Case Report

Primary small bowel melanomas: fact or myth?

Andreas V. Hadjinicolaou[1], Christopher Hadjittofi[2], Panagiotis G. Athanasopoulos[3], Rahul Shah[4], Aftab A. Ala[5]

[1]Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Headington, UK; [2]Department of Cardiothoracic Surgery, King's College Hospital, Denmark Hill, London, UK; [3]Department of HPB & Liver Transplant Surgery, Royal Free Hospital, London, UK; [4]Department of Gastroenterology, Frimley Park NHS Foundation Trust, Portsmouth Road, Frimley, Surrey, UK; [5]Department of Gastroenterology, Royal Surrey Hospital, Guildford, UK

Correspondence to: Dr. Andreas V. Hadjinicolaou. Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Headington, OX3 9DU, UK. Email: andreas.hadjinicolaou@merton.ox.ac.uk.

Abstract: Small bowel melanoma (SBM) is a rare entity, which often evades diagnosis and therefore presents late. Its origin, whether arising primarily or metastatically from an unidentified or regressed primary cutaneous melanoma, remains debatable. In this report, we present a rare case of primary SBM and review the current literature. A 60-year-old man presented with melena and microcytic anemia. A series of investigations including abdominal ultrasonography (US), esophago-gastro-duodenoscopy (EGD) and colonoscopy were normal. Abdominal computed tomography revealed no specific pathology. Subsequent capsule endoscopy identified a jejunal mass, which was confirmed on laparotomy, was resected, and histologically diagnosed as melanoma. Extensive postoperative clinical examination revealed no cutaneous lesions. This report discusses gastrointestinal (GI) malignant melanoma, and examines the evidence both for and against the existence of true primary vs. metastatic disease. Furthermore, this case highlights the capabilities of capsule endoscopy in identifying an extremely rare GI tumor, which evaded other diagnostic modalities. Finally, the origins and pathophysiology of this rare cancer are evaluated, with the aim of promoting early diagnosis and treatment, and therefore improving current poor outcomes.

Keywords: Bowel; capsule; endoscopy; intestine; melanoma

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Introduction

Primary small bowel malignant melanoma is rare, with a paucity of published reports. Whether these lesions arise as true small bowel primaries or represent metastases from unidentified cutaneous melanomas remains debatable. Similar to most small bowel tumors, small bowel melanoma (SBM) is typically difficult to diagnose, due to non-specific symptoms and difficult endoscopic access. The following report illustrates a case of SBM presenting with non-specific constitutional symptoms and upper gastrointestinal (GI) bleeding.

Case presentation

A 60-year-old Caucasian man was referred by his General Practitioner to his local Gastroenterology service with fatigue and iron-deficiency microcytic anemia (Hb =8.5 g/dL; MCV =76 fL; Serum ferritin =6 ng/mL). Additionally, the patient reported an isolated episode of melena on a background of chronic diarrhea without unintentional weight loss or anorexia.

His past medical history was notable for irritable bowel syndrome (IBS), first-degree hemorrhoids and a non-ST elevation myocardial infarction (NSTEMI), which was treated two years previously with coronary angioplasty and stenting of the right and left anterior descending coronary arteries. He received regular aspirin, clopidogrel, simvastatin, perindopril and bisoprolol. His family and social histories were unremarkable.

