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Primary Small Bowel Melanoma or Small Bowel Metastasis with Vanishing Primary Cutaneous Lesion

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Abstract

The small bowel represents one of the main sites for cutaneous melanoma metastasis; however, numerous cases of primary intestinal melanoma have recently been described. In view of this, we present the case of a 39-year-old woman admitted for nausea, heartburn, abdominal pain, change in bowel habits and weight loss. Contrast-enhanced CT revealed a small bowel mass. Surgical resection of a 6 cm ileal tumour with regional mesenteric lymphadenectomy and end-to-end anastomosis was performed. Histopathological findings indicated the presence of an ileal melanoma metastasis. Subsequent dermatological examination identified a cutaneous lesion on the right forearm, however no malignant cells were found at the histopathological exam. Whole body PET CT with FDG identified multiple frontal and parietal lesions. Genetic testing was positive for BRAF gene V600 E mutation. The patient underwent multiple neurosurgical procedures for the resection of cerebral metastases. Palliative external radiation and chemotherapy was also attempted. After approximately 2 years after the diagnosis, the patient died following multiple episodes of intracranial hypertension.

Keywords

Melanoma, Small Bowel, Cerebral Metastasis

1. Introduction

The incidence of malignant melanoma exhibited an ascending trend in recent

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years. This type of malignancy is characterised by an elevated affinity for the small bowel as metastasis site, more than half of melanoma patients exhibiting intestinal metastasis at autopsy. Although numerous cases of primary intestinal melanoma have been published, the possibility of melanoma developing directly from the intestinal mucosa represents an ongoing matter of debate, some authors suggesting that other organ involvement is associated with the regression of the primary cutaneous melanoma.

Most intestinal melanoma initially present with symptoms of small bowel obstruction. The mean survival of patients with metastatic melanoma amounting to approximately 5 months, possibly improved by surgical tumour resection.

The aim of this paper is to provide further insight into this disease and draw attention to the difficulty of differentiating between primary intestinal melanoma and intestinal melanoma metastasis with vanishing primary cutaneous lesion.

2. Case Presentation

A 39-year-old woman, with no previous medical history, presented with nausea, heartburn, diffuse abdominal pain, bloating, alternation between diarrhoea and constipation and involuntary weight loss of 4 kg in the past month.

Physical exam revealed slight tenderness on palpation in the hypogastrium. Bloodwork showed mild iron-deficiency anaemia (Hb 9.3 g/dl, ferritin 39 ng/ml) and a mild inflammatory syndrome (ESR 45 mm/h).

Abdominal ultrasound identified a digestive structure with thickened wall in the hypogastrium, in contact with the sigmoid colon and uterine body, without being able to distinguish its origin. Subsequently, lower digestive endoscopy was performed. No lesions were discovered at this level.

Contrast-enhanced CT scan of the abdomen and pelvis described a parenchymatous heterogeneously enhancing structure, of approximately 53/45 mm, involving the terminal jejunum or proximal ileum (**Figure 1**). Additionally, multiple lymphadenopathies along the superior mesenteric vascular pedicle were described.

Tumour markers CEA and CA125 were within normal values. Upper digestive endoscopy was also performed in order to exclude a celiac disease, but with no modification in this context. An antral gastritis was described, without any correlation with the actual disease.

Laparotomy was performed, with the resection of a 6 cm ileal tumour, located at 40 cm from the ileocecal valve, with regional mesenteric lymphadenectomy and end-to-end anastomosis. No postoperative incidents were reported and the patient was discharged after 4 days.

Pathology examination of the resected tumour identified a malignant cell proliferation with a mitotic rate of 11 atypical mitosis/10 HPF (**Figure 2**). None of the 35 ganglia removed exhibited malignancy features. Additional immunohistochemistry tests were positive for Melan-A, S100 and HMB45 (**Figure 2**). Thus,

