Gastritis Cystica Polyposa Concomitant with Gastric Inflammatory Fibroid Polyp Occurring in an Unoperated Stomach

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Abstract

The endoscopic examination of a 61-year-old male patient revealed a protruding lesion in the greater curvature of the lower third area of the stomach. The lesion, 17 mm in size, was resected completely with endoscopic submucosal dissection using an insulated-tip diathermic knife (IT-ESD). Histological examination of the protruding lesion revealed proliferation of fibroblasts and infiltration of inflammatory cells in the mucosa and submucosa, and it was diagnosed as an inflammatory fibroid polyp (IFP). Gastritis cystica polyposa (GCP) was presented adjacent to the IFP. This may be the first report of GCP concomitant with gastric IFP occurring in an unoperated stomach.
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Key words: gastric cysts, inflammatory polyp, neoplasm, insulated-tip diathermic knife, endoscopic submucosal dissection

Introduction

Inflammatory fibroid polyp (IFP) is a relatively rare disorder, which is thought to be clinically and histologically benign, and was first described as "polypoid fibroma" in 1920 by Konjetzny (1). Gastritis cystica polyposa (GCP), characterized by polypoid hyperplasia of the gastric mucosa, is an uncommon lesion that develops in patients who have undergone gastroenterostomy with or without gastric resection (2–5). GCP is rarely found in an unoperated stomach (4–6). There have been no previous case reports of gastric IFP concomitant with GCP. Herein, we report a case of GCP concomitant with gastric IFP occurring in an unoperated stomach, and treated by endoscopic submucosal dissection using an insulated-tip diathermic knife (IT-ESD).

Case Report

A 61-year-old man visited our hospital for further evaluation of abnormal radiographic findings of the stomach in a yearly physical checkup on October 13, 2001. No specific family or past medical history was identified. Routine hematological examination and biochemical tests were within normal limits. Serum anti-*Helicobacter pylori* (*H. pylori*) immunoglobulin G (IgG) antibody was positive. Endoscopic examination of the upper digestive tract revealed a protruding lesion, about 20 mm in diameter, in the pyloric gland area, in the greater curvature of the lower third area of the stomach (Fig. 1). The biopsy specimen obtained from the lesion revealed normal gastric mucosa. We had to make a differential diagnosis between a large hyperplastic polyp and a submucosal tumor covered with normal gastric mucosa. Endoscopic ultrasonography (EUS) with a miniature probe of 20 MHz frequency using the water filling method revealed a hypoechoic mass covered with a hyperechoic lesion that had anechoic areas in the second and third layers of the gastric wall (Fig. 2). This protruding lesion was surrounded by intestinal metaplastic mucosa. There were some red patches with erosions in the antrum, however, there was not any diffuse red area in the fundic area. The culture of gastric mucosa propagated the microaerophilic bacteria, *H. pylori*. On the basis of EUS findings, we could not deny that the tumor might be gastric cancer resembling a submucosal tumor or gastric cancer with a mucinous component. We suspected this patient had a submucosal tumor, but the definite diagnosis could not be made. The patient underwent an IT-ESD for histological confirmation. IT-ESD was performed as we previously described (7). The protruding lesion, 17×15×5 mm in size, was resected completely with a safe lateral

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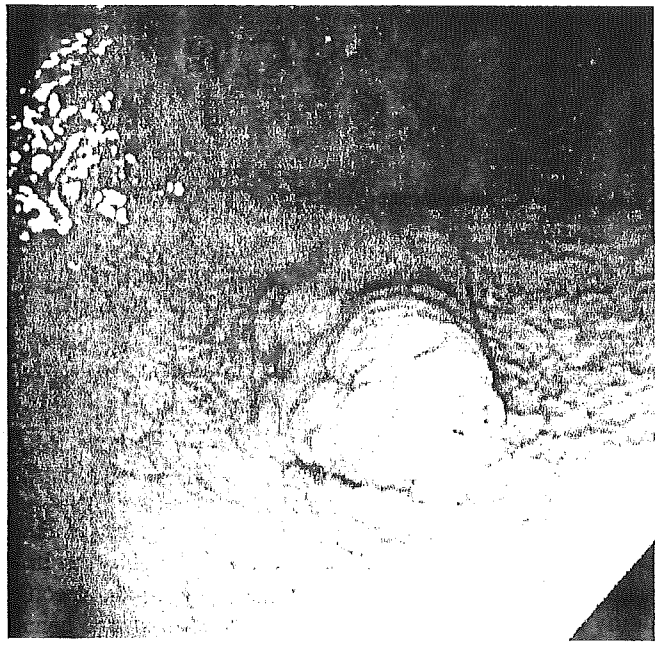

Figure 1. Endoscopic appearance of the elevated lesion in the greater curvature of the lower third area of the stomach. The lesion was covered with normal mucosa.

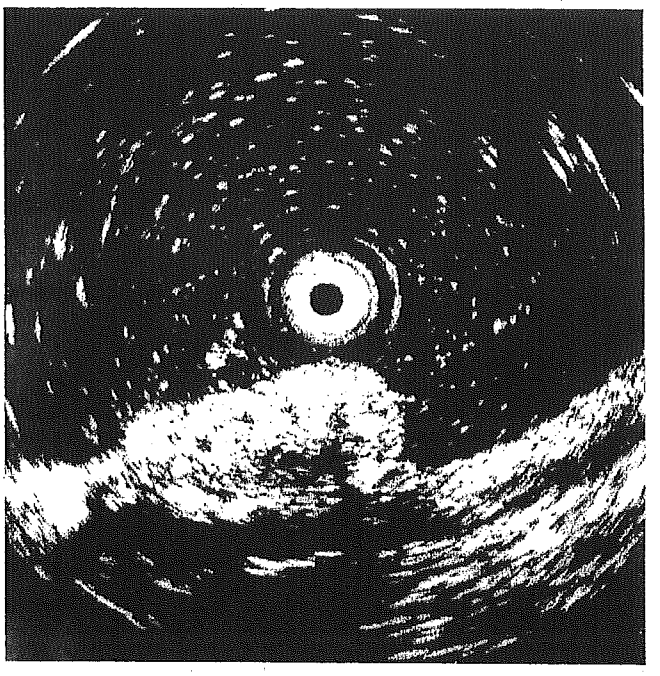

Figure 2. Endoscopic ultrasonography (EUS) revealed that a hypoechoic mass covered with hyperechoic lesion that had anechoic areas interrupted the second and third layers of the gastric wall.

and vertical margin, and resected specimen was 30×22 mm in size (Fig. 3). Histological examination of the protruding lesion revealed that the tumor was distributed from the mucosa to submucosal layer and multiple cysts were adjacent to the tumor (Fig. 4A). The proliferation of fibroblasts and the infiltration of inflammatory cells such as plasma cells and eosinophils were seen in the submucosal tumor (Fig. 4B). This tumor was diagnosed as gastric IFP. The elongation of the gastric foveolae along with hyperplasia and cystic dilatation of the gastric glands were seen (Fig. 4C). The protruding lesion was diagnosed as GCP concomitant with gastric IFP. Histologically, the tumor was surrounded by intestinal metaplastic mucosa. The postoperative course was uneventful. He has been under close periodic observation, and there is no evidence of disease 29 months after IT-ESD.

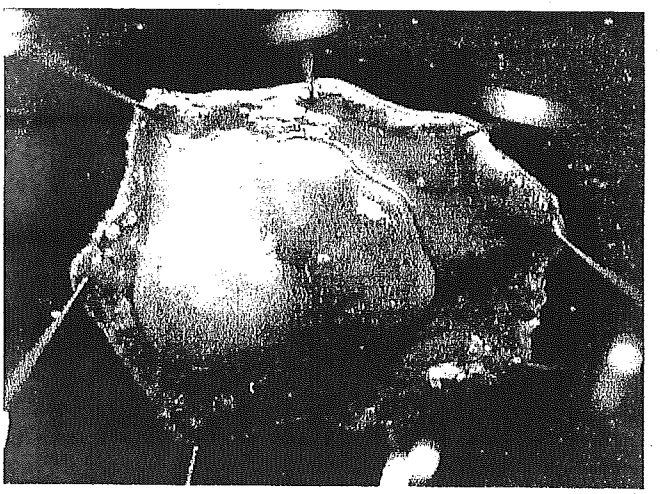

Figure 3. Macroscopic findings of the resected tumor. The resected specimen was 30×22 mm in size and the protruding lesion was resected completely with a safe lateral and vertical margin.

Discussion

IFP is a rare mucosal or submucosal lesion of the gastrointestinal tract that follows a benign course. Most of the fibroids reported were located in the mucosa and submucosa, although Ishikura et al (8) reported six lesions and we also reported one lesion (7) limited to the mucosa. The pathogenesis of IFP remains unknown. Endoscopic findings of IFPs are smooth sessile or pedunculated polyps. The final diagnosis of IFP depends on the pathological findings, however the histological findings of the biopsy specimen are often difficult to diagnose. In the present case, the tumor was completely resected by IT-ESD and the diagnosis of GCP concomitant with gastric IFP was made. This may be the first report of GCP concomitant with gastric IFP.

