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Management of occult obscure gastrointestinal bleeding patients based on long-term outcomes

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Abstract

Background: There is no consensus regarding the management of occult obscure gastrointestinal bleeding (OGIB) patients without a confirmed bleeding source. This study aimed to consider the management of occult OGIB patients based on their long-term outcomes.

Methods: We retrospectively enrolled 357 consecutive occult OGIB patients (203 men; mean age: 59.7 years) who underwent capsule endoscopy (CE) at Hiroshima University Hospital, Japan and were followed up for more than 12 months (mean follow-up period; 50.2 months). Patients were divided into three groups as follows: Group A consisted of 98 of 157 patients who had positive findings and indication for treatment, Group B consisted of 59 of 157 patients who had positive findings but no indication for treatment, and Group C consisted of 200 patients who had negative small-bowel findings. We examined the rate of positive CE findings, detection rate and details of bleeding sources, overt bleeding rate, the rate of anemia exacerbation, 5-year anemia exacerbation rate, and overall survival rate.

Results: The positive CE findings rate was 44% (157/357) and detection rate of bleeding source was 27% (98/357). The details of Group A were as follows: angioectasia ($n = 61$), nonspecific ulceration ($n = 10$), nonsteroidal anti-inflammatory drug-induced ulcer ($n = 8$), and others ($n = 19$). The details of Group B were as follows: erythema ($n = 31$), angioectasia ($n = 25$), and others ($n = 3$). There were no patients with overt bleeding in Group B. Although six patients had anemia exacerbation in Group B, they had angioectasia without a bleeding source.

Conclusion: The long-term outcomes of occult OGIB patients were good. Occult OGIB patients without bleeding source lesions may not require follow-up CE.

Keywords: capsule endoscopy, long-term outcomes, occult obscure gastrointestinal bleeding

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Introduction

Obscure gastrointestinal bleeding (OGIB) is broadly categorized into obscure overt and obscure occult bleeding based on the presence or absence of clinically evident bleeding.[1] There are various definitions of OGIB along with the change of technological advancements. Therefore, in this study, occult OGIB is defined as recurrent or persistent iron deficiency anemia (IDA) with or without a positive fecal occult blood test and no bleeding source identified by esophagogastroduodenoscopy and colonoscopy.[2] In Japan, the Japanese Gastroenterological Endoscopy Society developed the 'Clinical Practice Guidelines for Enteroscopy' which recommends capsule endoscopy (CE), a minimally invasive and well tolerated procedure, as a useful diagnostic endoscopic modality for OGIB patients.[3–6] However, occult and overt OGIB are not described separately in this guideline. We previously reported that not all

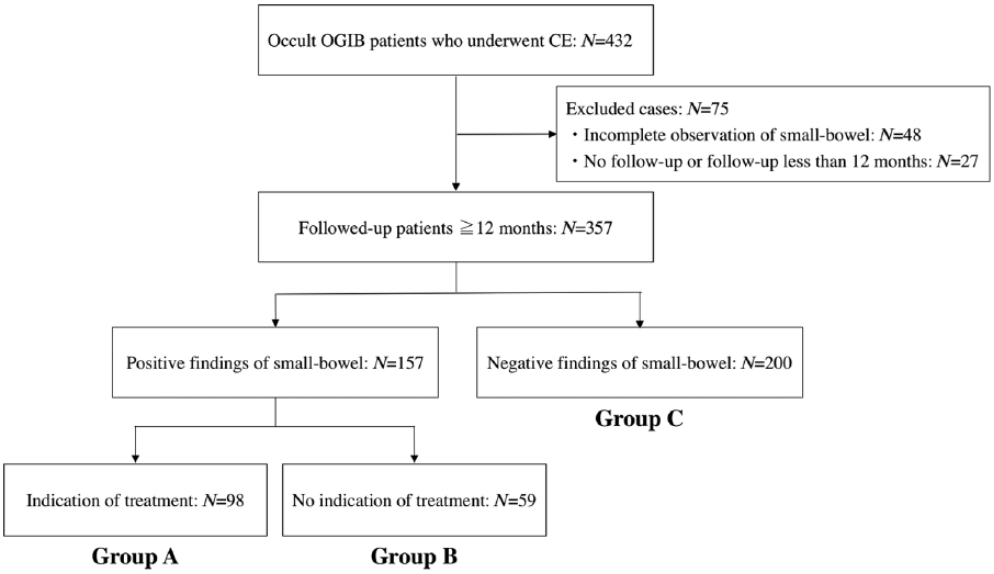

Figure 1. Flowchart of enrolled patients.
CE, capsule endoscopy; OGIB, occult obscure gastrointestinal bleeding.

