CLINICAL PROFILE ASSOCIATED WITH BLEEDING SMALL BOWEL TUMORS IN PATIENTS UNDERGOING CAPSULE ENDOSCOPY

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CLINICAL PROFILE ASSOCIATED WITH BLEEDING SMALL BOWEL TUMORS IN PATIENTS UNDERGOING CAPSULE ENDOSCOPY (Abstract): Since the development and implementation into clinical practice of the small bowel (SB) capsule endoscopy (CE), obscure gastrointestinal bleeding (OGIB) is no longer an answerless question. In many cases of SB pathology, a definite diagnosis is made by SBCE, while other cases, as SB tumors (SBT), require additional investigations. Our aim was to identify predictors for SBT as OGIB etiology. Material and methods: We retrospectively studied all patients with OGIB who underwent SBCE in a two-year period. Only patients with positive findings were included. Patients with SBTs were compared to patients with non-tumoral cause of OGIB, and analyses for possible associated clinical factors were performed. Results: 205 SBCE examinations were performed for OGIB. Positive findings were noted in 134 patients (male gender: 72; female gender: 62; age range 21-79): 25 cases of SBTs, and 109 cases with non-tumoral causes responsible for bleeding (angioectasia, Crohn’s disease, NSAIDs enteritis, and other). SBT patients underwent further investigations, for confirmation and stadialization. Patient’s age < 65 years, lack of anticoagulant treatment, and overt type of bleeding significantly associated with SBTs. Gender was not predictor for SBT. Surgery was the main therapeutic option for SBTs, significantly more frequently compared to the non-tumoral causes. Conclusion: Young age, overt bleeding and lack of anticoagulant treatment are factors associated with the final diagnosis of SBT. Because SBCE is only a visual technique and additional investigations are needed, predictors could anticipate the need for additional explorations and could help optimizing the investigational plan in terms of time and resources. Keywords: SMALL BOWEL TUMOR, OBSCURE GASTROINTESTINAL BLEEDING, IRON DEFICIENCY ANEMIA, SMALL BOWEL CAPSULE ENDOSCOPY.
 Actual guidelines from all over the world are now consensually sustaining the use of SBCE as first-line investigation whenever SB pathology is suspected unless absolute contraindication exists (2-4).

SBCE has made important contributions in the diagnostic work-up of obscure gastrointestinal bleeding, unexplained iron deficiency anemia (IDA), inflammatory bowel diseases - especially Crohn’s disease and inflammatory disease type unclassified, celiac disease, and small bowel tumors (SBT).

Since the use of SBCE, and thanks to various technical progresses aiming to improve its performance, OGIB is no longer an answerless question. Suspected small bowel bleeding, recognized recently as separate entity called middle gastrointestinal bleeding, represents the main indication for SBCE (5). Diagnostic yield of SBCE in suspected SB bleeding has raised to almost 70%, and the most frequent lesions found to be responsible are angiodysplasia, Crohn’s disease, various types of enteritis, and SBT (6, 7).

Traditionally, SBT are considered relatively rare, counting 5-8% from all gastrointestinal tract tumors (8). Small bowel is classically considered the most challenging part to be explored form the whole gastrointestinal tract, due to its “hidden” location, length and lack of ideal approach methods, both effective and safe. Not so long ago, data were showing that SBCE has doubled the rate of SBT diagnosis (9). According to recent analysis, SBCE has practically almost tripled it, the reason for this accomplishment being undoubtedly its capability to visualize in a relatively simple, non-invasive manner the entire small bowel (10). On the other hand, the most frequent circumstance for detecting SBT by SBCE is obscure (manifest or occult) gastrointestinal bleeding.

However, SBCE offers only a macroscopic view of the lesion. Therefore, the final and complete diagnosis of SBT is established after further investigations allowing histopathological analysis and, respectively, stadialization, or even only after surgical approach. Even if SBCE is the first line investigation for suspected SB pathology, any suspicion of SBT will require supplementary investigations. Thus, in terms of resources, anticipating the need of more explorations could optimize the work-up strategy.

Our aim was to identify predictors for SBT as cause of OGIB, so in the high probability of SBT, additional work-up should be timely previewed and consequently provided.

MATERIAL AND METHODS

Study design and patients

We retrospectively analyzed the clinical data and medical records of all patients with OGIB (overt or occult) who underwent SBCE in a two and a half-year period, from January 2019 to June 2021 in our tertiary referral care center. Only patients with positive findings, which were further concordant with the final diagnosis, were included in the final analysis.

This study was performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the institutional review board. All patients underwent SBCE examination after informed consent was signed. No additional consent was required for this study owing to its retrospective nature.

SBCE procedure

The third-generation CE system (PillCam SB3) was used, in combination with
RAPID reading software. All the procedures were performed after negative upper and lower gastrointestinal endoscopy. Patients were informed about the procedure and signed the informed consent. SBCE examination was performed after contraindications were excluded. They were prepared according to current guidelines, with 2 liters of polyethylene-glycol electrolyte lavage solution the day before the examination. Saurin’s classification was used for potential small bowel bleeding lesions (11).

