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Visual criteria in small bowel tumors detected by capsule endoscopy – morphological description and correlations with histological type

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Abstract

Introduction: Small bowel tumors (SBTs) are rare. The advent of small bowel capsule endoscopy (SBCE) revolutionized the diagnosis of small bowel pathology, the SBCE major breakthrough consequently doubled the diagnostic rate of SBTs. Being a visual technique, without ability to take biopsies, SBCE has limitations in the diagnostic work-up of SBTs. *Aim*: To assess if structured visual description of SBTs detected by SBCE correlates with the histological type. *Patients, Materials and Methods*: We included patients with SBTs, evaluated by SBCE and furthermore explored, for which a final histopathological diagnosis was made, either on biopsy tissue samples, or on surgical specimens, using routine techniques and immunohistochemistry. The SBCE findings and reports were reviewed in order to assess the main macroscopic features of the SBTs, which were further correlated with the histological type. *Results*: SBTs frequency at SBCE was 5.2%. All SBTs presented as protruding lesions. Features as size, color, type, shape, discoloration, presence of mucosa ulceration, bleeding stigmata or potential, contributed outlining a prototype. SBCE was accurate in terms of localization and suspected diagnosis. *Conclusions*: Even if SBCE is a purely visual technique, thorough examination and rigorous analysis of macroscopic features, as well as adoption of a structured terminology, may successfully predict the final diagnosis, empowering SBCE not only as a trust comrade in the diagnostic pathways of SBTs, but also as a valuable standalone technique mandating the final therapeutic decision.

Keywords: capsule endoscopy, small bowel tumors, macroscopic morphological criteria, histopathology.

Introduction

Although the small bowel (SB) represents 75% of the length of the gastrointestinal tract and 90% of its absorption surface, small bowel tumors (SBTs) are rare, counting for only approximately 3–6% of all gastrointestinal neoplasms and 1–3% of all gastrointestinal malignancies [1, 2]. There are several possible explanations for the relative rare incidence of SBTs compared to other gastrointestinal tumors, especially to the colorectal neoplasms: faster transit time, shorter contact of solid carcinogenic components with intestinal mucosa, lower bacterial population, and protective role of the mucosal lymphoid tissue.

The diagnosis of SBTs represents a true challenge for gastroenterologists. Besides their rarity, other conditions may render the diagnosis difficult: hardly accessible location by conventional examination tools, long asymptomatic periods and/or non-specific clinical picture.

However, the advent of small bowel capsule endoscopy (SBCE) revolutionized the diagnostic of SB pathology. Emerged from the need to overcome the examination techniques existent so far, the SBCE proved to be a safe and valuable tool for exploring the SB. The main indications of SBCE are obscure gastrointestinal bleeding (OGIB), unexplained iron deficiency anemia (IDA), Crohn's disease, suspected SBT. Studies showed superior diagnostic yields of SBCE to barium studies, computed tomography (CT) enterography, magnetic resonance (MR) enterography, and push enteroscopy, for detecting the SB lesions [3–6]. SBCE has become the first-line investigation for suspected SB pathology [7], and the SBCE major breakthrough consequently increased to double the diagnostic rate of SBTs [8, 9].

Nevertheless, SBCE has limitations in the diagnostic work-up of SBTs, among which the most important is the lack of capability of taking biopsies. It is a visual technique, which can offer a macroscopic description of the lesion, but cannot provide the definite diagnosis. Since only visual appearance is described, terminology has an important role for providing a portrait as suggestive as possible. In the same time, it has not the power to always accurately discriminate between the real tumors and pseudotumoral masses. Other inconveniences that could sometimes hamper the diagnostic yield are the low quality of visibility and the incomplete examination of the SB within the battery life time.

In order to achieve a final diagnosis, other investigations must follow SBCE. Both invasive and non-invasive examinations are required to provide a histological diagnosis and staging of the tumor, if malignant, described by SBCE. Surgery will follow if appropriate, providing complete pathological evaluation of the entire surgical specimen.

SBCE stands nowadays as a valuable tool for investigating the SB, and succeeding overcoming its main

limitations would assure it an even much more powerful position in the diagnostic work-up of the SBTs.

Aim

Our study aimed to assess if structured visual description of SBTs detected by SBCE correlates with the histological type.

Patients, Materials and Methods

Patients

We have conducted a retrospective observational study between January 1, 2011 and December 31, 2018, in the Institute of Gastroenterology and Hepatology, "Sf. Spiridon" Emergency Hospital of Iaşi, Romania, tertiary referral care center, including patients with SBTs, evaluated by SBCE and furthermore explored, for which a final histopathological diagnosis was made, either on biopsy samples, or on surgical specimens.

