



## Intestinal melanoma: A broad spectrum of clinical presentation

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### ABSTRACT

**INTRODUCTION:** Small intestine melanomas are rare and the most of them are metastases from primary cutaneous neoplasms.

**PRESENTATION OF CASE:** Below, we report two cases of small intestine metastatic melanoma with very different clinical presentation.

**DISCUSSION:** Still now, primary versus metastatic origin is often unclear. Small bowel melanoma is often asymptomatic. However, clinical picture can be various; it may occurs with non specific symptoms and signs of gastro-intestinal involvement, like chronic abdominal pain, occult or gross bleeding and weight loss, or with an emergency picture due to intestinal intussusception, obstruction or, rarely, perforation.

**CONCLUSION:** Small bowel melanoma is rare and the diagnosis done late. Imaging techniques are recommended in order to obtain early diagnosis of gastrointestinal metastases.

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### 1. Background

Primary and secondary malignant tumor of small intestine is rare. Most melanomas of the small intestine are metastases from primary cutaneous lesions, but melanoma can also develop as a primary mucosal neoplasm in the gastrointestinal tract [GI]. We report two cases of metastases of malignant melanoma of small bowel followed by a review of the literature.

### 2. Case report 1

A 17-year-old man was admitted to our Department in January 2000 due two-days of diffuse abdominal pain, constipation and vomiting. His past medical history was characterized by a diagnosis of cutaneous Clark V-level malignant melanoma in the occipital region made in January 1997, and treated with a surgical excision followed by immunotherapy. In September 1999, this tumor relapsed with a metastases in the left lateral-cervical region with nearby lymph node involvement. A complete markers screening showed an improvement of beta-HCG [8.5 mUI/ml; normal range 0–4 mUI/ml] and S100 [583 ng/l; normal range <250 ng/l]. A total body CT scan showed also the presence of partially necrotic lymph nodes in the left pulmonary hilum and in the abdominal cavity associated with a thickening of the some loops of small intestine with many bigger mesenteric lymph nodes. For this reason he had chemotherapy. At the admission in our Unit, patient presented fever, tachycardia, and a distended tender abdomen. Laboratory

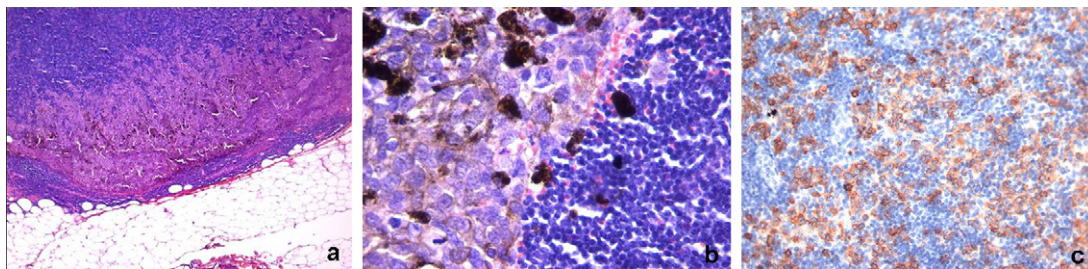
data revealed a moderate anemia and a slight leukocytosis. A laparotomy was performed. The exploration of the abdominal cavity showed a free enteric fluid and a mass of about 5 cm in diameter that included a neoplasm and a perforated ileal loop sided at 50 cm from ileocecal valve. An another neoplasm of 2 cm of diameter was found 70 cm from ligament of Treitz. The resection of both jejunal loops including the lesions and the related meso was done performing a manual entero-entero anastomosis. The pathologic examination of surgical specimen confirmed the size of both neoplasm detected at the laparotomy and showed that both tumors, at the section, had a white-yellowish aspect. The biggest neoplasm presented a large ulceration in the mucosa with an area of perforation. The histological analysis showed the presence of epithelioid cells from melanoma with malignant invasion of ten lymph nodes. At the immunohistochemical examination a strongly reactive for HMB-45, MelanA and S100 were detected. A diagnosis of melanoma metastases of the small intestine was done (Fig. 1a and b). The patient showed uncomplicated postoperative course and do not need of any adjuvant treatment. Two months after operation, both gastroscopy and colonoscopy were performed resulting negative for neoplastic lesions. He died 10 months after intestinal resection.

