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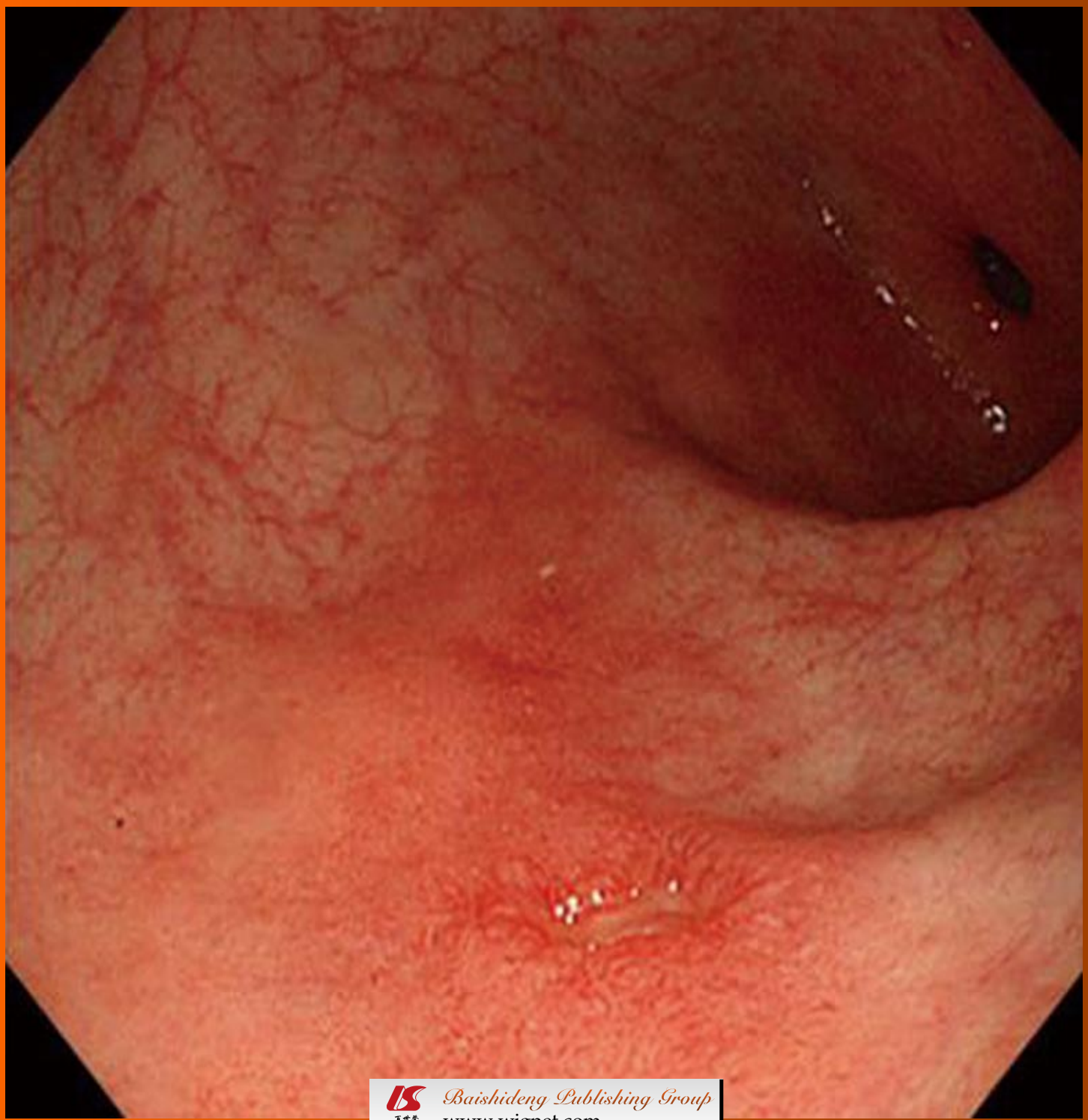

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EDITORIAL

Endoscopic and histopathological features of gastrointestinal amyloidosis

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Abstract

Amyloidosis is a rare disorder, characterized by the extracellular deposition of an abnormal fibrillar protein, which disrupts tissue structure and function. Amyloidosis can be acquired or hereditary, and systemic or localized to a single organ, such as the gastrointestinal (GI) tract. Clinical manifestations may vary from asymptomatic to fatal forms. Primary amyloidosis (monoclonal immunoglobulin light chains, AL) is the most common form of amyloidosis. AL amyloidosis has been associated with plasma cell dyscrasias, such as, multiple myeloma. Secondary amyloidosis is caused by the deposition of fragments of the circulating acute-phase reactant, serum amyloid A protein (SAA). Common causes of AA amyloidosis are chronic inflammatory disorders. Although GI symptoms are usually nonspecific, histopathological patterns of amyloid deposition are associated with clinical and endoscopic features. Amyloid deposition in the muscularis mucosae, submucosa, and muscularis propria has been dominant in AL amyloidosis, leading to polypoid protrusions and thickening of the valvulae conniventes, whereas granular amyloid deposition mainly in the propria mucosae has been related to AA amyloidosis, resulting in the fine granular appearance, mucosal friability, and erosions. As a result, AL amyloidosis usually presents with constipation, mechanical obstruction, or chronic intestinal pseudo-obstruction while AA amyloidosis presents with diarrhea and malabsorption Amyloidotic GI symptoms are mostly refractory and have a negative impact on quality of life and survival. Diagnosing GI amyloidosis requires high suspicion of evaluating endoscopists. Because of the absence of specific treatments for reducing the abundance of the amyloidogenic precursor protein, we should be aware of certain associations between patterns of amyloid deposition and clinical and endoscopic features.

Key words: Amyloidosis; Amyloid; Congo red; Endoscopy; Gastrointestinal tract; Histopathology

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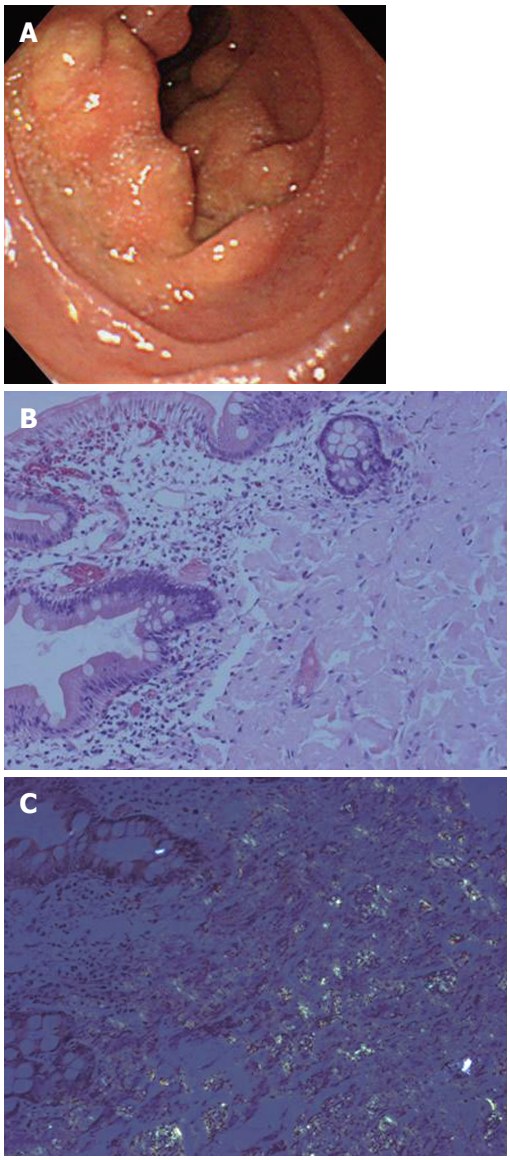

Figure 1 Endoscopic view of amyloid light chains amyloidosis in a 64-year-old man without multiple myeloma presenting abdominal fullness. A: Characteristic multiple yellowish-white polypoid protrusions and thickening of the folds in the descending duodenum are presented; B: Biopsy specimens showed marked homogenous eosinophilic deposition in the mucosae and submucosa (HE, × 40); C: Congo red stain confirmed a unique "apple-green" birefringence of the amyloid deposition under polarized light (× 40). All figures and legends are reproduced from[8] with permission from Elsevier.