Materials and Methods

Demographics, medical history, clinical examination data and paraclinical examinations results were collected from patients' medical files.

SBCE exams were performed according to current guidelines, after the contraindications were excluded and after the patient signed the informed consent for the procedure. Second- and third-generation of endoscopic capsules for SB examination (PillCam SB2 and PillCam SB3, Given Imaging, Yoqneam, Israel) were used. The evaluation of the SB was made after patients had fastened for 12 hours. The interpretation of the video recordings was made using Rapid Reader Software v.8. The SBCE findings and reports were reviewed in order to assess the main macroscopic features of the SBT, the presumed location, the transit time and any other significant finding. Concerning the appearance of the SB masses, the following parameters were analyzed: the number of lesions, the estimated size, the shape, the type, the color of the covering mucosa and the distribution pattern, the presence of an ulcer on its surface, the presence of bleeding or of stigmata of bleeding. The macroscopic morphological criteria which were analyzed and their respective variants of interpretation are presented in Table 1.

Table 1 – ***Main visual parameters and features described at SBCE***

Parameter	Variants
No. of lesions	Single Multiple
Size	Small Medium Large
Shape	Well defined Poorly defined
Type	Vegetant Submucosal
Color of the mucosa	Normal Discolored
Ulcer	Absent Present
Bleeding	Active bleeding Stigmata of bleeding Bleeding potential No bleeding potential

SBCE: Small bowel capsule endoscopy.

Spiral or single-balloon enteroscopy, with or without biopsy, followed SBCE in certain cases, and macroscopic features of SBT were also observed.

Complete staging was performed by CT or MR scans, and the patients were managed accordingly. If surgery was performed, data regarding the final histological diagnosis were collected.

All biopsy tissues and surgical specimens were routinely processed through fixation in 10% neutral buffered formalin, embedding in paraffin and sectioning. Five μm thickness sections were stained with Hematoxylin–Eosin (HE), van Gieson, and Alcian Blue. Immunohistochemistry tests were performed using standard techniques with appropriate positive and negative controls. The following antibodies were used: chromogranin A (Novocastra, 5H7, 1:400), synaptophysin (Novocastra, 27G12, 1:150), Ki67 (Novocastra, SP6, 1:250), discovered on GIST 1 (DOG1) (Novocastra, K9, 1:100), cluster of differentiation (CD) 117 (c-kit) (Novocastra, EP10, 1:200), alpha-smooth muscle actin (α-SMA) (Novocastra, asm-1, 1:50), CD34 (Novocastra, Qbend/10, 1:100), human melanoma black 45 (HMB45) (Novocastra, HMB45, 1:100), S100 (Novocastra, polyclonal, 1:150), cytokeratin (CK) AE1/AE3 (Novocastra, AE1/AE3, 1:250), CK7 (Novocastra, RN7, 1:100), CK20 (Novocastra, Ks20.8, 1:50), CD5 (Novocastra, 4C7, 1:150), CD10 (Novocastra, 56C6, 1:100), CD20 (Novocastra, L26, 1:150), B-cell lymphoma 6 (Bcl6) (Novocastra, LN22, 1:60), multiple myeloma oncogene 1 (MUM1) (Novocastra, EAU32, 1:100).

All morphological data were analyzed, correlating the descriptive features provided by SBCE with the definitive histological diagnosis.

Results

SBT frequency

Three hundred and two SBCE examinations were performed in the mentioned period in our center. The main indications were OGIB either overt or occult, and unexplained IDA, followed by suspected or known Crohn's disease, celiac disease, unexplained abdominal pain.

In 16 patients, SBCE showed findings consistent with SBTs; consequently, the calculated frequency of SBTs at SBCE for all indications was 5.2%. For two patients, a definitive diagnosis was not available. For the remaining 14 patients who entered the study, a histological diagnosis was provided, either by enteroscopy with biopsy or by analysis of surgical specimen if surgery was performed.

General characteristics – demographics, indications of examination, and histological diagnosis

Among the 14 patients, mean age 51±2 years, the majority were men (64% male, 36% female). The SBCE was indicated for overt OGIB (six cases, 43%), unexplained IDA with occult OGIB (five cases, 36%), or isolated abdominal pain (three cases, 21%). All the 14 patients were previously investigated by upper and lower endoscopy, without significant lesions.

Following SBCE, six patients, with duodenal or jejunal lesions, underwent enteroscopy. In two cases, the biopsy was not conclusive, and in four cases, a histological

diagnosis was made – two cases of stromal tumor (one duodenal, one jejunal), one case of SB lymphoma, and one case of metastatic melanoma, respectively. The two patients with stromal tumors, as well as the two patients with macroscopic suspicion were referred to surgery, and a complete histological diagnosis was established: one jejunal lipoma and one jejunal gastrointestinal stromal tumor (GIST) (Figure 1, A–D).

