



## Malignant gastrointestinal melanomas of unknown origin: Should it be considered primary?

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### TO THE EDITOR

We read with interest the article entitled: 'Jejuno-jejunal invagination due to intestinal melanoma' by Resta G, *et al*<sup>[1]</sup>. They reported a rare clinical case of a young woman with a bleeding jejunal melanoma, whose early clinical presentation was an intestinal invagination. The article is also referred to the rarity of gastrointestinal melanomas as well as their possible primary nature.

We would like to make a few comments about this and report our experience with a case series of gastrointestinal melanomas that have been proved of primary origin.

Malignant melanoma involving the gastrointestinal (GI) tract is mainly related to metastatic disease, the most common metastatic site of cutaneous melanoma<sup>[1-3]</sup>. Usually being asymptomatic, such metastases are diagnosed pre-mortem in 1.5%-4.49% of the patients<sup>[2-4]</sup>. GI metastases may not be clinically detected until after removal and potential cure of primary melanoma, mostly affecting the

small bowel, the stomach and the colon<sup>[2-8]</sup>. However, there is a portion of GI melanomas without any documented evidence of a primary lesion in the skin or elsewhere, even after thorough examination<sup>[9]</sup>. Incidence of GI melanotic metastases from unknown primary origin ranges from 4% to 9% in case series. A potential metastatic nature remains difficult to be formally excluded, because they can precede the identification of a primary site and regress spontaneously or it is too small to be identified by conventional clinical and laboratory investigations<sup>[6]</sup>. These cases might represent melanomas primarily derived from the alimentary tract<sup>[2,3,5,6,10]</sup>. However, they could not be documented as primary lesions because of the retrospectivity of such studies<sup>[5,10]</sup>.

Thus, identifying GI melanomas results in problems relating to histogenesis and determination of their primary or secondary nature. Primary mucosal melanomas are rare, mainly arising in head and neck, female genital tract, esophagus, anorectum and urinary tract<sup>[2,10-12]</sup>. GI melanomas' primary or secondary nature is often difficult to establish, giving rise to much controversies<sup>[10-12]</sup>. Esophagus and anorectum are considered to be the most frequent sites, while their existence in the remaining part of the GI tract is still debated<sup>[3,9]</sup>. Scattered cases, claimed to be of primitive origin, are occasionally reported in the literature<sup>[2,3,6,10,14-17]</sup>.

The proposed primary sources, from which melanomas are derived, are melanoblastic cells of the neural crest, which migrate to the ileum through the omphalomesenteric canal. However, this theory can only explain ileal melanomas. This discrepancy is addressed by the theory that intestinal melanomas could originate from APUD cells, which undergo neoplastic transformation in noncutaneous sites<sup>[14]</sup>.

Over the past two decades, we have documented five cases of solitary melanomas at the anorectum as well as the small intestine, claiming to be primary (Table 1). Our report includes three cases of melanoma located in the small intestine and two cases at the anorectum. These melanomas were considered as primitive of the gastrointestinal tract, after thorough investigation for another primary site elsewhere and a constant follow-up in patients after surgery. All underwent a thorough investigation whether they fulfill the criteria for primary GI melanomas. Clinical presentation included abdominal pain or cramping, palpable mass, diarrhea, GI bleeding, obstruction (Figure 1), intussusception or weight loss.

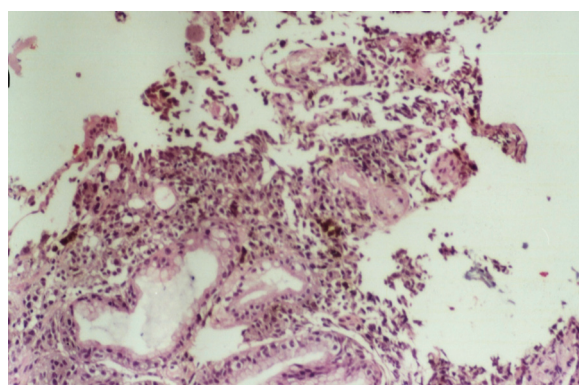
To establish the existence of primary GI melanomas,