GCP was first described by Littler and Gleibermann in 1972 (2). It is characterized histologically by elongation of the gastric foveolae along with hyperplasia and cystic

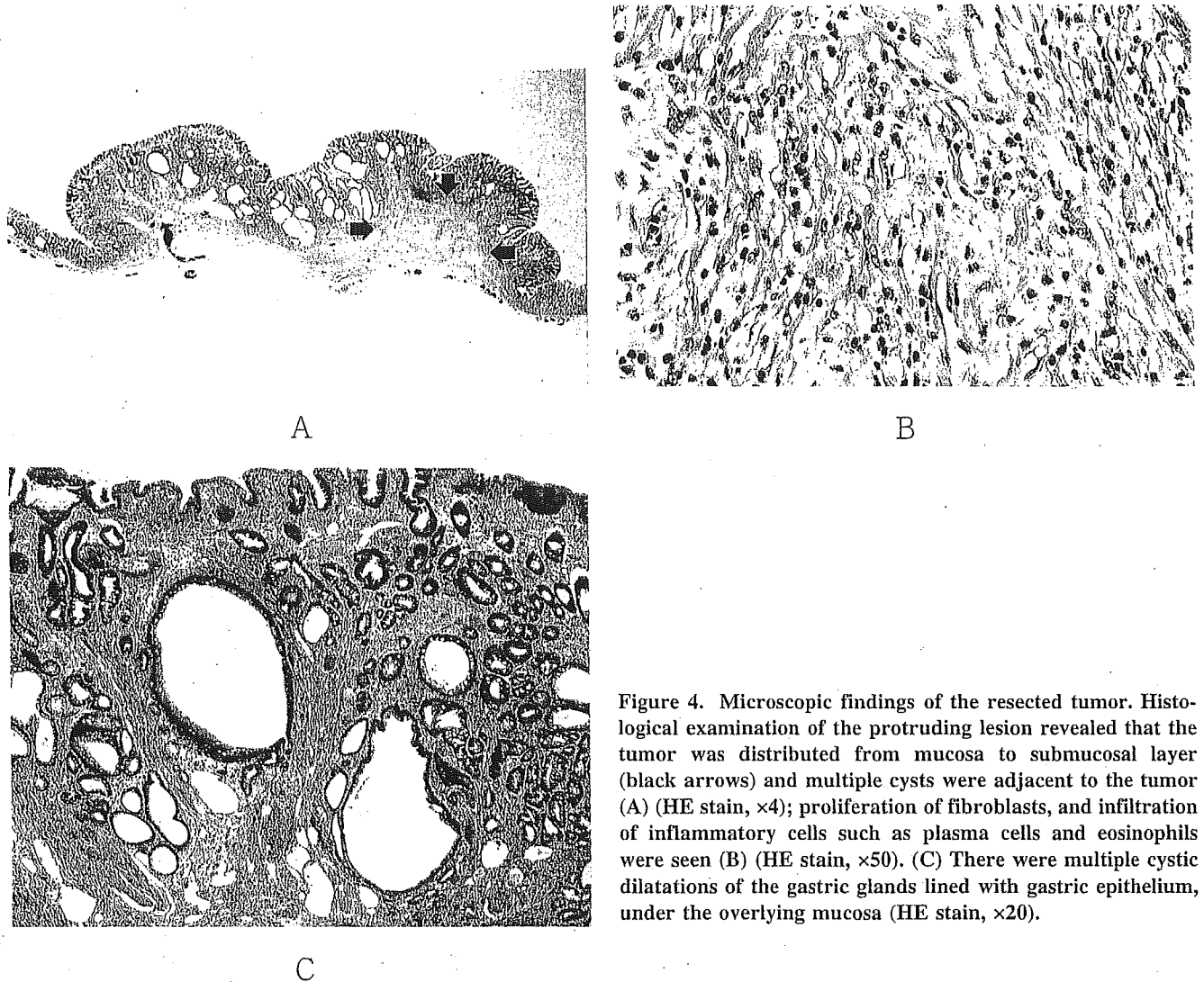

Figure 4. Microscopic findings of the resected tumor. Histological examination of the protruding lesion revealed that the tumor was distributed from mucosa to submucosal layer (black arrows) and multiple cysts were adjacent to the tumor (A) (HE stain, ×4); proliferation of fibroblasts, and infiltration of inflammatory cells such as plasma cells and eosinophils were seen (B) (HE stain, ×50). (C) There were multiple cystic dilatations of the gastric glands lined with gastric epithelium, under the overlying mucosa (HE stain, ×20).

dilatation of the gastric glands extending into the gastric submucosal layer (2–6). These lesions are usually found at the gastroenterostomy sites, presumably because of increased mucosal mobility accompanying peristaltic contractions and repair of the preanastomotic gastric mucosa after damage caused by reflux of duodenal contents (2, 9, 10). Koga et al described that there were 4 cases of GCP (9.5%) in their 42 patients who had once undergone gastrojejunostomy and received further surgery on account of various reasons (9). In Japan, there are many reports describing the association of GCP with early or small cancerous lesions in the remnant stomach (11, 12). Thus GCP has been proposed to be a possible precancerous lesion itself (13). GCP may rarely also develop in an unoperated stomach as in the present case. GCP in an unoperated stomach frequently occur in the gastric fundus (4–6). However, few cases with GCP in an unoperated stomach have been reported and further analysis of many cases is necessary in the future. GCP in an unoperated stomach has generally been assumed to be of congenital origin, mainly because of the lack of documented prior gastric ulceration or trauma (5, 14). However, the pathogenesis of GCP in an unoperated stomach is not clear. Thus further studies on the pathogenesis of GCP in an unoperated stomach are certainly necessary.

The pathogenesis of IFP remains unknown, however, some authors have proposed that IFP is caused by an allergic reaction to an inflammatory stimulus such as bacterial, chemical, traumatic, etc, or is a reactive lesion of fibroblastic or myofibroblastic nature (15). Gastric IFP frequently appears in the antrum (7), and the incidence of gastric IFP was reported to be 3.1% of one series of 5,515 gastric polyps by Stolte et al (16). Recently, Nishiyama et al (17) reported a case of IFP that morphologically changed after the *H. pylori* eradication therapy. They claimed that factors derived from gastric epithelial cells in response to *H. pylori* infection, such as inflammatory cytokines and growth factors, might affect the growth of IFPs. Their opinion is not proved although there is another report describing the relation between IFP and *H. pylori* infection (18). It is interesting that their report suggests the relationship between gastric IFP and *H. pylori*.

We could speculate possible pathogenetic relationships of gastric IFP with GCP as follows: 1) GCP occurs via stimulation of IFP and 2) IFP and GCP arise independently. The present case may indicate that some common factors are involved in the etiology of IFP and GCP, though there is no direct evidence at present. On the supposition, one of the factors may be *H. pylori*. However, there have been no reports describing the relationship between GCP and *H. pylori*. Further studies on the relationship between IFP and GCP are certainly necessary. The present case does not have direct evidence that IFP is related to GCP, however, we thought it would be valuable to report this case, since this may be the first report of GCP concomitant with gastric IFP occurring in an unoperated stomach. However, it is likely that there are latent patients with GCP concomitant with gastric IFP occurring in an unoperated stomach, which might be discovered by endoscopic resection in the future. Because both gastric IFP and GCP in an unoperated stomach are benign tumors and they are seldom resected by endoscopic resection or surgery.

The IT-ESD is a useful new endoscopic mucosal resection (EMR) method, which recently has been widespread in Japan. It is difficult to remove a complete tumor larger than 10 mm in diameter in one-piece by the usual strip biopsy method. However Ohkuwa et al (19) reported a one-piece resection rate of IT-ESD (between 11 and 20 mm) of 75% in 16 patients with adenocarcinoma or adenoma. As to the endoscopic treatment of gastric IFP, Nishio et al (20) reported a case of gastric IFP who revealed an increase in size of the IFP after incomplete endoscopic resection within a year. Thus, gastric IFP should be resected completely with a safe margin if EMR is performed. The lesion in the present case was about 20 mm, however, the result of IT-ESD was that we could resect this tumor completely and ensure a safe margin. Here, IT-ESD was an effective and safe therapy for a gastric protruding lesion of nearly 20 mm in diameter.

In conclusion, we report the first case of GCP adjacent to gastric IFP occurring in an unoperated stomach. The IT-ESD was a useful treatment method for GCP concomitant with IFP in the present case. There have been no previous case reports of GCP concomitant with gastric IFP. This case emphasizes that it is important to keep in mind that gastric IFP might be accompanied by GCP in an unoperated stomach though such a condition is extremely rare.

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GASTROENTEROLOGY

Stool decay-accelerating factor as a marker for monitoring the disease activity during leukocyte apheresis therapy in patients with refractory ulcerative colitis

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Abstract

Background and Aims: We have shown previously that concentrations of stool decay-accelerating factor (DAF; CD55), a complement regulatory protein, in patients with ulcerative colitis (UC) are increased in relation to the severity of the colonic mucosal inflammation. In the present study, we evaluated the usefulness of stool DAF as a marker for monitoring disease activity in patients with steroid-resistant active UC being treated with leukocyte apheresis performed with a centrifugal cell separator.

Methods: Twenty-one patients with active and steroid-resistant UC were treated with leukocyte apheresis once a week for 4 weeks, and stool DAF concentrations were determined weekly by immunoassay.

Results: After treatment, 11 (52%) of the 21 UC patients went into remission. Stool DAF concentrations decreased promptly and steadily in the responsive group. The difference reached statistical significance as soon as after the second apheresis session ($P < 0.003$), compared with values before the therapy and corresponding values in the non-responsive group ($P = 0.024$). The reduction in stool DAF concentrations after the second apheresis session was significantly greater in the responsive group (median 90%, range 22–90%) than in the non-responsive group (median −13%, range −307–94%) ($P = 0.008$). Hematological tests, that is, white blood cell (WBC) count and C-reactive protein, declined significantly during the apheresis therapy, but not in relation to therapeutic response.

Conclusion: Stool DAF concentration is a useful marker in the clinical response of UC patients to treatment with leukocyte apheresis.

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Key words: CD55, decay-accelerating-factor, leukocyte apheresis, ulcerative colitis.

INTRODUCTION

In the treatment of active ulcerative colitis (UC), leukocyte apheresis has been reported to be effective.[1–6] Apheresis is believed to exert its beneficial effects by removing activated leukocytes, including granulocytes and lymphocytes, and modulating altered immune responses. The effectiveness of apheresis is comparable to steroid therapy, even in patients whose colitis is refractory to conventional drug therapy.[4–6]

Assessment of the activity of intestinal inflammation is essential in the treatment of active UC. Laboratory markers such as white blood cell (WBC) count, platelet count, erythrocyte sedimentation rate and the acute phase protein, C-reactive protein (CRP), are useful in the evaluation of intestinal inflammation, but are not specific enough because often they are affected by drugs such as glucocorticoid or sulfasalazine. In the treatment with leukocyte apheresis, some of these markers, such as WBC and platelet counts, are decreased by apheresis itself and thus do not necessarily reflect the degree of intestinal inflammation.