On hospital admission, general physical examination

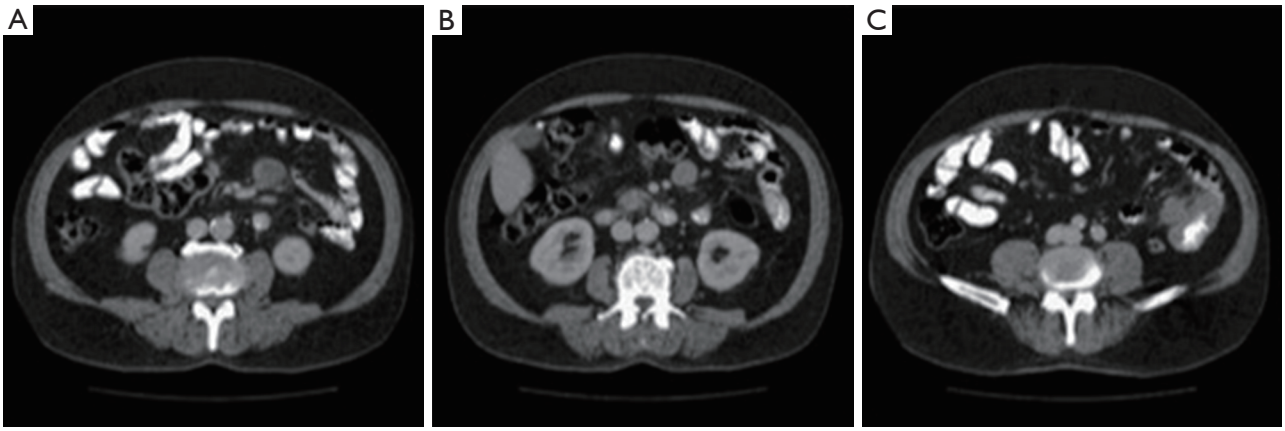

Figure 1 Abdominal CT demonstrating annular small bowel thickening and mesenteric lymphadenopathy.

revealed pallor without jaundice or lymphadenopathy. Abdominal, rectal examination and proctoscopy were unremarkable.

Laboratory investigations yielded Hb levels of 7.0 g/dL, a MCV of 72 fL and serum ferritin levels of 6ng/ml, thus confirming iron-deficiency microcytic anemia. Tumor marker assays (CEA, CA19-9, and PSA) fell within normal limits, and celiac serology was negative.

Abdominal ultrasonography (US), esophago-gastro-duodenoscopy (EGD) and colonoscopy revealed no pathology. During his inpatient stay, the patient developed melena and sepsis with acute kidney injury (AKI). Additional investigations revealed serum urea and creatinine levels of 43 mmol/dL and 730 μmol/dL respectively, alongside Hb and white blood cell (WBC) levels of 6.5 g/dL and 23,000/mm^3 respectively. Stool cultures isolated salmonella typhi. For this acute deterioration, the patient received cephalosporin treatment, intravenous fluids and two units of packed red cells, correcting the Hb to 10.9 g/dL. On stabilization and full recovery, he was discharged home for outpatient follow-up.

Within a few days however, he was readmitted with fever, melena, Hb levels of 8.3 g/dL and raised inflammatory markers (WBC =21,000/mm^3; CRP =211 mg/L). A new murmur was detected, with negative transthoracic and transesophageal echocardiograms. Blood and stool cultures, as well as hemolysis, autoantibody (ANA & ANCA) and HIV screening was negative.

Computed tomography (CT) demonstrated several sub-centimeter mesenteric lymph nodes and thickening of the small intestine and descending colon, but did not reveal any specific pathology (*Figure 1*).

Consequently, video capsule endoscopy (VCE) was performed, which identified an unequivocal sessile jejunal tumor with contact bleeding (*Figures 2,3*).

Exploratory laparotomy confirmed a mid-jejunal tumor without intra-abdominal metastases. Limited small bowel resection with end-to-end anastomosis and mesenteric lymph node sampling was performed. Postoperatively, a deep cervical lymph node was identified and excised. Immunohistochemistry of tissue biopsies revealed positive staining for melanoma markers S100, Melan-A, HMB45 and MIB1 (80% of cells) whereas chromogranin A, cytokeratin and CEA staining was negative (*Figure 4*). Further immunohistochemistry, with an identical staining pattern, identified infiltration by metastatic cancer cells within two out of seven mesenteric lymph nodes. Histology of both mesenteric and cervical lymph nodes confirmed the presence of invasive malignant melanoma (*Figure 5*).