**Data collection**

Patient-related variables, including age, gender, type of OGIB, and current anticoagulant treatment, were reviewed. The patients were classified into two groups according to the final diagnosis: patients with SBT and patients with non-tumoral cause for OGIB, respectively. The two groups were compared in order to assess clinical parameters associated with the diagnosis of SBT.

**Statistical analysis**

Categorical variables were reported as frequencies and percentages. Continuous variables are presented as mean ± standard deviation values, and differences between groups were statistically assessed using Fisher’s exact test. A two-sided P value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22.0 software (IBM SPSS Inc, Chicago, IL, USA).

**RESULTS**

**Baseline characteristics of patients and diagnostic yield of SBCE in OGIB**

In total, 205 patients underwent SBCE for OGIB in the above-mentioned period. SBCE found the responsible lesion in 134 patients, corresponding to a diagnostic yield of 65%.

The clinical characteristics of the 134 patients entering our study are presented in the Table I. We have noted a slight predominance for male gender among all patients. The majority of patients belonged to the young age group (age < 65 years), and the most frequent type of bleeding was the occult one. Approximately one fifth of the examined patients were taking anticoagulants, for associated cardio-vascular or neurological diseases.

**TABLE I.**

<table>
<thead>
<tr>
<th>Clinical characteristics of patients, findings at SBCE and type of intervention</th>
<th>Total number of patients = 134</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>64 ± 12.5</td>
</tr>
<tr>
<td>Range, years</td>
<td>21-79</td>
</tr>
<tr>
<td>Gender ratio</td>
<td>62/72 (46.3/53.7)</td>
</tr>
<tr>
<td>Women/Men, n (%)</td>
<td></td>
</tr>
<tr>
<td>Type of OGIB, n (%)</td>
<td></td>
</tr>
<tr>
<td>Overt</td>
<td>50 (37.3)</td>
</tr>
<tr>
<td>Occult</td>
<td>84 (62.7)</td>
</tr>
<tr>
<td>Patients with anticoagulant treatment, n</td>
<td>26</td>
</tr>
<tr>
<td>Further investigations, n</td>
<td>66</td>
</tr>
<tr>
<td>Type of lesion responsible for OGIB, n</td>
<td></td>
</tr>
<tr>
<td>SBT</td>
<td>25</td>
</tr>
<tr>
<td>GIST</td>
<td>13</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>6</td>
</tr>
</tbody>
</table>
Findings at SBCE

The interpretation of the lesions discovered by SBCE was made according to Sau-rin’s classification. Following SBCE, SBTs as etiology for OGIB were noted for 25 patients (18.6%), while for the remaining 109 patients (81.4%), non-tumoral causes were recorded. After complete work-up, consisting in further imaging or endoscopic investigations and/or surgical approach, a final histological diagnosis was established. The most frequent types of tumors were GIST and adenocarcinoma. Cases of neuroendocrine tumor and lymphoma were also recorded, as well as a case of jejunal ulcerated lipoma. Amid non-tumoral causes, the most frequent were represented by angioectasia, Crohn’s disease, NSAIDs enteropathy, and enteritis; other lesions were also described (diverticulum, parasitosis, intestinal tuberculosis).

The final management of the cases, consisted in medical treatment for the majority of cases, endoscopic or surgical treatment, according to the positive diagnosis. SBCE procedure-related complications, such as retention, did not occur in any of the cases.

Correlations between clinical characteristics of patients and the etiology of OGIB

The results of the analysis regarding patients’ age, type of bleeding, concomitant anticoagulant treatment according to the etiology of bleeding (tumoral lesion vs. non-tumoral cause, respectively) are showed in the Table II. Age group under 65, overt type of OGIB and lack of anticoagulant treatment significantly associated with SBT as cause of OGIB ($p<0.05$).

The comparative analysis regarding the need for further investigations and the type of therapeutic intervention according to the same two groups is shown in the Table III. With one exception, all the rest of the patients with SBT (24 out of 25) required additional investigations, significantly more compared to the patients with non-tumoral cause of OGIB (25 out of 109, respectively; $p<0.001$). In the same time, significantly more patients with tumoral bleeding needed surgery as therapeutic solution, while the most patients with non-tumoral bleeding were treated by medical or endoscopic interventions ($p<0.0001$).
Clinical profile associated with bleeding small bowel tumors in patients undergoing capsule endoscopy

**TABLE II.**

Clinical characteristics according to the etiologic diagnosis

<table>
<thead>
<tr>
<th></th>
<th>SBT, n Total = 25</th>
<th>Non-tumoral, n Total = 109</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women/men, n (%)</td>
<td>9/16 (36/64)</td>
<td>53/56 (48.7/51.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>Age group &lt;65/≥65, n</td>
<td>21/4</td>
<td>67/42</td>
<td>0.03*</td>
</tr>
<tr>
<td>Type of OGIB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overt/occult</td>
<td>18/7</td>
<td>32/77</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Anticoagulant treatment</td>
<td>1</td>
<td>25</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

*Significant p<0.05

**TABLE III.**

Diagnostic and therapeutic characteristics according to the etiological diagnosis

<table>
<thead>
<tr>
<th></th>
<th>SBT, n Total = 25</th>
<th>Non-tumoral, n Total = 109</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further imaging studies</td>
<td>24</td>
<td>42</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>23</td>
<td>2</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

*Significant p<0.05

**DISCUSSION**

SBT are rare, and their diagnosis is difficult. Clinical presentation of SBT is often non-specific. Even when the clinical index suspicion is high, choosing and applying the right methods of exploration is difficult. These are main the reasons for why, generally, the approach of the small bowel is considered a challenge.