INTRODUCTION

Amyloidosis is a rare disorder, characterized by the extracellular deposition of an abnormal fibrillar protein, which disrupts tissue structure and function. Types of amyloidosis are classified based on the identity of the respective precursor protein[1]. Amyloidosis can be acquired or hereditary, and systemic or localized to a single organ, such as the gastrointestinal (GI) tract. Clinical manifestations may vary from asymptomatic to fatal forms. We review the endoscopic and histopathological characteristics of GI amyloidosis with the presentation of our experiences.

TYPES OF AMYLOIDOSIS

Primary amyloidosis (monoclonal immunoglobulin light chains, AL) is the most common form of amyloidosis. AL amyloidosis has been associated with plasma cell dyscrasias, such as multiple myeloma. Secondary amyloidosis is caused by the deposition of fragments of the circulating acute-phase reactant, serum amyloid A protein (SAA). Common causes of AA amyloidosis are chronic inflammatory disorders and infections, including rheumatoid arthritis, Crohn's disease, familial Mediterranean fever, leprosy and tuberculosis[1,2]. Due to a predominance of infections before 1990, the AA/AL ratio was 1:3; however, the ratio has been 1:17 to 1:38 due to fewer chronic infections and an increasing recognition of AL amyloidosis[3]. Other types of amyloidosis are dialysis-related amyloidosis with the deposition of β_2-microglobulins, and autosomal dominant systemic amyloidosis, such as familial amyloidotic polyneuropathy (FAP) with the deposition of genetically variant transthyretin[1,2]. The incidence of the former has declined with the use of high flux hemodialysis.

THE ASSOCIATION OF CLINICAL FEATURES AND ENDOSCOPIC FINDINGS

Presentations of systemic amyloidosis include weakness, weight loss, neuropathy, cardiopathy, nephropathy and arthropathy, all of which can be refractory[1,2]. Among patients with systemic amyloidosis, the involvement in the GI tract is very common. The small intestine is most commonly affected in the GI tract[4,5]. Diagnosis requires confirmation of the presence of amyloid by histopathology using Congo red staining (Figure 1). Although GI symptoms are usually nonspecific and include macroglossia, dysphagia, abdominal pain, hemorrhage, constipation, diarrhea and malabsorption, patterns of amyloid deposition are associated with clinical and endoscopic features[6,7]. Amyloid deposition in the muscularis mucosae, submucosa and muscularis propria has been dominant in AL amyloidosis, leading to polypoid protrusions and thickening of the valvulae conniventes, whereas granular amyloid deposition mainly in the propria mucosae has been related to AA amyloidosis, resulting in the fine granular appearance, mucosal friability and erosions[6]. As a result, AL amyloidosis usually presents with constipation, mechanical obstruction or chronic intestinal pseudo-obstruction, while AA amyloidosis presents with diarrhea and malabsorption[6]. Typical endoscopic images of duodenal lesions in AL amyloidosis at our institute[8] are shown in Figure 1. Characteristic polypoid protrusions and thickening of the folds are presented. In Figure 2, gastroduodenal lesions in AA amyloidosis caused by rheumatoid arthritis are depicted. More friable duodenal mucosa and reddish colonic mucosa of AA amyloidosis caused by familial Mediterranean fever are disclosed in Figures 3 and 4. Table 1 shows a brief comparison of characteristics of AL and AA amyloidosis. In addition,

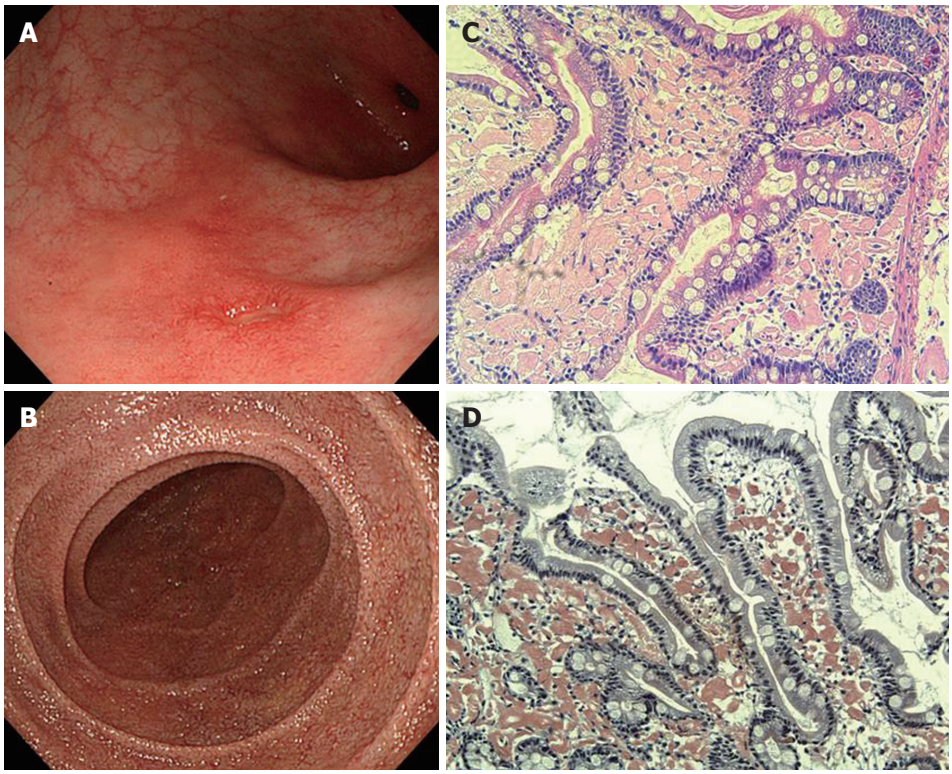

Figure 2 Endoscopic views of amyloid A amyloidosis in a 45-year-old woman with rheumatoid arthritis. A: A round ulcer surrounded by longitudinal reddish mucosa is presented in the gastric antrum. Histopathological examination confirmed amyloid deposition; B: Fine granular mucosa in the descending duodenum; C: Biopsy of the duodenal lesion showing marked amorphous eosinophilic deposition in the lamina propria mucosae (HE, × 100); D: Congo red staining showing amyloid deposition (× 100).

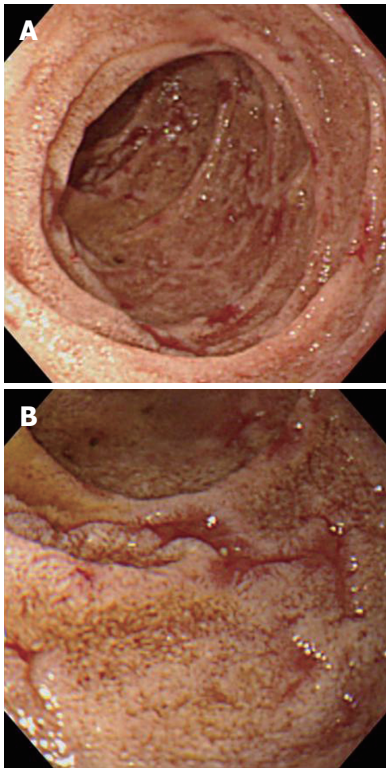

Figure 3 Endoscopic views of amyloid A amyloidosis in a 45-year-old man with familial Mediterranean fever. A: Friable granular mucosa with in the descending duodenum; B: Closer observation revealing whitish dilatated villi with multiple reddish erosions.