Given the above findings, a thorough examination of skin, scalp, oral mucosa, eyes and genital areas was carried out but failed to identify any suspicious lesions or dysplastic nevi. Retrospective scrutiny of medical records revealed that 26 years earlier, the patient underwent excision of a benign mole from the left arm. At that time, histopathological analysis revealed a cellular non-dysplastic nevus with partial regression and potential tendency towards malignancy but during six years of regular follow-up, there were no recurrences and the patient was therefore discharged from the dermatology clinic.

From one month postoperatively onwards, the patient was readmitted on multiple occasions, initially with sepsis, and subsequently with ileus. At four months postoperatively

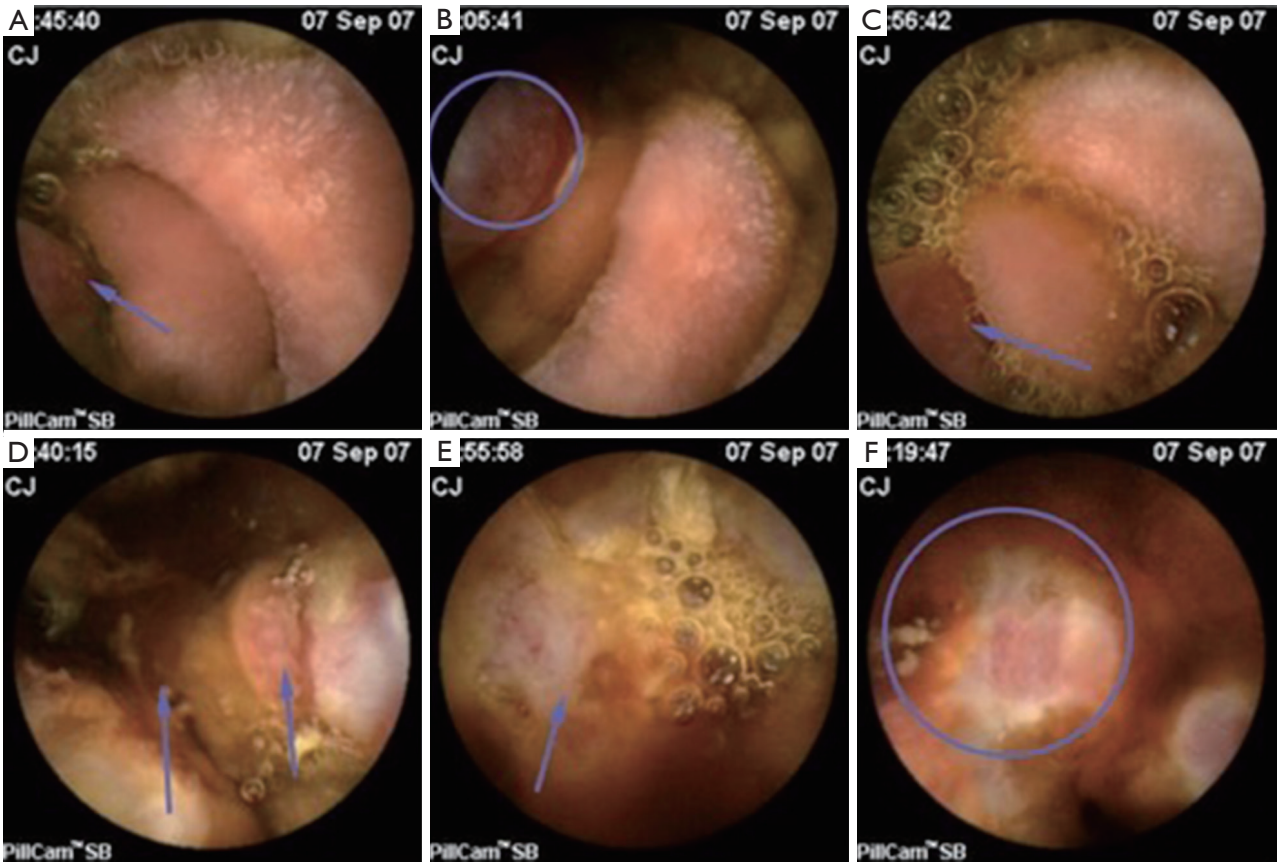

Figure 2 Capsule endoscopy views of small bowel tumor (annotated).

