Clinical Characteristics and Risk Factors for Rebleeding in Patients with Obscure Gastrointestinal Bleeding

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Abstract:
Objective With the advent of capsule endoscopy (CE) and double-balloon endoscopy (DBE), the diagnosis and treatment of obscure gastrointestinal bleeding (OGIB) have markedly progressed. However, rebleeding sometimes occurs and is difficult to diagnose and treat. The aim of the present study was to investigate the clinical features of OGIB and risk factors for rebleeding in our hospital.
Methods A total of 195 patients who underwent CE and/or DBE for OGIB in our hospital from January 2009 to July 2016 were included in the present study. We analyzed 168 cases of small intestinal OGIB, after excluding 27 cases of extra small intestinal bleeding. The clinical characteristics and risk factors related to rebleeding were retrospectively studied.
Results Among the 168 patients who were included in the analysis, 95 patients (56.5%) were male. The mean age was 64.5 years (range, 8 to 87 years). Hypertension (31.0%) was the most frequent comorbidity, followed by chronic kidney disease (19.0%). The final diagnoses were ulcerative lesions (n=50, 29.8%), vascular lesions (n=30, 17.9%), tumors (n=7, 4.2%), and diverticula (n=2, 1.2%). The bleeding source was undetermined in the remaining 79 cases (47.0%). Rebleeding was confirmed in 29 cases (17.3%). In a univariate analysis, chronic kidney disease, vascular lesion, and overt previous bleeding were significantly associated with the risk of rebleeding. A multivariate analysis showed that chronic kidney disease, vascular lesion, and overt previous bleeding were significantly associated with the risk of rebleeding.
Conclusion Patients with OGIB with overt previous bleeding, vascular lesions, and/or chronic kidney disease had a higher risk of rebleeding.

Key words: obscure gastrointestinal bleeding, overt previous bleeding, vascular lesions, chronic kidney disease

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Introduction

Obscure gastrointestinal bleeding (OGIB) is a form of gastrointestinal bleeding whose source is unknown, despite the performance of upper and lower gastrointestinal endoscopy. It accounts for 5% of all cases of gastrointestinal bleeding (1). Many of these cases are caused by small intestinal lesions (2). OGIB is classified into two subtypes in the American Journal of Gastroenterology Clinical Guideline: i) overt bleeding, manifesting as melena or hematochezia; and ii) occult bleeding, presenting as a positive fecal occult blood test with or without iron-deficiency anemia (3). Overt bleeding is further divided into two groups: i) overt ongoing bleeding (continuous bleeding); and ii) overt previous bleeding (previous bleeding). With the development of capsule endoscopy (CE) (4) and double-balloon endoscopy (DBE) (5), the diagnosis and treatment of OGIB have markedly progressed. However, rebleeding sometimes occurs, and most rebleeding cases are difficult to diagnose and treat. Thus, it is important to identify the characteristics of cases in which rebleeding occurs. The aim of the present study
was to investigate the clinical features of OGIB and risk factors for rebleeding.

**Materials and Methods**

**Study design and patients**

This was a single-center, retrospective study. Among 195 patients who underwent CE and/or DBE for OGIB in our hospital from January 2009 to July 2016, 27 patients in whom the source of bleeding was proven to be outside the small intestine were excluded. We investigated the clinical characteristics of the remaining 168 patients. Among these, 148 underwent CE alone, 8 underwent DBE alone, and 39 underwent both CE and DBE. Total enteroscopy was performed in 153 cases. CE was performed with a video capsule endoscopy device (PillCam SB2, or SB3; Given Imaging, Yokneam, Israel). The images were analyzed with the RAPID Reader 6 software program (Given Imaging) on a RAPID 5 or 6.5 workstation (Given Imaging). DBE was performed with a DBE system (FUJIFILM, Saitama, Japan) employed with a FUJIFILM EN-450T5, EN-530T, or EN-580T endoscope. The clinical characteristics and factors related to rebleeding were retrospectively studied. This study was conducted in accordance with Declaration of Helsinki and was approved by the Okayama University Hospital Ethics Committee in June 2018.

**Variables**

Medical records were retrospectively reviewed and evaluated for sex, age, comorbidities, oral medicine, clinical diagnosis, clinical course of the patient and outcome, and presence of rebleeding. Regarding deceased patients, the observation period was defined as the period until the day of death. Therapeutic intervention was defined as any of the various types of therapeutic intervention that were employed [e.g., endoscopic therapy, interventional radiology (IVR), medication, change of orally administered drugs, and surgery].

**Types of OGIB bleeding and definition of rebleeding**

As mentioned previously, OGIB was divided into three subtypes: overt ongoing bleeding, overt previous bleeding, and occult bleeding. In this study, rebleeding was defined as repeated visible bleeding or progressive anemia requiring repeated endoscopic examination. When the source of rebleeding was not confirmed in the small intestine, upper and lower gastrointestinal endoscopy were repeated in all cases.