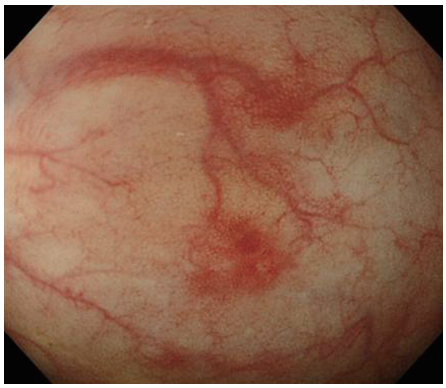

Figure 4 Endoscopic views of amyloid A amyloidosis in a 55-year-old man with familial Mediterranean fever. Patchy reddish mucosa was presented along with submucosal veins. Histopathological examination confirmed amyloid deposition.

submucosal hematoma, ulcers and hemorrhagic bullous colitis, which may be caused by amyloid infiltration, are other features in the setting of GI bleeding in AL amyloidosis[9,10]. Our experience with hemorrhagic colonic lesions in AL amyloidosis[11] is shown in Figure 5. Characteristic yellowish plaque-like infiltrative lesions, submucosal hematoma and ulceration are presented.

As for other types of amyloidosis, dialysis-related β2-microglobulin amyloidosis has a similar present ation to AL amyloidosis[12]. In FAP, endoscopic findings of GI tract are mostly a mild, fine, granular appearance and the

Table 1 Comparison of characteristics of amyloid light chains and amyloid A amyloidosis[1,2,6,7]

	amyloid light chains amyloidosis	amyloid A amyloidosis
Causes	Idiopathy and plasma cell dyscrasias	Chronic inflammatory disorders and infections
Deposition	Monoclonal immunoglobulin light chains	Serum amyloid A protein
Gastrointestinal site of amyloid deposition	The muscularis mucosae, submucosa and muscularis propria	The propria mucosae
Gastrointestinal symptoms	Constipation, mechanical obstruction and chronic intestinal pseudo-obstruction	Diarrhea, malabsorption and weight loss
Endoscopic and radiological features	Polypoid protrusions and thickening of the folds	Fine granular appearance and mucosal friability
Treatments	Prokinetic agents and myeloma-type chemotherapy	Control of the underlying inflammatory disorders

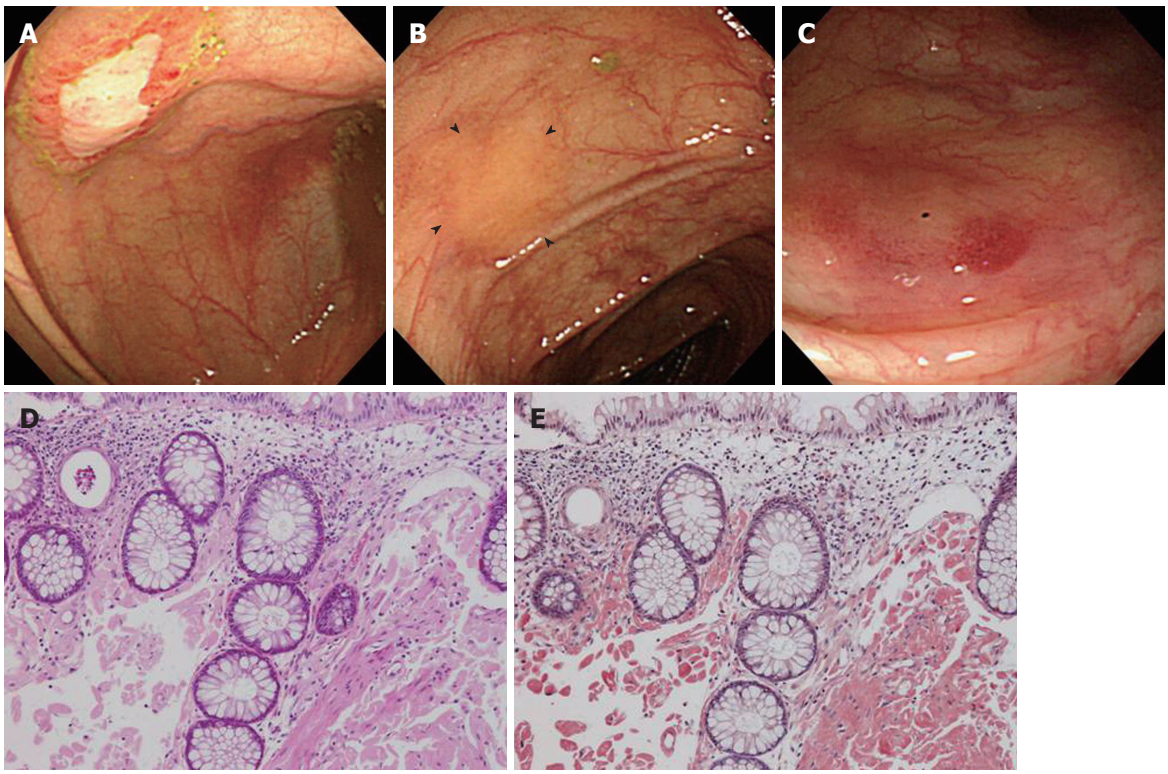

Figure 5 Endoscopic views of amyloid light chains amyloidosis in an 80-year-old woman without multiple myeloma presenting hematochezia. A: Colonoscopy showing a round ulcer in the cecum; B: A patchy yellowish plaque-like infiltrative lesion (arrowheads) relatively normal-appearing intervening mucosae in the transverse colon; C: A tiny submucosal hematoma within pinky plaque-like erythema in the sigmoid colon; D: Biopsy of the colonic lesion showing marked amorphous eosinophilic deposition in the mucosa and submucosa (HE, × 100); E: Congo red staining showing amyloid deposition (× 100). All figures and legends are reproduced from[11] with permission from BMJ Publishing Group Ltd.

amount of amyloid deposition in the mucosa is small compared with that in AL and AA amyloidosis. However, a significant amount of deposition is evident in the nerves of the GI tract, which may be the cause of severe diarrhea and malabsorption occasionally observed in FAP patients despite the mild macroscopic findings[13]. Although recent advances in endoscopy, including narrow-band imaging[14], capsule endoscopy[15,16] and double-balloon enteroscopy[17], have been widely applied to diagnose GI amyloidosis, plain radiographs and radiological barium examination, basic techniques, are still useful in evaluating GI amyloidosis, especially in the small intestine[18,19]. These methods can clearly reveal fold thickening of AL amyloidosis or fine granular mucosa of AA amyloidosis, which corroborate well with the histopathological findings[19,20].

TREATMENT OF AMYLOIDOSIS

Because of the absence of specific treatments for GI amyloidosis, therapy is aimed at reducing the abundance of the amyloidogenic precursor protein, leading to the improvement of amyloidotic organ dysfunction[1]. Treatment of AL amyloidosis includes myeloma-type chemotherapy with melphalan and prednisone and high-dose chemotherapy with hematopoietic stem cell transplantation. Prokinetic agents may benefit dysmotility-related symptoms. Treatment of AA amyloidosis is control of the underlying inflammatory disorders, leading to the reduction of SAA. Diarrhea and malabsorption are often refractory. Supportive measures such as total parenteral nutrition and antidiarrheal agents can be beneficial[1]. GI

tract surgery should be performed only if the benefits clearly outweigh the risks.

CONCLUSION

Amyloidotic GI symptoms are mostly refractory and have a negative impact on quality of life and survival. Diagnosing GI amyloidosis requires a high level of suspicion by the evaluating endoscopists; therefore, we should be aware of certain associations between patterns of amyloid deposition and clinical and endoscopic features.

