Impact of fecal occult blood on obscure gastrointestinal bleeding: Observational study

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Methods: Between February 2008 and August 2013, 202 patients with OGIB who performed both capsule endoscopy (CE) and FOBT were enrolled (mean age; 63.6 ± 14.0 years, 118 males, 96 previous overt bleeding, 106 with occult bleeding). All patients underwent immunochemical FOBTs twice prior to CE. Three experienced endoscopists independently reviewed CE videos. All reviews and consensus meeting were conducted without any information on FOBT results. The prevalence of SBDs was compared between patients with positive and negative FOBT.

Results: CE revealed SBDs in 72 patients (36%). FOBT was positive in 100 patients (50%) and negative in 102 (50%). The prevalence of SBDs was significantly higher in patients with positive FOBT than those with negative FOBT (46% vs 25%, P = 0.002). In particular, among patients with occult OGIB, the prevalence of SBDs was higher in positive FOBT group than negative FOBT group (45% vs 18%, P = 0.002). On the other hand, among patients with previous overt OGIB, there was no significant difference in the prevalence of SBDs between positive and negative FOBT group (47% vs 33%, P = 0.18). In disease specific analysis among patients with occult OGIB, the prevalence of ulcer and tumor were higher in positive FOBT group than negative FOBT group. In multivariate analysis, only positive FOBT was a predictive factors of SBDs in patients with OGIB (OR = 2.5, 95%CI: 1.4-4.6, P = 0.003). Furthermore, the trend was evident among patients with occult OGIB who underwent FOBT on the same day or a day before CE. The prevalence of SBDs in positive vs negative FOBT group were 54% vs 13% in patients with occult OGIB who underwent FOBT on the same day or the day before CE (P = 0.001), while there was no significant difference between positive and negative FOBT group in those who underwent FOBT two or more days before CE (43% vs 25%, P = 0.20).

Abstract

AIM: To elucidate the association between small bowel diseases (SBDs) and positive fecal occult blood test (FOBT) in patients with obscure gastrointestinal bleeding (OGIB).
CONCLUSION: The present study suggests that positive FOBT may be useful for predicting SBDs in patients with occult OGIB. Positive FOBT indicates higher likelihood of ulcers or tumors in patients with occult OGIB. Undergoing CE within a day after FOBT achieved a higher diagnostic yield for patients with occult OGIB.

Key words: Capsule endoscopy; Fecal occult blood test; Obscure gastrointestinal bleeding; Small bowel diseases; Timing

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Core tip: We investigated the association between small bowel diseases (SBDs) and a positive fecal occult blood test (FOBT) in patients with obscure gastrointestinal bleeding (OGIB). Positive FOBT may be useful for predicting SBDs in patients with occult OGIB. Positive FOBT indicates higher likelihood of ulcers or tumors in patients with occult OGIB. Undergoing capsule endoscopy within a day after FOBT achieved a higher diagnostic yield for patients with occult OGIB.

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INTRODUCTION

The fecal occult blood test (FOBT) is widely accepted as a colorectal cancer (CRC) screening tool, and several large cohort trials have shown a reduction in CRC mortality with use of the FOBT[1-7]. The FOBT detects occult bleeding from colorectal lesions, although it is assumed that the FOBT may also detect occult bleeding from small bowel diseases (SBDs). However, the usefulness of FOBT in detecting bleeding from the small bowel remains unknown.

Capsule endoscopy (CE) and balloon-assisted enteroscopy are now available for assessing SBDs in patients with obscure gastrointestinal bleeding (OGIB)[8-19]. Diagnosis of OGIB is made by excluding patients with a bleeding source which could be found by esophagogastroduodenoscopy (EGD) and colonoscopy[20]. OGIB is classified as either overt or occult OGIB. Occult OGIB is defined as iron-deficiency anemia (IDA) and/or a positive FOBT with no bleeding source found at the initial endoscopic evaluation[21]. OGIB was classified as overt or occult OGIB. Overt OGIB was defined as clinically perceptible bleeding that recurred or persisted after a negative initial endoscopic evaluation by EGD and colonoscopy. In comparison, occult OGIB was defined as IDA, with or without a positive FOBT[21]. IDA was diagnosed when all of the following criteria were fulfilled; hemoglobin (Hb) < 13.5 g/dL, serum ferritin < 65 ng/dL, mean corpuscular volume < 80 fl and mean corpuscular hemoglobin concentration < 28 pg.