We have previously shown that expression of decay-accelerating factor (DAF; CD55), a membrane-bound

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glycoprotein which inhibits the formation and promotes the catabolism of C3 and C5 convertases,[7] is enhanced in the colonic epithelial cells of UC mucosa[8] and that stool DAF concentrations in UC patients are increased in relation to the severity of mucosal inflammation.[9] These observations suggest that measurement of stool DAF could be a useful non-invasive method of monitoring intestinal disease activity in patients with UC. To test this possibility, we measured DAF concentrations in serially obtained stool specimens from patients with steroid-resistant active UC during treatment with leukocyte apheresis, using a centrifugal cell separator.

METHODS

Patients and study design

Twenty-one patients with active, steroid-resistant UC (13 females and eight males, mean age 35 years, age range 14–69 years) were studied. The diagnosis of UC was based on history, clinical symptoms, and endoscopic and histological findings. Nineteen patients had pancolitis and two had left-sided colitis. Disease activity was graded on the basis of clinical features and laboratory data according to the criteria of Truelove and Witts,[10,11] and endoscopic findings according to the method described by Matts.[12] All patients had been refractory to corticosteroid therapy for 1 month or more (mean dose of predonisolone, 30 mg/day; mean duration of therapy, 6.1 weeks). Clinical disease activity of the patients was severe ($n = 8$) and moderate ($n = 14$). Endoscopic findings were: Matts grade 4 ($n = 7$), 3 ($n = 10$) and 2 ($n = 4$).

Leukocyte apheresis was performed by use of a centrifugal separation apparatus (Multi Component System, Haemonetics, Braintree, MA, USA) once a week for 4 weeks. In each session, leukocyte-rich fractions of buffy coat layers were removed from 2000 to 2500 mL of patients' peripheral blood. Acid citrate dextrose solution was used as the anticoagulant. All medications the patients were currently taking, including aminosalicylates and corticosteorids, were continued at the same dose during the study period. After the completion of four apheresis sessions, the patients' disease activity was again assessed. Remission was defined as a reduction in the degree of clinical activity to mild and without hematochezia or better, and improvement of endoscopic findings to Matts grade 1 or 2 without contact bleeding. Disease activity and remission were determined by two gastroenterologists (MM and HO) who had no knowledge of the stool DAF levels of patients under evaluation. Hematological parameters, WBC count, platelet count and CRP were monitored once a week, and spontaneously passed stool samples (1–5 g) were obtained from each patient before and weekly after each apheresis session until the end of the study. The study was conducted according to the guidelines of the Declaration of Helsinki and our local Ethics Committee approved the study protocol. The objective of this study was explained to each patient before the study, and written informed consent was obtained from each patient.

Determination of decay-accelerating factor in stool specimens

Stool specimens were weighted and suspended in three times the weight of phosphate-buffered saline containing 1% bovine serum albumin, 0.05% Tween 20, and 1 mmol/L phenylmethylsulfonylfluoride with increased NaCl concentration (0.4 M) to reduce non-specific reactions as described.[13] The suspensions were centrifuged at 8000 g for a few seconds in a benchtop microfuge[14] and supernatants were collected and kept frozen at −80°C until use. Samples were coded, and the person doing the DAF assay had no knowledge of their origin.

Details of our methods for the measurement of stool DAF have been described.[9,13–16] Briefly, human DAF was purified from pooled human erythrocyte stroma, and mouse monoclonal antibodies to DAF were prepared.[17] Two of these mouse monoclonal antibodies (IgG1), clones 1C6 and 4F11, were used. The 1C6 antibody is directed to the active site on the DAF molecule, that is, short consensus repeat (SCR) 3, and the 4F11 antibody recognizes SCR 4.[18] The 1C6 monoclonal antibody was labeled with horseradish peroxidase as described.[19] The wells of microtiter plates were coated with 4F11 monoclonal anti-DAF antibody, and serially diluted stool supernatants were added to the wells. After washing, peroxidase-labeled 1C6 anti-DAF antibody was added. After further washing, bound 1C6 antibody was detected with 2,2′-azino-di-3-ethylbenzothiazoline-6-sulfonic acid as substrate. Optical densities at 415 nm were measured on an automated ELISA plate reader. A calibration curve was obtained from several dilutions of known quantities of purified DAF, and the concentrations of stool DAF were calculated. Samples were analyzed in duplicate and the results presented as ng/g stool.

Statistical analysis

For statistical analysis, the Mann–Whitney *U*-test, chi-squared test and Wilcoxon's signed rank test were used. Correlation was assessed using Spearman's rank correlation.

RESULTS

After leukocyte apheresis treatment, 11 (52%) of the 21 UC patients had gone into remission. No adverse event due to the treatment was observed. Clinical background characteristics, including disease activity level, were not different between the patients who responded to apheresis and those who did not (Table 1). Inflammatory markers were not significantly different between the two patient groups, except for slightly higher WBC counts in the non-responsive group ($P = 0.02$, Mann–Whitney *U*-test).

Stool DAF concentrations were determined once a week during apheresis therapy (Fig. 1). Before therapy, concentrations in the responsive group (38–2571 ng/g; median 226 ng/g) were not significantly different from

Table 1 Background characteristics of patients

	Responsive group ($n = 11$)	Non-responsive group ($n = 10$)
Age (years)†	34.9 ± 15.7	35.8 ± 17.8
Sex (male/female)	4/7	4/6
Disease activity‡ (severe/moderate/mild)	3/7/1	5/5/0
Endoscopic grade (Matts grade, 4/3/2)	4/6/1	3/4/3
Total/left colitis	9/2	10/0
Duration of disease (years)†	3.4 ± 3.9	4.8 ± 5.2
Daily dose of PSL (mg)†	31.0 ± 16.4	30.2 ± 28.5
WBC (μL)§	8400 (5400–18 400)*	13 950 (7400–25 000)
CRP (mg/dL)§	0.7 (0.0–33.9)	1.7 (0.1–1 6.5)
PLT ($\times 10^4$/μL)§	30.3 (19.5–57.8)	36.1 (17.4–78.7)
Stool DAF (ng/g)§	226 (38–2571)	303 (63–1138)

*$P = 0.02$ (Mann–Whitney U-test); †mean ± SD; ‡the severity of the illness by Truelove and Witts criteria;[10,11] §median (range). CRP, C-reactive protein; DAF, decay-accelerating factor; PLT, platelet counts; PSL, prednisolone; WBC, white blood cell count.

those in the non-responsive group (63–1138 ng/g; median 303 ng/g) (Table 1, Fig. 1). In the responsive group, stool DAF concentrations decreased promptly and steadily, reaching statistical significance as early as after the second apheresis session ($P = 0.003$, Wilcoxon's signed rank test), and after the third ($P = 0.008$) and the fourth sessions ($P = 0.008$) when compared with values before the therapy. In contrast, stool DAF concentrations in the non-responsive group were not significantly reduced until after the fourth apheresis session. The percent reduction (median 90%, range 22% to 99%) in stool DAF concentration in the responsive group after the second apheresis treatment was significantly greater than the corresponding value in the non-responsive group (median −13%, range from −307% to 94%) ($P = 0.008$, Mann–Whitney U-test). Stool DAF concentrations in the responsive group were significantly lower than concentrations in the non-responsive group after the second ($P = 0.024$), the third ($P = 0.013$) and the fourth ($P = 0.009$) apheresis sessions.

The patients' clinical disease activity was also assessed once weekly during apheresis therapy (Fig. 2). In the responsive group, the clinical disease activity decreased gradually, reaching statistical significance after the second apheresis session ($P = 0.035$, Wilcoxon's signed rank test), and after the third ($P = 0.007$) and the fourth sessions ($P = 0.003$) when compared with the activity before the therapy. However, decreases in the clinical disease activity in the non-responsive group also reached statistical significance after the second and later apheresis sessions ($P = 0.046$). When we assessed the relationship between stool DAF concentrations and the patients' clinical disease activity, stool DAF concentrations correlated significantly with the clinical severity of UC ($r = 0.57$, $P < 0.0001$, Spearman's rank correlation) (Fig. 3).

In the hematological parameters of the two patient groups, significant decreases were observed in platelet counts ($P < 0.01$, Wilcoxon signed-rank test), CRP ($P < 0.05$) and WBC counts ($P < 0.05$) in the responsive patients, but similar decreases were observed also in the non-responsive patients.

DISCUSSION

In this study we serially measured stool DAF concentrations during leukocyte apheresis treatment in patients with UC refractory to corticosteroid therapy. The major finding was that measurement of stool DAF is useful as a simple, non-invasive means for evaluating the effectiveness of leukocyte apheresis therapy. The monitoring of stool DAF appears to be useful in predicting the effectiveness of apheresis therapy; when the therapy was ultimately effective, a decrease in stool DAF concentrations usually became evident as early as after the second apheresis session.

Apheresis of leukocytes from the circulation of UC patients is reportedly often effective even when the disease is refractory to conventional drug therapy.[4–6] Among several methods for leukocyte apheresis, we used a centrifugal cell separator, which has been shown to be effective in steroid-refractory UC.[6] A major advantage of leukocyte apheresis treatment is a lower frequency of adverse events. Reported side-effects of leukocyte apheresis are only minor, such as nausea or vomiting, which improve soon after the treatment,[5,6] as was the case in our study.