Table 1 Patients' data

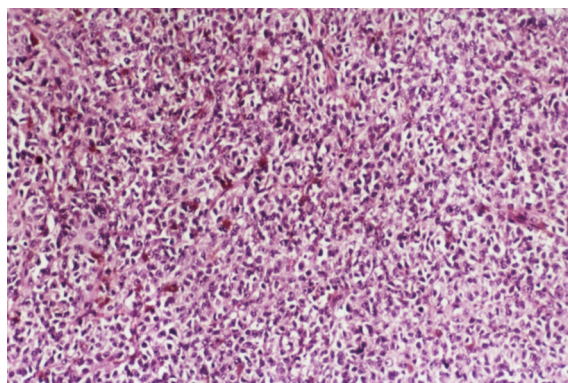
Patient/Sex	A/m	B/f	C/f	D/m	E/f
Age (yr)	72	45	56	48	68
Location of melanoma	Small bowel	Small bowel	Small bowel	Anorectum	Anorectal juncture
Size of melanoma	12 cm × 6 cm × 6 cm	Multiple tan-black lesions, ranging from 0.5 to 2 cm	4 cm × 5 cm	7.5 cm × 6 cm × 2.7 cm	6 cm × 5 cm × 3 cm
Complains on admission	Intermittent right abdominal pain	Abdominal cramping, diarrhea, black stools since a month	Strangulated umbilical hernia	3-mo history of 2-3 kg weight loss, stools mixed with blood	Pruritus, tenesmus, bleeding during defecation
Physical examination	Palpable mass in the right lower quadrant	Acute abdomen	Strangulation	Digital rectal examination: obstructive mass, just above the dentate line	Digital rectal examination: obstructive mass, blood
Preoperative work-up	CT scan: abdominal mass attached to the right colon	Plain X-rays: small bowel obstruction	No specific finding	Biopsy: ulcerated melanoma	Endoscopy: dark brown, partially ulcerated lesion
Operation	Exploratory laparotomy-segmental enterectomy	Laparotomy-segmental enterectomy	Hernioplasty-segmental enterectomy	Abdominoperineal resection	Sigmoidectomy-ileoanal anastomosis
Findings in operation	A mass found 30 cm distal to the Treitz ligament, causing partial obstruction	Intussusception, 40 cm in length-multiple tan-black lesions	Hernial sac: ileum with a 4 cm × 5 cm mass	Melanoma extended through the muscularis propria into the subserosa	Ulcerated melanotic lesion
Adjuvant therapies	Declined further treatment	No	No	No	No
Metastases	No infiltrated mesenteric lymph nodes	No	The whole thickness of the wall, 3/16 lymph nodes infiltrated	4/9 lymph nodes infiltrated	Extending to the serosa, 6/7 infiltrated local lymph nodes
Postoperative course	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful
Follow-up	Died 1 yr	Disease-free 2 yr	Died 6 mo	Died 1 yr	Died 3 mo



**Figure 1** An abdominal CT scan section showing an obstructive luminal mass at the jejunum proved to be of melanotic nature.



**Figure 3** Colonic malignant melanoma originated at the anorectum (HE, x 100).

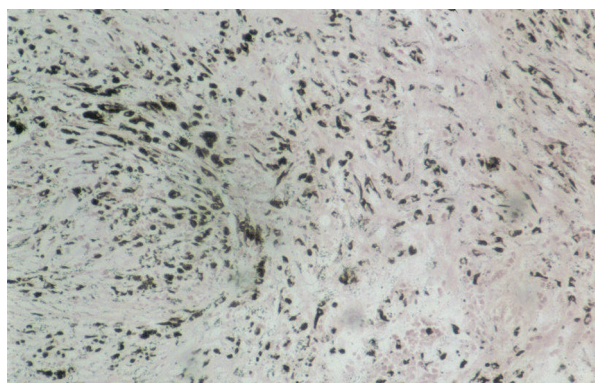


**Figure 2** Melanoma of the small intestine with submucosal infiltration. Numerous pleomorphic tumor cells with melanin deposits are viewed (HE, x 250).