### 3. Case report 2

A 60-year-old woman was admitted to our department in February 2008 due to anemia and diffuse abdominal pain of duration of about one week. Her past medical history was unremarkable. At physical examination, an ovalar tumor of about 10 × 5 cm in size was detected in the mesogastric region, leading us to considered the possibility of a gastric or duodenal neoplasm. Laboratory data were within normal limits except for a moderate anemia. Gastroenterological workup, including gastroscopy and colonoscopy, was

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**Fig. 1.** (a) A global view of lymph nodes analyzed in hematoxylin-eosin that shows the metastatic area subside in the sub capsular region (E-E; original magnification 25×); (b) a particular of melanocytes population associated with hemosiderin deposit. On the right it is presents a residual lymph node parenchima (E-E; original magnification 400×); (c) immunohistochemical assay for Melan-A shows positive cells among negative lymphoid cells. (Melan-A, original magnification 100×.)

normal. A computerized tomography [CT] scan revealed a regular circumferential thickness of jejunum loop with a moderate swelling upstream in mesogastric region, suggesting the presence of a neoplasm and a series of nodular lesions in the right side of parietal peritoneum of about 5 cm in size. A complete neoplastic markers screening resulted only in a slight rise of  $\beta$ HCG [6.64 mUI/ml; normal range 0–4 mUI/ml]. She underwent to a laparotomy, due to the presence of jejunal neoplasm, which revealed the presence of two jejunal masses; the greatest one was localized 60 cm from ligament of Treitz, the second mass was found 70 cm from the first. Moreover, a neoplasm of about 5 cm of diameter was found in the right side of parietal peritoneum. A double jejunum resection (Fig. 2) with end-to-end anastomosis associated with excision of peritoneal neoplasm was performed.

The pathology report confirmed the presence of a white-yellowish tumour of  $7 \times 4 \times 2$  cm in size in the proximal jejunum, the neoplasm extended up to the mucosa causing focal areas of ulceration. A  $3 \times 2 \times 1.3$  cm tumour was found in the distal jejunum with similar macroscopic characteristics. The histological examination showed that tissue was highly atypical, with an epithelial aspect (Fig. 3a). Immunohistochemical stains revealed that the neoplastic cells were strongly reactive for HMB-45, Melan A, S100 (Fig. 3b). A mesenteric lymph node was affected by metastasis. This picture was compatible for metastases from melanoma. The post-operative course was regular and uneventful. The patient underwent a deep clinical and laboratory examinations in order to find a possible cutaneous lesion, and an Ophthalmologic consultation, but no primary malignant melanoma was found. Therefore, neoplasms were considered metastases of a spontaneous regression of a cutaneous melanoma. After surgery the patient underwent to six chemotherapy sessions. In October 2009 the patient noticed the arising of a neoplasm in the left dorsal-lumbar region, which

the CT showed to be  $8.5 \times 4.4 \times 3$  cm in size, solid, and heterogeneously vascularised with necrotic areas. The tumour was excised. The histological and immunohistochemical examination revealed that the cells were strongly reactive for HMB-45, Melan A, MIB-1; therefore it was made diagnosis of metastases of melanoma. Three months later she developed recurrent multiple bone metastases and in March 2010 she died.