For the evaluation of disease activity and the efficacy of treatment in UC, symptoms often are non-specific and hematological tests such as WBC count and platelet count are decreased by apheresis itself. Indeed, these markers declined significantly during the apheresis therapy, but not in relation to the therapeutic response. Invasive examinations, such as radiography and colonoscopy, although useful and informative, may be a burden to patients when the disease is active. Measurement of stool DAF concentration, non-invasive means for monitoring the degree of intestinal inflammation, appears suitable for this purpose, especially in the treatment with leukocyte apheresis. Not

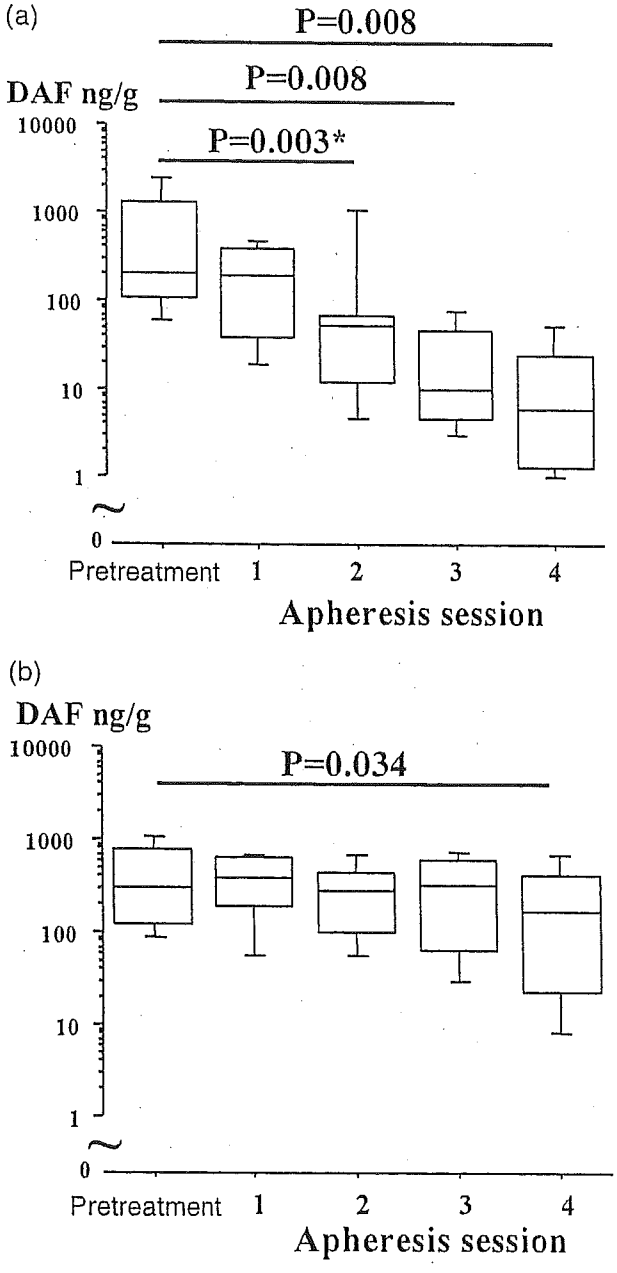

Figure 1 Weekly stool decay-accelerating factor (DAF) concentrations during apheresis treatment. (a) Apheresis responsive group; (b) apheresis non-responsive group. Dark bars represent median values, boxes represent interquartiles (the 25th and 75th percentiles), and error bars indicate the 10th and 90th percentiles. *Wilcoxon signed-rank test.

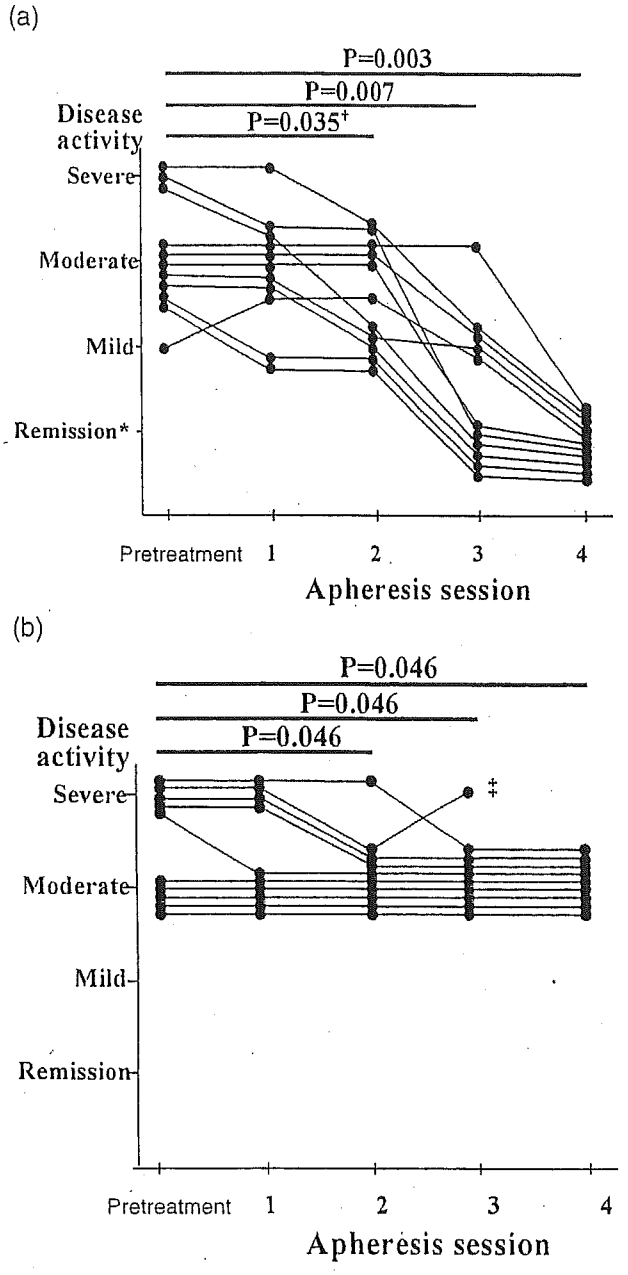

Figure 2 Weekly alterations of the disease activity during apheresis treatment. (a) Apheresis responsive group; (b) apheresis non-responsive group. The patients' disease activity was assessed according to the criteria of Truelove and Witts.[10,11] *Clinical activity of mild and without hematochezia or better. †Wilcoxon signed-rank test. ‡This patient was operated after the third apheresis session due to refractory bleeding.

only does the test accurately reflect disease activity,[9] it has been shown to be reliable and easy to perform.[13,14] DAF is resistant to proteolytic enzymes, such as trypsin,[20] so it is not affected by the abundant proteolytic enzymes derived from inflammatory cells that enter the colonic lumen during active UC. DAF is heat-resistant[21] and can be measured reliably in stools kept for at least 1 day at room temperature.[9] Other fecal proteins such as calprotectin,[22,23] a calcium-binding protein present in neutrophilic granulocytes,[24] and tumor necrosis factor-α,[25] have been proposed as surrogate markers of intestinal inflammation in inflammatory bowel disease. To our knowledge, these proteins have not been studied in the evaluation of leukocyte apheresis treatment.

DAF in stools possibly comes from several sources. We have shown that the colonic epithelia of active UC and colorectal cancer cells overexpress DAF on the

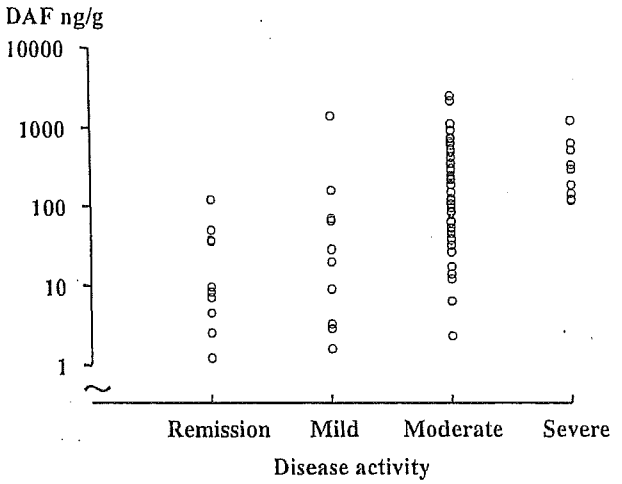

Figure 3 Stool decay-accelerating factor (DAF) concentration by patients' clinical disease activity in ulcerative colitis (UC). Stool DAF concentrations correlated significantly with the clinical severity of UC ($r = 0.57$, $P < 0.0001$, Spearman's rank correlation).

luminal surface[8,26] and that DAF is released into the colonic lumen from colorectal cancer cells by way of cleavage at the site of the membrane-bound anchor.[27] Thus, the first source is from colonic epithelial cells in the mucosal lesion and the second source of DAF may come from inflammatory cells passing into the colonic lumen. We have recently reported that serum concentrations and surface expression on WBC of DAF are increased in patients with active UC.[28] In active UC, inflammatory cells enter the colonic lumen through the diseased mucosa. Indeed, several proteins derived from neutrophils reportedly are increased in the stools of patients with active UC.[29,30] Plasma membranes of erythrocytes also are rich in DAF.[7] However, it is not likely that DAF in stools is derived from erythrocytes because we found no correlation between the amounts of DAF and hemoglobin in stools of UC patients in our previous study.[9]

We conclude that measurement of stool DAF concentrations may be useful in monitoring disease activity in patients with UC during leukocyte apheresis therapy, and as an early predictor of response to the therapy. A large-scale, prospective study of these possibilities is now warranted.

ACKNOWLEDGMENTS

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Conflict of interest statement: Dr Motowo Mizuno, Dr Teizo Fujita and Dr Takao Tsuji have patented the method for the detection of stool DAF.

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Digestive Endoscopy (2005) **17**, 331–333

HOW I DO IT

CLINICAL APPLICATION OF AN INDWELLING NEEDLE FOR ESOPHAGEAL VARICES IN ENDOSCOPIC INJECTION SCLEROTHERAPY WITH SIMULTANEOUS LIGATION

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Endoscopic injection sclerotherapy (EIS), in which a sclerosing agent is infused into esophageal varices, is advantageous in obstructing a blood-supplying route; however, accurate intravascular infusion is technically difficult. To achieve accurate continuous intravascular infusion that does not depend on respiration or vomiting reflex, we developed an indwelling needle for esophageal varices. This indwelling needle facilitated intravascular puncture, as demonstrated for conventional puncture needles, and stabilized infusion of a sclerosing agent. Furthermore, EIS with ligation (EISL) prevented hemorrhage after the needle was removed. EISL with an indwelling needle may improve the treatment results.

Key words: endoscopic injection sclerotherapy (EIS), endoscopic injection sclerotherapy with ligation (EISL), esophageal varix, indwelling needle.