**Definition of the endoscopic findings and diagnoses**

The endoscopic findings were classified as follows: no abnormality, ulcerative lesions (i.e., erosion or ulcer), vascular lesions (i.e., angiectasia, Dieulafoy lesions, or arteriovenous malformation), tumors, diverticula and others. The final diagnosis was made based on the endoscopic findings at not only the first bleeding episode but also rebleeding episodes. The endoscopic diagnosis was performed and discussed by two expert endoscopists (S.K and Y.B). Only definite findings of bleeding were regarded as positive findings.

**Comorbidities and medications**

Hypertension, chronic kidney disease (CKD), diabetes mellitus, ischemic heart disease, liver cirrhosis, malignant tumors, and hematologic disease were investigated as comorbidities. In this study, CKD was defined by a creatinine level that exceeded the standard laboratory value in our hospital. CKD was further divided into two groups as severe CKD (eGFR<30 mL/min/1.73 m²) or moderate CKD (eGFR 30 to <60 mL/min/1.73 m²). Antithrombotic drugs

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**Table 1. Patient Characteristics.**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>n=168</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male), n (%)</td>
<td>95 (56.5)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>64.5 (8-87)</td>
</tr>
<tr>
<td>Comorbidity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>52 (31.0)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>32 (19.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30 (17.9)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>29 (17.3)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>27 (16.1)</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td>13 (7.7)</td>
</tr>
<tr>
<td>Hematologic disease</td>
<td>10 (6.0)</td>
</tr>
<tr>
<td>Antithrombotic drugs, n (%)</td>
<td>60 (35.7)</td>
</tr>
<tr>
<td>Anti-platelet/Anticoagulant</td>
<td>42</td>
</tr>
<tr>
<td>NSAIDs, n (%)</td>
<td>57 (33.9)</td>
</tr>
<tr>
<td>aspirin/Non-aspirin</td>
<td>35/27</td>
</tr>
<tr>
<td>PPI, n (%)</td>
<td>90 (53.6)</td>
</tr>
</tbody>
</table>

NSAIDs: nonsteroidal anti-inflammatory drugs, PPI: proton-pump inhibitor

**Table 2. The Final Diagnosis of OGIB Cases.**

<table>
<thead>
<tr>
<th></th>
<th>Positive group (n=104)</th>
<th>Negative group (n=64)</th>
<th>Total (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular lesions</td>
<td>28</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>Ulcerative lesions</td>
<td>49</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Tumors</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Diverticulum</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unclassified</td>
<td>18</td>
<td>61</td>
<td>79</td>
</tr>
</tbody>
</table>

OGIB: obscure gastrointestinal bleeding
were classified into antiplatelet drugs (e.g., aspirin and thienopyridine) and anticoagulants (e.g., warfarin and direct oral anticoagulants). Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, cyclooxygenase (COX) inhibitors (e.g., loxoprofen and diclofenac), and selective COX2 inhibitors (e.g., celecoxib, etodolac, and meloxicam). Proton-pump inhibitors (PPIs) included omeprazole, esomeprazole, lansoprazole, and rabeprazole. The potassium-competitive acid blocker (P-CAB) vonoprazan was not included because it was not administered to any of the patients.

Statistical analysis

Sequential data were expressed as the mean and median. Categorical data were compared using the chi-squared test or Fisher’s exact test. Variables with p values of <0.05 in the univariate analysis were included in the multivariate logistic regression models. All statistical analyses were performed using the JMP Pro for Windows software program (version 13). P values of <0.05 were considered to indicate statistical significance.

Table 4. Rebleeding Rates after Therapeutic Intervention.

<table>
<thead>
<tr>
<th>Therapeutic intervention</th>
<th>OGIB cases</th>
<th>Vascular lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total, n</td>
<td>Rebleeding, n</td>
</tr>
<tr>
<td></td>
<td>(%) incidence ratio</td>
<td>(%) incidence ratio</td>
</tr>
<tr>
<td>Hemostatic treatment</td>
<td>52</td>
<td>11 (21.1)</td>
</tr>
<tr>
<td>Endoscopic therapy</td>
<td>24</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>15</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td>IVR</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Oral administration change/addition</td>
<td>28</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Addition of other drugs</td>
<td>13</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>NSAIDs change</td>
<td>10</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Antithrombotic drug change</td>
<td>5</td>
<td>2 (40.0)</td>
</tr>
</tbody>
</table>

IVR: interventional radiology, NSAIDs: nonsteroidal anti-inflammatory drugs, OGIB: obscure gastrointestinal bleeding.

Results

Patient characteristics

Table 1 shows the clinical characteristics of patients in this study. Among 168 patients, 95 (56.5%) were male, and the mean age was 64.5 years (range, 8-87 years). One-hundred fourteen patients (67.9%) had one or more comorbidities: hypertension was the most common (31.0%), followed by CKD (19.0%), diabetes mellitus (17.9%), ischemic heart disease (17.3%), and liver cirrhosis (16.1%). Sixty patients (35.7%) were taking oral antithrombotic drugs. Forty-two patients were using antiplatelet drugs and 31 were using anticoagulant drugs (including combined use). Fifty-seven patients (33.9%) were using NSAIDs, including aspirin (aspirin, n=35; NSAIDs other than aspirin, n=27). Ninety patients (53.6%) were using PPIs. The median period of observation was 31.5 months. 20 patients died during the observation period. The primary cause of death was progression of comorbidities (n=15). The other causes included sepsis, multiple organ failure, and unknown origin.