factors associated with positive CE findings in cases of occult OGIB are clear, but small-bowel lesions should be suspected in patients with occult OGIB and a high platelet count.[7] We also reported that small-bowel CE is effective in diagnosing small-bowel lesions with occult OGIB. CE detection rates and CE identification of various small-bowel diseases do not differ between occult *versus* overt OGIB patients.[7] However, there is no consensus regarding the management of occult OGIB patients without bleeding sources. This study aimed to evaluate the presence or absence of bleeding sources, the necessity of treatment, and rebleeding rate in occult OGIB patients.

Methods

Patients

A total of 432 consecutive patients with occult OGIB presented to Hiroshima University Hospital, Japan between February 2009 and March 2016. Among them, we excluded 75 patients due to inability to visualize the entire small bowel (48 patients), no follow up or follow up less than 12 months (27 patients). Thus, we retrospectively enrolled 357 patients (203 men; mean age: 59.7 years: mean follow-up period: 50.2 months) in this study as follows; 157 of 357 patients had positive small-bowel findings by CE, and 200 of 357 patients had negative small-bowel findings by CE. We classified three groups as follows: Group A consisted of 98 of 157 patients who had positive findings and indication for treatment, Group B consisted of 59 of 157 patients who had positive findings but no indication for treatment, and Group C consisted of 200 patients who had negative small-bowel findings. The flowchart of patients through the study is shown in Figure 1. Yano–Yamamoto's endoscopic classification of small-bowel vascular lesions was used to classify any identified vascular lesions.[8] The indication of treatment for small-bowel lesions is as follows: vascular lesions of Yano–Yamamoto's endoscopic classification except for Type 1a without oozing in our previous report,[9] and obvious bleeding sources from ulcerative lesions or tumors.

CE procedure

CE was performed using a PillCam® SB2 or SB3 video capsule (Covidien, Mansfield, MA, USA). Sensor arrays were attached to the patient's abdomen and data recorders were attached to a belt around the waist. Patients swallowed the capsules with a solution of dimethicone in the sitting position after a 12-h overnight fast. Patients were allowed to perform their normal activities immediately thereafter. After 8 h, the sensor arrays and the recording device were removed. Using the Rapid Reader 6.5 software or the RAPID 8

workstation (Covidien, Mansfield, MA, USA), we analyzed the images. The CE digital image stream was reviewed and interpreted independently by two experienced professionals who had reviewed images from >200 patients; no patient information was provided to these examiners. Diagnoses were reached by consensus.

Evaluation of occult OGIB

Occult OGIB was defined as recurrent or persistent IDA or a positive fecal occult blood test. IDA was diagnosed according to standard criteria, that is, a blood hemoglobin concentration of <13.8 g/dl for men, <11.5 g/dl for postmenopausal women, and <11 g/dl for premenopausal women, with a plasma ferritin level of <30 mg/l and a mean corpuscular volume of <80 fl.[10] Occult blood in the stool was detected by immunochemical fecal occult blood test. Transabdominal ultrasonography or abdominal computed tomography were performed to uncover stenosis of the gastrointestinal tract or small-bowel disease before CE in all patients.[11] The indication for iron preparation was a blood hemoglobin concentration of <10.0 g/dl in principle.

We evaluated clinical characteristics and prognosis after initial CE in Groups A, B and C. Clinical characteristics were age, sex, comorbidity, drug history, mean time from the first OGIB episode to CE, mean hemoglobin before CE, and blood transfusion in particular. Prognosis after initial CE was based on overt bleeding, anemia exacerbation (hemoglobin levels decreased >2.0 g/dl), 5-year anemia exacerbation rate, and 5-year overall survival (OS) rate.

This study was conducted in accordance with the Declaration of Helsinki. All patients were informed of the risks and benefits of CE, and each provided written informed consent for the use of patients' data. This study protocol was approved by the Institutional Review Board of Hiroshima University Hospital, Japan (Approval number: E-763).

Statistical analysis

Patients were classified based on the presence or absence of findings in the small bowel by CE. Between-group differences were evaluated using Student's t test for quantitative data and Chi-square test for categorical data. Yates' correction or Fisher's exact test was used as required. All tests were two-sided, and a p-value <0.05 was considered statistically significant. Survival was analyzed by the Kaplan–Meier method and comparisons between subgroups were examined by the log rank test. All analyses were performed using JMP12 (SAS Institute Inc., Cary, NC, United States).