FOBTs were performed for patients with occult OGIB or previous overt OGIB. Patients with clinically perceptible bleeding at the time of the FOBT were excluded. Patients with a cardiac pacemaker, past history of bowel obstruction, or refusal to provide written informed consent were also excluded.

Capsule endoscopy procedures

CE was performed using Pillcam® SB or SB2 (Given Imaging Ltd., Yoqneam, Israel). The preparation for CE involved fasting for 12 h and administration of 40 mg simethicone just before CE. Eating was allowed 5 h after CE ingestion. During the examination, patients could move freely. Sensor array and recording devices were removed 8 h after CE ingestion.

Three experienced endoscopists independently reviewed the CE images using Rapid® 6.5 Access software (Given Imaging Ltd., Yoqneam, Israel) or Rapid® 6.5 Access software. The reading speed of the CE videos was 15-20 frames per second in the dual-view mode. The endoscopists were blinded to the FOBT results and an independent review was held to reach a consensus on the CE findings.

Fecal occult blood test

All study patients underwent immunochemical FOBTs (Eiken Chem, Tokyo, Japan) prior to CE. Two tubes were collected for FOBT, if possible. A positive test was accepted at a threshold of 100 ng/mL for the higher reading of the two tubes.

MATERIALS AND METHODS

Study design

We conducted a retrospective analysis in accordance with the Declaration of Helsinki with the approval of the ethical committee of the University of Tokyo (Tokyo, Japan). The aim was to investigate the association between FOBT and SBDs detected by CE in patients with OGIB.

Patients

Between February 2008 and August 2013, we enrolled 202 patients with OGIB who underwent CE and FOBT. OGIB was defined as recurrent or persistent overt/visible bleeding, IDA, or a positive FOBT with no bleeding source found at the initial endoscopic evaluation[21]. OGIB was classified as overt or occult OGIB. Overt OGIB was defined as clinically perceptible bleeding that recurred or persisted after a negative initial endoscopic evaluation by EGD and colonoscopy. In comparison, occult OGIB was defined as IDA, with or without a positive FOBT[21]. IDA was diagnosed when all of the following criteria were fulfilled; hemoglobin (Hb) < 13.5 g/dL, serum ferritin < 65 ng/dL, mean corpuscular volume < 80 fl and mean corpuscular hemoglobin concentration < 28 pg.

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Table 1  Baseline characteristics of the study patients (n = 202) n (%) 

| Characteristic               | Positive FOBT | Negative FOBT | P value |
|------------------------------|---------------|---------------|---------|
| Age (yr)
 1 Mean ± SD; 2 Number of patients. CE: Capsule endoscopy; OGIB: Obscure gastrointestinal bleeding; NSAIDs: Non-steroidal anti-inflammatory drugs; BUN: Blood urea nitrogen. |
| Gender (Male/Female)         | 118 (58)/84 (42) | 106 (52) | 0.9 |
| Indications of CE           | 102 (50) | 100 (50) | 0.7 |
| Previous overt OGIB         | 96 (48) | 90 (45) | 0.06 |
| Occult OGIB                 | 106 (52) | 106 (52) | 0.7 |
| FOBT Positive FOBT          | 100 (50) | 100 (50) | 0.7 |
| Negativ FOBT                | 102 (50) | 100 (50) | 0.7 |
| The time discrepancy between the FOBT and CE | 8.5 (0-156) d | 8.5 (0-156) d | 0.9 |
| FOBT findings of the small bowel | 11 (11) | 11 (11) | 0.9 |
| Ulcer                       | 13 (6) | 13 (6) | 0.9 |
| Erosion                     | 37 (18) | 37 (18) | 0.9 |
| Angiectasia                 | 22 (11) | 22 (11) | 0.9 |
| Tumor                       | 8 (4) | 8 (4) | 0.9 |
| Active bleeding             | 19 (9) | 19 (9) | 0.9 |
| Daily using drugs           | NSAI Ds | 18 (9) | 0.9 |
| Aspirin                     | 44 (22) | 44 (22) | 0.9 |
| % of capsule obtained cecum image | 83% | 83% | 0.9 |
| Blood test1                 | Hemoglobin (g/dL) | 10.6 ± 2.3 | 10.6 ± 2.3 | 0.9 |
| BUN (mg/dL)                 | 17.9 ± 10.6 | 17.9 ± 10.6 | 0.9 |
| Creatinine (mg/dL)          | 1.25 ± 1.69 | 1.25 ± 1.69 | 0.9 |
| Serum iron (µg/dL)          | 65.7 ± 56.2 | 65.7 ± 56.2 | 0.9 |
| Ferritin (ng/mL)            | 95.4 ± 20.1 | 95.4 ± 20.1 | 0.9 |