INTRODUCTION

A study of endoscopic injection sclerotherapy (EIS), an intravascular infusion procedure, has reported that infusion of a sclerosing agent into a blood-supplying route decreases the recurrence rate.[1,2] However, skilled techniques are required to puncture varices that move with respiration under an endoscope and continuously infuse a sclerosing agent using conventional puncture needles. Previous studies have used an indwelling puncture needle for accurate intravascular infusion; however, this procedure is not generally used. One reason is that when an indwelling puncture needle is used, the thickness of the barrel may increase the risk of hemorrhage with the removal of the needle. We performed simultaneous combination therapy with EIS and endoscopic variceal ligation (EVL) (modified EIS; i.e. EIS with ligation (EISL))[3–5] as standard treatment for esophageal varices. As the puncture site is ligated at the removal of a needle, EISL does not cause hemorrhage. Therefore, the risk of hemorrhage may be extremely low even when a thick indwelling needle is used. We report an indwelling needle for esophageal varices, the application of which has been facilitated by EISL.

MATERIALS AND METHODS

To prepare a taper-shaped indwelling needle for esophageal varices, the sheath end of a type C 23 G Barixer puncture needle for esophageal varices (Top Inc., Tokyo, Japan) was heated with a burner, extended, and cut at an appropriate point. The needle was sterilized with ethylene oxide gas before use. We used a GIF-Q240X scope (Olympus, Tokyo, Japan). EVL was performed using a pneumatic EVL device (Sumitomo Bakelite Co. Ltd, Tokyo, Japan).

For EISL with an indwelling needle for esophageal varices, an oral-side balloon was initially set at an area 1–2 cm from the end, and an EVL device was set at the scope end. For antisepsis, 100% ethanol was infused into the forceps pore. A scope was inserted to a varix, and the balloon was dilated. An indwelling puncture needle was inserted through the forceps pore to puncture the varix. After backflow of blood was confirmed, the inner cylinder was removed, and the barrel was inserted into the varix. Under direct vision, 5% ethanolamine oleate (EOI) was infused into the varix, involving a blood-supplying route. After the end of infusion, suction was performed during puncture. EVL involving the puncture site was performed (Fig. 1).

The indwelling needle that we produced has no adhesive area, and its shape was formed using heat. There is no difference in the basic structure between this needle and commercially available puncture needles, and the safety may be similar. An intensity test of the processed area was conducted to confirm the safety of this needle.

The present patient was treated in Kuniyoshi Hospital. The use of an indwelling needle has been approved by the Ethics Committee of this hospital. After explaining the procedure to the patient, written informed consent was obtained.

CASE REPORT

A 71-year-old female had an underlying disease of liver cirrhosis (type C). Endoscopy revealed an esophageal varix (F3, CB, Lm, RC(3+)),[6] and preventive treatment was performed.

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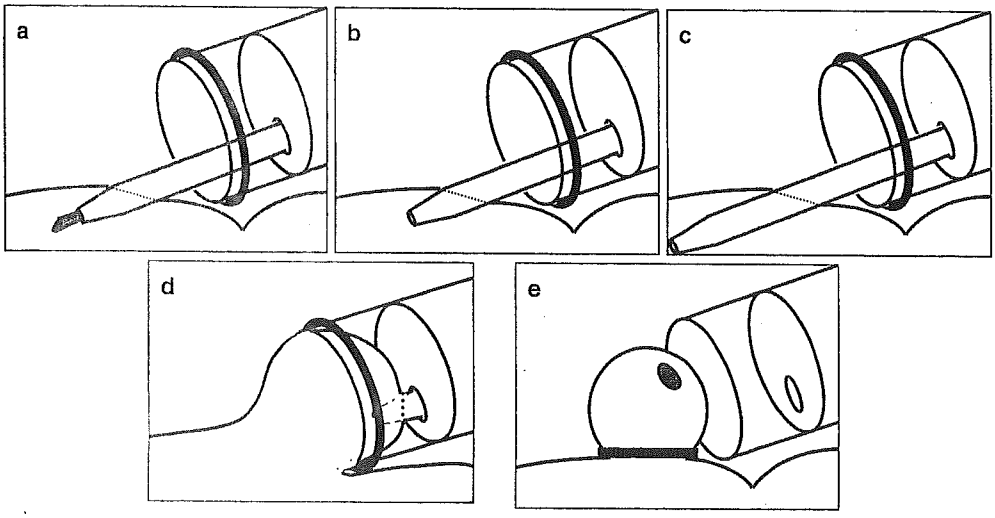

Fig. 1. (a) After puncture of the varix, backflow is confirmed. (b) The inner cylinder is removed. (c) The barrel is inserted, and 5% ethanolamine oleate is infused. (d) Suction is performed while pulling the puncture needle. (e) The lesion site involving the puncture site is ligated.

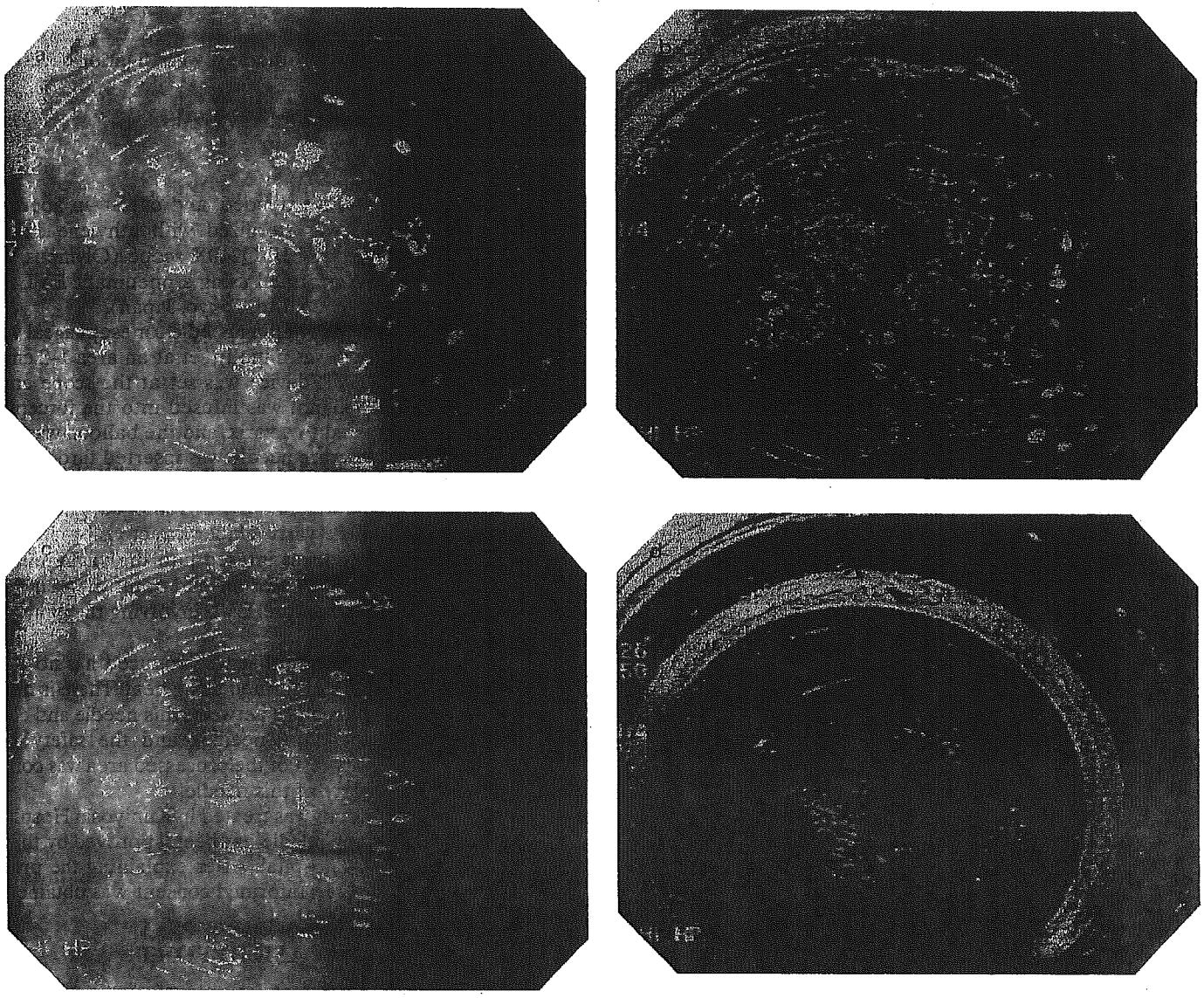

Fig. 2. (a) Before puncture. (b) After puncture, backflow is confirmed. (c) A sclerosing agent is infused via an indwelling needle. (d) After endoscopic variceal ligation there was no hemorrhage.

According to the Child-Pugh classification, the grade was evaluated as B. EISL was performed four times; in the first course, 10 mL EOI was infused into a blood vessel, and influx of EOI from the cardiac venous plexus to the left gastric vein was observed. In the second course, influx of EOI to the posterior gastric vein was observed after intravascular infusion of EOI at 10 mL. In the third course, influx of the sclerosing agent to the capillaries around the upper stomach was observed after intravascular infusion of EOI at 3 mL. In the fourth course, EVL alone was performed. After treatment, the endoscopic findings suggested FO and RC(–). There were no complications. This procedure stabilized intravascular infusion of the sclerosing agent (Fig. 2).

DISCUSSION

Endoscopic injection sclerotherapy,[7,8] in which intravascular infusion of a sclerosing agent is given, is a rational therapeutic procedure for obstructing a blood-supplying route. However, complete EIS; that is, infusion of a sclerosing agent into a blood-supplying route is often difficult in some patients.

Concerning EVL,[9–13] even less skilled therapists can perform complete treatment; therefore, the sufficient treatment response may be readily achieved, which leads to the underestimation of EIS in comparison to EVL. If the EIS procedure becomes simple and accurate, the therapeutic effects and assessment of EIS may improve.

We have developed a simple and accurate procedure so that therapists can perform complete EIS; namely, EISL, in which the puncture site is simultaneously ligated during EIS, and this indwelling needle for varices. The use of an indwelling needle for infusing a sclerosing agent eliminates the influence of respiration or vomiting reflex during infusion, facilitating accurate infusion of a sclerosing agent into a blood-supplying route, such as the left gastric vein. Conventional puncture needles were used by therapists for intravascular infusion, which depended on their skill. This requires high concentration. When an indwelling needle is used, relatively less skilled therapists can perform the procedure without stress, to a similar standard as skilled experts.