Results

Table 1 shows patient characteristics per study group. Comorbidity and drugs overlapped in three groups. There was no significant difference among the three groups in sex, anticoagulants, mean time from the first OGIB episode to CE, mean hemoglobin before CE, or blood transfusion. In comorbidity, there were significantly more patients with chronic liver disease in Group B (83%, $n = 49$) than in Group A (49%, $n = 48$) and Group C (40%, $n = 80$; $p < 0.05$). Age (≧60 years old) was significantly greater in Group A (88%, $n = 86$) than Group B (68%, $n = 40$; $p < 0.05$). Moreover, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was significantly higher in Group A (27%, $n = 26$) than Group B (8%, $n = 5$; $p < 0.05$). The rate of positive CE findings was 44% (157/357). Positive CE findings of Group A and Group B are shown in Table 2. Positive CE findings in Group A included vascular lesions, ulcerative lesions, tumors, and others. The details were as follows: vascular lesions (angioectasia 61 patients, Type 1a with oozing 37 patients, Type 1b 24 patients), hemangioma (5 patients), ulcerative lesions (nonspecific ulceration 10 patients, NSAID-induced ulceration 8 patients, and Crohn's disease 3 patients), tumors (primary carcinoma 2 patients, metastatic carcinoma (hepatocellular carcinoma) 2 patients, gastrointestinal stromal tumor (GIST) 2 patients, malignant lymphoma 2 patients), and others (intestinal tuberculosis 2 patients, radiation enteritis 1 patients). The positive CE findings in Group B were as follows; erythema 31 patients, angioectasia (Type 1a without oozing) 25 patients, lymphangioma two patients, and lipoma one patients. Treatment methods for Group A are shown in Table 3. Angioectasia and hemangioma were treated by endoscopic hemostasis in all cases. Nonspecific ulcer and radiation enteritis were treated by mucosal protectant, NSAIDs-induced ulcer was treated by mucosal protectant after stopping NSAIDs, and Crohn's disease was treated by 5-aminosalicylic acid. Primary carcinoma, metastatic carcinoma, and GIST were treated surgically.

Table 1. Clinical characteristics of occult OGIB patients.

	Group A	Group B	Group C
	n = 98	*n* = 59	*n* = 200
Sex			
Male	52 (53)	33 (56)	112 (56)
Female	46 (47)	26 (44)	88 (44)
Age (years)[a]			
<60	12 (12)	19 (32)	66 (33)
⩾60	86 (88)	40 (68)	134 (67)
Comorbidity*			
Cardiovascular disease	14 (14)	3 (5)	22 (11)
Chronic renal disease	7 (7)	3 (5)	8 (4)
Chronic liver disease[b]	48 (49)	49 (83)	80 (40)
Chronic respiratory disease	3 (3)	0 (0)	5 (3)
Cerebrovascular disease	4 (4)	2 (3)	7 (4)
Drugs*			
Anticoagulants			
(+)	27 (28)	8 (14)	29 (15)
(–)	71 (72)	51 (86)	171 (86)
NSAIDs[c]			
(+)	26 (27)	5 (8)	26 (13)
(–)	72 (73)	54 (92)	174 (87)
Mean time from the first OGIB episode to CE, days	28	30	34
Mean hemoglobin before CE, g/dl	10.9	10.7	11.3
Blood transfusion			
(+)	20 (20)	15 (25)	29 (15)
(–)	78 (80)	44 (75)	171 (85)
Mean follow-up period, month	58.8	41.7	50.1

*overlapped *n* (%).
[a]Group A *versus* Group B, $p < 0.05$,
[b]Group A *versus* Group B, $p < 0.05$, Group B *versus* Group C, $p < 0.05$,
[c]Group A *versus* Group B, $p < 0.05$.
CE, capsule endoscopy; OGIB, obscure gastrointestinal bleeding; NSAID, nonsteroidal anti-inflammatory drug.

Malignant lymphoma was treated surgically and/or with chemotherapy.

With regard to prognosis after initial CE, no patients in Group A had overt bleeding or anemia

Table 2. Positive CE findings.