Statistical analysis
The prevalence of SBDs was compared between patients with positive and negative FOBTs. We analyzed an association between the FOBT and the prevalence of each SBD, such as erosion, ulcer, angiectasia, tumor or active bleeding. We also analyzed the association between the timing of the FOBT and the prevalence of SBDs.

All statistical analyses were performed using the JMP 10 statistical software program (SAS Institute Inc., North Carolina, United States). In all analyses, means were compared using an unpaired Student’s t-test. Frequency distributions were compared using Fisher’s exact probability test or χ² test. Multivariate analysis was conducted using multivariate unconditional logistic regression analysis. A P value < 0.05 was considered statistically significant.

RESULTS
Baseline characteristics of the study patients
Baseline clinical characteristics of the study patients are summarized in Table 1. A total of 202 OGIB patients (mean age 63.6 ± 14.0 years; 118 males) received both CE and FOBT during the study period. Ninety-six patients (48%) had previous overt OGIB and 106 patients (52%) occult OGIB. The FOBT was positive in 100 (50%) and negative in 102 (50%) patients. The time discrepancy between the FOBT and CE was similar for overt and occult OGIB (11.9 vs 5.3 d, P = 0.09). CE revealed significant lesions of the small bowel in 72 patients (36%), identified as ulcers in 13 (6%), erosions in 37 (18%), angiectasias in 22 (11%), tumors in 8 (4%) and active bleeding in 19 (9%) patients. There were some patients that had several types of SBD simultaneously. The mean of the three kappa values (reviewer A vs B, A vs C, B vs C) was 0.9.

A comparison of baseline characteristics between the positive and negative FOBT groups is summarized in Table 2. Between the two groups, there was no significant difference in the number of patients using drugs such as non-steroidal anti-inflammatory drugs (NSAI Ds), aspirin or warfarin daily. There was no significant difference in the levels of hemoglobin, blood urea nitrogen, creatinine, serum iron or ferritin between the positive and negative FOBT groups.

Association between the FOBT and the prevalence of SBDs detected by CE
The prevalence of SBDs in the positive and negative FOBT groups is shown in Table 3. The prevalence of SBDs was significantly higher in patients with a positive
FOBT than in those with a negative FOBT (46% vs 25%; OR = 2.5; 95%CI: 1.4-4.5; P = 0.002). In the disease-specific analysis, the prevalences of ulcers and active bleeding were higher in patients with a positive FOBT. The prevalence of ulcers in the small bowel was significantly higher in the positive FOBT group than the negative FOBT group (11% vs 2%; OR = 6.2; 95%CI: 1.30-28.6; P = 0.009). Similarly, the prevalence of active bleeding was significantly higher in the positive FOBT group than the negative FOBT group (15% vs 4%; OR = 4.3; 95%CI: 1.4-13.5; P = 0.007). There was no significant difference in the prevalence of erosions, angiectasias or tumors between the positive and negative FOBT groups.

When patients were divided into occult and previous overt OGIB groups, a significant difference in the prevalence of SBDs was observed between the positive and negative FOBT groups. Patients with overt OGIB, the prevalence of SBDs was significantly higher in the positive FOBT group than the negative FOBT group (45% vs 18%; OR = 3.9, 95%CI: 1.6-9.5; P = 0.002). In other words, the mean sensitivity and specificity of FOBT for SBDs in the occult OGIB group were 74% and 42%, respectively, while the accuracy of FOBT for SBDs in the occult OGIB group was 63%.