The reason why an indwelling needle has not commonly been used is the limitation of hemorrhage from the puncture site after the removal of the needle. The hole of an indwelling needle is larger than that of a standard puncture needle; therefore, hemorrhage from the puncture site may readily occur, and hemostasis may be difficult. To eliminate this limitation, EISL,[14] which we report as standard treatment for esophageal varices,[4] should be performed. In this procedure, the puncture site is ligated at the removal of the needle, reducing the risk of hemorrhage.

The use of an indwelling needle for esophageal varices may make EIS and EISL via intravascular infusion simpler and more accurate, emphasizing the significance of sclerotherapy for obstructing a blood-supplying route.

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Unusual Metastasis of Hepatocellular Carcinoma to the Esophagus

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Abstract

This report describes a case of metastatic hepatocellular carcinoma (HCC) presenting as a polypoid mass in the lower esophagus. The patient was a 63-year-old man with HCC. An endoscopic examination revealed a pedunculated polypoid mass, about 3 cm in diameter, at the lower part of the esophagus. The biopsy specimen obtained from the tumor revealed that the mass consisted of a pseudoglandular arrangement of tumor cells, and the tumor was diagnosed as metastatic HCC. There were no symptoms due to esophageal tumor. He died of progressive hepatic failure. Cases of premortem-diagnosed esophageal metastasis from HCC are extremely rare.
(Internal Medicine 44: 444–447, 2005)

Key words: hepatocellular carcinoma, hematogenous metastasis, esophageal varix, gastric invasion, esophageal metastasis

Introduction

Metastasis to the esophagus is extremely rare, being present in less than 0.4% of patients with hepatocellular carcinoma (HCC) (1). This metastasis is presumed to be caused by tumor thrombi infiltrating via the portal system, at which point they are disseminated by hepatofugal portal blood flow to the gastrointestinal (GI) tract (2, 3). We present here a rare case of premortem-diagnosed esophageal metastasis from HCC.

Case Report

The patient was a 63-year-old man, 165 cm tall and weighing 52.3 kg. He visited our hospital for further evaluation of space-occupying lesions in the liver on April 23, 2002. He had a past medical history of HCC in 1998 at another institute. No specific family history was identified. At his first visit to our hospital, his body temperature was 36.8 °C, blood pressure was 94/50 mmHg, and radial pulse rate was 60 beats/min and regular. Moderate anemia was observed, but he did not have jaundice. A neurological examination revealed no abnormal findings and there was no lymphadenopathy.

Laboratory tests on April 23, 2002 showed a red blood cell count of $286\times10^4/\mu l$, a white blood cell count of 7,100/μl, and a platelet count of $11.0\times10^4/\mu l$. The hemoglobin concentration was 10.6 g/dl. The liver function tests revealed: aspartate aminotransferase, 61 IU/*l* (normal range [NR] 2–39); alanine aminotransferase, 43 IU/*l* (NR 2–39); total protein 6.1 g/dl (NR 6.5–8.1); serum albumin 2.1 g/dl (NR 3.8–5.2); alkaline phosphatase, 380 IU/*l* (NR 96–310); leucin amino peptidase, 100 IU/*l* (NR 45–71); γ-glutamyltranspeptidase, 22 IU/*l*; cholinesterase, 0.10 ΔpH (NR 0.6–1.2); lactate dehydrogenase, 298 IU/*l*; and total bilirubin, 2.1 mg/dl (NR 0.1–0.4). With respect to renal function, blood urea nitrogen was 13.6 mg/dl and creatinine was 0.8 mg/dl. Serological studies for hepatitis B virus were negative, however, hepatitis C virus was positive. A test for C reactive protein revealed a level of 0.10 mg/dl. Urinary protein and sugar were negative. Regarding tumor markers, carbohydrate antigen 19-9 was negative, however, carcinoembryonic antigen (CEA) and alpha fetoprotein (AFP) were high at 9.8 ng/ml (NR ≦5 ng/ml) and 4,130 ng/ml (NR ≦10 ng/ml), respectively. Abdominal CT on April 23, 2002 revealed a 3 cm low density area in the liver segment 8 treated at another institute with percutaneous ethanol injection and multiple space-occupying lesions (about 2 cm in diameter) in the liver in segment 2, 4, 5 and 6. The patient underwent intrahepatic arterial infusion (IAI) therapy with cisplatin (CDDP) 20 mg/m^2, day 1 and 5-fluorouracil 300 mg/m^2 days 1–5, repeated every week in May 2002. However, after 3 times of IAI, the

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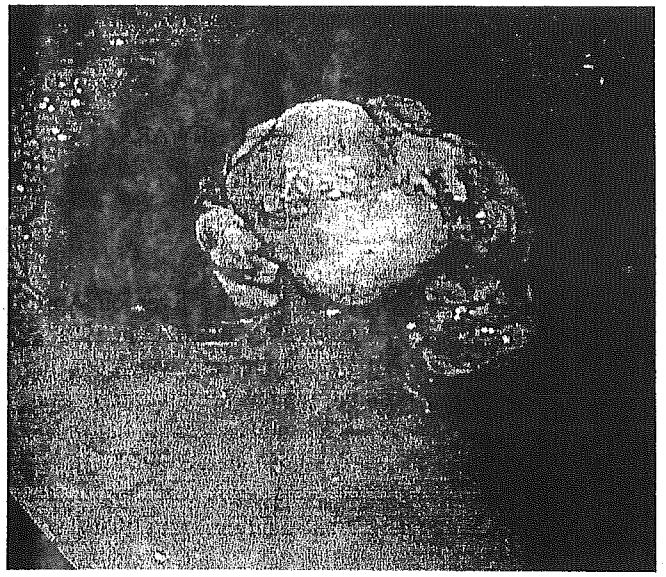

Figure 1. Endoscopic appearance of the elevated lesion in the esophagus. The lesion presented as a polypoid mass, about 3 cm in diameter.

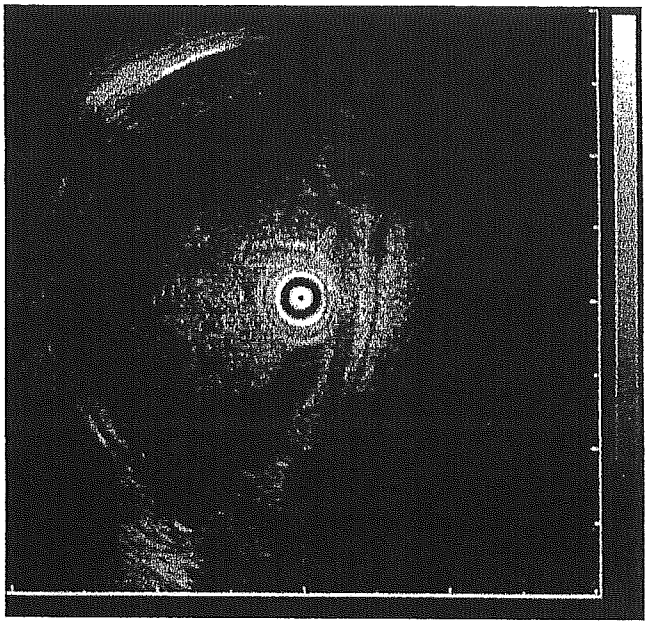

Figure 2. Endoscopic ultrasonography (EUS) revealed a polypoid mass with a mosaic echo pattern.

serum level of AFP had reached 9,005 ng/ml in June 2002. Thereafter, chemotherapy was stopped and he underwent palliative therapy.

Endoscopic examination of the upper digestive tract on January 17, 2003 revealed no abnormal findings except for F2 (enlarged and tortuous) esophageal varices. He underwent endoscopic examination again because of epigastric discomfort on April 17, 2003. It revealed a soft pedunculated polypoid mass, about 3 cm in diameter, at the lower part of the esophagus (Fig. 1). Esophageal varices were seen at the anal side of the tumor, however, it was unclear whether the tumor was connected to an esophageal varix. The tumor was slightly stained by lugol staining. Endoscopic ultrasonography (EUS) with a miniature probe of 20 MHz frequency using the water filling method revealed a polypoid mass with a mosaic pattern (Fig. 2). The arterial-dominant phase of dynamic CT showed enhancement of the esophageal tumor (Fig. 3). Abdominal CT on April 3, 2003 revealed space-occupying lesions in the liver in segment 2 and a direct invasion of HCC to the posterior gastric wall (Fig. 4). However, the existence of portal thrombus was not recognized on the abdominal CT. The biopsy specimen obtained from the esophageal lesion revealed that the tumor cells with pseudoglandular arrangement were covered with squamous cell epithelium (Fig. 5). They represented a positive immunohistochemical reaction for AFP. The pedunculated polypoid mass of the esophagus was diagnosed as a metastatic tumor from HCC. No therapy was done for the metastatic esophageal tumor or direct invasion of HCC to the posterior gastric wall because there were no symptoms due to the esophageal tumor, and GI bleeding did not occur at any time during his entire clinical course. Follow-up endoscopy on June 23, 2003 revealed that the metastatic tumor of the esophagus was slightly enlarged. The serum level of AFP had reached 596,090 ng/ml on July 9, 2003. He died of progressive hepatic failure on July 23, 2003. Autopsy was not permitted.

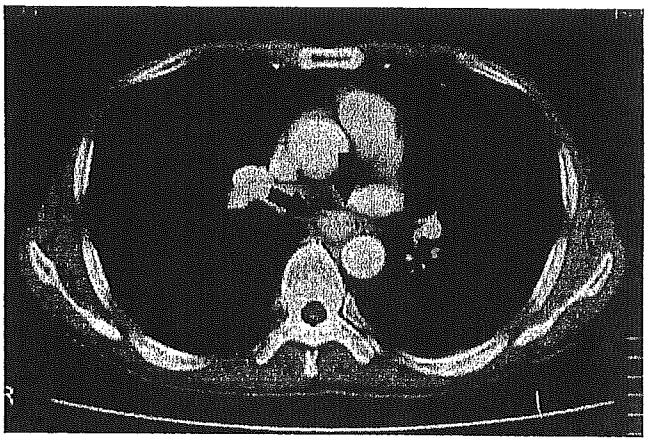

Figure 3. CT of the chest showed enhancement of the esophageal tumor (arrows).