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ORIGINAL ARTICLE

Transnasal and standard transoral endoscopies in the screening of gastric mucosal neoplasias

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Abstract

AIM: To compare the diagnostic performances of transnasal and standard transoral esophagogastroduodenoscopy (EGD) in gastric cancer screening of asymptomatic healthy subjects.

METHODS: Between January 2006 and March 2010, a total of 3324 subjects underwent examination of the upper gastrointestinal tract by EGD for cancer screening, with 1382 subjects (41.6%) screened by transnasal EGD and the remaining 1942 subjects (58.4%) by standard transoral EGD. Clinical profiles of the screened subjects, detection rates of gastric neoplasia and histopathology of the detected neoplasias were compared between groups according to the stage of *Helicobacter pylori* (*H. pylori*)-related chronic gastritis.

RESULTS: Clinical profiles of subjects did not differ significantly between the two EGD groups, except that there were significantly more men in the transnasal EGD group. During the study period, 55 cases of gastric mucosal neoplasias were detected. Of these, 23 cases were detected by transnasal EGD and 32 cases by standard transoral EGD. The detection rate for gastric mucosal neoplasia in the transnasal EGD group was thus 1.66%, compared to 1.65% in the standard transoral EGD group, with no significant difference between the two groups. Detection rates using the two endoscopies were likewise comparable, regardless of *H. pylori* infection. However, detection rates when screening subjects without extensive chronic atrophic gastritis (CAG) were significantly higher with standard transoral EGD (0.70%) than with transnasal EGD (0.12%, $P < 0.05$). In particular, standard transoral EGD was far better for detecting neoplasia in subjects with *H. pylori*-related non-atrophic gastritis, with a detection rate of 3.11% compared to 0.53% using transnasal EGD ($P < 0.05$). In the screening of subjects with extensive CAG, no significant differences in detection of neoplasia were evident between the two endoscopies, although the mean size of detected cancers was significantly smaller and the percentage of early cancers was significantly higher with standard transoral EGD.

CONCLUSION: These results strongly suggest that the diagnostic performance of transnasal endoscopy is

suboptimal for cancer screening, particularly in subjects with *H. pylori*-related non-atrophic gastritis.

Key words: Transnasal endoscopy; Gastric cancer; Gastric adenoma; Atrophic gastritis; *Helicobacter pylori*; Cancer screening

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INTRODUCTION

To address the high mortality rate associated with gastric cancer, a nationwide program of gastric cancer screening has been introduced throughout Japan as a public service sponsored by local governments. In 2007, a total of 6 385 118 individuals underwent these screenings, resulting in the detection of 5606 cases of gastric cancer[1]. This screening program utilizes barium x-ray with photofluorography as a standard screening test and is considered effective in reducing the cancer mortality rate[2-5]. However, the sensitivity of barium X-ray is by no means high, reaching only 39% for early cancer[6]. To cope with this problem and improve the quality of screening, esophagogastroduodenoscopy (EGD) has gradually been adopted in several workplaces, local communities for organized screening and in health check-up institutions, including private health assessment clinics for opportunistic screening. A total of 211 821 subjects underwent cancer screening using EGD in 2007, according to the annual report of the Japanese Society of Gastroenterological Screening[1]. Since EGD is an unpleasant examination for subjects, evoking anxiety, pharyngeal discomfort, nausea, the gag-reflex and choking, and has been associated with adverse effects such as cardiovascular accidents[7-9], this screening method is highly dependent on the skill of the endoscopist. The limited number of highly experienced endoscopists thus represents a major limitation to the feasibility of widespread cancer screening using EGD. Transnasal EGD using a small-diameter endoscope is more patient-friendly than standard transoral EGD, is safer, with little impact on the cardiopulmonary and autonomic nerve systems[10-13], and provides good operability. Transnasal EGD is thus more acceptable for patients and appears to be better suited to endoscopic cancer screening. However, because the luminous intensity and quality of endoscopic images varies greatly depending on differences in endoscope diameter, the screening performance of transnasal EGD for gastric cancer, particularly with regard to early cancer, must be determined carefully in the setting of cancer screening. The present study compared screening performance for gastric mucosal neoplasia (adenoma or cancer) between transnasal EGD and standard transoral EGD. In addition, the morphological and biological characteristics of gastric mucosal neoplasia are influenced by the stage of *Helicobacter pylori* (*H. pylori*)-related chronic gastritis[14-18], which thus seems likely to influence the diagnostic ability of these two EGDs. We therefore compared screening by transnasal and standard transoral EGDs according to the stage of *H. pylori*-related chronic gastritis.

MATERIALS AND METHODS

Subjects comprised 3324 patients [1442 men, 1882 women; mean (SD) age, 53.4 (15.4) years] who underwent EGD for screening of the upper gastrointestinal tract in our health assessment clinic between January 2006 and March 2010. All subjects were essentially symptom-free and each was free to choose between transnasal and standard transoral EGD. The transnasal EGD group included 1382 subjects [684 men, 698 women; mean (SD) age, 53.4 (15.4) years] and the standard transoral EGD group included 1942 subjects [758 men, 1184 women; mean (SD) age, 53.5 (15.4) years]. Standard transoral EGD was performed using a GIF-Q260 or prototype GIF-Y0004 endoscope (Olympus, Tokyo, Japan), whereas transnasal EGD was performed using a GIF-N260 or prototype GIF-Y0022 endoscope (Olympus) or an EG-530N2 endoscope (Fuji Film Medical, Tokyo, Japan). Outer diameters of the standard endoscopes were larger than those of transnasal endoscopes: GIF-Q260, 9.2 mm; GIF-Y0004, 7.7 mm; GIF-N260, 4.9 mm; GIF-Y0022, 5.4 mm; and EG-530N2, 5.9 mm. Sizes of the charge-coupled device for the two standard endoscopes were the same and about 30% larger than those of the GIF-N260 and GIF-Y0022 transnasal endoscopes. The optical system in EG-530N2 differs from those of the other endoscopes but image quality for the EG-530N2 was equivalent to that with the other two transnasal endoscopes. Standard endoscopes were equipped with two light guides, while transnasal endoscopes were equipped with either single (GIF-N260) or double light guides (GIF-Y0022 and EG-530N2); the visual field of the transnasal endoscopes were dark compared with the standard endoscopes, due to the smaller number of light guide fibers. Viewing angles of all standard and transnasal EGDs were 140° and 120°, respectively. The tip flexion capability of en-

Table 1 Clinical profiles of the subjects screened by transnasal or transoral endoscopy and clinicopathological characteristics of detected gastric mucosal neoplasia (mean ± SD) *n* (%)

	Total subjects	Subject screened	
		By transnasal EGD	By transoral EGD
No. of screened subjects	3324	1382	1942
Age (yr)	53.4 ± 15.4	53.4 ± 15.4	53.5 ± 15.4
Males	1442 (43.4)	684 (49.4)[a]	758 (39.0)
Smokers	678 (20.4)	267 (19.3)	411 (21.1)
Helicobacter pylori-infected subjects	1202 (40.2)	510 (39.8)	692 (40.5)
CAG-positive subjects	1360 (40.9)	560 (40.5)	800 (41.2)
No. of subjects with gastric neoplasia/DR	55/0.0165	23/0.0166	32/0.0165
Location of neoplasia (U/M/L)	20/15/20	8/7/8	12/8/12
Adenoma cases/DR	12/0.0036	3/0.0022	9/0.0046
Location of adenoma (U/M/L)	2/4/6	0/2/1	2/2/5
Size of adenoma (mm)	10.5 ± 7.0	9.7 ± 4.0	10.8 ± 7.9
Cancer cases/DR	43/0.0129	20/0.0145	23/0.0118
Location of cancer (U/M/L)	18/11/14	8/5/7	10/6/7
Size of cancer (mm)	27.3 ± 16.7	32.6 ± 19.5[a]	22.3 ± 12.8
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	12/1/15/13	6/1/5/8	6/0/12/5
With intestinal-type cancer	33 (76.7)	18 (90.0)[a]	15 (65.2)
Depth of invasion (m/sm/pm-)	20/10/13	5/7/8	15/3/5
With early cancer	30 (69.7)	12 (60.0)	18 (78.3)

[a]$P < 0.05$ *vs* transoral esophagogastroduodenoscopy (EGD). CAG: Chronic atrophic gastritis; DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach.

doscopes was 210° up, 90° down and 100° right and left, with the exception of GIF N260, a two-way angulation transnasal endoscope, which showed flexion capability of 210° up and 120° down in a single plane. All endoscopes used in the present study were equipped with a forceps channel (diameter, 2 mm).