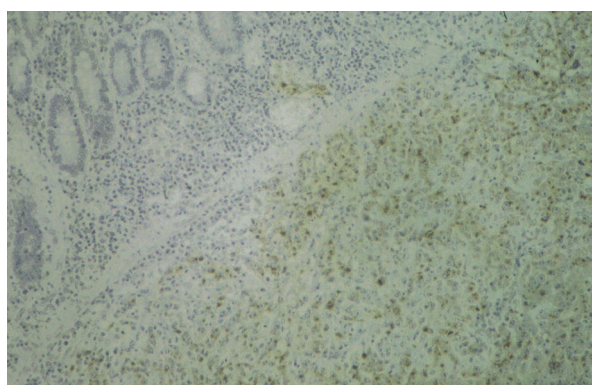
certain criteria have been developed. Suggestive characteristics of primitive nature include lack of concurrent

or previous removal of a melanoma or atypical melanotic lesion from the skin, lack of other organ involvement, *in situ* change in the overlying or adjacent GI epithelium and disease free survival of 12 mo after diagnosis<sup>[18]</sup>. The latter, recognized histologically by the presence of atypical melanotic cells in the basal layer of the epithelium and extending in a “pagetoid” fashion into the more superficial epithelium, may be reported in 40%-100% of primary GI melanomas<sup>[5,17]</sup>. Histologically, the tumor cells show varying proportions of spindled cells and epithelioid areas, the latter is characterized by large, pleomorphic cells with large eosinophilic nucleoli and abundant cytoplasm (Figures 2 and Figure 3). Cells frequently are poorly cohesive, particularly in the more epithelioid areas. Tumors may show abundant melanin pigment, confirmed histochemically by a Masson Fontana stain (Figure 4), within stromal macrophages and tumor cells. They may be even completely amelanotic. Stains that do not depend upon the presence of melanin pigment include S100 and the more specific HMB-45 (Figure 5). Electron microscopy demonstrates melanosomes and

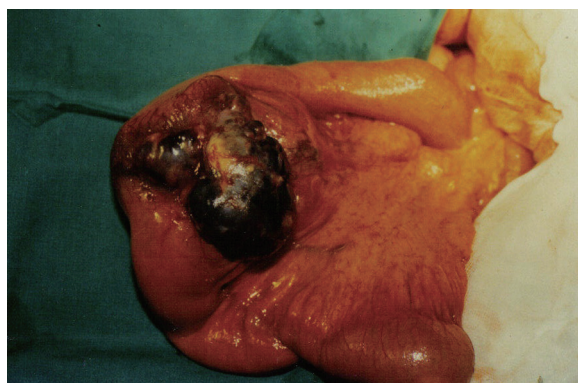




**Figure 4** Melanoma of the small intestine stained with Masson-Fontana. Plenty of granules of melanin are viewed (x 100).



**Figure 5** Melanoma of the small intestine stained with HMB-45 (x 100).



**Figure 6** Surgical specimen of a segmental enterectomy for a primary melanoma located at the jejunum. A few lymph nodes of the mesentery proved to be infiltrated.

premelanosomes in the tumor cells. Immunohistochemical stains for HMB-45 and Masson-Fontana have increased the diagnostic sensitivity of the biopsy and cytologic evaluation.

Regardless the exact origin of the melanotic lesion of the GI tract, the treatment of choice should be a curative-intent en block resection of the tumor with sufficient free margins and mesentery (Figure 6)<sup>[5,13]</sup>. Surgical palliation in non-curable melanomas aims at relieving obstruction and/or bleeding<sup>[8,12]</sup>. Surgery, if curative, has a relatively

low morbidity and mortality and long-term disease-free survival<sup>[2,4,7]</sup>. Systemic adjuvant therapy has a limited role. Chemotherapy using cisplatin, dacarbazine and tamoxifen has been applied, but the response rates are extremely low<sup>[2,15]</sup>. Melanomas that arise on mucosa surfaces appear to be more aggressive and are associated with worse prognosis than cutaneous melanomas. This may be related to delayed diagnosis, an inherently more aggressive behavior of mucosal melanomas or earlier dissemination because of the rich lymphatic and vascular supply of the GI tract mucosa.

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