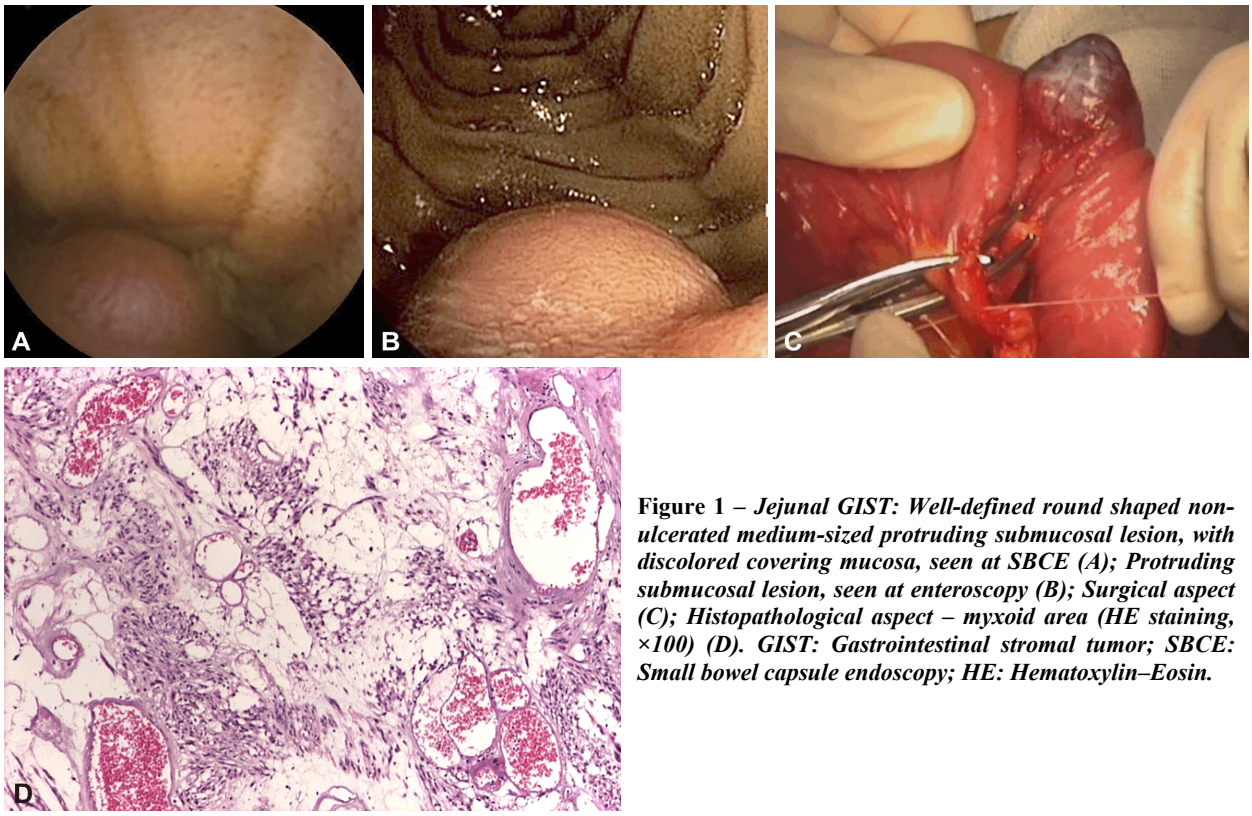


Figure 1 – ***Jejunal GIST: Well-defined round shaped non-ulcerated medium-sized protruding submucosal lesion, with discolored covering mucosa, seen at SBCE (A); Protruding submucosal lesion, seen at enteroscopy (B); Surgical aspect (C); Histopathological aspect – myxoid area (HE staining, ×100) (D). GIST: Gastrointestinal stromal tumor; SBCE: Small bowel capsule endoscopy; HE: Hematoxylin–Eosin.***

The patient with SB lymphoma had a complete staging and referred to the Department of Onco-Hematology. The case of metastatic melanoma had an oncological management. The remaining eight patients were directly referred to surgery immediately after SBCE; the final diagnosis confirmed the previous suspicion – GIST (Figure 2, A and B) in another three cases, adenocarcinoma in three cases (one jejunal, and two ileal – Figure 3, A–C), and neuroendocrine tumors (NETs) in two patients (Figure 4, A–D).

