Taken together, our data suggests that long-term *H. pylori* infection is associated with CD133-positive cell infiltration into the gastric mucosa. Celecoxib treatment might suppress CD133-positive cell migration via the reduction of CCR2 expression levels. Further studies are needed to clarify the mechanisms driving *H. pylori* infection-induced CD133-positive cell migration and its link to the progression of chronic gastritis into gastric cancer.

Acknowledgement

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ENDOSCOPIC IMAGE OF INTEREST

RARE CAUSE OF OBSCURE GASTROINTESTINAL BLEEDING DUE TO PYOGENIC GRANULOMA IN THE ILEUM DETECTED BY CAPSULE ENDOSCOPY AND TREATED WITH DOUBLE BALLOON ENDOSCOPY

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Pyogenic granuloma is a lobular capillary hemangioma that occurs mostly on the skin, and occasionally on the mucosal surface of the oral cavity, but very rarely in the gastrointestinal tract. We report the case of a 63-year-old woman who suffered from palpitations, and iron deficiency anemia for 5 years. Esophagogastroduodenoscopy and colonoscopy could not reveal significant bleeding focus. She had not received medical treatment except for oral iron. Capsule endoscopy revealed a bleeding focus in the small intestine. Afterwards, we carried out double balloon endoscopy to treat the lesion. We found a subpedunculated polyp in the small intestine at 100 cm away from ileocecal valve by double balloon endoscopy and resected it endoscopically. The histological features of the polyp were consistent with pyogenic granuloma. Anemia had improved gradually without giving oral iron after polypectomy.

Key words: capsule endoscopy, double balloon endoscopy, obscure gastrointestinal bleeding, pyogenic granuloma, small intestine.

INTRODUCTION

The source of gastrointestinal (GI) bleeding can be identified in most cases by conventional upper or lower GI endoscopy, but approximately 5% of all GI bleeds remain undiagnosed. Obscure gastrointestinal bleeding (OGIB) is defined as bleeding from the GI tract that persists or recurs without an obvious etiology after esophagogastroduodenoscopy (EGD) and colonoscopy (CS). The bleeding source of OGIB is frequently located in the small intestine, and it has been easily detected since capsule endoscopy (CE) and double balloon endoscopy (DBE) came into practical use. CE and DBE are highly effective in diagnosing the bleeding origin of OGIB.[1,2] Additionally DBE is a new method that allows visualization, tissue sampling, and therapeutic intervention of a variety of pathologies throughout the small intestine.

Pyogenic granuloma occurs commonly on the skin of the head, face, hands and upper trunk, but it is extremely rare in the GI tract except for the oral cavity. Also, it is very rare to identify pyogenic granuloma as the cause of OGIB, although various types of tumors were found in the small intestine by DBE.[3] We report a case of pyogenic granuloma in the small intestine detected by CE and subsequently treated by DBE.

CASE REPORT

A 63-year-old woman had suffered from palpitations and iron deficiency anemia since 2002 and her hemoglobin level was approximately 4 mg/dL (normal range: 12–16 g/dL). She had no medical history nor took any medicine, including non-steroidal anti-inflammatory drugs (NSAIDs). EGD and CS failed to reveal a significant bleeding focus. After giving oral iron, her symptoms improved and her hemoglobin level was approximately 10 mg/dL. However, her primary doctor stopped oral iron because her serum ferrous level was becoming extremely high in 2007. Subsequently, she complained of palpitations and shortness of breath and her hemoglobin level decreased to 6 mg/dL. She underwent EGD, CS, abdominal CT, and bleeding scintigraphy, but no significant lesions could be detected.

She was then referred to our hospital in order to examine the entire small intestine. Laboratory test results of her first visit to our hospital included red blood cell count of $260 \times 10^4/mm^3$ ($400–500 \times 10^4/mm^3$), hemoglobin level of 8.7 g/dL and hematocrit level of 26.5% (33–43%). Results of fecal occult blood tests were positive. We first carried out CE which revealed a little oozing protruded focus with fresh blood in the ileum (Fig. 1). Afterwards, we carried out DBE for treatment and found a subpedunculated polyp with a smooth surface in the small intestine 100 cm away from the ileocecal valve (Fig. 2). We identified this polyp as the bleeding focus because there was no other lesion in the entire small intestine. The polyp was resected by endoscopic mucosal resection, because the non-lifting sign of this polyp was negative. The polyp was 7 mm in diameter and shaped like a hemisphere with a smooth surface. Her hemoglobin level increased from 8.7 to 10.1 g/dL 1 week after polypectomy, thereby confirming that the anemia was caused by bleeding from the polyp. Histological examination of the resected polyp showed proliferation of blood capillaries and

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microvessels densely accompanying inflammatory cell infiltration and granulation tissue (Fig. 3). Because proliferation of blood vessels came from the submucosal layer, we diagnosed it as a pyogenic granuloma and it was considered the cause of the anemia.

DISCUSSION

Pyogenic granuloma is called granuloma telangiectaticum or lobular capillary hemangioma and was first described in 1897 by two French surgeons, Poncet and Dor. Macroscopically, this lesion reveals polypoid growth with a subpedunculated configuration. Microscopically, its structure is the same as capillary hemangioma with a lobulated formation. The distinctive histopathological characteristics of pyogenic granuloma are proliferation and lobular arrangement of capillary-sized vessels with inflamed and edematous stroma and endothelial cell swelling. It is accompanied by ulceration on its surface and granulation with infiltration of inflammatory cells, including neutrophils. Pyogenic granuloma is a benign lesion and its mechanism of occurrence is considered to be that a damaged dense part of an arteriovenous anastomosis has developed capillary proliferation as a reaction to injury. However, the precise etiology is unknown. Pyogenic granuloma usually occurs in the skin and mucosal surfaces, and GI involvement is rare except for the oral cavity. Because the small intestine is long, tortuous, distant from both ends of the digestive tract and in an unfixed position, deep insertion and clinical diagnosis of the small intestine was difficult until recently. For these reasons, pyogenic granuloma of the small intestine is extremely rare.[4] However, similar cases will be found in the future in proportion to the prevalence of CE and DBE. Furthermore, recently, pyogenic granuloma of the GI tract, except for the small intestine, treated by endoscopic resection, not by surgical resection, has been reported. Endoscopic treatment is relatively easy, safe, and of low cost for small-sized pyogenic granuloma of the GI tract.[5]

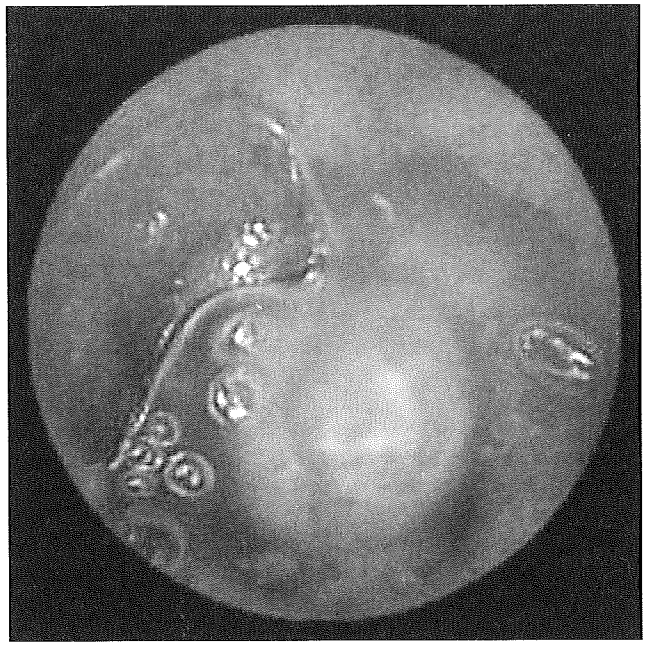

Fig. 1. Capsule endoscopy findings of a little oozing protruded focus with blood in the ileum.

It is necessary to resect pyogenic granuloma including arteriovenous anastomosis under the tumor endoscopically, because incomplete resection might cause recurrence. In this case, we considered that the lesion remained in the mucosal layer or the submucosal layer, because the non-lifting sign of the polyp was negative. However, medium-sized blood vessels were observed to proliferate histologically at the cut margin. It was difficult to determine whether the vertical resection margin was positive or negative on the resected specimen, because proliferated vessels seemed to continue from the submucosal layer. It is difficult to see the remaining part of the arteriovenous anastomosis under the submucosal layer in the endoscopically treated specimen. Therefore, careful surveillance will be needed after polypectomy. The prognosis of pyogenic granuloma is good and there has been no report of malignant changes so far.

In summary, GI pyogenic granuloma is a rare cause of OGIB. Awareness of such an infrequent benign lesion makes it easy to diagnose and treat properly. Finally, the incidence of lesions of the small intestine, including pyogenic granuloma, will probably increase by using CE and DBE, and many of them might be treated with DBE in the future.