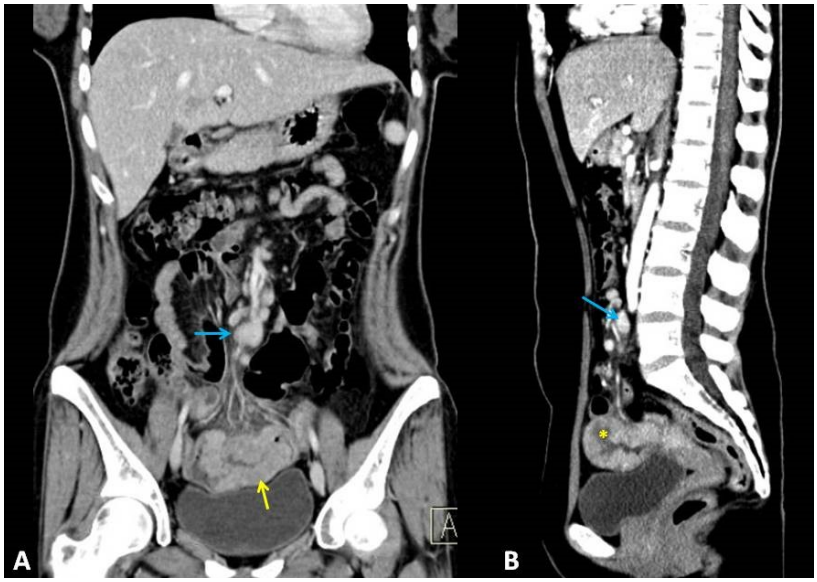

Figure 1. Abdomen and pelvis contrast-enhanced CT scan findings: The coronal (A) and sagittal (B) reconstructions depict a segmental small bowel thickening at the jejunal-ileal junction (yellow arrow), with necrosis (asterisk) and multiple satellite mesenteric lymphadenopathies (blue arrows).

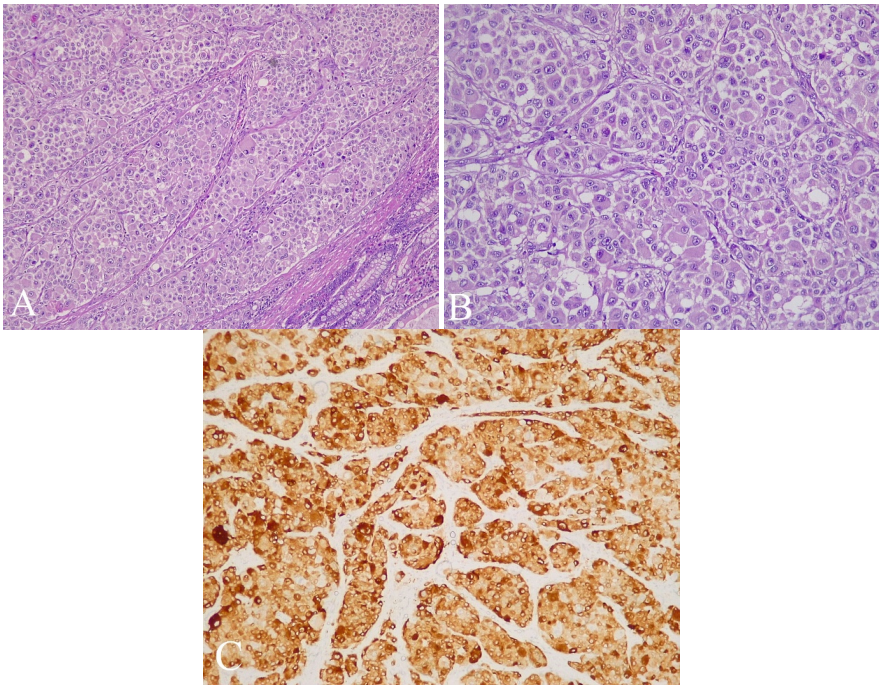

Figure 2. Histopathological findings: Hematoxylin and eosin stain (A 10×, B 40×) showing a malignant cell proliferation with a mitotic rate of 11 atypical mitosis/10 HPF. Immunohistochemical depiction of a melanocytic intestinal lesion positive for Melan-A (C 40×).

these histopathological features indicated the presence of a melanoma ileal metastasis.

In consequence, the patient underwent thorough dermatology examination,

which identified a lesion suggestive of a superficial spreading melanoma on the right forearm. The lesion was promptly surgically removed. Pathology examination described a small number of melanophages spread across the superficial dermis and inflammatory infiltrate around capillaries, suggestive of chronic irritation. No malignant cells were identified on the examined specimens.

Whole body PET CT scan with 18-fluor-deoxi-glucose (FDG) was performed in order to identify the primary tumour or other concurrent metastases (Figure 3). The examination revealed no other lesions in the thorax, abdomen or pelvis. However, significant vasogenic cerebral oedema of the left centrum semiovale and multiple frontal and parietal hypermetabolic lesions were identified.

The PET CT findings prompted brain MRI evaluation which identified a total of 7 metastases both in the supratentorial and infratentorial regions (Figure 4).