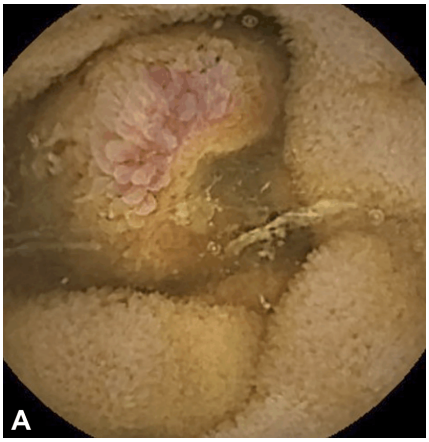
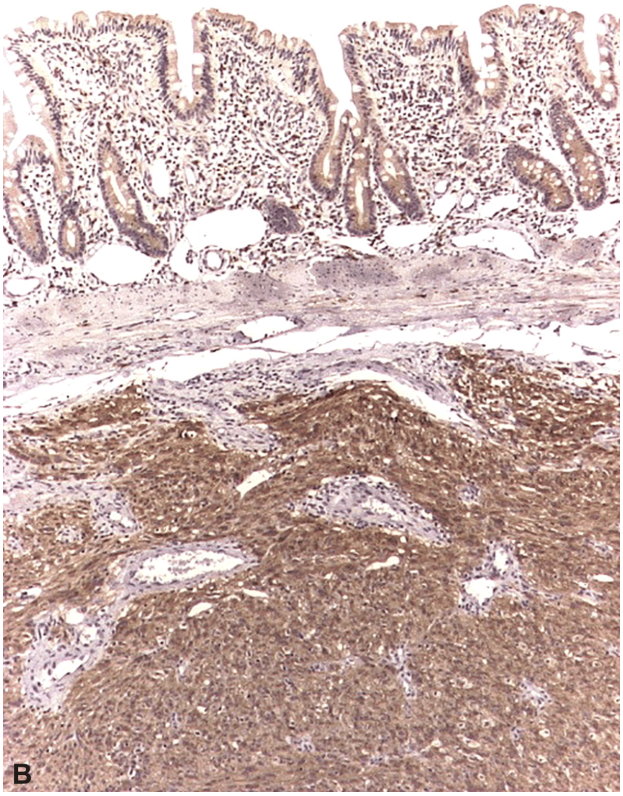


Figure 2 – ***Jejunal GIST: Well-defined shaped ulcerated protruding submucosal lesion, seen at SBCE (A); Histopathological aspect – CD117 (c-kit) diffusely positive in tumor cells (Anti-CD117 antibody immunomarking, ×100) (B). GIST: Gastrointestinal stromal tumor; SBCE: Small bowel capsule endoscopy; CD117: Cluster of differentiation 117.***