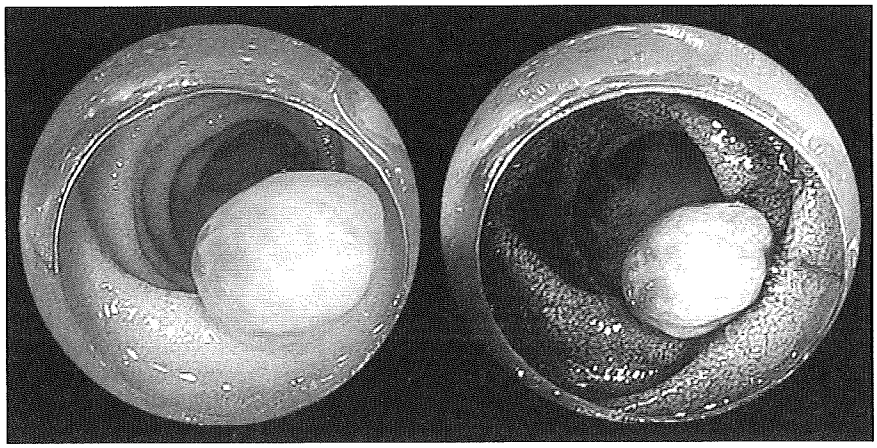

Fig. 2. Double balloon endoscopy findings of a subpedunculated polyp in the small intestine 100 cm away from the ileocecal valve.

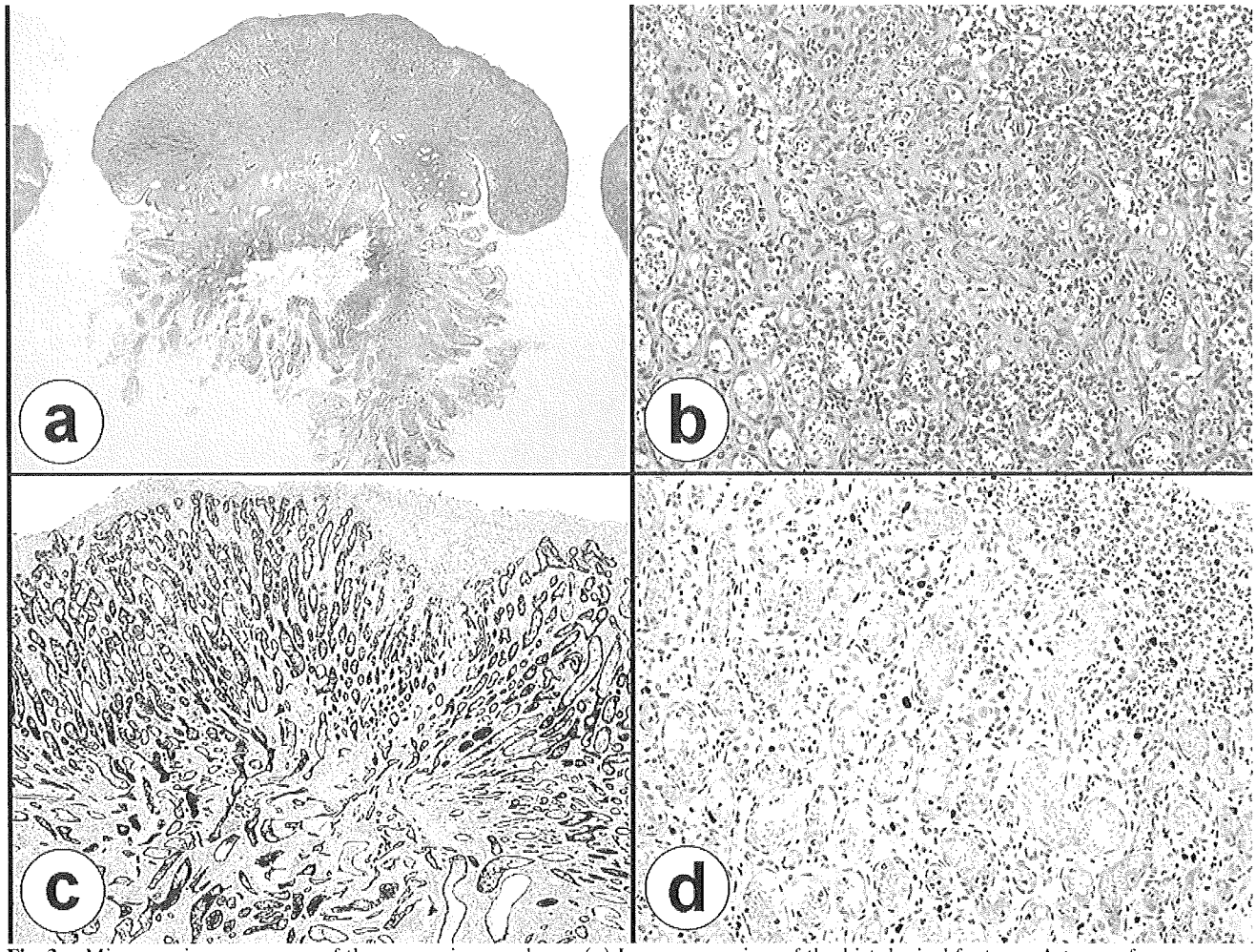

Fig. 3. Microscopic appearance of the pyogenic granuloma. (a) Low-power view of the histological features. A torose focus comes from the submucosal layer (original magnification ×20). (b) High-power view of microscopic features. Remarkable inflammatory cell invasion and granulation tissues are noted (original magnification ×200). (c) Immunostaining for von Willebrand Factor; proliferation of blood capillaries and blood vessels is evident (original magnification ×100). (d) Immunostaining for Ki-67; Ki-67 is positive in capillary endothelial cells and inflammatory cells. The labeling index is fairly low in both cell types (original magnification ×200).

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ORIGINAL ARTICLE—ALIMENTARY TRACT

The appearance of rosette-like esophageal folds ("esophageal rosette") in the lower esophagus after a deep inspiration is a characteristic endoscopic finding of primary achalasia

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Abstract
Background In healthy subjects who inspire deeply the lower esophagus usually opens, and the esophageal palisade vessels (EPVs) become visible. However, in patients with achalasia, the full extent of the EPVs does not become visible and, in addition, rosette-like esophageal folds appear in the lower esophagus. The aim of this study was to investigate whether or not these changes at the lower esophagus are characteristic findings of achalasia.
Methods A total of 34 patients with achalasia and no esophageal dilatation following deep inspiration were compared with 34 sex- and age-matched control subjects. Following a deep inspiration, the lower esophagus of all study cohorts was evaluated on (1) whether or not the full extent of the EPVs was visible, (2) whether or not rosette-like esophageal folds appeared in the lower esophagus, and (3) whether or not there were any gastric lesions.
Results One patient had secondary achalasia, and the remaining 33 patients had primary achalasia. In the control subjects, the full extent of the EPVs was clearly visible after a deep inspiration, and no esophageal folds appeared in the lower esophagus. In contrast, in the achalasia patients, EPVs were not observed in all patients after a deep inspiration, and rosette-like esophageal folds appeared in 33 of the 34 patients.
Conclusion After a deep inspiration, the non-visibility of the EPVs and the appearance of rosette-like esophageal folds at the lower esophagus, which we have called "esophageal rosette", are characteristic endoscopic findings of primary achalasia.

Keywords Endoscopic findings of achalasia · Esophageal rosette · Esophagogastric junction · Palisade vessels · Primary achalasia

Introduction

Achalasia is a primary motility disorder of unknown etiology that is characterized by esophageal aperistalsis and the failure of the lower esophageal sphincter (LES) to relax on swallowing [1]. The functional obstruction at the level of the LES causes dysphagia and the regurgitation of esophageal content. Achalasia is not difficult to diagnose if the esophagus is dilated and if there is abnormal liquid and/or retention of food in the esophagus. Esophageal dilatation and tapered deformity of the distal esophagus generally occur with advancement of the condition and are visible as radiological manifestations of the disease [1, 2]. If these findings are not present, achalasia may not be diagnosed for a long period of time, and psychological factors can be considered to be the cause of the symptoms. Esophageal manometry provides a definitive method of differentiating achalasia from other esophageal motor disorders. In Asian countries, including Japan, however, esophageal manometry is not commonly used; instead, when a patient with dysphagia visits a hospital, the first examination carried out is an esophagogastroduodenoscopy (EGD). It is important, therefore, to determine other characteristic findings of achalasia in order to accurately diagnose this condition in

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patients who do not have the most common findings on barium swallow, such as dilatation of the esophagus and abnormal liquid and/or retention of food in the esophagus.

In our hospital, when we evaluate the esophagogastric junction (EGJ), we always request that a patient inspire deeply while the lower esophagus is being inflated with air, which results in the lower esophagus opening and the esophageal palisade vessels (EPVs) above the EGJ becoming visible (Fig. 1). However, when we ask patients with achalasia to inspire deeply, we have noticed that the full extent of the EPVs does not become visible and, in addition, rosette-like esophageal folds appear at the luminal of center of the lower esophagus (Fig. 2). Given the fact that the LES is located in the lower esophagus, such observations may be important findings for the early diagnosis of achalasia. The aim of this study, therefore, was to investigate whether or not such changes in the lower esophagus are characteristic findings of achalasia.