Pathogenesis of FOBT in patients with occult OGIB
The association between FOBT and each SBD was analyzed (Table 4). In patients with occult OGIB, the prevalence of ulcers, tumors and active bleeding were significantly higher in the positive FOBT group than the negative FOBT group (7% vs 0% for ulcers, P = 0.049; 7% vs 0% for tumors, P = 0.049; 13% vs 0% for active bleeding, P = 0.008, respectively), while there was no significant difference in the prevalence of erosions and angiectasias between the positive and negative FOBT groups.

Predictive factors of SBDs in patients with OGIB
Table 5 summarizes the results from the univariate analysis of predictive factors for SBDs in patients with OGIB. Among age, gender, FOBT, OGIB (overt or occult), hemoglobin level (≤ 10.6 g/dL or > 10.6 g/dL), NSAIDs, aspirin and/or other anticoagulants, only positive FOBT was a significant factor (P = 0.002). Overt OGIB and a hemoglobin level ≤ 10.6 g/dL had P values < 0.3. Multivariate analysis using these three factors revealed that only a positive FOBT was an independent predictive factor for SBDs in patients with OGIB (OR = 2.5; 95%CI: 1.4-4.6; P = 0.003) (Table 6).

Influence of FOBT timing on CE detection
We analyzed the timing of FOBT and the prevalence of SBDs. The average duration between FOBT and CE was 8.5 d (0-129 d). We divided the study patients based on those who underwent FOBT on the same day or the day before CE (n = 114) vs those who underwent FOBT 2 or more days before CE (n = 85). The prevalence of SBDs was significantly higher in the positive than the negative FOBT group among patients who underwent FOBT on the same day or the day before CE (55% vs 24%, P = 0.0007). In contrast, there was no significant difference in the prevalence of SBDs between the positive and negative FOBT groups among patients who underwent FOBT 2 or more days before CE (40% vs 28%, P = 0.24).

Among patients with occult OGIB who underwent FOBT on the same day or the day before CE, the prevalence of SBDs was significantly higher in the positive than the negative FOBT group (54% vs 13%,
P = 0.001), while there was no significant difference between the positive and negative FOBT groups in those who underwent FOBT 2 or more days before CE (43% vs 25%, P = 0.20) (Figure 2). In contrast, among patients with previous overt OGIB, there was no significant difference in the prevalence of SBDs between the positive and negative FOBT groups, regardless of the FOBT timing.

**DISCUSSION**

The present study estimated the association between the prevalence of SBDs and the FOBT in patients with OGIB. The study revealed that the prevalence of SBDs was significantly higher in patients with a positive FOBT than in those with a negative FOBT among patients with OGIB. Multivariate analysis revealed that a positive FOBT was an independent predictive factor for SBDs in patients with OGIB (OR = 2.5, 95%CI: 1.4-4.6, P = 0.003). Although a positive FOBT comprises part of the definition of occult OGIB, the clinical impact of FOBT on SBDs has not been elucidated. The present study indicated that a positive FOBT was useful for predicting the presence of SBDs in patients with occult OGIB. Furthermore, in disease-specific analysis, the prevalence of ulcers, tumors and active bleeding were significantly higher in the positive than the negative FOBT group among patients with occult OGIB, while there was no significant difference in the prevalence of erosions or angiectasias. It is assumed that ulcers and tumors undergo continuous bleeding, which can be detected by FOBT, while erosions and angiectasias do not bleed constantly, and some additional factors such as anticoagulant drugs or hypertension could provoke bleeding intermittently.