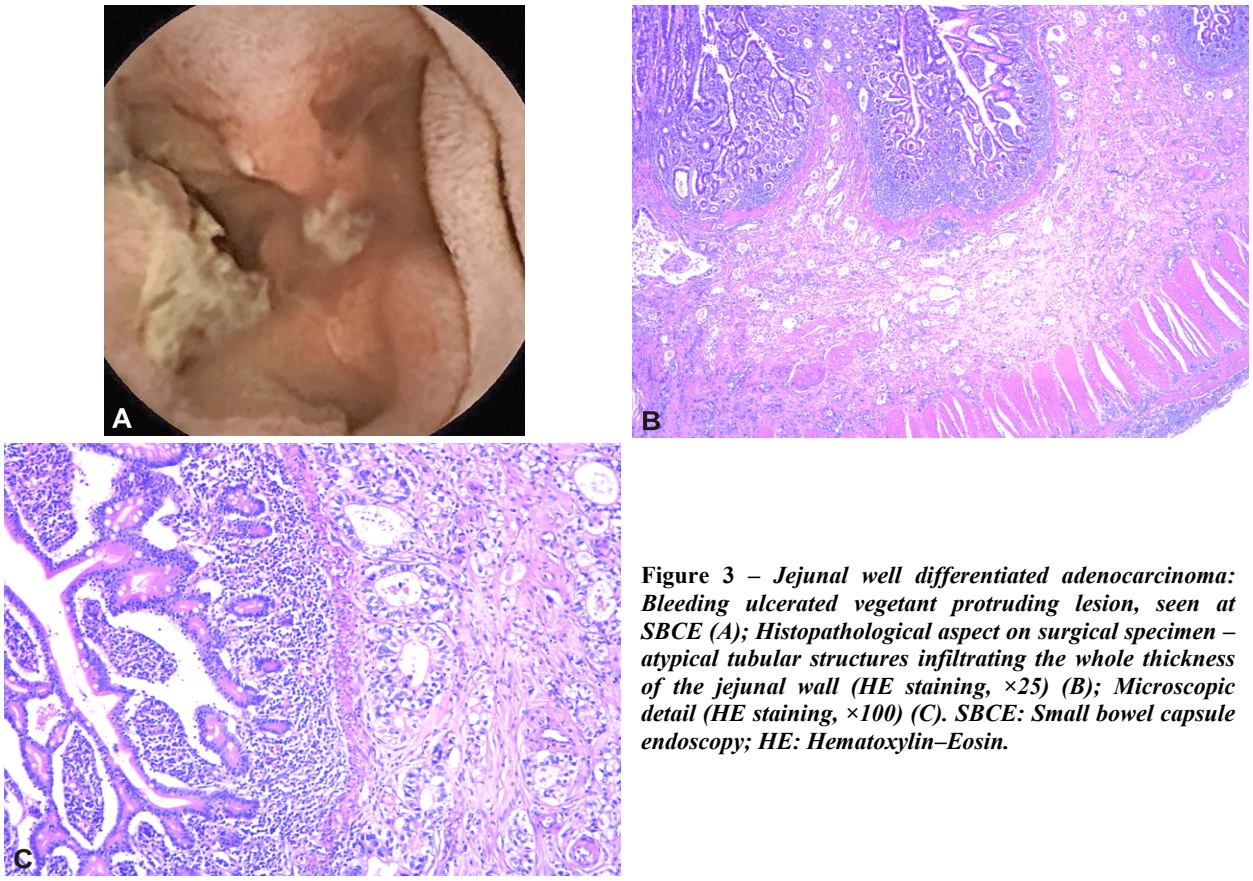


Figure 3 – ***Jejunal well differentiated adenocarcinoma: Bleeding ulcerated vegetant protruding lesion, seen at SBCE (A); Histopathological aspect on surgical specimen – atypical tubular structures infiltrating the whole thickness of the jejunal wall (HE staining, ×25) (B); Microscopic detail (HE staining, ×100) (C). SBCE: Small bowel capsule endoscopy; HE: Hematoxylin–Eosin.***