Figure 3 Capsule endoscopy video showing the sessile small bowel tumour (1).
Available online: http://www.asvide.com/articles/947

he developed spastic paraparesis and severe pneumonia which prompted CT of the head, chest, abdomen and pelvis along with magnetic resonance imaging (MRI) of the brain. Imaging confirmed multiple brain, lung and bone metastases. Prior to any palliative treatment, the patient died of progressive disease and sepsis.

Discussion

Malignant melanomas are relatively common cancers making up around 2% of all tumors (2-4). The vast majority of melanomas are cutaneous but non-cutaneous tumors such as ocular, leptomeningeal, oral, nasopharyngeal, esophageal, bronchial, vaginal, anorectal and nail-bed melanomas (in descending order of frequency) occur, albeit very rarely (4,5). Only 3–4% of all melanomas originate in mucosal membranes as primaries (6).

GI tract malignant melanoma is rare and may either represent metastasis from a primary cutaneous site or a true primary tumor arising from the GI mucosa. Certain experts believe that primary intestinal melanomas derive from melanoblastic neural crest cells which migrate via

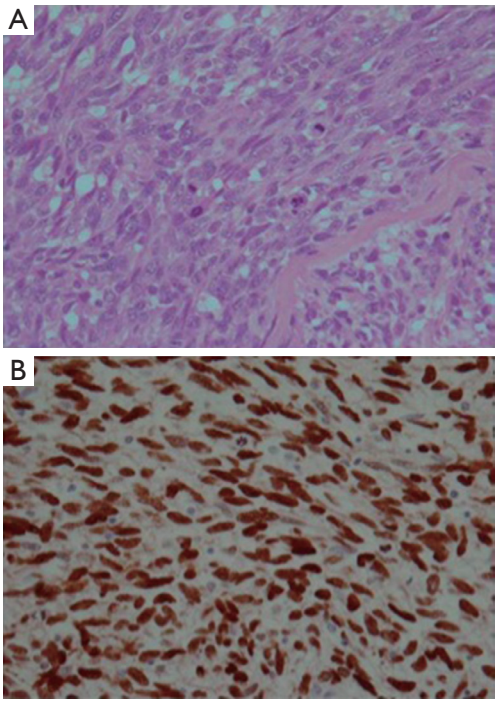

Figure 4 Immunohistochemistry of tumor biopsy revealing melanoma cells. (A) H&E staining (×100); (B) positive S100 staining (×100).

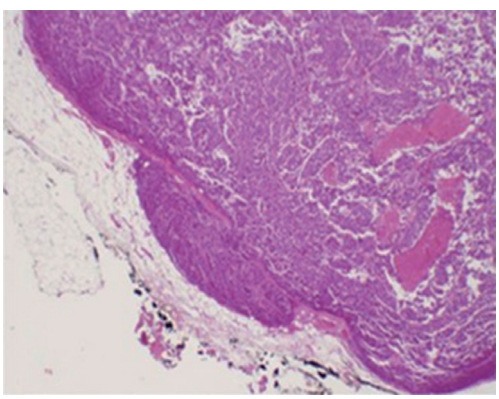

Figure 5 Lymph node architecture replaced by invading malignant melanoma cells with capsular breach (H&E staining; ×10).

the omphalomesenteric canal to the distal ileum whereas others postulate that these tumors originate from enteric neuroendocrine non-cutaneous tissue in the form of amine precursor uptake decarboxylase (APUD) cells that have undergone neoplastic transformation (7,8). The former hypothesis could certainly explain the presence of melanomas in the ileum whereas the latter would also account for the remaining non-ileal intestinal malignant melanomas (9). Other authors suggest that the cancer cells arise from neuroblastic Schwann cells of the intestinal autonomic nervous system (10). However, the most intriguing theory is that primary small intestinal melanomas do not exist as a distinct clinical entity but are instead secondary deposits from a primary cutaneous melanoma which has either regressed or remained indolent and undiagnosed (6,11,12).