Discussion

Autopsy and surgical series have suggested the presence of metastases of HCC in the lung (18.1–49.2%), lymph

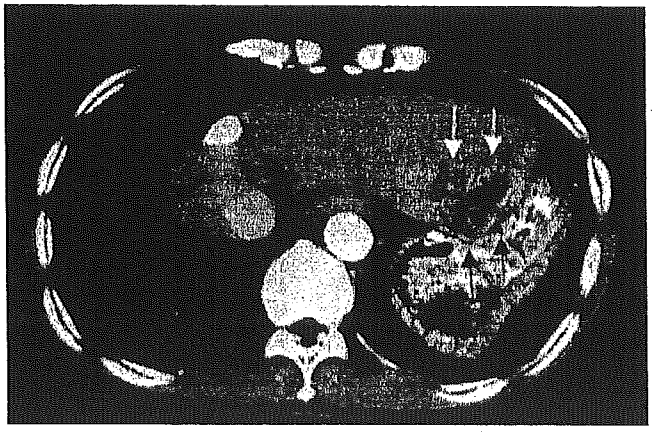

Figure 4. Abdominal CT revealed space-occupying lesions in the liver (white arrows) and direct invasion of hepatocellular carcinoma to the posterior gastric wall (black arrows).

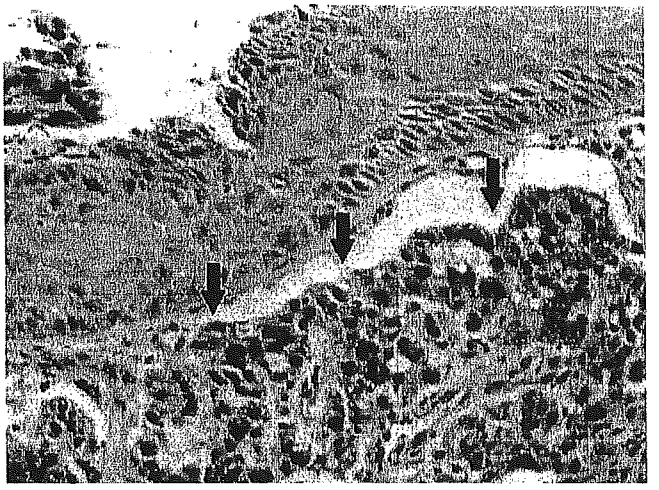

Figure 5. Histological examination of the biopsy specimen obtained from the esophageal protruding lesion revealed that the tumor cells with pseudoglandular arrangement were covered with squamous cell epithelium (arrows) (HE stain, ×10).

nodes (26.5–41.7%), bone (4.2–16.3%), and adrenal glands (8.4–15.4%) (4–6). The incidence of premortem-diagnosed GI tract involvement is typically low in most studies, with some reporting rates of between 0.5 and 2% (3, 7). In most reports, the involved site was the duodenum, stomach, colon, or jejunum, and the presumed mode of metastasis was usually direct invasion to the contiguous GI tract via adhesion to the serosal side of the tumor. Metastasis to the esophagus is extremely rare, being present in less than 0.4% of patients with HCC (1).

A MEDLINE search of the English language literature, revealed that only 5 cases of esophageal metastasis from HCC including the present case have been reported in the last 15 years (8–10) (Table 1). Major symptoms of metastatic esophageal tumor from HCC include dysphagia and GI bleeding. However, 3 cases including the present case were asymptomatic.

Arakawa et al (11) investigated the gastric wall and the esophagus in 55 autopsy cases with HCC associated with cirrhosis, and found that 31 cases (56.4%) had distant hematogenous metastases, including 12 cases (38.7%) of variceal tumor thrombi. Thus hematogenous spread, caused by tumor thrombi infiltrating via the portal system and being disseminated by hepatofugal portal blood flow to the esophagus, seems to be the possible route of esophageal metastasis. In four cases excluding the present case shown in Table 1, the esophageal metastasis might have occurred through the aforementioned route. Kume et al (9) reported a case of metastatic HCC of the esophagus occurring at a site of endoscopic variceal band ligation, and suggested that endoscopic therapy of the esophageal varices was a possible cause of the implantation. They explained the mechanism of esophageal metastasis caused by the therapy of esophageal varices as follows; tumor emboli in the portal system were trapped at the site where the variceal bloodstream had been interrupted by endoscopic variceal ligation (EVL), and the metastatic tumor had then grown and broke through the ulcer base due to EVL, producing a polypoid mass. We speculated that esophageal metastasis from HCC may occur on the basis of variceal tumor emboli plus other conditions such as rupture of esophageal varices. However, in the present case, there was no history of therapy of the esophageal varices, and no evidence of apparent rupture of esophageal varices; moreover, we could not recognize the existence of portal thrombus on the abdominal CT. Thus the causative mechanism of the esophageal metastasis from HCC in the present case has yet to be clarified. The abdominal CT of this patient revealed a direct invasion of HCC to the posterior gastric wall when the esophageal tumor was detected. Therefore, the direct invasion of HCC to the gastric wall and the inflow of the tumor cells from the left gastric vein to the esophageal varices might affect the esophageal metastasis.

To diagnose GI tract metastasis of HCC, endoscopic examination is necessary. However, there have been few reports on the endoscopic findings of premortem-diagnosed esophageal metastasis from HCC. A review of the literature indicated that the most common abnormal findings include a polypoid mass and a submucosal tumor (8–10). If endoscopic biopsy reveals a lack of available tumor tissue or poorly differentiated tissue, image evaluations such as CT, EUS, or angiography are necessary to differentiate between primary cancer and GI metastasis from HCC. Cho et al (10) reported that the major CT and angiography findings with respect to esophageal metastasis from HCC were hypervascular tumors resembling HCC. They also described that EUS findings of the esophageal metastasis from HCC revealed a poorly defined lesion with a mosaic pattern. In the present case, CT images demonstrated tumor staining similar

Table 1. Summary of the 5 Cases of Esophageal Metastasis from Hepatocellular Carcinoma Reported in the Past 15 Years

	Author	Age	Sex	Year	Symptoms	Size (cm)	Shape	Serum AFP (ng/ml)	Therapy for esophageal metastatic tumor	Outcome
1	Sohara 8)	54	M	2000	melena	ND	submucosal tumor	4,987	–	dead
2	Sohara 8)	46	M	2000	hematemesis	ND	polypoid	990	–	dead
3	Kume 9)	56	M	2000	dysphagia, tarry stools	ND	submucosal tumor	12,200	–	dead
4	Cho 10)	50	M	2003	dysphagia, hematemesis	ND	polypoid	elavated	RT+TAI	dead
5	Present case	63	M	2004	–	3	polypoid	4,130	–	dead

ND: not described, RT: radiation therapy, TAI: transcatheter arterial infusion.

to that of the primary tumor in the liver and enhanced mass, and EUS showed a mosaic pattern tumor. The findings of the imaging examinations in the present case were compatible with those of a metastatic esophageal tumor from HCC.

Cases of premortem-diagnosed esophageal metastasis from HCC are extremely rare, however, it is likely that there are many latent patients with esophageal metastasis from HCC who might be incidentally discovered in the future, because many patients with the terminal stage of HCC are not closely followed by endoscopic examinations. In the present case, the esophageal metastatic tumor, which was considered to have increased in size rapidly, was discovered incidentally by endoscopic examination, although only esophageal varices had been seen 3 months previously.

In conclusion, we report a rare case of premortem-diagnosed esophageal metastasis from HCC. Endoscopists should be aware that esophageal metastasis from HCC may exhibit the aforementioned endoscopic characteristics, it may exhibit rapid growth as in the present case, and it may cause dysphagia or GI bleeding, although the present patient had no symptoms due to the esophageal tumor.

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□ ORIGINAL ARTICLE □

Treatment of Elderly Patients with Early Gastric Cancer by Endoscopic Submucosal Dissection Using an Insulated-tip Diathermic Knife

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Abstract

Objective **In recent years, the number of elderly patients with early gastric cancer (EGC) has steadily been increasing. In our institute, endoscopic submucosal dissection (ESD) involving the use of an insulated-tip diathermic knife (IT-ESD) was introduced for the treatment of mucosal gastric carcinoma in 1996. The purpose of this study was to evaluate the effectiveness of IT-ESD for the treatment of elderly patients with EGC.**

Materials and Methods **A total of 144 patients with EGC were treated at Shikoku Cancer Center in the 5-year period from January 2000 to December 2004, including 53 patients over 75 years old. The performance status (PS) for all patients was less than 2. We compared patient's backgrounds, the one-piece resection rate, complete resection (CR) rate, operation time, bleeding rate, perforation rate, blood pressure, and peripheral oxygen saturation (SpO_2) between patients over 75 years of age (elderly group) and the remaining 91 younger patients (non-elderly group).**

Results **The rate of having underlying disease was significantly higher for the elderly group ($p<0.05$) and we found no significant difference for the one-piece resection rate, CR rate, operation time, bleeding rate, and perforation rate between the 2 groups. There were also no significant differences for the frequency of the use of oxygen, pressor and depressor between the 2 groups.**

Conclusion **There was no significant difference in the outcome resulting from ESD between the 2 groups. Our study proves that ESD is a feasible treatment for elderly patients with EGC PS of less than 2.**
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Key words: gastric cancer, endoscopic mucosal resection, complication, monitoring

Introduction

Endoscopic mucosal resection (EMR) of early gastric cancer (EGC) is effective for the treatment of mucosal malignancies, but one-piece resection is often not achieved by conventional EMR (1). Endoscopic submucosal dissection (ESD) techniques using a variety of knives, such as the insulated-tip diathermic knife (IT-knife), hook knife or flex knife, have been developed in Japan (2, 3) and high one-piece resection rates have been reported (1, 3). The number of elderly patients with EGC has steadily been increasing, however, there has been no report describing the result and feasibility of the ESD using an insulated-tip diathermic knife (IT-ESD) for the elderly patients with EGC. The purpose of this study was to evaluate the effectiveness of IT-ESD for elderly patients with EGC.