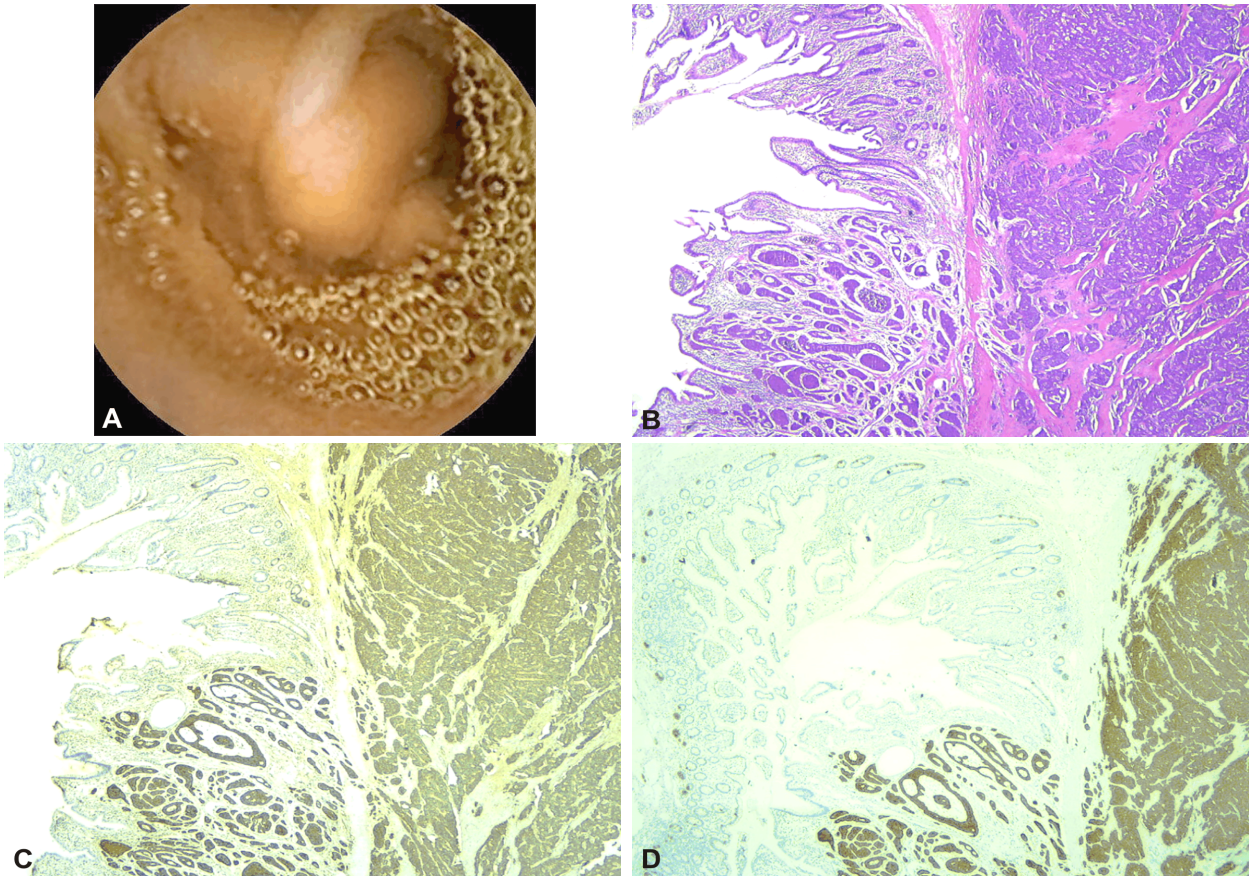


Figure 4 – ***Ileal NET G1: Poorly-defined shaped ileal protruding submucosal lesions, seen at SBCE (A); Histopathological aspect on the surgical specimen – isle and trabecular architecture, monomorphic tumor cells, low mitotic rate, infiltrative growing (HE staining, ×25) (B); Chromogranin A – intense diffuse positivity in tumor cells (Anti-chromogranin A antibody immunomarking, ×25) (C); Synaptophysin – intense diffuse positivity in tumor cells (Anti-synaptophysin antibody immunomarking, ×25) (D). NET: Neuroendocrine tumor; SBCE: Small bowel capsule endoscopy; HE: Hematoxylin–Eosin.***

The demographics, clinical characteristics of patients, SBCE indication, and histopathological diagnosis of patients with SBTs are presented in Table 2.

Table 2 – ***Characteristics, SBCE indication, and histological diagnosis of patients with SBTs***

Patient, No.	Gender, age [years]	SBCE indication	Histological diagnosis after enteroscopy with biopsy	Histological diagnosis after surgery
1. GM	M, 54	Overt OGIB	Jejunal GIST	Jejunal GIST
2. FR	M, 48	Unexplained IDA	Inconclusive biopsy	Jejunal GIST
3. FI	F, 52	Abdominal pain	Duodenal GIST	Duodenal GIST
4. LM	F, 62	Overt OGIB	NA	Jejunal GIST
5. DV	M, 25	Overt OGIB	NA	Jejunal GIST
6. BM	F, 71	Overt OGIB	NA	GIST
7. PT	M, 65	Overt OGIB	NA	Jejunal adenocarcinoma
8. MV	M, 70	Abdominal pain	NA	Ileal adenocarcinoma
9. BD	F, 61	IDA	NA	Ileal NET G2
10. CI	F, 59	Abdominal pain	NA	Ileal NET G1
11. BA	M, 32	IDA	Lymphoma	NA
12. OI	M, 54	Overt OGIB	Metastatic melanoma	NA
13. SC	M, 64	IDA	Inconclusive biopsy	Ulcerated lipoma
14. EC	M, 68	IDA	NA	Ileal adenocarcinoma

SBCE: Small bowel capsule endoscopy; SBTs: Small bowel tumors; M: Male; F: Female; OGIB: Obscure gastrointestinal bleeding; IDA: Iron deficiency anemia; GIST: Gastrointestinal stromal tumor; NA: Not available; NET: Neuroendocrine tumor.

Macroscopic morphological criteria

For all the lesions proved as SBTs, the cardinal designation term was "protruding lesion". All SBTs presented as intraluminal mass lesions, small, medium or large.

The majority of lesions (11 cases) were single, while in three cases, multiple protruding lesions with similar characteristics were described: two cases of multicentric NETs and one case of metastatic melanoma.

After tumor size estimation, lesions were classified into small (lymphoma, melanoma, NET), medium (GIST, adenocarcinoma, NET) and large (GIST, lipoma).

Regarding the type of the lesion, the submucosal type of the lesion was observed in all the cases confirmed latter as GIST, NET or lipoma. For the three cases of adenocarcinoma, a vegetant phenotype was described.

The shape was described as well defined (mainly round) or poorly defined. All cases of GISTs were well defined as shape, with visible limits from the adjacent mucosa. On the contrary, adenocarcinoma and NET presented poorly defined shape, either irregular or barely identified besides surrounding mucosa.

An important feature was the color. None of the SBTs presented normal colored mucosa, even in the cases of submucosal tumors. Discolored covering mucosa was described in all cases of submucosal tumors: GIST had a purplish shade surface, NETs appeared as whitish-colored masses, while the jejunal lipoma had smooth slightly discolored aspect. The patient with metastatic melanoma had atypical lesions, white ulcerated protruding masses, being proved after biopsy as amelanotic melanoma. The distribution pattern of the discolored mucosa was also analyzed, and we found that for almost all cases (13 out of 14) the modified aspect was localized, while only for one case (the SB lymphoma), there was a diffusely modified aspect of the mucosa.