In both groups, a sedative (midazolam, 2.5-5 mg/body) was provided for subjects who desired it. All endoscopic examinations were performed by a single endoscopist with 20 years' experience in gastrointestinal endoscopy. Narrow-band imaging, flexible spectral imaging color enhancement or indigo carmine spraying was applied for full observation when considered necessary. Chronic atrophic gastritis (CAG), defined as chronic gastritis with open-type atrophy in the background gastric mucosa according to the definitions of Kimura *et al*[19], was diagnosed by endoscopic observation, whereas *H. pylori* infection was diagnosed by histopathological analysis using Giemsa staining of endoscopically biopsied mucosal samples obtained from the greater curvature of the gastric body and antrum. Furthermore, on the basis of previous reports[20,21], subjects with *H. pylori*-related chronic gastritis were examined after being divided into the following 4 groups according to the stage of *H. pylori*-related chronic gastritis: Group A, *H. pylori*-negative and CAG-negative; Group B, *H. pylori*-positive and CAG-negative; Group C, *H. pylori*-positive and CAG-positive; and Group D, *H. pylori*-negative and CAG-positive. Among the subjects screened, the status of *H. pylori*-related chronic gastritis in the background stomach was able to be analyzed in 2987 subjects.

Histopathological assessment of gastric mucosal neoplasias, adenoma and cancer was performed on resected specimens obtained by endoscopy or surgery. Early gastric cancers were defined as those confined to the mucosa or submucosa. Advanced cancers were defined as those invading into the muscularis propria or beyond. Pathologically, gastric cancer cases were classified into intestinal type or diffuse type, according to Lauren's classification[22]. The ethics committee of Wakayama Medical University approved the protocol of the present study and informed consent was obtained from all subjects prior to participation.

Statistical analysis

Data were analyzed using SPSS version 11.0 (SPSS, Chicago, IL, USA) and STATA (STATA, College Station, TX, USA). Differences were tested for significance using analysis of variance for comparisons between groups and Scheffe's LSD test for comparisons between pairs of groups. The χ^2 test and Fisher's exact test were used to compare categorical variables. For all comparisons, values of $P < 0.05$ were considered statistically significant.

RESULTS

Between January 2006 and March 2010, a total of 3324 subjects underwent examination of the upper gastrointestinal tract by EGD for cancer screening, with 1382 subjects (41.6%) screened by transnasal EGD and the remaining 1942 subjects (58.4%) by standard transoral EGD. Clinical profiles of subjects in the two endoscopy groups are shown in Table 1. Although significantly more men were included in the transnasal EGD group than in the standard transoral EGD group, no significant differences in age, smoking habits, *H. pylori* infection or extent of concomitant CAG were seen between groups. Endoscopy screening identified 55 cases of gastric mucosal

Table 2 Screening performance of the two esophagogastroduodenoscopies in subjects with or without *Helicobacter pylori* infection (mean ± SD) *n* (%)

	Total subjects (*H. pylori* analyzed)	*H. pylori*	
		Positive	Negative
Screened by transnasal EGD			
Screened subjects	1280	510	770
Age (yr)	53.4 ± 15.4	56.8 ± 13.6[c]	50.2 ± 14.3
Males	623 (48.7)[a]	268 (52.5)[a]	355 (46.1)[a]
Smokers	247 (19.3)	118 (23.1)[c]	129 (16.7)[a]
Subjects with gastric neoplasia/DR	21/0.0164	16/0.0314[c]	5/0.00649
Location of neoplasia (U/M/L)	7/6/8	4/6/6	3/0/2
Adenoma cases/DR	3/0.0023	3/0.00589	0/0
Size of adenoma (mm)	9.7 ± 4.0	9.7 ± 4.0	0
Cancer cases/DR	18/0.0141	13/0.0255[c]	5/0.00649
Size of cancer (mm)	31.2 ± 19.5	25.5 ± 13.3	46.0 ± 28.2
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	6/1/4/7	5/0/4/4	1/1/0/3
With intestinal-type cancer	16 (88.9)	12 (92.3)	4 (80)
Depth of invasion (m/sm/pm-)	5/6/7	4/5/4	1/1/3
With early cancer	12 (66.7)	10 (76.9)	2 (40)
Screened by transoral EGD			
Screened subjects	1707	692	1015
Age (yr)	53.5 ± 15.4	56.3 ± 14.7[c]	51.8 ± 14.8
Males	655 (38.4)	298 (43.1)	357 (35.2)
Smokers	354 (20.7)	141 (20.3)	213 (21.0)
Subjects with gastric neoplasia/DR	33/0.0193	26/0.0376[c]	6/0.00591
Location of neoplasia (U/M/L)	12/8/12	10/8/9	2/0/3
Adenoma cases/DR	9/0.0052	5/0.00722	4/0.00394
Size of adenoma (mm)	10.8 ± 7.9	13 ± 11.5	10 ± 4.08
Cancer cases/DR	23/0.0135	21/0.0303[c]	2/0.00197
Size of cancer (mm)	22.3 ± 12.8	23.2 ± 13.4	20 ± 0
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	6/0/12/5	6/0/10/5	0/0/2/0
With intestinal-type cancer	15 (65.2)	14 (66.7)	1 (50)
Depth of invasion (m/sm/pm-)	15/3/5	13/3/5	2/0/0
With early cancer	18 (78.3)	14 (76.2)	2 (100)

[a]$P < 0.05$ *vs* transoral, [c]$P < 0.05$ *vs Helicobacter pylori* (*H. pylori*)-negative. DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach; EGD: Esophagogastroduodenoscopy.

neoplasia (detection rate, 1.65%), with gastric cancers in 43 subjects (detection rate, 1.29%) and adenomas in 12 subjects (detection rate, 0.36%). Of these, 23 cases were detected by transnasal EGD (detection rate, 1.66%) and 32 cases by standard transoral EGD (detection rate, 1.65%). Detection rates for screening using the two different types of endoscopes were thus almost equivalent (Table 1). The detection rate of adenoma was higher in the standard transoral EGD group (0.46%) than in the transnasal EGD group (0.22%), but no significant differences in detection rate, size or location of adenoma were evident between groups. The detection rate of gastric cancer likewise did not differ significantly between groups, at 1.45% for transnasal EGD and 1.18% for standard transoral EGD. However, mean size of detected lesions was significantly smaller with standard transoral EGD. The percentage of early cancers tended to be higher for standard transoral EGD (78.3%) than for transnasal EGD (60%), although no significant difference was apparent. Locations and morphological types of detected cancers did not differ significantly between groups, although standard transoral EGD detected depressed-type cancers located in the upper third of the stomach more frequently. With regard to the histopathological type of detected cancers, standard transoral EGD detected significantly more non-intestinal-type cancers (i.e. diffuse-type cancers) than transnasal EGD.