Materials and methods

Patients with achalasia who were self- or physician-referred to the Nippon Medical School Hospital between January 2002 and June 2009 were enrolled in this study. The achalasia patient group comprised 34 patients (16 males and 18 females; mean age 51.6, range 28–76 years) with no esophageal dilatation (<35 mm) on barium swallow and who were diagnosed with achalasia using esophageal high-resolution manometry. All patients with achalasia had dysphagia on a daily basis, the median duration of which was 36 months (interquartile range 12–60 months). In each case, age- and sex-matched asymptomatic control subjects were selected (34 patients, 16 males and 18 females; mean age 51.6 years, range 28–76 years) from patients who had visited our hospital. None of the control subjects had hiatus hernia, defined as apparent separation of the EGJ and the diaphragm impression by greater than 2 cm at endoscopy. The control subjects underwent an EGD but showed no localized lesions in the esophagus, stomach, or duodenum. They also stated that they had no history of upper gastrointestinal disease or any related symptoms, including dysphagia, regurgitation, or chest pain. Informed consent was obtained from all subjects, and the study was conducted according to the provisions of the Declaration of Helsinki.

Esophageal manometry

Esophageal manometry was performed with a 21-channel manometric assembly (Dentsleeve, Wayville, Australia). Ten side holes, which were spaced at 1-cm intervals, starting at 3 cm above the distal end of the assembly, monitored pressure from the proximal stomach, LES, and distal esophagus. A further seven side holes, spaced at 2-cm intervals, monitored pressure from the distal to the proximal esophagus, and four side holes, at 3, 6, 10, 13 cm above the most proximal of the 2-cm interval side holes, monitored pressure from the proximal esophagus to the pharynx.

Each lumen was perfused with degassed distilled water at 0.15 ml/min by a low compliance manometric infusion pump (Dentsleeve). Data were digitized with a computer, and the digitized signals were displayed, stored, and analyzed using Trace! Software (Dr. G.S. Hebbard, Royal Melbourne Hospital, Melbourne, Australia).

Subjects were studied in the sitting position after fasting overnight. The manometric assembly was passed via an anesthetized nostril and positioned so that the most proximal of the 1-cm interval side holes was 2 cm above the LES. The subjects were then allowed to adapt to the assembly for 10 min. Baseline recordings of LES pressure were made for 5 min, after which primary peristalsis was assessed.

Primary peristalsis and residual LES pressure, after a swallow, were assessed in response to ten swallows of a 5-ml water bolus, with each swallow separated by a 30-s interval. Patterns of LES pressure were analyzed using the profile of pressure across the full extent of the ten 1-cm spaced side-hole array, which straddled the EGJ. Incomplete relaxation of the LES was defined as the mean of the ten lowest residual LES pressures, relative to the gastric baseline, within 5 s of a swallowing of more than 4 mmHg [3]. Diagnosis of achalasia by esophageal manometry is made when esophageal aperistalsis and incomplete relaxation of the LES is present in a patient.

Endoscopy

Following the diagnosis of achalasia by esophageal manometry, EGD was performed on all patients while in a fully conscious state, and the EGJ was always evaluated before the endoscope was inserted into the stomach. Observation of the EGJ was as follows: patients were requested to inspire deeply while air was put into the lower esophagus, at which time the lower esophagus usually opened and the EPVs above the EGJ could be observed. The lower esophagus was evaluated based on: (1) whether or not the full extent of the palisade vessels was visible and (2) whether or not the appearance of rosette-like esophageal folds at the lower esophagus could be seen after a deep inspiration. In addition to the above, we also examined whether or not there were any esophageal or gastric lesions. After evaluating the lower esophagus, we examined the stomach and the duodenum in all patients. All endoscopic examinations were evaluated by a sole endoscopist (K.I.).

Results

Gastric and duodenum lesions

Of the 34 patients with achalasia diagnosed by esophageal high-resolution manometry, one had gastric cardia cancer. This case, therefore, was secondary achalasia due to the invasion of the LES by gastric cardia cancer. The pathology of the resected specimen showed a moderately differentiated tubular adenocarcinoma invading the subserosa. The remaining 33 patients had primary achalasia.

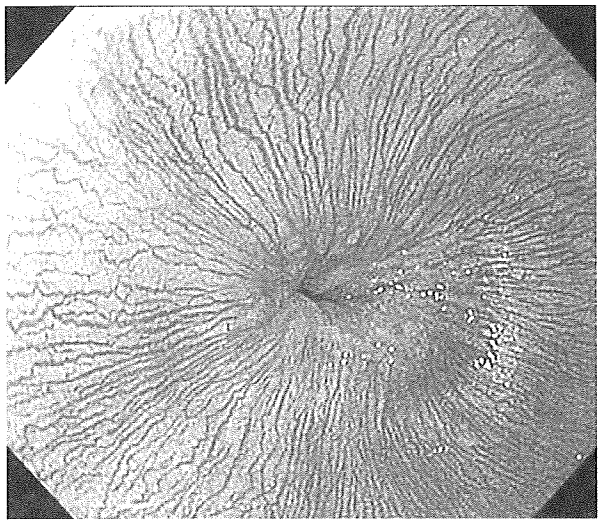

Fig. 1 Endoscopic finding of the esophagogastric junction in healthy subjects after a deep inspiration. The esophageal palisade vessels are visible in the lower esophagus

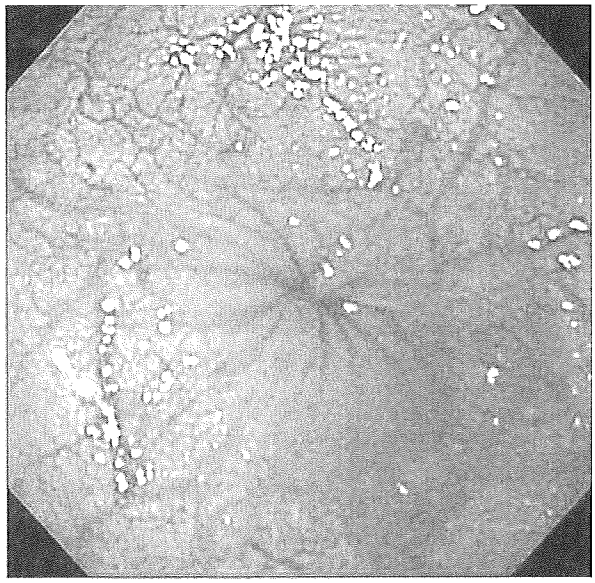

Fig. 2 Endoscopic finding of the esophagogastric junction in patients with primary achalasia who had no dilatation after a deep inspiration. The appearance of rosette-like esophageal folds at the luminal center of the lower esophagus is observed, and the esophageal folds are distributed in all directions

Retained liquid or food in the esophagus

There was no retention of abnormal liquid or food in the esophagus in either group (Table 1).

Esophageal palisade vessels

In the control subjects, the full extent of the EPVs was clearly visible after a deep inspiration, and the lower ends of the EPVs were observed. After a deep inspiration, however, the EPVs were not visible in 28 of the 34 patients, and in the remaining six patients they were only partially visible. Therefore, in the achalasia group, the full extent of the EPVs was not observed (Table 1).

Table 1 Esophageal endoscopic findings in patients with achalasia and control subjects

Esophageal endoscopic findings	Achalasia group	Control group
Existence of retained abnormal liquid or food in the esophagus	0/34 (0%)	0/34 (0%)
Visibility of the full extent of the esophageal palisade vessels after a deep inspiration	0/34 (0%)	34/34 (100%)
Existence of the rosette-like esophageal folds at the lower esophagus	33/34 (97.1%)	0/34 (0%)

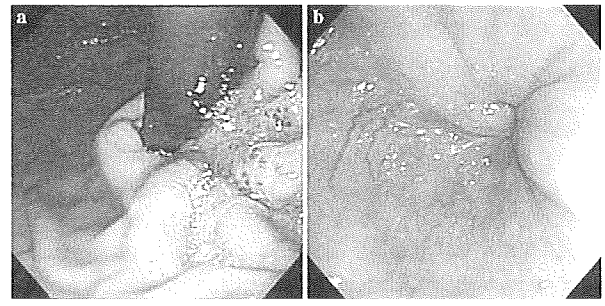

Fig. 3 Endoscopic finding in a patient with secondary achalasia due to the invasion of the lower esophageal sphincter with gastric cardia cancer. Pathology of the resected specimen showed a moderately differentiated tubular adenocarcinoma invading the subserosa. **a** Gastric cardia cancer with converging folds was observed at the lesser curvature of the gastric cardia. **b** Uneven esophageal folds were observed at the lower esophagus, after a deep inspiration

The appearance of rosette-like esophageal folds in the lower esophagus after a deep inspiration

In the control subjects, no folds were formed at the lower esophagus after a deep inspiration. In contrast, in 33 of the 34 patients with achalasia, rosette-like esophageal folds were observed at the luminal center of the lower esophagus (Table 1). In the one patient with gastric cardia cancer (secondary achalasia) (Fig. 3a), esophageal folds were observed, but these folds were unevenly distributed (Fig. 3b) and not rosette-like in appearance.

