showed hyperacidity [6]. The results have not been consistent. Ashida *et al.* [1] reported that gastric acidity was enhanced in patients with intractable gastric ulcers, suggesting that there is also a relationship between gastric acid secretion and the healing rate. Hunt *et al.* [5] reported that duodenal ulcer healing rates showed a significant correlation with suppression of 24-hour hydrogen ion activity, but gastric ulcers did not.

There was no significant difference in gastric emptying between UL4 and UL2 or 3 patients, although gastric emptying was slightly delayed in the UL4 patients. Previous studies indicated that ulcers of the angulus were associated with delayed gastric emptying [2]. We suggest the following mechanism may be responsible: Deeper ulcers more markedly damage the muscularis propria, thereby reducing gastric motor function and causing a delay in gastric emptying, resulting in intractable lesions.

CONCLUSION

UL4 was intractable, and more readily recurred. Furthermore, it is suggested that background factors such as smoking and alcohol drinking, as well as local factors such as *H. pylori* infection and hyperacidity, are involved in the etiology of UL4.

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