Next, we compared detection rates of gastric mucosal neoplasia using the two different EGDs according to the status of *H. pylori* infection (Table 2) and the extent of CAG (Table 3). Mean age of screened subjects was significantly higher in the *H. pylori*-positive group and in the CAG-positive group than in their respective negative counterparts, and no significant differences in mean age of screened subjects were seen between the two EGD groups when stratified into subgroups according to positivity for *H. pylori* infection or the extent of CAG. However, the percentage of men was significantly higher in the transnasal EGD group irrespective of *H. pylori* status or the extent of CAG. In the *H. pylori*-negative group, the percentage of smokers was significantly higher among subjects screened by standard transoral EGD than by transnasal EGD, while the *H. pylori*-positive group showed no significant difference in the percentage of smokers between EGD groups. No significant difference in the percentage of smokers was seen between EGD groups, regardless of CAG status.

Detection rates of gastric mucosal neoplasia using

Table 3 Screening performance of the two esophagogastroduodenoscopies in subjects with or without chronic atrophic gastritis (mean ± SD) *n* (%)

	Total subjects	CAG	
		Positive	Negative
Screened by transnasal EGD			
Screened subjects	1382	560	822
Age (yr)	53.4 ± 15.4	60.3 ± 11.8[c]	47.0 ± 14.5
Males	684 (49.4)[a]	316 (56.4)[a]	368 (44.8)[a]
Smokers	267 (19.3)	121 (21.6)	146 (17.8)
Subjects with gastric neoplasia/DR	23/0.0166	22/0.0286[c]	1/0.00122[a]
Location of neoplasia (U/M/L)	8/7/8	8/6/8	0/1/0
Adenoma cases/DR	3/0.0022	3/0.00536	0/0
Size of adenoma (mm)	9.7 ± 4.0	9.7 ± 4.0	0
Cancer cases/DR	20/0.0145	19/0.0315[c]	1/0.00122
Size of cancer (mm)	32.6 ± 19.5[a]	34.1 ± 18.8[a]	5 ± 0
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	6/1/5/8	6/1/4/8	0/0/1/0
With intestinal-type cancer	18 (90.0)	18 (94.7)	0 (0)
Depth of invasion (m/sm/pm-)	5/7/8	4/7/8	1/0/0
With early cancer	12 (60.0)	11 (57.9)[a]	1 (100)
Screened by transoral EGD			
Screened subjects	1942	800	1142
Age (yr)	53.5 ± 15.6	62.3 ± 11.4[c]	47.3 ± 14.2
Males	758 (39.0)	363 (45.3)	395 (34.6)
Smokers	411 (21.2)	165 (20.6)	246 (21.6)
Subjects with gastric neoplasia/DR	32/0.0164	24/0.0300[c]	8/0.0070
Location of neoplasia (U/M/L)	12/8/12	8/7/9	4/1/3
Adenoma cases/DR	9/0.0046	7/0.00875[c]	2/0.00175
Size of adenoma (mm)	10.8 ± 7.9	11.7 ± 8.8	7.5 ± 3.5
Cancer cases/DR	23/0.0118	17/0.0213[c]	6/0.00525
Size of cancer (mm)	22.3 ± 12.8	19.4 ± 11.7	31.4 ± 12.1
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	6/0/12/5	6/0/9/2	0/0/3/3
With intestinal-type cancer	15 (65.2)	12 (70.6)[c]	2 (33.3)
Depth of invasion (m/sm/pm-)	15/3/5	13/2/2	2/1/3
With early cancer	8 (78.3)	15 (88.2)	3 (50.0)

[a]$P < 0.05$ *vs* transoral; [c]$P < 0.05$ *vs* CAG-negative. CAG: Chronic atrophic gastritis; DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach; EGD: Esophagogastroduodenoscopy.

each of the two EGDs were significantly higher in the *H. pylori*-positive group than in the negative group (Table 2). No significant differences in the detection rate of neoplasia, as either adenoma or cancer, or in the size or percentage of early cancers were found between the two EGDs, irrespective of *H. pylori* infection. The percentage of morphologically depressed and histologically diffuse-type cancer tended to be higher among cancers detected by standard transoral EGD than by transnasal EGD, irrespective of *H. pylori* infection, but no significant differences were evident. Table 3 shows the results of screening by the two EGDs according to CAG status. The detection rate for gastric mucosal neoplasia was significantly higher among CAG-positive subjects than among negative subjects, regardless of the type of endoscope. In CAG-positive subjects, 65% (30/46) of detected neoplasias were located in the lower two-thirds of the stomach, 50% (23/46) showed an elevated-type morphology and 87% (40/46) displayed intestinal-type histology. No significant differences in the detection rate of neoplasia, morphological or histological types or location were noted between the two EGD groups. However, mean size of the cancer detected was significantly smaller and the percentage of early cancers was higher with standard transoral EGD than with transnasal EGD. Among CAG-negative subjects, 44.4% (4/9) of detected neoplasias were located in the upper third of the stomach and all cancers detected showed depressed- or ulcerated-type morphology. Seventy-one percent (5/7) displayed diffuse-type histology and 42.9% of cases (3/7) showed complications of nodular gastritis. Detection rates of neoplasia were significantly higher in the standard transoral EGD group (0.70%) than in the transnasal EGD group (0.12%, $P < 0.05$). This reflects the high rate of cancer detection for standard transoral EGD in the CAG-negative stomach.

Finally, screening for gastric mucosal neoplasias using the two different EGDs was analyzed according to the stages of *H. pylori*-related chronic gastritis. Mean age in each stage group increased in a stepwise manner with the progression of *H. pylori*-related chronic gastritis from Group A to Group D, and no significant differences were found between the two EGD groups in any stage. The transnasal EGD group showed a higher proportion of men than the transoral group throughout all stages, with significant differences in Groups A and C. In Group A, the standard transoral EGD group included significantly more smokers than the transnasal EGD group,

Table 4 Screening performance of the two esophagogastroduodenoscopies according to the stages of *Helicobacter pylori*-related chronic gastritis (mean ± SD) *n* (%)

	Group A	Group B	Group C	Group D	Total subjects (*H. pylori* analyzed)
Screened by transnasal EGD					
Screened subjects	572	189	321	198	1280
Age (yr)	45.3 ± 13.8	49.2 ± 14.6[c]	59.8 ± 12.1[c]	63.4 ± 12.8[c]	53.4 ± 15.4
Males	257 (44.9)[a]	74 (39.3)	194 (60.2)[a]	98 (49.4)	623 (48.7)[a]
Smokers	89 (15.6)[a]	43 (22.8)[a]	75 (23.3)	40 (20.2)	247 (19.2)
Subjects with gastric neoplasia/DR	0/0	1/0.0053[a,c]	15/0.0466[c]	5/0.0253	21/0.0164
Location of neoplasia (U/M/L)	0	0/1/0	4/5/6	3/0/2	7/6/8
Adenoma cases/DR	0/0	0/0	3/0.0093	0/0	3/0.0023
Size of adenoma (mm)	0	0	9.7 ± 4.0	0	9.7 ± 4.0
Cancer cases/DR	0/0	1/0.00532	12/0.0373	5/0.0253	18/0.0141
Size of cancer (mm)	0	5 ± 0	27.3 ± 12.3	46.0 ± 28.2	31.2 ± 19.5
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	0	0/0/1/0	5/0/3/4	1/1/0/3	6/1/4/7
With intestinal-type cancer	0 (0)	0/1 (0)	12/12 (100)	4/5 (80)	16/18 (88.9)
Depth of invasion (m/sm/pm-)	0	1/0/0	3/5/4	1/1/3	5/6/7
With early cancer	-	1 (100)	8 (66.7)	2 (40)	12 (66.7)
Screened by transoral EGD					
Screened subjects	751	257	435	264	1707
Age (yr)	46.0 ± 12.6	46.6 ± 15.4	60.9 ± 11.8[c]	64.0 ± 11.4[c]	53.5 ± 15.4
Males	247 (32.9)	95 (37.0)	203 (46.7)	110 (41.7)	655 (38.4)
Smokers	167 (22.2)	39 (15.2)	102 (23.4)	46 (17.4)	354 (20.7)
Subjects with gastric neoplasia/DR	0/0	8/0.0311[c]	18/0.0414[c]	6/0.0227	32/0.0187
Location of neoplasia (U/M/L)	0	4/1/3	6/7/5	2/0/4	12/8/12
Adenoma cases/DR	0/0	2/0.00778	3/0.00689	4/0.0152	9/0.0052
Size of adenoma (mm)	0	7.5 ± 3.53	8.0 ± 13.9	10 ± 4.08	10.8 ± 7.9
Cancer cases/DR	0/0	6/0.0233	15/0.0345	2/0.00758	23/0.0134
Size of cancer (mm)	0	31.4 ± 12.1	19.4 ± 12.5	20 ± 0	22.3 ± 12.8
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	0	0/0/3/3	6/0/7/2	0/0/2/0	6/0/12/5
With intestinal-type cancer	0 (0)	2/6 (33.3)	12/15 (80)	1/2 (50)	16/24 (66.7)
Depth of invasion (m/sm/pm-)	0	2/1/3	11/2/2	2/0/0	15/3/5
With early cancer	-	3 (50)	13 (86.7)	2 (100)	18 (78.3)