Discussion

The EGJ is defined differently in Japan than in Western countries based on different endoscopic diagnostic criteria. In Western countries, the upper limit of the gastric fold is considered to be the landmark of the EGJ [4–6], while in Japan, the distal end of the lower EPVs is used as the endoscopic landmark of the EGJ [7–9]. This diagnostic criterium has been approved by The Japan Esophageal Society [10]. To observe the EPVs accurately, it is essential to evaluate them after the patient has inspired deeply. We always evaluate the short segment Barrett's esophagus or the esophageal mucosal break after a deep inspiration. Based on our experience using this method for observing the EPVs, we noticed that in patients with achalasia, the full extent of the EPVs was either not visible or it was only partially visible. We also noticed that rosette-like esophageal folds appeared at the luminal center of lower esophagus in almost all patients with achalasia.

In this study, in six patients with achalasia, the EPVs were partially visible after a deep inspiration, but in the remaining 28 patients, they were not visible at all. In addition, rosette-like esophageal folds at the lower esophagus could be observed in 33 of the 34 patients with achalasia. In contrast, in the age- and sex-matched asymptomatic control subjects, the full extent of the EPVs was visible, and esophageal folds at the lower esophagus were not. These results strongly suggest that, after a deep inspiration, the non-visibility of the EPVs and the appearance of rosette-like esophageal folds at the lower esophagus are endoscopic findings that characterize achalasia.

The LES is thought to be positioned in the same place as the EPVs; consequently, because patients with achalasia have an incomplete LES relaxation, the LES does not open. However, the oral side, which is above the LES, does open, resulting in the appearance of rosette-like esophageal folds. The appearance of rosette-like esophageal folds after a deep inspiration may well be an endoscopic characteristic finding of achalasia, but care should be taken because in cases where the inspiration is insufficient, it is possible that similar findings can also be observed in healthy subjects. It is important, therefore, to try to evaluate the EPVs after the patient has inspired deeply.

In this study, one of the 34 patients with achalasia had gastric cardia cancer invading the subserosa; this was therefore a case of secondary achalasia due to the invasion of the LES by gastric cardia cancer. There was a difference in the appearance of the esophageal folds between those patients with primary achalasia and the one patient with secondary achalasia. The esophageal folds of the former were distributed in all directions, taking on a rosette-like in appearance. In the one patient with secondary achalasia, however, the esophageal folds were unevenly distributed. In cases where rosette-like esophageal folds appear in the lower esophagus after a deep inspiration, it is highly possible that patients have primary achalasia.

Based on our results, we conclude that, after a deep inspiration, the non-visibility of the EPVs and the appearance of rosette-like esophageal folds in the lower esophagus, which we have called "esophageal rosette", are characteristic endoscopic findings of primary achalasia. We therefore strongly suggest that an attempt to observe the EPVs, after a deep inspiration, is a useful procedure in the diagnosis of achalasia and of "Barrett's mucosa" and reflux esophagitis.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Predictors of a better outcome of pneumatic dilatation in patients with primary achalasia

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Abstract
Objective Pneumatic dilatation (PD) has been widely used in the treatment of primary achalasia. The aim of this study was to evaluate the effectiveness of PD and its predictive factors in Japanese patients with primary achalasia.
Methods Fifty-five consecutive patients were treated using PD (Rigiflex balloon dilator). Diagnosis was established through radiographic and/or esophageal manometry. All patients underwent a pre-designed clinical evaluation prior to and 6 months after PD treatment. We defined success of PD as 6 months or more of clinical remission, with a total score (0–4) ≤ 2, a decrease in the total score ≥ 1 and the score for each item ≤ 1. Possible predictive factors to response were analyzed.
Results Successful PD was achieved in 41 of 55 (74.5%) patients. The median age (58.0 years) in the successful group was significantly older than in the failure group (37.5 years), but there were no differences in other factors between the groups. When the cut-off value was set at 40 years of age, the success rate of PD in the >40-year age group was 85.7%, while the <40-year age group achieved a rate of only 38.5%. Multivariate logistic regression analysis also demonstrated that older age was the only independent factor associated with the success of PD. There was no perforation related to PD.
Conclusions PD is a safe and effective treatment for achalasia, particularly in older patients who experience a better outcome than younger patients.

Keywords Achalasia · Pneumatic dilatation · Dysphagia

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Introduction

Achalasia, characterized by esophageal aperistalsis and incomplete relaxation of the lower esophageal sphincter (LES) with swallowing, is the most common primary esophageal motor disorder of the esophagus [1, 2]. Dysphagia, regurgitation, chest pain, and weight loss are among the most recognized clinical features of the disease [3, 4]. The aim of therapy in patients with achalasia is to reduce distal obstruction, which can be treated by botulinum toxin injection, pneumatic dilatation (PD) or surgical esophagomyotomy [3]. For many authors, PD is considered the first-line therapy in esophageal achalasia that can result in remission in 67–90% of patients [3]. Surgical myotomy should be offered to patients who do not respond to PD [5]. However, it is important to know PD outcomes and possible predictive response factors that can help select the group of patients most likely to benefit from early surgery. In Japan, however, there are few data regarding PD in patients with primary achalasia.

The aim of this study was to evaluate the effectiveness of PD and its predictive factors in Japanese patients with primary achalasia and to assess its safety and any adverse effects.

Methods

This was a prospective study in which 55 patients were included consecutively. Patients had been previously

diagnosed with primary esophageal achalasia between January 2002 and December 2007 in the Nippon Medical School Hospital. All patients were included in the PD protocol and were clinically assessed before PD, undergoing a barium esophagram, esophagogastroscopy and esophageal manometry. Patients were excluced if they had previously received PD or surgical esophagomyotomy or had secondary achalasia. Patients were not treated with any drugs that could have altered the PD result.

Clinical evaluation

At the initial investigation and at each subsequent visit, the main symptoms (dysphagia and regurgitation) were evaluated and each was given a score between 0 and 2 (almost no symptoms = 0, occasional symptoms = 1 and daily symptoms = 2). Patients were considered to have reached clinical remission when the total scores (0–4) were ≤ 2, a decrease in the total score was ≥ 1 and each item was ≤ 1. Chest pain and body weight loss were also investigated. The success of PD was defined as 6 months or more of clinical remission.

Radiographic and endoscopic study

The maximum diameter of the esophageal body was measured before PD using a barium esophagram. The definition of achalasia by radiographic study is dilatation of the esophagus of more than 35 mm and/or liquid or food retention in the esophagus with the lower esophagus having the appearance of a "bird's beak." Achalasia was classified into three groups based on the maximum diameter of the esophageal body (<35 mm, 35–59 mm, ≥ 60 mm). Secondary achalasia was ruled out by an endoscopic examination of the cardia area.

Esophageal manometry

Esophageal manometry was performed with a 21-channel manometric assembly (Dentsleeve, Wayville, Australia). Ten side holes, which were spaced at 1-cm intervals starting at 3 cm above the distal end of the assembly, monitored pressure from the proximal stomach, LES and distal esophagus. An additional seven side holes, spaced at 2-cm intervals, monitored pressure from the distal to the proximal esophagus; four side holes located at 3, 6, 10, 13 cm above the most proximal of the 2-cm interval side holes monitored pressure from the proximal esophagus to the pharynx.

Each lumen was perfused with degassed distilled water at 0.15 mL/min using a low compliance manometric infusion pump (Dentsleeve). Data were digitized with a computer and the digitized signals were displayed, stored, and analyzed using Trace! Software (Dr G.S. Hebbard, Royal Melbourne Hospital, Melbourne, Australia).

Subjects were studied in the sitting position after fasting overnight. The manometric assembly was passed via an anaesthetized nostril and positioned so that the most proximal of the 1-cm interval side holes was 2 cm above the LES. The subjects were then allowed to adapt to the assembly for 10 min. Baseline recordings of LES pressure were made for 5 min, after which primary peristalsis was assessed.

Primary peristalsis and the lowest residual LES pressure were assessed in response to 10 swallows of a 5-mL water bolus. Each swallow was separated by a 30-s interval. For the analysis of patterns of LES pressure, the profile of pressure was used across the full extent of the ten 1-cm spaced, side-hole array that straddled the esophagogastric junction. Incomplete relaxation of the LES was defined as the mean of the 10 lowest residual LES pressures within 5-s of swallowing more than 4 mmHg compared to the gastric baseline [6]. Diagnosis of achalasia by esophageal manometry is made when esophageal aperistalsis and incomplete relaxation of LES is present in a patient.