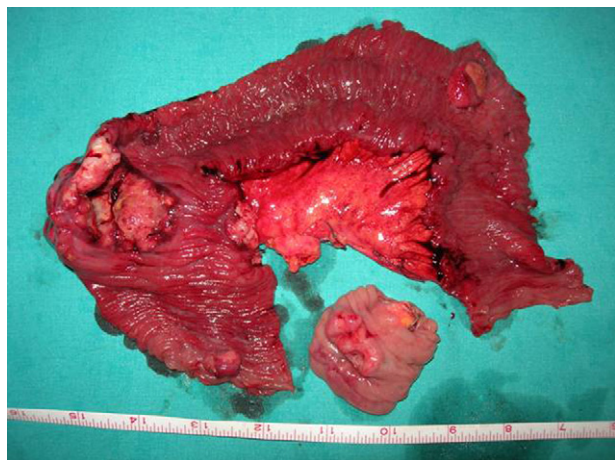
#### 4. Discussion

GI tract malignant melanoma is an uncommon form of neoplasm that may be either primary or metastatic; it can be localized in different sites from the oral cavity up to anus and the most common includes small bowel.<sup>1</sup> The distinction between primary or metastatic small bowel melanoma remain difficult to establish. Primary intestinal melanoma seems to be associated with a worse prognosis and a more aggressive behaviour due to rapidly growth for a rich vascular and lymphatic supply of the intestinal mucosa respect to metastatic one.<sup>2</sup> Mishima,<sup>3</sup> postulated that the primary melanoma of the small intestine might arise from schwannian neuroblast cells associated with the autonomic innervations of the gut. Other authors reported its origin in melanoblastic cells of the neural crest which migrate to the distal ileum through omphalomesenteric canal<sup>4</sup> or in APUD cells. However, some researchers suggest that primary melanoma of the small bowel does not exist as a separate clinical entity and that all small bowel melanomas are metastatic lesions from unknown or regressed primary cutaneous melanoma.<sup>5</sup> The frequency of an unknown primary cutaneous tumor site is estimated to be about 26% of cases.<sup>6</sup>

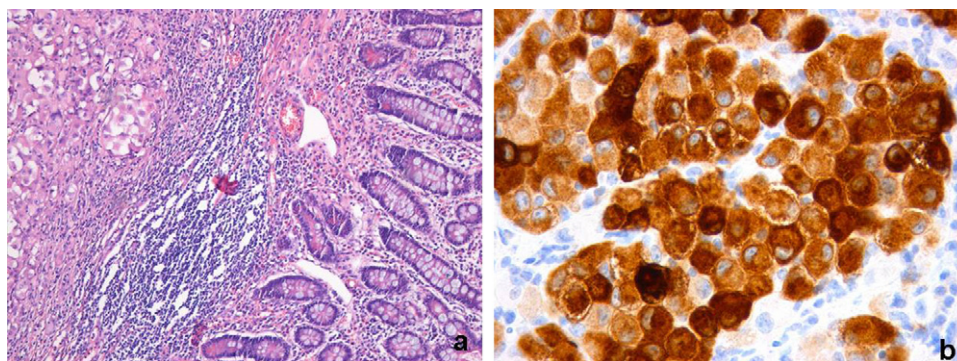
Blecker et al.<sup>1</sup> propose the following criteria for a diagnosis of primary melanoma of small bowel: presence of a solitary mucosal lesion in the intestinal epithelium, absence of melanoma or atypical melanocytic lesions of the skin and presence of intramucosal melanocytic lesions in the overlying or adjacent intestinal epithelium.

GI melanoma metastases are present in more than a quarter of patients with melanoma at autopsy, but only in 1–4% of patients the diagnosis is made during the life.<sup>7</sup> Metastases of melanoma are often multiple in the GI tract and can also be extra-intestinal.

Bender et al.,<sup>8</sup> defined four different types of metastatic melanoma of the small bowel: cavitory, infiltrating, exoenteric, and polypoid [often called a target or bull's-eye lesion]. These four types are not always distinct. In addition, they may be either pigmented or amelanotic. Histological features of metastatic intestinal melanoma that develop after spontaneous regression of primary cutaneous melanoma include lymphocytic infiltration of the dermis with melanophages, vascular proliferation and reparative fibrosis.<sup>9</sup> A clear distinction between primary intestinal melanoma and intestinal metastatic deposits can be difficult when considering histopathological features alone.<sup>10</sup>



**Fig. 2.** Surgical specimen after double jejunum resection.



**Fig. 3.** (a) Submucosal neoplastic nodule of intestinal metastatic melanoma. Overlying mucosa is normal (E-E; Original magnification 100×); (b) neoplastic cells are positive to Melan A (Melan A; original magnification 400×).