Malignant melanoma is the commonest malignancy to metastasize to the GI tract (2,3). Although GI tract metastases are observed in up to 50–60% of malignant melanomas, clinical evidence of GI involvement with ante-mortem diagnosis comes to light in only 1–5% of cases (13-17). Interestingly, an estimated 10–26% of primary GI melanomas in fact represent metastases from occult cutaneous sites, and even in cases with a known primary site of malignant melanoma, GI metastases are discovered after an average of 54 months (and perhaps as long as 15 years later), if at all (16,18).

Malignant melanoma is also the commonest cancer to specifically metastasize to small bowel, comprising 50–70% of small bowel secondary cancers (19). Furthermore, although melanoma can metastasize to any GI tract site from mouth to anus, the jejunum and ileum, are most commonly involved (14). This might be partly attributed to the fact that melanoma cells show significant surface expression of the chemokine receptor CCR9, which might promote transmigration and homing of tumor cells to the small intestine, where the CCR9 ligand, CCL25, is strongly expressed (20).

In contrast to secondary metastases, primary SBM is exceptional. An extensive literature review identified only 26 reports describing potential cases of SBM based on the absence of a cutaneous or other primary site (*Table 1*). Biologically, the rarity of such tumors is not unexpected and can be explained by the lack of melanocytes in the small intestine; this is in contrast to the anorectum and even the esophagus where these cells are often naturally present (6,21,22).

It is currently challenging to differentiate between primary and secondary SBM (6,7). The clinical importance of this distinction lies within the differential in prognosis. Prognosis is worse for primary intestinal melanomas which tend to grow faster and more aggressively than metastatic tumors perhaps due to the rich lymphovascular supply available in the intestinal mucosa (46). In terms of prognosis, both primary and secondary GI malignant melanomas are worse than the conventional cutaneous

equivalents, with a 5-year survival of only 10% and median survival of 4–6 months (4,12,23).

Criteria devised to support the diagnosis of true primary melanomas of the small intestine consist of:

(I) The existence of a single solitary tumor in the intestinal mucosa;
(II) The presence of other intramucosal melanocytic lesions in the surrounding intestinal epithelium;
(III) The absence of cutaneous or mucosal malignant melanoma or other atypical melanocytic skin lesions such as dysplastic nevi (14).

In contrast to primary GI melanoma, which is characteristically solitary, GI metastases from cutaneous melanoma are often multiple and co-existent with metastases to additional systems. The presence of melanophages and lymphocytic infiltration along with neovascularisation and healing fibrosis in the dermis provides additional histological evidence of a previous primary cutaneous malignant melanoma which metastasized to the small intestine before spontaneously regressing (6). Secondary small intestinal melanoma can be infiltrating, polypoid, cavitating or exoenteric and any type can be either pigmented or non-pigmented (47).

Clinical diagnosis of SBM is difficult, due to the non-specific nature of its symptoms and signs. Non-specific GI features include rectal bleeding (melena, hematochezia, and occult blood), which is the commonest symptom, along with chronic persistent abdominal pain, vomiting, diarrhea, weight loss and asymptomatic anemia. Acute presentations with intussusception and perforation are rare; nevertheless, an awareness of these possibilities is important (20,48-53). Endoscopy and colonoscopy almost universally fail to identify small intestine pathology as reported in all the cases reviewed in the literature (*Table 1*). Alternative diagnostic modalities must be considered, such as US, CT, barium/technetium studies, positron emission tomography (PET) and capsule endoscopy, the latter of which permitted a diagnosis in this case.