The presence of ulcer on the surface of the SBT was noticed by SBCE in four cases of the stromal tumor, in all the three cases of adenocarcinoma, and in the melanoma case. The other two cases of stromal tumor, the two cases of NET, and the lymphoma had no obvious ulcer on their surface. For the patient with lipoma, during enteroscopy the ulcerated aspect was observed. In the same time, it must be mentioned that the macroscopic examination of the surgical specimen performed afterwards in the two cases of GIST revealed the presence of ulcer on the surface of the tumor, on the side not visualized by the SBCE.

The active bleeding or the stigmata of recent bleeding were important features, as well as the estimated potential of bleeding of the lesion. For the patients who had OGIB or unexplained IDA as indications for SBCE, the detection of bleeding or potentially bleeding lesions had a positive diagnostic role. The images provided by the SBCE revealed actively bleeding in two cases of GIST and in one case of SB adenocarcinoma, stigmata of recent bleeding in the case of melanoma and bleeding potential in the other two ulcerated cases of GIST and in the other two cases of adenocarcinoma. The lesions with no active, recent or potential of bleeding corresponded to the cases investigated for other reasons than overt OGIB, namely IDA, or abdominal pain.

General description and ***characteristic features*** of SBTs, by histological type, as seen at SBCE, are presented in Table 3; beside the so-called common characteristic features, ***additional peculiar features*** have been described, for some of the SBTs. For instance, large stromal tumors had unseen versants which were afterwards proved to be ulcerated. Adenocarcinomas presented as vegetant or ulcerated-vegetant masses, with obstructive effect, proven by the large amount of time the capsule passed around the tumor. The NET tumors were multicentric, presenting as multiple similar multilevel lesions. The case of SB lymphoma presented diffuse discolored modified mucosa, with abnormal villi all around the tumor. The metastatic melanoma appeared as multiple ulcerated lesions, with similar localization, size, and shape; it was a particular case of amelanotic melanoma, proved by enteroscopy with biopsy. The lipoma was described as a large sized submucosal tumor, with incompletely visible versants, with smooth slightly discolored covering mucosa.

Table 3 – ***General description and characteristic features of SBT, by histological type***

Type of SBT (No. of cases)	General term	Common characteristic features (No. of cases) at SBCE	Additional peculiar features
GIST (6)	Protruding lesion	Single Well-defined shape Medium/large Submucosal mass Discolored surface Ulcerated (4)/ non-ulcerated (2) Bleeding (2)/ non-bleeding (4)	Hidden side

Type of SBT (No. of cases)	General term	Common characteristic features (No. of cases) at SBCE	Additional peculiar features
Adenocarcinoma (3)	Protruding lesion	Single Medium Poorly-defined shape Ulcerated Bleeding (1)/ non-bleeding (2)	Vegetant aspect Obstructive effect
NET (2)	Protruding lesion	Multiple Small/medium Poorly-defined shape Submucosal mass Discolored surface Non-bleeding	Multilevel lesions
Lymphoma (1)	Protruding lesion	Multiple Small Discolored surface Non-ulcerated Non-bleeding	Diffuse discolored modified mucosa Abnormal villi
Metastatic melanoma (1)	Protruding lesion	Multiple Small Discolored surface Ulcerated Stigmata of bleeding	Multiple similar lesions
Lipoma (1)	Protruding lesion	Single Large Well-defined shape Submucosal mass Non-ulcerated	Smooth light surface Hidden side

SBT: Small bowel tumor; SBCE: Small bowel capsule endoscopy; GIST: Gastrointestinal stromal tumor; NET: Neuroendocrine tumor.

Discussions

SBCE is nowadays recommended as first-line investigation for suspected SB pathology [7], with incontestable proved value in the diagnostic work-up of OGIB, unexplained IDA, celiac disease, suspicion of SBT, unexplained abdominal pain, after negative or inconclusive upper and lower endoscopy. The major indications for SBCE remain OGIB and unexplained IDA, which are in the same time the main circumstances of discovery of SBTs [10].

The frequency of SBTs at SBCE varies widely in the literature; the prevalence is between 1.6% as reported by Pasha *et al.* in a meta-analysis including 1000 examinations [11] and much higher, above 10% in other studies with lower number of patients, as reported by Almeida *et al.* [12] or Marmo *et al.* [13]. The differences in prevalence probably rely mainly on the size of the series, as highlighted by Rondonotti *et al.* in a multicenter European study, who described an inverse correlation between the number of the procedure performed and the frequency of detection of SBTs [9]. In the same time, other circumstances may explain the differences in prevalence, such as inclusion criteria or lack of definitive diagnosis. In our study, the frequency of SBTs at SBCE for all indications was 5.2%, comparable with other studies of similar size. The frequency was calculated taking into account the lesions subsequently proved as SBT, while only the patients with definitive histopathological diagnosis entered the study. Thus, the analysis did not include those cases for which a final diagnosis was not microscopically confirmed.