Pneumatic dilatation

Four physicians (YT, KI, NK, HS), using a Rigiflex balloon dilator (Microvasive, Milford, MA, USA), performed all procedures on patients who had fasted overnight. First, a guide wire was placed endoscopically into the stomach and the dilator was positioned across the gastroesophageal junction over the guide wire under fluoroscopic control. The balloon was then inflated three times over the course of 180 s at 60-s intervals. During the first dilatation, the balloon was gradually inflated up to 3–4 psi in 20–30 s, followed by a second dilatation reaching 4–5 psi and a third dilatation of 5–7 psi. The pressure of the balloon was determined by the pain-threshold of individual patients. This method of carrying out PD has a long history of use in our hospital, with no serious side-effects (e.g. perforation). The first treatment of dilatation was always performed with a 30-mm diameter balloon. Dilatations were performed under sedation with intravenous injections of pentazocine (7.5–15 mg) and hydroxyzine (12.5–25 mg).

Protocol of iterative pneumatic dilatations

A second treatment using a 35-mm diameter balloon was performed a week after initial treatment if clinical remission had not been achieved. The dilatations were considered to have failed and the patients were proposed for a surgical esophagomyotomy if clinical remission had not been achieved following the second treatment. For patients in clinical remission, scheduled visits were planned at

2 months and then every 6 months after the last PD. The main symptoms were evaluated at each visit. Endoscopy examination was consistently carried out 12 months following the last PD; December 2008 served as the end-point for final clinical evaluation.

In case of a relapse after a 6-month period of clinical remission, a subsequent treatment of PD was performed with the same protocol. Subsequent treatment commenced from the last dilator size at which clinical remission was achieved. However, in case of a relapse within 6 months after clinical remission, the dilatations were considered to have failed and patients were proposed for a surgical esophagomyotomy.

Statistical analysis

Frequencies, percentages and medians (interquartile range) were used in the descriptive statistics of the clinical variables. The effect of factors that predict the success response to PD in patients was first assessed using a univariate analysis with the Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables. Possible predictive response factors to PD were determined by multivariate analysis based on a logistic regression model: age, gender, total symptom score, dilatation of esophagus, weight loss, basal LES pressure, lowest residual LES pressures after a swallow, and the number of months of having symptoms prior to the first dilatation. A p value <0.05 was considered statistically significant.

Results

Fifty-five patients were treated for esophageal primary achalasia in our hospital between 2002 and 2007. Forty-five of 55 patients were diagnosed using esophageal manometry, but the remaining 10 patients were diagnosed using an esophagogram because esophageal dilatation and the bend of the lower esophagus made it difficult to place the manometric catheter into the stomach. The clinical characteristics and demographic data of patients are summarized (Table 1).

Outcome of PD

After the first treatment of PD, remission was achieved in 44 of 55 (80.0%) patients. Forty-two of 44 (95.5%) patients required 1 dilatation and 2 (4.5%) patients needed 2 dilatations to achieve remission. Three patients experienced recurrence within 6 months after the first treatment; as a result, PD was successfully achieved in 41 of 55 (74.5%) patients. PD failed to achieve clinical remission in 14 of 55 (25.5%) patients, who were then offered surgery.

Table 1 Clinical characteristics and demographic data of patients with achalasia

Age (years)	54.0 (40.5–66.0)
Gender (male/female)	25/30
Weight loss (kg)	3.0 (0–8.0)
Duration of symptoms (months)	36.0 (18.0–87.0)
Dysphagia	55/55 (100%)
Regurgitation	45/55 (81.8%)
Chest pain	9/55 (16.4%)

Median (interquartile range)

Predictive PD response factors

The median age in the successful group was 58.0 years (47.8–66.0), which is significantly older than that of the failure group 37.5 years (27.0–58.0). Otherwise, there were no differences in other factors between the groups (Table 2). The success rate of PD in the >40 year age group ($n = 42$) was 85.7% (36/42) when the cut-off value was set at 40 years of age, but it was only 38.5% (5/13) in the <40 year age group ($n = 13$) (Fig. 1). Those under 30 had no clinical remission after PD. Multivariate logistic regression analysis also demonstrated that older age was the only independent factor (Odds ratio = 1.070, 95% confidence interval 1.009–1.133, $p < 0.0227$) associated with the success of PD.

Follow up

The follow-up period after the first PD in the 41 patients with successful PD ranged between 12 and 74 months (28.0 months (19.8–41.5)). Three (7.3%) of these patients experienced a clinical recurrence after PD at 8, 18, and 24 months, respectively. The patient, who experienced recurrence at 8 months after PD, refused further PD treatment and instead received a surgical esophagomyotomy. The remaining 2 patients again received PD treatment and achieved clinical remission.

Complications

There was no perforation related to PD. During follow-up, 3 of 41 patients who had successful PD had reflux esophagitis of grade B of the Los Angeles classification.

Discussion

The main symptoms of achalasia are dysphasia, regurgitation and chest pain; all are symptoms usually used to parameters of the effectiveness of PD. Most of our patients had dysphagia and regurgitation but only approximately 9

Table 2 Univariate analysis of factors associated with the success of pneumatic dilatation

Factor	Pneumatic dilatation		Univariate
	Success	Failure	*P* value
Clinical presentation			
Age	58.0 (47.8–66.0)	37.5 (27.0–58.0)	0.0141
Gender (male/female)	20/21	5/9	0.3966
Total symptom score	3 (3–4)	3 (3–4)	0.4989
Body weight loss (kg)	5.0 (0–8.0)	2.5 (0–8.0)	0.3846
Duration of symptoms (months)	36.0 (24.0–81.0)	36.0 (15.0–96.0)	0.7241
Esophageal dilatation (<35 mm/35–59 mm/≥60 mm)	13/20/8	6/7/1	0.5080
Manometric findings			
Basal LES pressure (mmHg)	20.0 (15.2–27.6)	25.3 (18.7–38.6)	0.1348
Lowest residual LES pressure (mmHg)	14.6 (10.4–17.5)	15.6 (13.7–24.1)	0.2543
Esophageal body pressure	4.0 (−3.1–5.5)	5.0 (3.8–5.9)	0.222

Median (interquartile range)
LES lower esophageal sphincter

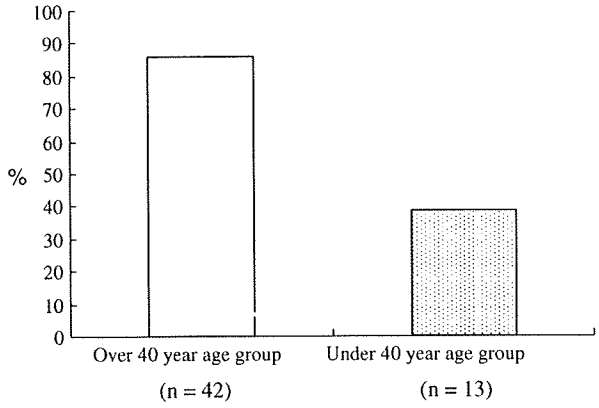

Fig. 1 The difference in the success rate of pneumatic dilatation between age groups below and above 40 years

(16.4%) had chest pain. Considering these results, we excluded chest pain as a parameter of the effectiveness of PD.

The cumulative effectiveness of PD for achalasia was 74.5% in our study, although a previous study reported effectivness around 80%—a little lower than a previous study [3]. The number of PDs used in 53 of 55 patients was one only; therefore, most of the balloons used in the PDs were 30 mm. The cumulative effectiveness of 30 mm balloons was 74% in previous studies [3], a result similar to that of our study when the diameter of the balloon is taken into account.

With regard to the number of PDs, it is thought that dilatations should continue until clinical remission is achieved. The American Society for Gastrointestinal Endoscopy recommends a second dilatation session if a single attempt (size of the balloon dilatator unspecified) does not produce satisfactory relief. Surgery is usually the next course of action if the second dilatation fails [7]. The results of previous PD procedures we have carried out lead us to conclude that most patients who responded effectively to PD were able to achieve a clinical remission with only one treatment. For these reasons, if patients did not achieve clinical remission after the second treatment we regarded them as having failed PD treatment. Repeated PDs cause adhesions to the outside of the LES and adhesions make operating difficult. Because the effectiveness of surgery is good enough [3], we believe that repeated PDs should not be performed. The reduced number of PDs may also have had an affect on our cumulative effectiveness of PD, which is a little lower than that of previous studies.

It has been previously reported that the inflation pressure of PD was 8–15 psi [8–10]; however, in our method, it was 3–7 psi. Although dilatations were performed under sedation, increasing the inflation pressure of the balloon was problematic for patients who complained of severe pain as pressure increased. The lower inflation pressure of the balloon may have also been a factor in the cumulative effectiveness of our PD results.