VCE is a reliable, safe, minimally invasive diagnostic tool for small bowel disease with excellent diagnostic yield and is considered the gold-standard small intestine imaging modality (54,55). Our literature review suggests that men are more frequently affected than women, with a male-to-female ratio of 1.8 (20 *vs*. 11 cases), and that the ileum (n=20; 50%) and jejunum (n=10; 42%) are the most commonly involved GI sites (*Table 1*). There was only one case of solitary duodenal involvement, and one case that was considered as a primary SBM despite GI multifocality (*Table 1*). Although VCE can provide extremely useful information, in the absence of approachable extra-intestinal lesions, a tissue diagnosis of jejunal or ileal melanoma can only be achieved surgically.

Therapeutics in SBM are a field in need of development. Chemotherapy, immunotherapy and target therapy all have a role in medical treatment of SBM but they are almost invariably used palliatively. In cases of bowel obstruction, perforation or significant bleeding, emergency laparotomy for resection is mandatory. Nevertheless, the influence of surgery on morbidity and mortality is unclear. According to one study, neither elective nor emergency operations for secondary GI melanoma had any effect on postoperative morbidity or mortality (56). On the other hand, two separate studies reported that surgical intervention significantly reduced mortality and also suggested that complete resection (with histological evidence) was superior to incomplete removal in terms of mean survival (31.6–48.9 *vs.* 5.4–9.6 months) (57,58). In this context, clinical guidelines recommend that resection of the affected intestine should be wide with suitable margins of normal bowel proximal and distal to the lesion, and should include resection of the associated affected mesentery and lymph nodes (21). The relevant data from *Table 1* in our study show that 1-year survival post resection was only 50% (8/16 cases), with half of the operated patients dying within a year postoperatively, as a result of tumor recurrence and/or progression.

In conclusion, primary SBM is a rare entity, which can exist asymptomatically for long periods of time and as such, is often diagnosed at an advanced stage, where treatment options are limited. The pathophysiology remains debatable. In our case, the possibility of a regressed or unidentified extra-intestinal site cannot be absolutely excluded. Whether or not primary SBM is a true entity remains to be clarified. Nevertheless, clinicians including Dermatologists, Gastroenterologists, General Practitioners, General Surgeons, Oncologists and Radiologists should maintain a degree of vigilance when encountering vague presentations suggestive of upper GI malignancy. As with any malignancy, a timely and accurate diagnosis affords patients with more therapeutic options.

Learning points

- Cutaneous melanoma can metastasize to any site in the GI tract, the commonest being the jejunum and ileum;
- GI melanomas are rare, and their true identity, whether primary or secondary, remains to be clarified;