Materials and Methods

We retrospectively reviewed the records of patients admitted to Shikoku Cancer Center with gastric cancer between January 2000 and December 2004. The patients, who had severe underlying disease such as heart disease, respiratory disease, liver disease, or bleeding tendency, were excluded from the indication of ESD in our institute, however, there were no patients who had severe underlying disease in this study. The patients, who had drugs to promote bleeding such as ticlopidine, aspirin or warfarin, underwent ESD after a definite term of discontinuance of drugs. All patients fulfilled the following criteria: 1) diagnosed as having mucosal gastric carcinoma by endoscopic findings or endoscopic ultraso-

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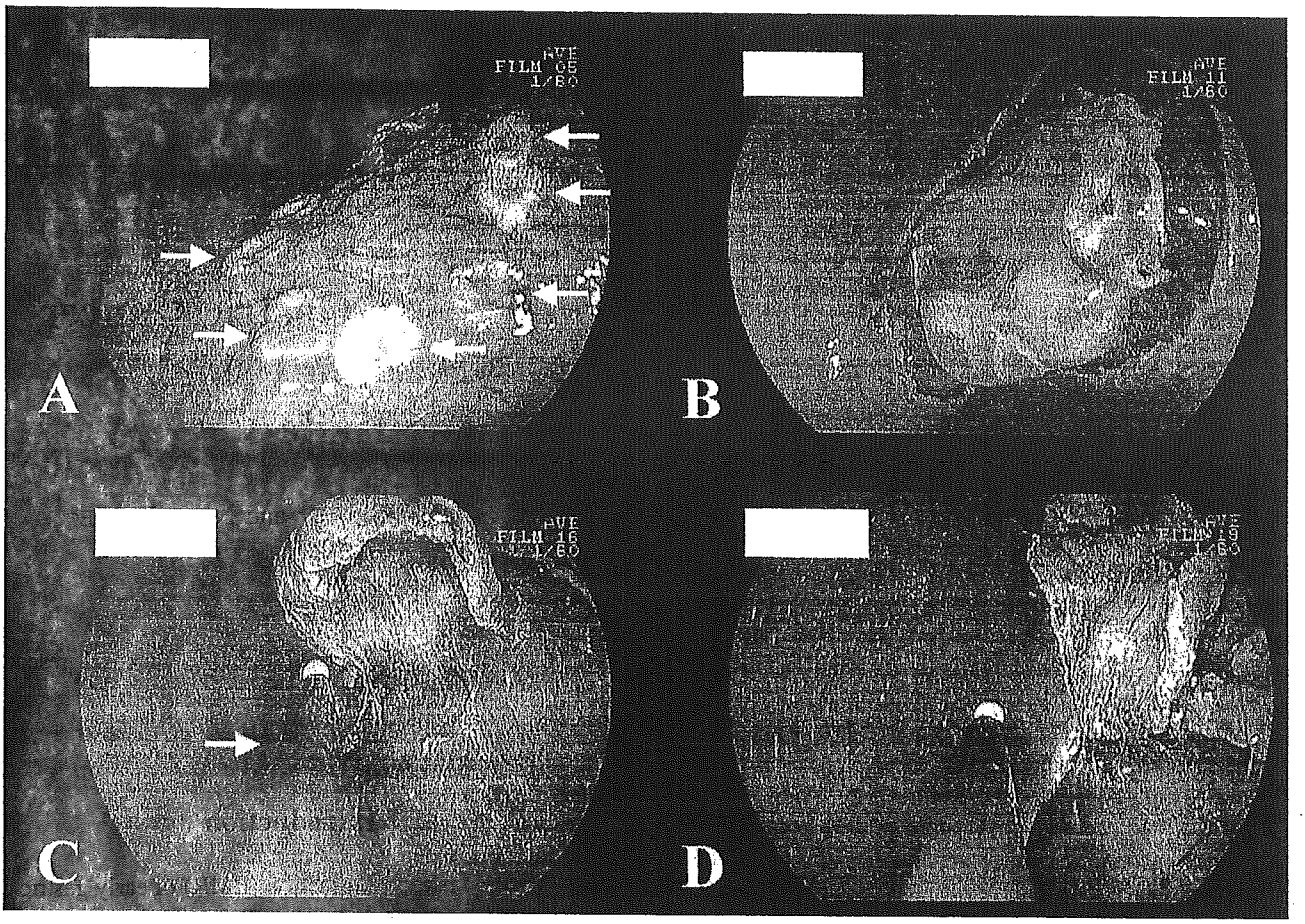

Figure 1. The procedure of IT-ESD; (A) marks (white arrows) are made at several points along the outline of the lesion with a coagulation current. (B) completion of the IT-knife cutting around the lesion with a safe lateral margin. (C) abrasion of the submucosal tissue under the circumcised area with IT-knife (white arrow). (D) the tumor is completely resected with IT-knife and without using snaring.

nography, 2) had a biopsy specimen obtained from the lesion that revealed differentiated adenocarcinoma, 3) did not have an ulceration in the lesion, and 4) the diameter of their lesion was up to 30 mm. There were no patients with aforementioned conditions who underwent endoscopic therapy other than ESD such as laser therapy. In our institute, if the size of the mucosal cancer is over 20 mm up to 30 mm in diameter, the patient can undergo ESD if it is their wish. The performance status (PS) of each patient was less than 2 on the Eastern Cooperative Oncology Group (ECOG) scale. IT-ESD was performed under informed consent. Midazolam and pethidine hydrochloride were used for conscious sedation during ESD. If the patient's systolic blood pressure was over 160 mmHg, we used a depressor (nicardipine 0.5–2 mg/body) and if the patient's systolic blood pressure was below 80 mmHg, we used a pressor (etilefrine 5–10 mg/body). If the patient's peripheral oxygen saturation (SpO_2) was below 90%, nasal oxygen therapy was carried out.

IT-ESD technique

IT-ESD was performed as we previously described (3, 4): 1) marks were made at several points along the outline of the lesion with a coagulation current, using a marking tip (Type KD-1L; Olympus) (Fig. 1A), 2) an injection of 20 ml of saline containing 0.0025% epinephrine was carried out just outside the marks to prevent perforation until the mucosa around the lesion was raised. 3) a hole (about 2 mm) for inserting the ceramic ball of the IT-knife into the submucosal layer was made with hot biopsy forceps on the raised mucosa. 4) starting from the hole made by hot biopsy forceps, the mucosa just outside the marks with the IT-knife was incised. 5) after completion of the IT-knife cut around the lesion with a safe lateral margin (Fig. 1B), the submucosal tissue under the circumcised area was abraded with it (Fig. 1C), 6) as the abrasion made progress, the circumcised area shrank gradually, 7) the specimen was then either completely resected using the IT-knife (Fig. 1D), or finally removed using a conventional polypectomy snare if it was attached only to a pedicle. In more than half of the patients

Table 1. Characteristics of Patients and Lesions in the Control Group and the Pathway Group

	Elderly group	Non-elderly group	P value
Number of patients	53	91	
Mean age (years)	78.2±3.8	64.7±7.4	
Male: Female	34 : 19	74 : 17	
Mean size of the lesion (mm)	12.2	13	NS
Frequency of the underlying disease (%)	57	33	<0.05
heart diseases	1.9	5.5	
hypertension	28	7.7	
respiratory diseases	7.5	2.2	
liver diseases	7.5	5.5	
diabetes mellitus	9.4	14	
other diseases (cerebral infarction etc.)	9.4	5.5	
Frequency of the anticoagulant therapy (%)	11	8.8	NS

NS: not significant.

in this study, we cut down the lesions with an IT-knife and without using snaring.

Histological assessment

A gastrointestinal pathologist evaluated the ESD specimens with special attention to the depth of tumor invasion and the lateral and deep margins of the excision. Resected specimens were cut into 2 mm slices according to the Japanese Classification of Gastric Carcinoma (5) and evaluated as to whether cancerous glands were present or absent at the margin of each slice.

Definition of complete and incomplete resection

When one-piece resection could be performed, it was easy to evaluate the completeness of the resection histologically. The efficacy of resection was determined according to the completeness of the resection: when the tumor was resected as a single fragment, contained within the mucosal layer and when the margin was definitely free of tumorous glands, resection was considered to be complete. If the lesion was resected as 2 or more fragments, resection was also defined as complete if the margin of the fragment containing the tumor was free from tumorous glands and the additional fragments did not contain any tumorous glands. However, with resection of multiple fragments it is difficult to reconstruct the lesion accurately and to evaluate the resected margin histologically. Therefore, multifragment resections were defined as incomplete when tumorous glands were present in 2 or more fragments histologically, even if endoscopically the lesion had been completely removed. If the lateral margin of the lesion could not be evaluated histologically because of the effects of the electrosurgical current or mechanical damage, the resection was defined as being incomplete.

Complications

Bleeding and perforation were two major complications of ESD. The bleeding group was defined as patients who required endoscopic management using methods such as clip placement and/or monopolar electrocoagulation to stop the bleeding.

Clinical data

Clinical data were recorded from patients who were admitted to Shikoku Cancer Center for ESD between January 2000 and December 2004. Patients admitted during this period were divided into an elderly group and a non-elderly group. The elderly group was composed of patients over 75-years old and the non-elderly group was composed of patients younger than 75-years old. Patients, who were 75-years old, were included in the elderly group. The patients' backgrounds, the one-piece resection rate, complete resection (CR) rate, operation times, bleeding rate, perforation rate, blood pressure, and SpO_2 were compared among the groups.

Statistics

Values are expressed as means±SD. Statistical analysis was performed using the unpaired Student's *t*-test and the chi-square test. A P value of less than 0.05 was considered to be significant.

Results

There were 53 patients in the elderly group and 91 in the non-elderly group. The diagnosis of mucosal gastric carcinoma was confirmed pathologically for 130 patients, but 14 patients had submucosal invasion. Three of 25 patients with over 20 mm had submucosal invasion.

The number of patients classified into each group and the clinical data for IT-ESD is shown in Table 1. The mean ages were 78.2±3.8 years (range, 75 to 91 years) in the elderly group and 64.7±7.4 years (range, 45 to 74 years) in the non-elderly group, respectively. The mean size of the lesions