Endoscopic findings at the first procedure and final diagnosis

We investigated the endoscopic findings of 168 patients at the first bleeding episode. Endoscopic findings were positive in 104 patients (positive group), while no abnormalities were detected in 64 patients (negative group). The 104 patients in the positive group had ulcerative lesions (erosion and/or ulcer, n=49), vascular lesions (angiectasia, Dieulafoy lesions, and/or arteriovenous malformation, n=28), tumors (n =7), diverticulum (n=2), and unclassified lesions (n=18). In contrast, among the 64 patients in the negative group, vascular lesions (n=2) and ulcerative lesions (n=1) were detected at the second or subsequent bleeding event. Thus, the final diagnoses of 89 patients were as follows: ulcerative lesions (n=50), vascular lesions (n=30), tumors (n=7), and diverticulum (n=2) (Table 2). Seventy-nine patients were unclassified or impossible to diagnose.

Table 5. Clinical Risk Factors for Rebleeding.

<table>
<thead>
<tr>
<th></th>
<th>No rebleeding</th>
<th>Rebleeding</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=139</td>
<td>n=29</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>80</td>
<td>15</td>
<td>0.57</td>
</tr>
<tr>
<td>Over 70 years</td>
<td>59</td>
<td>13</td>
<td>0.81</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>20</td>
<td>7</td>
<td>0.21</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>21</td>
<td>11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>6</td>
<td>3</td>
<td>0.23</td>
</tr>
<tr>
<td>Antithrombotic drugs</td>
<td>49</td>
<td>11</td>
<td>0.79</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>24</td>
<td>3</td>
<td>0.33</td>
</tr>
<tr>
<td>Vascular lesions</td>
<td>16</td>
<td>14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Overt previous bleeding</td>
<td>65</td>
<td>22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Therapeutic intervention</td>
<td>41</td>
<td>11</td>
<td>0.38</td>
</tr>
</tbody>
</table>

NSAIDs: nonsteroidal anti-inflammatory drugs.
Details of rebleeding cases

Rebleeding was confirmed in 29 patients (17.3%). In the positive group, rebleeding was observed in 21 patients (20.2%), with vascular lesion (n=12) being the most frequent diagnosis in cases of rebleeding. There was only one case in which a final diagnosis could not be obtained. In contrast, among the 64 patients in the negative group, rebleeding occurred in 8 patients (12.5%). In three cases, vascular lesions (n=2) and ulcerative lesions (n=1) were identified at the second or subsequent bleeding episode. However, a final diagnosis could not be obtained in 5 cases (62.5%). In the total population of 168 patients, rebleeding occurred in 29 patients (17.3%): vascular lesions (n=14), ulcerative lesions (n=9), and unclassified lesions (n=6). In this study, vascular lesions were the most frequent cause of rebleeding (Table 3). The median observation period from the first bleeding episode to rebleeding was 4 months.

Detail of rebleeding cases after therapeutic intervention

Among 168 patients with OGIB, 52 underwent therapeutic intervention such as endoscopic treatment, surgery, and oral administration change at the first event. Rebleeding occurred in 11 patients (21.1%). Vascular lesions were the most frequent cause of rebleeding (7 patients). In the 11 patients, 5 patients (55.6%) occurred rebleeding after endoscopic treatment. On the other hand, no rebleeding occurred after surgery or IVR (Table 4). In the patients who underwent a therapeutic intervention, rebleeding rate was higher in those with overt previous bleeding (n=9, 81.8%) than in those with occult bleeding (n=2, 18.2%).

Risk factors for rebleeding

We investigated risk factors for rebleeding. In the univariate analysis, CKD, vascular lesions, and overt previous bleeding were significantly associated with higher risk of rebleeding (Table 5). Intake of any antiplatelet, anticoagulant, or combination use was not a risk factor of rebleeding (Table 6). In the multivariate analysis, CKD, vascular lesions, and overt previous bleeding were independent risk factors of rebleeding (Table 7).

With respect to the relationship between CKD and rebleeding, the rebleeding rate of patients with normal kidney function was 13.2%. In contrast, the rebleeding rate in moderate CKD was 33.3%, and that in severe CKD was 35.2% (Figure). The rebleeding rate in overt bleeding and occult bleeding cases were 22.5% (23 of 102 patients) and 9.1% (6 of 66 patients), respectively. The rebleeding rate in overt bleeding was significantly higher than that in occult bleeding (p=0.02). Additionally, the rebleeding rate in overt previous bleeding and others were 25.6% (22 of 86 patients) and 8.6% (7 of 81 patients), respectively (p<0.01). The rate of overt previous bleeding was significantly higher than that in other bleeding types.

Discussion

We investigated clinical features of patients with OGIB. In this study, we diagnosed OGIB according to the diagnos-
The rebleeding rates according to the renal function. CKD: chronic kidney disease.


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