In our study, indications for SBCE were OGIB (43%) and unexplained IDA (36%), followed by unexplained abdominal pain (21%). As already stated by now, OGIB and IDA remain the main revealing circumstances of SBTs, due to their bleeding potential. Regarding abdominal pain as indication for SBCE, the overall diagnostic yield of SBCE is variable, but rather low in different series, facilitating diagnosis in 9–24% of cases [14–16]. Even in the studies that reported the highest diagnostic yields, the spectrum of significant lesions included mostly inflammatory lesions and much scarcely SBTs [16, 17]. However, in our study, chronic unexplained abdominal pain was the cardinal symptom which justified further investigations and permitted a diagnostic of SBTs in three cases, among which one case of duodenal GIST, one case of adenocarcinoma and one case of NET.

Following SBCE, individualized work-up decisions were made. Some cases were further explored by enteroscopy with biopsy. Enteroscopy provided in some cases a more accurate description of the lesion, and in the same time, offered localization information. For SBCE, lesion localization is difficult, because of the lack of landmarks; conventionally, lesions are described as situated in one of the three tertiles of the SB, and also as projected in one of the four abdominal quadrants. However, SBCE was accurate, a correspondence of the sites of the lesions being noticed, as described by SBCE, enteroscopy and surgery. The biopsies performed during enteroscopy provided or not a histological diagnosis; the cases with positive results were: ulcerated GIST, lymphoma and metastatic melanoma, inconclusive biopsies being from protruding lesions developed in the submucosa. In some cases, patients were referred to surgery immediately after SBCE, being given the macroscopic features, localization and bleeding complications (GIST with overt bleeding, ileal NET, suspicion of adenocarcinoma with bleeding or obstructive effect). Therefore, SBCE gains value as standalone technique mandating therapeutic decision.

The appearance of SBT at SBCE was the main parameter when describing the lesions. The macroscopic description of SBT in structured terminology and enriched with individual observations permitted framing the findings in certain supposed types of SBTs. All SBTs are defined as protruding lesions, and afterwards a sum of parameters is added, in order to enrich the description. Features as size, color, type, shape, presence of ulceration on the surface of the mucosa, bleeding stigmata or potential, contributed outlining a prototype. Furthermore, some peculiar characteristics were noticed, and even if they are not yet be not extrapolated, they may be highly indicative: large-sized stromal tumors have "hidden" areas at SBCE where an ulcer might exist, adenocarcinomas present with prolonged transit time of the SBCE, NETs may present as multilevel lesions. The size of the lesion seemed correlating with the circumstances of diagnosis: little-sized lesions, discovered in clinical circumstances of abdominal pain or unexplained IDA were subsequently proved as aggressive type (NET, lymphoma, SB metastases), while medium- or large-sized lesions were rather discovered in more dramatic circumstances, revealed by the hemorrhagic complications (GIST, adenocarcinomas). The discoloration of the covering mucosa, as well as the appearance of the adjacent mucosa, was also indicative parameters, as presented.

Undoubtedly, empowering the SBCE predicting the most accurately possible the definitive diagnosis equally preoccupied the gastroenterologists and the researchers [18]. There have been registered much progress in SBCE

technology, in terms of image resolution, wider angle view, software innovations, such as flexible spectral imaging color enhancement [19] or the "optical biopsy", including the wireless spectroscopic compact photonic for detecting microscopic malignancy [20]. Nevertheless, no matter how much SBCE will progress as technique, it will remain an artificial smart one. Only the human intelligence and sense could empower SBCE as highest valuable and not only purely visual technique.

Conclusions

SBCE has become a valuable tool in the investigation of SB pathology. Its real advantages, consisting in safety, non-invasiveness, and patients' comfort may be counter-balanced by its limitations, mainly lack of capability for biopsy and lack of therapeutic abilities. However, the introduction of SBCE doubled the diagnostic rate of SBTs, and even if, so far, SBCE has been considered a visual technique, with no discriminating power between different histological types, we may affirm that thorough examination and rigorous analysis of macroscopic features may successfully predict the final diagnosis. SBCE proved to be both a trust comrade in the diagnostic pathways of SBTs, and a valuable standalone technique guiding the definitive therapeutic decision.

Conflict of interests

The authors declare that they have no conflict of interests.

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