It is important to know the predictive response factors to PD in lasting clinical improvement. Multivariate analysis demonstrated that older age was the only independent factor associated with a better response to PD. In fact, patients who were referred for surgery after PD had failed had a median age of 37.5 years. Setting the cut-off value at 40 years of age resulted in a 87.8% cumulative effectiveness of PD in the >40-year age group but only 42.9% in the <40-year age group. Our result is consistent with other published data showing that older patients respond favorably to PD compared with younger patients [11–14], although it is not clear why older patients are more responsive to PD. Two or three small tears are usually at the position of the LES after PD, but no tear was present when PD was performed in a younger patient of 12 years. In other younger patients who had no response to PD, tears were smaller and shallower than in those of older patients, who experienced clinical remission after PD. The LES

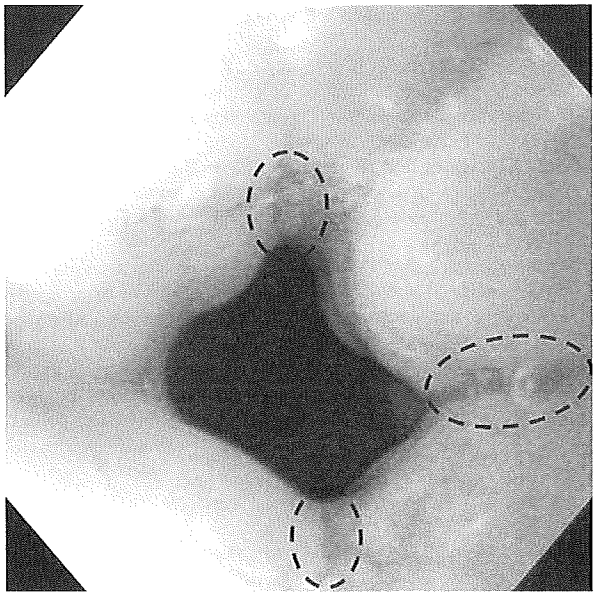

Fig. 2 An endoscopic picture after pneumatic dilatation (*PD*) of a young male patient of 26 years, who had no response to PD, reveals three very small, shallow tears

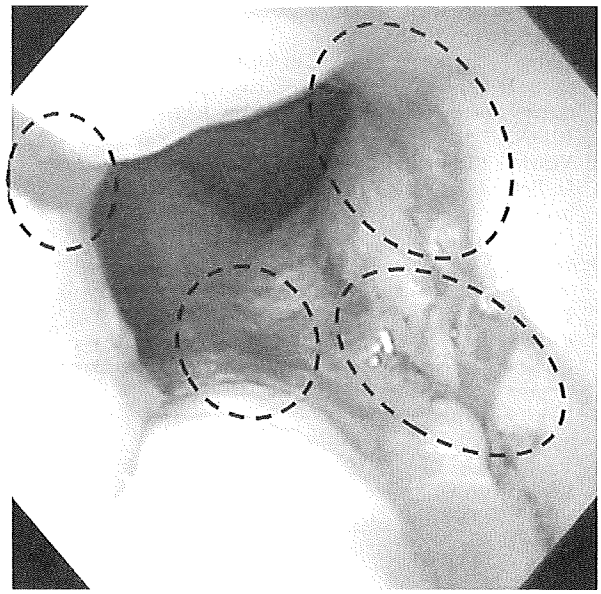

Fig. 3 An endoscopic picture of clinical remission after PD in a 79-year-old female. Unlike the tears in the younger patient who had no response to PD, four larger, deeper tears are evident

muscle, therefore, in younger patients may be more flexible, one of the possible reasons why younger patients with achalasia did not respond favorably to PD. Figure 2 shows an endoscopic picture after PD, in a 26-year-old male patient who had no response to PD and Fig. 3 shows an endoscopic picture of a 79-year-old female patient who had a clinical remission after PD.

A previous study reported that women had a better outcome from a single dilatation [15] and that patients with a long history of dysphagia had greater success from PD compared with those with a short history [3]. In our study, however, gender and symptom duration, among others, were not factors in the response to PD.

Esophageal perforation is the most serious complication of PD. More recent studies indicate that the rate of esophageal perforations conducted with a Rigiflex balloon dilator is around 0.5–3.0% [15–17]. However, no patients in our study had an esophageal perforation during treatment from PD. Our results confirm that the method we used for PD characterized by a low number of PDs and low inflation pressure of the balloon was therapeutically safe. The most frequent complication is gastroesophageal reflux (GERD); the prevalence of GERD following PD varies widely between 2 and 38% [18, 19]. This may be due to differences in the diagnostic criteria of GERD used in these studies. In our study, 4 (9.8%) of 41 patients, with remission after PD, had reflux esophagitis with grade B of the Los Angeles classification, which responds well to proton pump inhibitors.

In conclusion, PD is an effective and safe treatment for achalasia and the major factor associated with a better outcome is older age. No patients younger than 30 years responded to PD, suggesting that in lieu of this therapy patients younger than 30 years should be offered a surgical esophagomyotomy.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

The prokinetic effect of mosapride citrate combined with omeprazole therapy improves clinical symptoms and gastric emptying in PPI-resistant NERD patients with delayed gastric emptying

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Abstract
Background Previous studies have shown that non-erosive reflux disease (NERD) patients are less sensitive to proton pump inhibitor (PPI) treatment than patients with erosive reflux disease. The aim of this study was to investigate whether treatment with prokinetics in addition to omeprazole therapy would improve clinical symptoms, gastric emptying and esophageal peristalsis in PPI-resistant NERD patients with or without delayed gastric emptying.
Methods Subjects were 64 consecutive patients presenting with typical symptoms of PPI-resistant NERD ($n = 44$) and 20 healthy volunteers. PPI-resistant NERD patients underwent mosapride citrate (15 mg/day) and omeprazole (20 mg/day) co-therapy for 12 weeks. We evaluated the clinical symptoms as well as gastric emptying and esophageal manometry before and after combined therapy. We measured both acylated- and des-acylated plasma ghrelin levels by the ELISA method. The primary endopoint was to investigate whether co-administration of mosapride citrate and omeprazole would improve clinical symptoms and gastric emptying in PPI-resistant NERD patients with delayed gastric emptying.
Results T_{max} value in PPI-resistant NERD patients was significantly higher than in healthy volunteers. Combination therapy with the prokinetic agent mosapride citrate and omeprazole significantly improved reflux symptoms and T_{max} value in $T_{max} > 65$ min NERD patients. Co-therapy also significantly reduced des-acylated-ghrelin levels in NERD patients with delayed gastric emptying.
Conclusions Administration of mosapride citrate in addition to omeprazole improved gastro-esophageal reflux and gastric emptying in PPI-resistant NERD patients with delayed gastric emptying.

Keywords Non-erosive reflux disease · 5-HT_4 receptor agonist · Acylated-ghrelin · Gastric emptying

Introduction

About one-fifth of the adult population in Western countries experiences typical weekly symptoms of gastro-esophageal reflux disease (GERD), such as heartburn and regurgitation [1]. Recently, we have come to realize that the majority of GERD patients do not have any endoscopically visible lesions in the distal part of the esophagus. Several mechanisms have been proposed for the pathogenesis of non-erosive reflux disease (NERD), including visceral hypersensitivity, prolonged contraction of the esophagus and psychological factors [2–4]. Therefore, it is clear that NERD is an umbrella concept covering heterogenous subgroups of patients with different mechanisms responsible for their symptoms. It has been shown that between 33 and 50% of NERD patients presenting with heartburn do not have any evidence of pathological acid reflux during 24-h esophageal pH testing [5, 6]. Indeed, several studies have demonstrated that NERD patients are less sensitive to proton pump inhibitor (PPI) treatment than patients with erosive reflux disease [7–9].

In fact, some recent studies have suggested that the pathogenesis of NERD may differ from that of erosive

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GERD or Barrett's esophagus [10, 11]. The physiology of the lower esophageal sphincter, so fundamental to the pathophysiology of all manifestations of GERD, is intimately related to that of the gastric fundus and cardia. In other studies, gastric distention significantly increased the transient lower esophageal sphincter relaxation (tLESR) [11–13]. To date, there are no available data regarding the relationship between gastric motility and NERD patients.

Mosapride citrate is a prokinetic agent known to stimulate the serotonin 5-hydroxytryptan-4 (5-HT_4) receptor, increase acetylcholine release from the parasympathetic nerve endings, and promote bowel motility and gastric emptying [14]. Some previous studies have revealed that mosapride citrate decreases acid reflux to the esophagus in GERD patients and improves gastric emptying in healthy volunteers and diabetic patients for both solids and liquids [15, 16]. Therefore, in this study, we investigated whether mosapride citrate and omeprazole co-therapy could alleviate clinical symptoms in PPI-resistant NERD patients by improving gastric emptying and esophageal peristalsis.