The association between the FOBT and the prevalence of SBDs in OGIB patients remains to be determined. Levi et al.[25] studied the association between FOBT and SBDs among patients with occult OGIB. Ten of 26 patients with SBDs had a positive FOBT, while only 2 of 25 patients without SBDs had a positive FOBT. They concluded that significant lesions detected by CE in the small bowel could explain a positive FOBT, similar to the results found here. On the other hand, Chiba et al.[26] assessed the small bowel using CE in asymptomatic FOBT-positive patients with a negative colonoscopy. Among 53 asymptomatic patients with a positive FOBT and a negative colonoscopy, there were no findings of a high potential for bleeding, which

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**Table 5 Univariate analysis of predictive factors for small bowel diseases in patients with obscure gastrointestinal bleeding**

| Factor                        | OR   | 95% CI   | P value |
|-------------------------------|------|----------|---------|
| Age (yr)                      |      |          |         |
| > 64                          | 1.2  | 0.67-2.2 | 0.52    |
| ≤ 64                          | 1    |          |         |
| Sex                           |      |          |         |
| Male                          | 1    |          |         |
| Female                       | 1.1  | 0.61-2.0 | 0.75    |
| FOBT                          |      |          |         |
| Positive                     | 2.5  | 1.4-4.5  | 0.002   |
| Negative                     | 1    |          |         |
| OGIB                          |      |          |         |
| Overt                        | 1.4  | 0.78-2.5 | 0.27    |
| Occult                       | 1    |          |         |
| Hemoglobin level (g/dL)       |      |          |         |
| ≤ 10.6                       | 1.5  | 0.81-2.6 | 0.21    |
| > 10.6                       | 1    |          |         |
| Medication                   |      |          |         |
| NSAIDs                        | 0.67 | 0.23-2.0 | 0.47    |
| Aspirin and/or other anticoagulants | 0.83 | 0.45-1.6 | 0.57    |

FOBT: Fecal occult blood test; OGIB: Obscure gastrointestinal bleeding; NSAIDs: Non-steroidal anti-inflammatory drugs; CI: Confidence interval.

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**Table 6 Multivariate analysis of predictive factors for small bowel diseases in patients with obscure gastrointestinal bleeding**

| Factor            | OR    | 95% CI   | P value |
|-------------------|-------|----------|---------|
| Positive FOBT     | 2.5   | 1.4-4.6  | 0.003   |
| Overt OGIB        | 1.4   | 0.78-2.6 | 0.25    |
| Hemoglobin level  |       |          |         |
| ≤ 10.6 g/dL       | 1.2   | 0.68-2.3 | 0.48    |

FOBT: Fecal occult blood test; OGIB: Obscure gastrointestinal bleeding; CI: Confidence interval.
Fecal occult blood for small-bowel diseases

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Background

Although several large cohort trials have shown a reduction in colorectal cancer mortality with use of the fecal occult blood test (FOBT), the usefulness of FOBT for detection on bleeding from the small bowel is unknown. Capsule endoscopy (CE) is now available for assessing small bowel diseases (SBDs) in patients with obscure gastrointestinal bleeding (OGB) or patients who have possibilities for SBDs. Although a positive FOBT is a component of an occult OGB diagnosis, the association between FOBT and SBDs detected by CE remains unknown.

Research frontiers

FOBT is widely used for colorectal cancer screening and several large cohort trials have shown a reduction in colorectal cancer mortality with use of FOBT. CE is now available for assessing SBDs in patients with obscure gastrointestinal bleeding or patients who have possibilities for SBDs. CE makes a large contribution to following examinations or therapies for SBDs.

Innovations and breakthroughs

In this study, the authors investigated the association between SBDs and a positive FOBT in patients with OGB. The prevalence of SBDs was significantly higher in patients with positive FOBT than those with negative FOBT. In particular, among patients with occult OGB, the prevalence of SBDs was higher in positive FOBT group than negative FOBT group, while there was no significant difference in the prevalence of SBDs between positive and negative FOBT group among patients with previous overt OGB. Furthermore, undergoing CE within a day after FOBT achieved a higher diagnostic yield for patients with occult OGB.

Applications

The study results suggest that positive FOBT may be useful for predicting SBDs in patients with occult OGB and undergoing CE may be performed within a day after FOBT.

Peer review

The authors investigated the association between SBDs and a positive FOBT in patients with OGB. The prevalence of SBDs was higher in positive FOBT group than negative FOBT group in patients with occult OGB (45% vs 18%, \( P = 0.002 \)). Positive FOBT may be useful for predicting SBDs in patients with occult OGB. Positive FOBT indicates higher likelihood of ulcers or tumors in patients with occult OGB. Undertaking CE within a day after FOBT achieved a higher diagnostic yield for patients with occult OGB.

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