Recent studies show how the high incidence of metastases of melanoma in the small bowel may be due to the presence, on human melanoma cells, of a particular chemokine, CCR9, that it is likely a “homing receptor” for melanoma of the small bowel. In fact, it participates in the enhanced motility of melanoma cells and its ligand, CCL25, is strongly expressed in the small bowel.<sup>11</sup>

The time frame period between diagnosis of primary malignant melanoma and the identification of metastases at a gastrointestinal level varies between 2 and 180 months and most of them is detected only during autopsy.<sup>6</sup>

The melanoma of the small bowel is often asymptomatic. When it produce symptoms, they can be varying from chronic abdominal pain [17–64%], occult or gross bleeding [26–84%] and weight loss [10–47%].<sup>6</sup> Due to the unspecified clinical picture it needs to exclude other causes of abdominal pain in order to be sure of the diagnosis. Sometimes, small bowel melanoma occurs with an emergency clinical picture due to intestinal obstruction or intestinal intussusceptions and, rarely, to bowel perforation. To date, only six cases of perforation due to melanoma intestinal metastasis have been reported<sup>11–15</sup> and less than twenty cases of small bowel intussusception secondary to metastatic skin melanoma have been reported up to 2007.<sup>16</sup>

Due the rarity of occurrence of small bowel melanoma, the unspecificity of clinical complaints and the difficulty to explore the intestinal loops with the common instrumental procedures, preoperative diagnosis of small intestine melanoma results often difficult to perform. Different imaging techniques [Echo, TC, PET, capsule endoscopy] may give a suspicion of intestinal neoplasm, however the final diagnosis can be obtained only after surgical exploration. The sporadic nature and the small numbers of patients reported in the literature with a primary small bowel melanoma led the surgeons to not gain a standardization of treatment. A wide intestinal resection including the resection of the mesentery with lymph nodes remains the treatment of choice also because it seems to be associated with low morbidity and the mortality rate; in case of obstruction, perforation or serious hemorrhage an emergency surgical treatment is mandatory. Before considering a possible elective surgery, In case of non-urgent symptoms, first it is important to value intestinal or extra-intestinal spread. Gutman et al.,<sup>17</sup> studied indications for surgery of GI melanoma metastases. Half of their patients underwent elective surgery and 22% required emergency surgery for bowel obstruction or gross GI hemorrhage. They reported that the indications for surgery both elective and emergency had no impact on postoperative survival. On the other hand, Ollila et al. reported that surgical intervention improved survival significantly, especially when resection was complete on microscopic examination.<sup>18</sup> In their study, the median survival period after complete surgical resection of GI metastases was 48.9 months while only 5.4 months after incomplete resection and the 5-years

survival rate was 41% after complete resection. Branum et al. also reported significantly longer survival after complete resection of GI metastases than after incomplete resection, the mean survival period being 31.6 months versus 9.6 months.<sup>19</sup> Actually a standardized systemic therapy is missing. Treatment of metastatic disease include chemotherapy, immunotherapy and target-therapy. They can be useful as a palliative treatment in metastatic intestinal melanoma but at the moment their role is unclear.<sup>20</sup>

## 5. Conclusion

Primary melanoma of small bowel is rare; they are always metastatic lesions from regressed primary cutaneous melanoma. The diagnosis is often late and the patients undergo emergency surgery.

Because the high incidence of gastrointestinal metastases, in patients with an history of cutaneous melanoma who complaints abdominal pain and/or anemia, the employ of the modern imaging techniques applied for the study of small bowel is recommended in order to obtain an early diagnosis of gastrointestinal metastases.

## Conflict of interest statement

There are no conflicts of interest.

## Funding

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## Ethical approval

The local ethics committee approved the study.

## Consent

Written informed consent was obtained from the patients for publication of this case report and accompanying images.

## Author contributions

Rosalia Patti and Gaetano Di Vita made the study design and contributed to the preparation of the manuscript writing.

Giovanni Guergio, Matilde Cacciatori and Valentina Territo contributed to the collection and analysis of data.

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