After having proved along the years the usefulness, together with its non-invasive character, SBCE became the first line investigation method recommended when small bowel pathology is suspected.

However, a positive diagnosis at SBCE examination is not always the final diagnosis. The identification and the right description of a typical, benign lesion at SBCE usually represents the last step before applying the right treatment, but the diagnosis of SBT in patients undergoing SBCE is usually an intermediate cornerstone across a long investigational path. Finding a tumoral mass at SBCE is followed, as appropriate, by anterograde or retrograde enteroscopy with biopsy, and further entero-CT or entero-IRM in order to establishing the extension.

At the same time, another challenge in the diagnosis of SBT are represented by the cases of false SBT, which require, especially in the case of submucosal lesions, thorough differential diagnosis with the bulges having similar appearance. Several criteria and scores have been proposed along the years, as predictive methods to differentiate between the true masses and the innocent bulges (12, 13).

Thus, knowing the factors associated with the SBT could help anticipate the diagnosis and plan in a timely manner the diagnostic sequence and the therapeutic decision.

Epidemiological studies showed that, according to gender, men are more prone to develop malignant SBT (14). In our analysis, there was a higher predominance of male patients in the SBT group, but male gender was not predictive for the diagnosis of SBT.

In our study, the main indication for OGIB was represented by the occult bleed-
ing, with IDA. A significant lower proportion of patients with occult OGIB had tumoral lesions as cause for their anemia (8%), while more than one third of patients with overt OGIB had SBT at SBCE (36%, p<0.05). Consequently, overt OGIB associates with higher frequency of SBT diagnosis. Lower diagnostic yield of SBCE in IDA, compared to overt bleeding, has been stated by many studies so far (15,16). Additionally, anemia itself has many and often combined causes and mechanisms and may become relatively common in the elderly population. Thus, when SBCE is performed for IDA, there are usually less chances to have a diagnosis. This is also how we could further explain the higher proportion of patients aged under 65 in the SBT group, compared to that in the non-tumoral group (84% versus 61%, respectively, p = 0.27).

Anticoagulant treatment was associated in our analysis with the non-tumoral cause of OGIB. Minor lesions bleeding may be triggered by the anticoagulant medication. In the lack of anticoagulant drugs, they would have probably remained silent. So, minor lesions are prone to manifest and be discovered more frequently when the patient follows this type of treatment, for various, especially cardio-vascular, comorbidities. SBT present a bleeding potential by themselves, so they do not need an extra trigger factor for hemorrhagic exteriorization.

As discussed before, identifying a tumoral mass at SBCE implies further work-up. In our study, in order to complete the diagnosis, all patients with SBTs underwent additional investigations (enteroscopy with biopsy, entero-CT, and/or entero-IRM), while only 38% of patients with non-tumoral lesions at SBCE needed supplementary exploration before the therapeutic decision (p<0.05).

Depending on the type, dimension and extension, SBTs have usually surgical indication. In our study, one single SBT was benign, with the final histological diagnosis established after surgery - jejunal ulcerated lipoma. The bleeding potential, and the lack of a histological diagnosis after enteroscopy with biopsy, justified the surgical approach. Metastatic SBTs are rare, but they exist, and they may complicate with bleeding; a particular case of metastatic melanoma was diagnosed in our analysis with metastatic melanoma, managed by conservative treatment, with no surgery involved. The other case in our study which did not require surgery was a case of SB lymphoma, which was referred to the hemato-oncologist.

Capsule retention is a complication with 1-2% overall occurrence rate, with various frequencies reported depending on the indication of the examination, the highest in known CD (17, 18).

For OGIB, retention rate was 1.3% in a large European single-center 10-year experience (19). Nor retention or other complication occurred in our analysis, probably due to the prior work-up which excluded patients with high obstruction risk from the SBCE examination.

CONCLUSIONS

Age under 65, overt bleeding and lack of anticoagulant treatment sketch the profile of the patients with SBT; these patients will also be those who will require additional investigation methods and, finally, will have surgery as therapeutic option.

A complete early characterization of the clinical profile of the patient is of upmost importance, before deciding the diagnostic work-up. Some clinical characteristics may associate, as we showed, with a higher probability of having a tumoral lesion responsi-
ble for their bleeding. Being prepared of advance in front of such patients may assure a temporal gain and a more fluent investigation algorithm, finally reflected into the right therapeutic option choice.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

REFERENCES