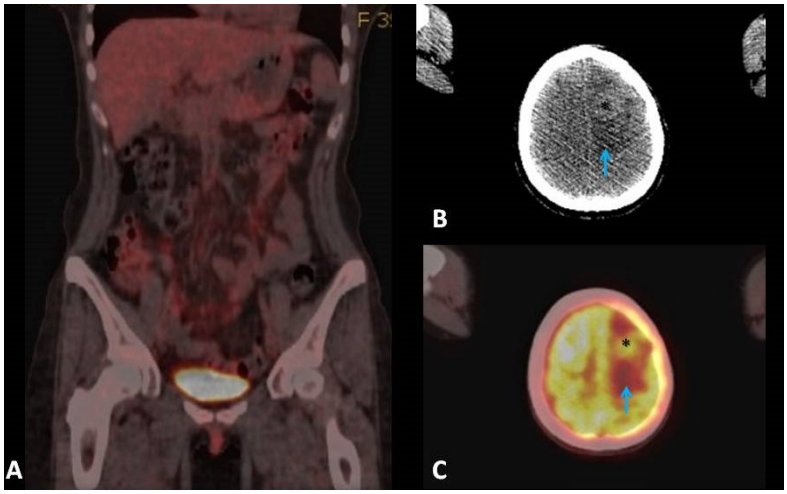

Figure 3. FDG PET-CT findings: The coronal reconstruction (A) showed no signs of relapse or abdominal or pelvic metastases. Cerebral axial reconstruction (B) (C) revealed left frontal vasogenic oedema (blue arrows) surrounding a nodular aria suggestive of a cerebral tumour (asterisk).

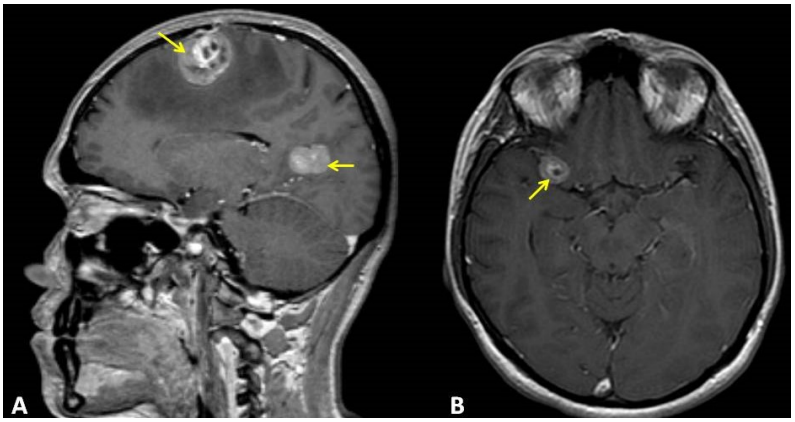

Figure 4. Contrast-enhanced MRI findings: T1 sagittal (A) and axial (B) reconstructions reveal multiple nodular cortico-subcortical lesions located in the supratentorial and infratentorial regions suggestive of cerebral metastases. The largest ones are located in the left frontal and parietal-occipital lobe and right frontal lobe (yellow arrows).

To complete the investigations, mutational status of BRAF gene was determined, V600E (c.1799T > A) mutations being detected.

From this moment on, the patient underwent four neurosurgical gamma-knife procedures for the resection of cerebral metastases in the span of 18 month. Moreover, palliative external radiation (30 Gy in 10 fractions) and chemotherapy (dabrafenib 150 mg twice daily and trametinib 2 mg twice daily) were attempted. The patient maintained a good clinical status throughout treatment, although progressive disease was detected after 12 months under this treatment. Chemotherapy was therefore supplemented with nivolumab 3 mg/kg every 2 weeks.

The patient neurological status gradually worsened and further progression of the disease was confirmed after 5 months from the addition of nivolumab. The patient was multiple times admitted for episodes of intracranial hypertension treated with iv corticoids and mannitol, eventually succumbing after approximately 2 years from diagnosis.

3. Discussion

The small bowel is rarely a site for development of primary tumours, most tumours arising at this site being metastatic in nature [1].

Skin melanoma is the most frequent malignancy to develop small bowel metastasis, namely up to one third of small bowel metastasis are due to melanoma [2], followed by breast and pulmonary cancer [3]. A possible explanation for the affinity of melanoma for the small bowel resides in the presence of surface chemokine CCR9 on melanoma cells that binds to the CCL25, particularly found on intestinal cells [4]. Most melanoma metastasis are located in the jejunum and ileum [5], but it can spread to any gastrointestinal segment. Although 60% of autopsies on melanoma patients reveal intestinal involvement, only 4% of intestinal metastases are diagnosed ante-mortem [6].

We found a few other case reports that described the presence of melanoma at different levels of the gastrointestinal tract, such as the oral cavity, oesophagus, small and large bowel, rectum and anal canal, with no detectable cutaneous melanoma at the time of diagnosis [7]-[15]. Through immunohistochemical stains such as HMB-45 and S100, the presence of melanocytes has been detected at the aforementioned digestive sites [16]. The migration of melanoblastic cells originating in the neural crest to the distal ileum by means of the omphalomesenteric canal, might account for the development of primary intestinal melanoma [17]. Another possible mechanism involves the development of primary intestinal melanoma from the Schwannian neuroblast cells that form the enteric nervous system [18].