Group A ($n = 98$)		Group B ($n = 59$)	
Vascular lesions		Vascular lesion	
Angioectasia	61 (62)	Angioectasia	25 (42)
Type 1a with oozing	37 (38)	Type 1a without oozing	25 (42)
Type 1b	24 (24)	Tumors	
Hemangioma	5 (5)	Lymphangioma	2 (3)
Ulcerative lesions		Lipoma	1 (2)
Nonspecific ulceration	10 (10)	Others	
NSAID-induced ulceration	8 (8)	Erythema	31 (53)
Crohn's disease	3 (3)		
Tumors			
Primary carcinoma	2 (2)		
Metastatic carcinoma	2 (2)		
Gastrointestinal stromal tumor	2 (2)		
Malignant lymphoma	2 (2)		
Others	3 (3)		

n (%).
CE, capsule endoscopy; NSAID, nonsteroidal anti-inflammatory drug.

exacerbation after treatment for bleeding sources. In Group B, no patients had overt bleeding, and six patients had anemia exacerbation although they used iron preparations. The details of these cases are shown in Table 4. All patients had angioectasia (Type 1a without oozing) at initial CE with no bleeding sources. Although all patients underwent follow-up CE, there were no bleeding sources identified. We diagnosed the exacerbation of anemia related to primary disease. Figure 2 shows 5-year anemia exacerbation rates after initial CE. There were significant differences among the three groups ($p < 0.0001$). With respect to OS rate after initial CE, there were no significant differences among Groups A, B, and C ($p = 0.3313$; Figure 3)

Discussion

In the present study, we classified patients into three groups based on the diagnosis of occult OGIB patients because we aimed to evaluate the presence or absence of bleeding sources and the necessity of treatment. Our study revealed that 27% of occult OGIB patients had bleeding sources in the small bowel. The most frequent bleeding sources of occult OGIB were vascular lesions and these lesions were good indicators of endoscopic hemostasis.[9,12] After treatment for bleeding sources, no patients had overt bleeding or anemia exacerbation during the follow-up periods.

There are several reports about the risk factors for ulcerative and vascular lesions of the small bowel diagnosed by CE or double-balloon endoscopy in OGIB patients. With respect to ulcerative lesions, NSAIDs were identified as the most important in patients with overt OGIB. With respect to vascular lesions, liver cirrhosis (LC) and hemodialysis were identified as important risk factors in patients with overt OGIB. In addition, LC, hematologic disease, and the lowest hemoglobin levels were identified in patients with occult OGIB.[13,14]

Regarding rebleeding after treatment, we previously reported that a good outcome could be expected for patients who undergo total enteroscopy and receive

Table 3. Treatment methods for small-bowel lesions.

Diagnosis	Number of cases	Treatment method
Vascular lesions		
Angioectasia	61 (62)	Endoscopic hemostasis
Hemangioma	5 (5)	Endoscopic hemostasis
Ulcerative lesions		
Nonspecific ulceration	10 (10)	Mucosal protectant
NSAID-induced ulceration	8 (8)	Stopping NSAIDs and Mucosal protectant
Crohn's disease	3 (3)	5-ASA
Tumors		
Primary carcinoma	2 (2)	Surgery
Metastatic carcinoma	2 (2)	Surgery
Gastrointestinal stromal tumor	2 (2)	Surgery
Malignant lymphoma	2 (2)	Surgery, Chemotherapy
Others	3 (3)	Surgery, Drug

n (%).
NSAID, nonsteroidal anti-inflammatory drug; 5-ASA, 5-aminosalicylic acid.

proper treatment for the source of bleeding in the small bowel.[15] Aoki and colleagues[16] reported that the rebleeding rate was lower for single ulcerations than for multiple ulcerations in OGIB patients with ulcerative lesions. Moreover, small-bowel vascular lesions have a higher rate of rebleeding compared with other lesions, even after endoscopic interventions.[17] Yung and colleagues[18] reported that a negative CE provides adequate evidence of a subsequently low risk of rebleeding and such patients could therefore be safely managed with watchful waiting. However, patients who have rebleeding after 2 years may need to be investigated for a new source of blood loss. In the previous studies, rebleeding rate of overt and occult OGIB patients was 0% after a negative CE over a 12-month follow-up period.[19,20] However, the rebleeding rate was 11% after negative CE over a 17-month follow-up period, and 35.7% over a 32-month follow-up period. Thus, increased rebleeding rates are reported with longer follow-up periods.[21,22] OGIB patients with a negative CE have a potential risk of rebleeding and close observation is warranted, and alternative modalities should be considered in clinically suspicious cases.[23]

A few studies have reported the long-term outcome of OGIB patients. Tan and colleagues[24] reported that the rebleeding rate of OGIB patients was 28.6% during a median follow-up period of 48 months, compared with 13.7% for patients with negative CE findings. Nevertheless, further investigation and close follow up of OGIB patients, including those with negative CE findings, is necessary. Moreover, Ribeiro and colleagues[25] reported that patients with OGIB and negative CE had a significantly lower rebleeding rate and can be safely followed up without intervention. However, the authors also demonstrated that a higher rate of red blood cell transfusion prior to CE and an overt bleed are associated with a higher rebleeding risk; thus, it is reasonable to consider that these patients may benefit from at least 1 year of follow up. Follow up is necessary because rebleeding occurs after negative CE in occult OGIB patients.