Materials and methods

Patients

Forty-four consecutive patients presenting with typical symptoms of PPI-resistant NERD and 20 healthy volunteers were enrolled after upper gastrointestinal endoscopy and abdominal ultrasonography. Participants were recruited from September 2006 to April 2008. The diagnosis of NERD was based on typical reflux-associated symptoms (QUEST score >4 points) that occurred at least twice a week for at least 6 months before diagnosis in the absence of visible esophageal mucosal breaks at endoscopy. The exclusion criteria included severe heart disease, renal or pulmonary failure, liver cirrhosis, severe systemic illness and history of malignant disease. Patients with previous gastroduodenal surgery and those on recently used NSAID or anticoagulant medication were also excluded. *H. pylori* infection was determined by both the ^{13}C-urea breath test and histological identification. Healthy volunteers were recruited from a general pool of medical students and doctors. Written informed consent was obtained from all subjects prior to undergoing upper gastrointestinal endoscopy and abdominal ultrasonography for evaluation of dyspeptic symptoms. The study protocol was approved by the Ethical Review Committee of the Nippon Medical School Hospital.

Study protocol

Proton pump inhibitor-resistant NERD was diagnosed when 4-week omeprazole treatment (20 mg/day) failed to improve clinical symptoms (QUEST score >4 points) in NERD patients. PPI-resistant NERD patients were treated with the prokinetic agent mosapride citrate for 12 weeks in addition to omeprazole (20 mg/day). We evaluated clinical symptoms as well as gastric emptying and esophageal manometry twice in this study; the first evaluation was done after 4-week omeprazole treatment prior to mosapride citrate co-therapy, and the second evaluation after 12-week mosapride citrate (15 mg/day) administration in addition to omeprazole (20 mg/day) (Fig. 1). All study personnel and participants were blinded to treatment assignment for the duration of the study. In addition, we evaluated gastric emptying and esophageal manometry blindly.

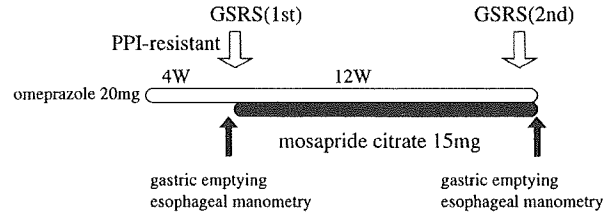

Fig. 1 Study protocol. PPI-resistant NERD was diagnosed when 4-week omeprazole treatment (20 mg/day) failed to improve clinical symptoms in NERD patients. PPI-resistant NERD patients were treated for 12 weeks with combined mosapride citrate (15 mg/day) and omeprazole (20 mg/day) therapy. Clinical symptoms, gastric emptying and esophageal manometry were evaluated before and after combined therapy

Endoscopic assessment of NERD

The patients were evaluated by endoscopy for reflux-associated disease if they complained of typical heartburn symptoms, i.e., a burning feeling rising from the stomach or lower chest up toward the neck at least twice a week [17] for a period of at least 6 months prior to examination.

Clinical symptoms

GI symptoms were assessed based on the GSRS questionnaire, which proved reliable and valid for the evaluation of GI symptoms [18, 19]. The GSRS consists of 15 items, each rated on the 7-point Likert scale (1–7), ranging from "no discomfort at all" to "very severe discomfort." The scores for abdominal pain, reflux, diarrhea, indigestion and constipation subscales were calculated by averaging the scores of the items completed within an individual subscale, with higher scores indicating more severe symptoms. After combined therapy, patients experiencing no discomfort at all for a particular symptom were considered cured for that clinical symptom; that is, when the GI score for each symptom such as abdominal pain, reflux, diarrhea, indigestion, and constipation improved to a score 1.

Measurement of gastric motility

Sodium acetate (water soluble) for emptying of liquids was used as a tracer (Cambridge Isotope Laboratories; Cambridge, MA). Probes were analyzed by non-dispersive infrared spectroscopy (IRIS, Wagner Analyzentechnik; Bremen, Germany). The subject's own production of 300 mmol CO_2 per m^2 body surface and per hour was set as default value. Integrated software solutions calculated the half gastric emptying time ($T_{1/2}$) and the lag phase (T_{max}) as the point of maximum gastric emptying according to Hellmig et al. [20]. Hellmig et al. [20] have also reported that the gastric emptying of liquid meals was similar to that of solid meals. T_{max} value >65 min indicated disturbance of gastric emptying [21].

Study protocol for gastric emptying of liquids

The liquid test meal consisted of 100 mg of ^{13}C-acetate dissolved in 200 ml of a liquid meal (Racol, 1 ml/1 kcal; Otsuka Pharmacia Company; Tokyo, Japan). Breath samples were taken at 0, 10 s, 5, 10, 15, 20, 30, 40, 50, 60, 75 and 90 min after ingestion. The patients were instructed not to drink, eat or smoke during the test.

Recording methods

Esophageal manometry was performed with a 21-channel manometric assembly (Dentsleeve; Wayville, Australia). We used ten-side holes, which were spaced at 1-cm intervals starting at 3 cm above the distal end of the assembly to monitor the pressure from the proximal stomach, LES and distal esophagus. We used another seven side holes, spaced at 2-cm intervals, to monitor the pressure from the distal to the proximal esophagus and four side holes at 3, 6, 10, and 13 cm above the most proximal of the 2-cm interval side holes to monitor the pressure from the proximal esophagus to the pharynx. Each lumen was perfused with degassed distilled water at 0.15 ml/min by a low compliance manometric infusion pump (Dentsleeve). The data were digitized with a computer, and the digitized signals were displayed, stored and analyzed using Trace Software (Dr GS Hebbard, Royal Melbourne Hospital; Melbourne, Australia).

Study protocol for esophageal manometry

The subjects were examined in the sitting position after fasting overnight. The manometric assembly was passed via an anesthetized nostril and positioned so that the most proximal of the 1-cm interval side holes was 2 cm above the LES. The subjects were then allowed to adapt to the assembly for 10 min. Baseline recordings of LES pressure were made for 5 min, and then primary and secondary peristalsis was assessed. The primary peristalsis was assessed in response to ten swallows of a 5-ml water bolus. Each swallow was separated by a 30-s interval. Secondary peristalsis was triggered by esophageal distention using a 20-ml air bolus, which was injected rapidly by hand into the mid-esophagus through an infusion port located 11 cm above the LES. After 20 s, each stimulus was followed by a dry swallow to clear any residual air. Each stimulus was repeated five times [22].

Intraluminal esophageal pH recording

Twenty-four-hour esophageal pH values were monitored in nine PPI-resistant NERD patients with delayed gastric emptying who consented to the monitoring for assessment of the severity of acid reflux in the esophagus. The study was carried out on an outpatient basis, after at least 6 h of fasting. A Digitrapper Mark III recorder (Synectics Medical, Stockholm, Sweden) was used. An antimony pH catheter (Zenetics Medical; Salt Lake City, UT) was inserted intranasally and positioned 5 cm above the lower esophageal sphincter. Patients then underwent 24-h pH monitoring, and diaries were provided for them to record their symptoms during the study period. At the end of the 24-h recording period, data were transferred to a commercially available software program (Esophagogram, Gastrosoft; Stockholm, Sweden). Patients were encouraged to maintain normal activity and sleep schedules. Meals (total 1,500 kcal, fat 25%) were given at 9:00 a.m. (breakfast), 12:30 p.m. (lunch) and 7:30 p.m. (supper).

Data analysis

The primary and secondary peristalsis was classified as successful if a pressure wave of more than 12 mmHg at the three proximal esophageal recording sites (16, 19 and 22 cm above the LES) and of more than 25 mmHg at the middle and distal esophageal recording sites progressively traversed all of the esophageal recording sites. Peristaltic progression was defined as a peristaltic velocity of <6 cm/s. The criteria of failed peristalsis were failure of a pressure wave of more than 12 mmHg at the three proximal esophageal recording sites, failure to traverse each of the esophageal recording sites, or a peristaltic velocity of more than 6 cm/s between the recording sites at 2 and 22 cm above the LES [15]. Normal secondary peristalsis was defined as the occurrence of four or more complete peristaltic responses to the five air boluses [17].

Tracings were reviewed, meals periods were timed, changes in body position were noted and the time that symptoms were recorded was compared with the information written in the diaries. The pathological acid reflux (abnormal acid exposure time) is considered present when intra-esophageal pH falls below 4 for >4.2% of the time

[23]. Analysis of pH tracing was done as follows: (1) the time period percentage with an esophageal pH of <4.0 was calculated as a proportion of the recording periods and (2) acid reflux was defined as those periods when the pH in the esophagus dropped to below 4.0.

Measurement of plasma ghrelin levels

We then measured the plasma ghrelin levels to evaluate their association with gastric motility. Blood was drawn into chilled tubes containing EDTA-2Na (1 mg/ml) and aprotinin (500 U/ml), and the plasma was taken after immediate centrifugation and stored at −30°C until assay. Plasma immunoreactive ghrelin concentrations (acylated- and des-acylated) were measured in duplicate using a commercial radioimmunoassay (Phoenix Pharmaceuticals; Belmont, CA). The intra-assay coefficient of variation (CV) was 8.1%, and the inter-assay CV, 9%. The range of detection was 10–1,280 pg/ml.