[a]$P < 0.05$ *vs* transoral; [c]$P < 0.05$ *vs* previous stage. *H. pylori*: *Helicobacter pylori*; DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach; EGD: Esophagogastroduodenoscopy. Group A: *H. pylori* (-), chronic atrophic gastritis (CAG) (-); Group B: *H. pylori* (+), CAG (-); Group C: *H. pylori* (+), CAG (+); Group D: *H. pylori* (-), CAG (+).

while Group B included significantly more smokers in the transnasal EGD group than in the standard transoral EGD group. No neoplasias were detected in Group A (*H. pylori*- and CAG-negative), which comprised of subjects with an infection-free healthy stomach (Table 4). In Group B (*H. pylori*-positive, CAG-negative), representing subjects with an *H. pylori*-infected non-atrophic stomach, the detection rate of gastric mucosal neoplasia was significantly higher in the standard transoral EGD group (3.11%) than in the transnasal EGD group (0.53%, $P < 0.05$). In Group C (*H. pylori*- and CAG-positive) and Group D (*H. pylori*-negative, CAG-positive), no significant differences in detection rates were found between endoscopy groups. Mean size of the detected cancer was smaller and the proportion of early cancers was higher in the standard transoral EGD group, although the difference was not significant. Furthermore, no significant differences in location, morphological type or histopathological type of detected cancers were seen, irrespective of differences in the endoscope used.

DISCUSSION

Previous studies have reported that the diagnostic accuracy of transnasal EGD is equivalent to that of standard transoral EGD for the detection of esophagogastric lesions, including gastric cancer[23-30]. However, despite recent advances in endoscopic technologies, small-diameter endoscopes used for transnasal EGD still show disadvantages when compared to standard endoscopes, due to lower luminous intensity, lower resolution of endoscopic images, a narrow field of view, low maneuverability and low biopsy performance, all of which are attributable to the small diameter of the endoscope[31]. Yoshida *et al*[30] found no significant differences in detection rates of early gastric cancer and adenoma between transnasal and standard transoral EGD, but also noted that gastric cancers may be overlooked by transnasal EGD when performed by less-experienced endoscopists. Furthermore, Hayashi *et al*[32] investigated the detection of early gastric cancer ⩽ 2 cm in diameter using the two different EGDs and indicated that transnasal EGD offers inadequate diagnostic yield compared with standard transoral EGD. Supporting those findings, the present results strongly suggest that, although detection rates of gastric mucosal neoplasia might not differ significantly between transnasal and standard transoral EGDs, mean sizes of the detected cancers were significantly larger with transnasal EGD. In addi-

tion, percentages of early or diffuse-type cancers, which require higher resolution for detection, were lower among cancers detected by transnasal EGD. Of note, the difference in detection rates of diffuse-type cancer between the two EGDs was significant. Hayashi *et al*[32] also reported that ultra thin endoscopes were less efficient in screening for lesions located in the upper third of the stomach, due to the narrower field of view and low luminous intensity. Diffuse-type cancer tends to develop from fundic gland mucosa located mainly in the gastric body[14,15,17], providing a possible explanation for the low diagnostic performance of transnasal EGD in detecting diffuse-type cancer. However, the present study found no significant differences in the locations of detected neoplasias between the two EGDs. Screening performance of transnasal EGD thus seems to remain suboptimal compared with standard transoral EGD, at least in the detection of subtle mucosal changes presented by small-sized cancers or by diffuse-type cancers with biologically infiltrating characteristics.

The proliferation and growth of neoplastic cells derived from the stomach mucosa is widely accepted to be regulated by the acidic environment in the gastric lumen. The morphological and biological characteristics of gastric mucosal neoplasia are under the influence of the stage of *H. pylori*-related chronic gastritis[14-16]. With the development of gastric atrophy together with intestinal metaplasia, intra-luminal pH in the stomach becomes less acidic and mucosal neoplasia with an elevated or protruding morphological type and intestinal histological type tends to become more prevalent[14-17]. Conversely, chronic active inflammation of the stomach, regardless of the existence of gastric atrophy, directly induces histologically diffuse-type cancer, which tends to develop in the non-atrophic stomach and is thus usually morphologically depressed or ulcerated[14,15,17,18]. The natural history of *H. pylori*-related chronic gastritis can be classified into four stages (Groups A-D), based on the establishment of *H. pylori* infection or CAG[20,21]. In the present study, the screening performance of transnasal EGD according to each of the four stages of *H. pylori*-related chronic gastritis was also investigated in comparison with standard transoral EGD. No gastric cancers were detected among subjects with an *H. pylori*-negative healthy stomach (Group A), while establishment of *H. pylori* infection (Group B) was associated with the development of gastric mucosal neoplasias. The incidence of gastric mucosal neoplasias increased significantly as the extent of CAG increased from Group B to Group C. In Group B (subjects with *H. pylori*-infected non-atrophic stomach), the detection rate of gastric mucosal neoplasia was significantly lower with transnasal EGD than with standard transoral EGD, representing the detection rate of gastric cancer. Types of cancers detected in Group B were predominantly depressed or ulcerated type morphologically and diffuse type histologically, supporting the reported clinicopathological characteristics of cancers developing from a non-atrophic stomach[14,15,17]. The present results clearly indicate that the screening performance of transnasal EGD is low for detecting the above-mentioned types of cancer developing against a background of the non-atrophic stomach. Meanwhile, in Groups C and D, comprising subjects with extensive CAG, no significant differences in detection rates of gastric mucosal neoplasia were seen between the two EGDs. As postulated in the multistep model of stomach carcinogenesis, a major proportion of cancers develop from the stomach mucosa with extensive CAG together with intestinal metaplasia in regions with a high risk for cancer, including Japan[14,15,17,18]. Consistent with this, 83.0% of gastric mucosal neoplasias (82.9% of cancers) developed in Groups C and D. In these groups, intestinal-type cancer predominated histopathologically and 50% of detected neoplasias were morphologically elevated or protruding, compatible with clinicopathological findings of cancer developing from extensive CAG[14-17]. Based on the observed detection rates for the two EGDs, screening performance of transnasal EGD appears comparable to that of standard transoral EGD in detecting this major type of cancer. However, the significantly smaller size of detected cancers and the significantly higher percentage of early cancers among cancers detected by standard transoral EGD suggest great room for improvement in the diagnostic performance of transnasal EGD for cancer screening in subjects with extensive CAG. Meanwhile, the present study has some limitations. Firstly, in our country gastric cancer screening is being carried out as a public health service and a non-negligible number of people underwent the screening by endoscopy. Thus, the detection rate of gastric mucosal neoplasia is to some extent under the influence of the time intervals between the previous EGD and the EGD performed in the present study. In both groups of the two EGDs, around 55% of the study subjects underwent the cancer screening by EGD in the previous year. The proportion of the subjects who underwent EGD within the last 3 years was 11% and 18% in transnasal and standard transoral EGD, respectively. As for the remaining subjects, no information about the previous EGD is available. Secondly, in general the incidence of gastric neoplasia is higher in males compared to females. In the present study, the number of male subjects included in the transnasal EGD group was significantly higher than in the transoral EGD group. Thus, the screening performance of transnasal EGD might have been overestimated, although it still remains suboptimal compared with that of standard transoral EGD. Since tolerability, acceptability and safety of transnasal EGD with a small-diameter endoscope are better than standard transoral EGD, transnasal EGD has been increasingly used for gastric cancer screening[30-32]. However, the present results indicate that the screening performance of transnasal EGD remains suboptimal, even in subjects with extensive CAG, which represents a key route of stomach carcinogenesis in Japan. Furthermore, in screening for the small proportion of cancers developing from the *H. pylori*-infected non-atrophic stomach, small-diameter endoscopes are clearly