Some authors argue that there is no primary intestinal melanoma, implying that either cutaneous lesions were failed to be diagnosed or underwent complete regression by the time of metastasis detection [19]. Cutaneous melanoma regression is a fairly common finding, encountered in up to 37% of all melanomas [20], occasionally leaving no trace of the initial malignant lesion. The histologi-

cal aspect left behind cutaneous regression is characterised by decreased number of melanoma cells, dermis fibrosis, inflammation, melanophages, ectatic blood vessels, epidermal attenuation and/or apoptosis of keratinocytes or melanocytes [21]. In our case, some of these histopathological elements have been described after examining the excised cutaneous lesion, but no certain cutaneous melanoma regression diagnosis could be reached.

The degree of spontaneous regression of the primary cutaneous lesion has been linked with survival in melanoma patients. Thin melanomas are more likely to metastasize depending on the degree of cutaneous regression; after 77% of the primary cutaneous tumour has regressed, solid organ metastases are more likely to be diagnosed [22].

While some authors argue that there is no such entity as primary gastrointestinal melanoma, notwithstanding cases where no primary cutaneous lesion could be identified after rigorous dermatological examination [19], others defined a series of diagnostic criteria for primary small bowel melanoma. Sachs *et al.* [23] outlined the following criteria according to which a primary small bowel diagnosis could be reached: 1) solitary melanoma lesion confirmed by histopathology, 2) no other organ involvement except regional lymph nodes and 3) disease-free survival of 12 months minimum following diagnosis. According only to the aforementioned criteria, our case does not qualify for the diagnosis of primary small bowel melanoma, as only one of the three criteria was met, namely the histopathologic confirmation of the presence of melanoma at a small bowel site. In our case, approximately four months had elapsed before the diagnosis was confirmed and further investigations were performed for the identification of other organ involvement, therefore the second criterion cannot be considered fulfilled.

Usually, intestinal melanoma manifests as an acute bowel obstruction [24], the underlying mechanism being enteric intussusception [25]. Other possible symptoms are abdominal pain, change in bowel habits, haematemesis, melena and weight loss [26]. Our patient presented no signs of acute bowel obstruction or digestive bleeding.

Usually, abdominal ultrasound is the first examination employed in the evaluation of cutaneous melanoma patients with digestive symptoms, although it renders a weak diagnostic performance, as in the case of our patient where the exact location of the tumour could not be established only through abdominal ultrasound. In addition, upper and lower digestive endoscopy systematically fails to identify small bowel lesions [27]. Therefore, additional diagnostic procedures are being investigated. Our patient presented a tumour at approximately 40 cm from the ileocecal valve, a site not accessible by conventional endoscopy. As enteroscopy could not be performed in our medical unit, further radiological examinations were employed (contrast enhanced CT scan).

Considering the frequent small bowel involvement in patients with cutaneous melanoma, Albert *et al.* [28] attempted with a multicentric prospective study, to design an algorithm for the detection of small bowel metastasis using faecal oc-

cult blood test, gastroscopy, ileo-colonoscopy and video-capsule endoscopy (VCE). 390 patients with stage I-IV melanoma patients were evaluated. Small bowel melanoma metastasis was identified in 28.6% of stage IV patients, 1.7% of stage III and in none of the stage I-II patients. The study underlines the potential role of VCE in the detection of small bowel metastasis, as no additional lesions were identified by further conventional endoscopy in these patients. Moreover, a positive faecal occult blood test indicated a poor survival rate in stage III and IV melanoma.

Gastrointestinal melanoma metastases are usually diagnosed at 2 to 180 months after the detection of the primary tumour [29], but their development remains possible even years after the curative treatment of the primary lesion [30]. Stage IV melanoma patients usually have a mean survival of 5.3 months [31], however in addition to symptomatic relief, considerably increased survival time has been observed in stage IV patients who underwent tumour resection [32]. In the case of our patient, a 2-year survival was achieved after the resection of the initial small bowel tumour, followed by multiple resections of the cerebral metastases.

According to Janavicius *et al.* [33], patients with melanoma brain metastases achieved better overall survival when treated with combined treatment modalities: surgery followed by radiotherapy (26.6 months overall survival), combining surgery, radiotherapy and systemic therapy (18.7 months overall survival), and also radiotherapy followed by systemic therapy (13.8 months overall survival). In the presented case, combined therapy was offered (surgery, radiotherapy and chemotherapy with dabrafenib, trametinib and nivolumab) achieving a longer survival than the average presented by Janavicius *et al.*

In conclusion, although in most cases it cannot be distinguished between primary intestinal melanoma or small bowel metastasis with no detectable primary cutaneous lesion, all patients require urgent diagnosis and management, as its prognosis remains poor.

Conflicts of Interest

None of the authors declared a conflict of interest.

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