Table 1 Published cases of primary small bowel melanoma

Case	Sex	Age	Symptoms	Location	Diagnostic method	Mesenteric lymphadenitis	Treatment	Outcome	Reference
1	F	46	n/a	Distal ileum	n/a	n/a	Surgery	No follow-up	(7)
2	F	70	Abdominal pain; constipation; vomiting; GI bleeding	Distal ileum	Barium enema	No	Surgery	No follow-up	(8)
3	M	72	Abdominal pain	Proximal jejunum	CT	No	Surgery	Death at 1 year	(9)
4	F	45	Abdominal pain; diarrhea; GI bleeding	n/a	Abdominal radiograph	No	Surgery	Disease free at 2 years	(9)
5	F	56	Strangulated umbilical hernia	Ileum	Surgical exploration	Yes	Surgery	Death at 6 months	(9)
6	M	72	Abdominal pain; weight loss; anorexia; GI bleeding	Ileum	CT	Yes	Surgery	Disease-free at 1 year	(21)
7	M	73	n/a	n/a	n/a	n/a	Surgery	No follow-up	(22)
8	M	25	Abdominal pain; fever; weight loss; diarrhea	Proximal ileum	US & CT	No	Surgery	Disease-free at 1 year	(23)
9	M	46	n/a	n/a	n/a	Yes	Surgery	No follow-up	(24)
10	M	43	n/a	Ileum	n/a	Yes	Surgery	No follow-up	(24)
11	M	37	n/a	Ileum	n/a	No	Surgery	Disease-free at 2 years	(25)
12	M	57	Abdominal pain; vomiting; constipation	n/a	US & CT	Yes	Surgery	Hepatic & para-aortic node recurrence at 1 year	(26)
13	M	81	Melena; fatigue	Ileum	VCE & CT	Yes	Surgery	Disease-free at 5 months	(27)
14	M	73	Diarrhea; weight loss	n/a	CT & bowel transit studies	n/a	Surgery	No follow-up	(28)
15	n/a	n/a	Abdominal pain; weight loss	Ileum	n/a	n/a	n/a	n/a	(29)
16	F	75	n/a	n/a	n/a	n/a	Surgery	No follow-up	(30)
17	F	42	Abdominal pain; diarrhea	Duodenum; jejunum; ileum	Abdominal radiograph; endoscopy	Yes	None	Death from advanced disease	(31)
18	F	42	n/a	Jejunum	n/a	Yes	Surgery	No follow-up	(32)
19	F	26	n/a	Ileum	n/a	Yes	Surgery	No follow-up	(33)
20	M	38	Abdominal mass; constipation; weight loss	Ileum	Surgical exploration	Yes	Surgery	Disease-free at 21 months	(34)
21	M	78	GI bleeding	n/a	n/a	n/a	Surgery	Disease-free at 3 months	(35)
22	M	30	Abdominal pain; GI bleeding	Duodenum	Follow-through studies; endoscopy	n/a	Surgery	Recurrence at 4 months; death at 8 months	(36)

Table 1 *(continued)*

Table 1 *(continued)*

Case	Sex	Age	Symptoms	Location	Diagnostic method	Mesenteric lymphadenitis	Treatment	Outcome	Reference
23	F	36	Abdominal pain; fever; indigestion	Terminal ileum	US & CT	No	Surgery	Recurrence at 1 year	(37)
24	M	58	Abdominal pain; vomiting	n/a	CT	No	Surgery	Death from recurrent/ progressive disease at 7 months	(38)
25	M	76	Abdominal pain; GI bleeding; weight loss; anorexia	Jejunum	Follow-through study; CT	No	Surgery	No follow-up	(39)
26	M	71	GI bleeding	Jejunum	Double-contrast barium enema	Yes	Surgery	Death from recurrent/ progressive disease at 7 months	(40)
27	M	71	Abdominal pain; weight loss	Jejunum	Abdominal CT scan	n/a	Surgery	No follow-up	(41)
28	F	48	Abdominal pain; hematemesis; weight loss; GI bleeding	Jejunum	CT	Yes	Surgery	Disease-free at 1 year	(42)
29	M	60	Abdominal pain & mass; vomiting	Jejunum	US & surgical exploration	Yes	Surgery	No follow-up	(43)
30	F	41	Abdominal pain; weight loss; diarrhea	Jejunum	Surgical exploration	No	Surgery	Disease-free at 53 months	(44)
31	M	77	Abdominal pain; melena	Jejunum	CT	No	Surgery	No follow-up	(45)
32	M	60	Melena	Jejunum	VCE	Yes	Surgery	Death from progressive disease & sepsis at 1 month	Current study

n/a, not available/not reported; GI, gastrointestinal; CT, computed tomography; US, ultrasonography; VCE, video capsule endoscopy.

- GI melanoma can present insidiously and non-specifically, evading common diagnostic modalities;
- A degree of suspicion in unexplained anemia and melena can expedite the diagnosis of GI melanoma;
- Capsule endoscopy is a safe, minimally invasive and high-yielding investigation for small bowel pathology.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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