In the present study, when the bleeding source was not identified by CE, our data showed that the exacerbation of anemia was related to a primary disease. These results showed that

Table 4. Cases of anemia exacerbation during follow up.

No.	Sex	Age (years old)	Comorbidity	Drugs	Platelet count (/μl)	Initial CE findings	Follow-up CE findings	Follow-up period (month)
1	Male	54	CKD	None	25.2×10^4	Angioectasia (Type 1a without oozing)	No change	30
2	Male	61	LC	None	8.6×10^4	Angioectasia (Type 1a without oozing)	No change	12
3	Female	73	LC	None	7.3×10^4	Angioectasia (Type 1a without oozing)	No change	25
4	Male	75	LC	Anticoagulants	5.4×10^4	Angioectasia (Type 1a without oozing)	No change	14
5	Female	82	LC	None	5.3×10^4	Angioectasia (Type 1a without oozing)	No change	32
6	Male	85	LC	NSAIDs	6.5×10^4	Angioectasia (Type 1a without oozing)	No change	18

CE, capsule endoscopy; CKD, chronic kidney disease; LC, liver cirrhosis; NSAID, nonsteroidal anti-inflammatory drug.

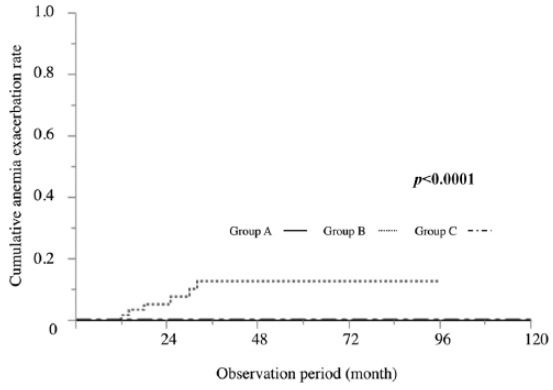

Figure 2. Anemia exacerbation rate after initial CE.
CE, capsule endoscopy.

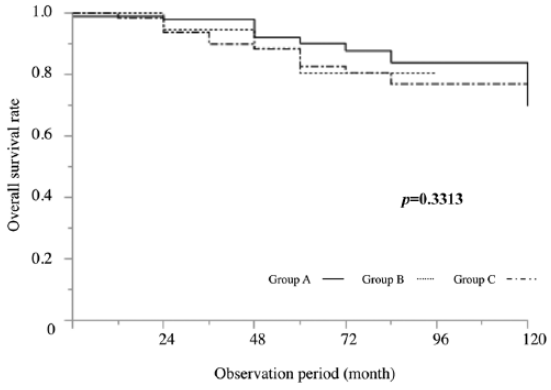

Figure 3. Overall survival rate after initial CE.
CE, capsule endoscopy.

follow-up CE for occult OGIB patients may unnecessary after initial CE. Thus, it is important to manage occult OGIB patients without obvious bleeding sources in clinical practice. However, for patients with anemia exacerbation during follow up, it may be necessary to consider reassessment through various measures including laboratory tests or alternative imaging modalities. Moreover, in Group B, five of six patients, who had anemia exacerbation had LC. According to these results, we could interpret chronic liver disease as a risk factor for occult OGIB with minor CE findings such as angioectasia Type 1a without oozing.

Our study has some limitations which need to be acknowledged. First, this study was a retrospective analysis. Second, the sample size was relatively small. Third, our study group was recruited from a single center, and our observation period was relatively short (135 patients were followed up for more than 5 years, and 222 patients were for less than 5 years.). Therefore, a large-scale study is needed to address these limitations.

In conclusion, the long-term outcomes were favorable because occult OGIB patients who underwent treatment for bleeding sources did not have overt bleeding or anemia exacerbation

during the follow-up period. Moreover, occult OGIB patients who had no bleeding sources did not have rebleeding during the follow-up period. Therefore, based on our findings, occult OGIB patients without a confirmed bleeding source may not require follow-up CE.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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