Measurement of serum pepsinogen I and II

Serum PGI and II levels were measured using E Plate Pepsinogen I and II (Eiken Chemical Co., Ltd.) using cutoff levels of PGI < 70 μg/L + PGI/II ratio <3 as low PG levels (L-PG) and PGI < 30 μg/l + PGI/II ratio <2 as very low PG levels (VL-PG) according to the instructions of the manufacturer.

Statistical analysis

For statistical evaluation of group data, Student's *t* test for paired data and analysis of variance (ANOVA) for multiple comparisons were followed by Scheffe's *F* test. Mann–Whitney *U* test was used for analysis of categorical data. A *P* value of <0.05 was considered statistically significant.

Results

Characteristics of PPI-resistant NERD patients

BMI scores did not vary significantly between the two groups of patients and healthy volunteers (Table 1). There was also no significant variation in *H. pylori* positivity rates between PPI-resistant NERD patients with delayed gastric emptying and those without (Table 1). The pepsinogen I/II ratio in PPI-resistant NERD patients with or without delayed gastric emptying and healthy volunteers was 5.68 ± 2.4, 5.72 ± 1.9 and 6.71 ± 1.8, respectively. There was no significant difference in the pepsinogen I/II ratio among the three groups (Table 1).

T_{max} value in PPI-resistant NERD patients

We then used the ^{13}C-acetate breath test to calculate the T_{max} value as a marker of gastric emptying of liquids and compared gastric motility among PPI-resistant NERD patients and healthy volunteers. The T_{max} value in PPI-resistant NERD patients was significantly higher than that in healthy volunteers (Fig. 2).

Mosapride citrate combined with omeprazole improves reflux symptoms and T_{max} value in PPI-resistant NERD patients with delayed gastric emptying

To elucidate the possibility that the prokinetic effect of mosapride citrate improved gastro-esophageal reflux symptoms via its effect on gastric emptying, we measured the T_{max} value and clarified whether administration of mosapride citrate in addition to omeprazole affected gastric emptying in PPI-resistant NERD patients with or without delayed gastric emptying. Mosapride citrate in combination with omeprazole therapy significantly improved the T_{max} value in PPI-resistant NERD patients with delayed gastric emptying (Fig. 3). Combined therapy significantly improved T_{max} value in 83% (20/24) of PPI-resistant NERD patients with delayed gastric emptying. We also investigated whether mosapride citrate combined with omeprazole improved the upper GI symptoms and lower GI symptoms. Mosapride citrate combined with omeprazole significantly improved reflux symptoms in the T_{max} > 65 min group of NERD patients compared to that in the T_{max} < 65 min group (Fig. 4).

In some T_{max} > 65 min NERD patients ($n = 9$), we investigated whether combined mosapride citrate and omeprazole treatment affects the acid exposure time and the frequency of acid reflux using 24-h pH monitoring.

Table 1 Characteristics of the patients

	Sex	Age	BMI	HP positivity (%)
Healthy volunteer ($n = 20$)	M 14 F 6	46.2 ± 12.8	21.8 ± 1.2	15
PPI-resistant NERD ($n = 24$) (T_{max} > 65 min)	M 10 F 14	44.2 ± 8.1	22.9 ± 2.1	33
PPI-resistant NERD ($n = 20$) (T_{max} < 65 min)	M 12 F 8	41.2 ± 7.9	23.1 ± 1.7	30

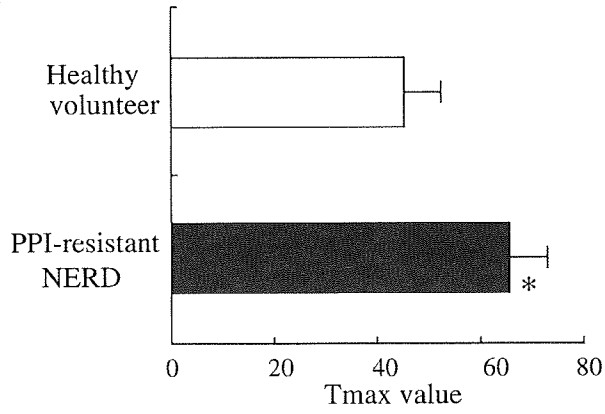

Fig. 2 T_{max} value in PPI-resistant NERD patients and healthy volunteers. The T_{max} value in PPI-resistant NERD patients was significantly higher than in healthy volunteers. *Versus healthy volunteers, $P < 0.05$

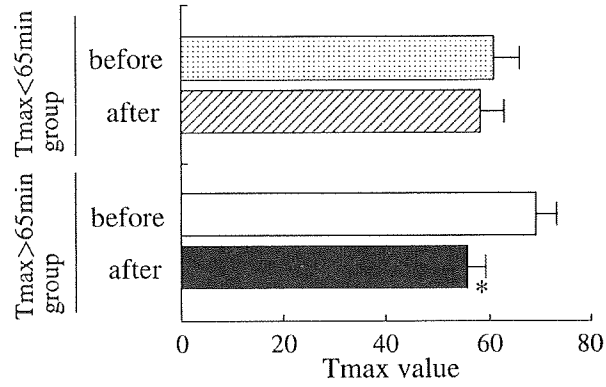

Fig. 3 Mosapride citrate combined with omeprazole improves T_{max} value in PPI-resistant NERD patients with delayed gastric emptying. Mosapride citrate significantly improved ($P < 0.05$) the T_{max} value in $T_{max} > 65$ min NERD patients. *Versus T_{max} value in $T_{max} > 65$ min NERD patients before combined therapy, $P < 0.05$

There was no abnormal acid exposure time (0.1 ± 0.08%) in nine PPI-resistant NERD patients with delayed gastric emptying under 4-week omeprazole treatment. In addition, there was no difference in the acid exposure time (0.1 ± 0.08 and 0.07 ± 0.06%) and the frequency of acid reflux (5.2 ± 3.2, 3.6 ± 3.4) in nine PPI-resistant NERD patients with delayed gastric emptying between before and after combined therapy.

Esophageal secondary peristalsis in PPI-resistant NERD patients after combined mosapride citrate and omeprazole therapy

To elucidate the possibility that the prokinetic effect of mosapride citrate improved gastro-esophageal reflux symptoms via its effect on esophageal peristalsis, we measured secondary esophageal peristalsis in NERD

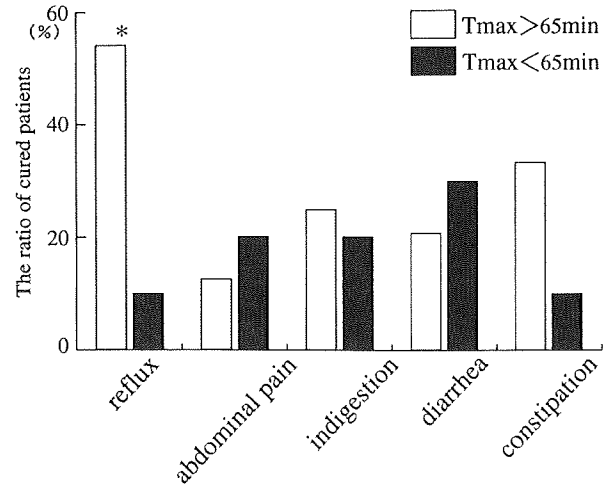

Fig. 4 The ratios of NERD patients with $T_{max} > 65$ min and $T_{max} < 65$ min cured with mosapride citrate and omeprazole co-therapy. Mosapride citrate significantly improved reflux symptoms in PPI-resistant NERD patients with T_{max} value > 65 min. In contrast, mosapride citrate did not improve any clinical symptoms in PPI-resistant NERD patients with T_{max} value < 65 min. *Versus the ratio of cured patients after 12 weeks of treatment with mosapride citrate combined with omeprazole in PPI-resistant NERD patients with $T_{max} < 65$ min, $P < 0.05$

patients with or without delayed gastric emptying. Although mosapride citrate and omeprazole co-therapy increased the amplitude of primary esophageal peristalsis in some cases (Fig. 5a, b), combined mosapride citrate and omeprazole therapy did not affect primary esophageal peristalsis in most of cases. In addition, mosapride citrate and omeprazole co-therapy did not significantly increase esophageal secondary peristalsis in PPI-resistant NERD patients with or without delayed gastric emptying (Fig. 5c).

Plasma ghrelin levels in PPI-resistant NERD patients after combined mosapride citrate and omeprazole therapy

Mosapride citrate combined with omeprazole did not significantly increase acylated ghrelin levels in PPI-resistant NERD patients with or without delayed gastric emptying (Fig. 6). In contrast, mosapride citrate combined with omeprazole significantly reduced des-acylated ghrelin levels in PPI-resistant NERD patients with delayed gastric emptying (Fig. 6).

Discussion

The major findings in this study are as follows: (1) T_{max} values, one of the markers of gastric emptying, were significantly higher in PPI-resistant NERD patients than in