inadequate compared with standard endoscopes. Evaluation of the accuracy of transnasal EGDs in cancer screening must await the results of long-term follow-up studies. However, the present findings offer compelling evidence that the introduction of small-diameter endoscopes into cancer screening first requires improvements in the low image quality of transnasal EGD due to low resolution, low luminous intensity and narrow angle of view.

Special attention should be paid to the screening of individuals with *H. pylori* infection of the non-atrophic stomach. This group of subjects as a whole is not considered to be at high risk of cancer, with an annual incidence rate of around 0.1% in Japan[20,21,33]. However, considering the rapid growth and high malignant potential of the diffuse-type cancer that tends to arise in this group, together with the subtle endoscopic findings present in the early stage, use of high-performance endoscopy is strongly recommended. We have recently reported that a group of subjects with non-atrophic stomach at high risk for diffuse-type cancer can be identified using serum pepsinogen (PG) levels (PG I > 70 ng/mL; PG I / II ratio ≤ 3.0)[33]. We believe that cancer screening in such individuals should be performed cautiously using standard transoral EGD. In the near future, high-performance, small-diameter endoscopes will surely be developed and are likely to contribute greatly to the establishment of highly efficient cancer screening programs. However, with the currently available small-diameter endoscopes, cancer screening should be performed meticulously based on ample experience with standard transoral EGD and also with full knowledge of the limitations and characteristics of small-diameter endoscopes.

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COMMENTS

Background

Transnasal esophagogastroduodenoscopy (EGD) is more acceptable for patients and has been increasingly applied for gastric cancer screening. Previous studies showed that the diagnostic accuracy of transnasal EGD was equivalent to that of standard transoral EGD for the detection of esophagogastric lesions. However, the screening performance of transnasal EGD for gastric mucosal neoplasias must be determined carefully because of its lower luminous intensity and lower quality of endoscopic images.

Research frontiers

In the present study, the diagnostic ability of transnasal and standard transoral EGD for gastric cancer screening has been evaluated from various points of view. Especially, the screening performance of both EGDs has been investigated according to the stages of *Helicobacter pylori* (*H. pylori*)-related chronic gastritis.

Innovations and breakthroughs

The results have clearly demonstrated that the diagnostic performance of transnasal EGD remains suboptimal for cancer screening, particularly in subjects with *H. pylori*-infected non-atrophic stomach.

Applications

Based on the present results, special attention should be paid to the cancer screening of the subjects with *H. pylori*-infected non-atrophic stomach, who are at high risk for diffuse-type cancer, and transoral EGD is strongly recommended for such individuals. The results of the authors' previous study have already revealed that such individuals can be identified using serum pepsinogen levels.

Peer review

Nakata *et al* compared the diagnostic performances of transnasal and standard transoral EGD in gastric cancer screening of asymptomatic healthy subjects. A total of 3324 subjects including 1382 screened by transnasal EGD and 1942 screened by standard transoral EGD were enrolled. They concluded that the diagnostic performance of transnasal endoscopy is suboptimal for cancer screening, particularly in subjects with H. pylori-related atrophic gastritis. This is a well-written paper describing an extensive experience in the use of transnasal endoscopy for gastric cancer screening.

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AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011
Miami, FL 33101, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011
San Francisco, CA 94143, United States

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 04-05, 2011
13th Duesseldorf International Endoscopy Symposium
Duesseldorf, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

February 24-26, 2011
2nd International Congress on Abdominal Obesity
Buenos Aires, Brazil

February 26-March 1, 2011
Canadian Digestive Diseases Week
Westin Bayshore, Vancouver
British Columbia, Canada

March 03-05, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL 32614, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011
Birmingham, England, United Kingdom

March 17-19, 2011
41. Kongress der Deutschen Gesellschaft für Endoskopie und Bildgebende Verfahren e.V.
Munich, Germany

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology 2011
Jacksonville, FL 34234, United States

March 25-27, 2011
MedicReS IC 2011 Good Medical Research
Istanbul, Turkey

April 07-09, 2011
International and Interdisciplinary Conference Excellence in Female Surgery
Florence, Italy

April 15-16, 2011
Falk Symposium 177, Endoscopy Live Berlin 2011 Intestinal Disease Meeting, Stauffenbergstr. 26
Berlin 10785, Germany

April 18-22, 2011
Pediatric Emergency Medicine: Detection, Diagnosis and Developing Treatment Plans
Sarasota, FL 34234, United States

April 20-23, 2011
9th International Gastric Cancer Congress, COEX, World Trade Center, Samseong-dong
Seoul 135-731, South Korea

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

April 28-30, 2011
4th Central European Congress of Surgery
Budapest, Hungary

May 07-10, 2011
Digestive Disease Week
Chicago, IL 60446, United States

May 12-13, 2011
2nd National Conference Clinical Advances in Cystic Fibrosis
London, England, United Kingdom

May 21-24, 2011
22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
Venise, Italy

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn
Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV Spigc II ESYS, Napoli, Italy

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
Barcelona, Spain

September 10-11, 2011
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 10-14, 2011
ICE 2011-International Congress of Endoscopy, Los Angeles Convention Center, 1201 South Figueroa Street
Los Angeles, CA 90015, United States

September 30-October 1, 2011
Falk Symposium 179, Revisiting IBD Management: Dogmas to be Challenged, Sheraton Brussels Hotel
Brussels 1210, Belgium

October 19-29, 2011
Cardiology & Gastroenterology Tahiti 10 night CME Cruise
Papeete, French Polynesia

October 22-26, 2011
19th United European Gastroenterology Week
Stockholm, Sweden

October 28-November 02, 2011
ACG Annual Scientific Meeting & Postgraduate Course
Washington, DC 20001, United States

November 11-12, 2011
Falk Symposium 180, IBD 2011: Progress and Future for Lifelong Management, ANA Interconti Hotel, 1-12-33 Akasaka, Minato-ku
Tokyo 107-0052, Japan

December 01-04, 2011
2011 Advances in Inflammatory Bowel Diseases/Crohn's & Colitis Foundation's Clinical & Research Conference
Hollywood, FL 34234, United States

WJGE World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
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GENERAL INFORMATION

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The columns in the issues of *WJGE* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in gastrointestinal endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGE*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal endoscopy.

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Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

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Format

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
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