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# Asymptomatic jejunal metastatic melanoma. A case report of anemia of uncertain origin

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## ABSTRACT



Gastrointestinal metastases from cutaneous melanoma are rare and usually asymptomatic, with most patients not being clinically diagnosed throughout their lifetime.

We report a case of how melanoma may metastasize insidiously in the small bowel. Unexplained iron deficiency anemia was assumed to be the result of underlying gastrointestinal bleeding. Therefore, the diagnosis of jejunal metastasis from cutaneous melanoma was suggested based on imaging findings and made through the histopathological examination.

According to the international guidelines, the patient underwent the complete excision of the primary tumor and therapeutic lymph node dissection. Furthermore, an adjuvant treatment was required to reduce the risk of recurrence.

Both immunotherapy and surgical therapy have been shown to be effective, providing long-term survival in this case.

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## Introduction

Intestinal melanoma is a rare form of cancer that can be either primary or metastatic. Primary small bowel melanoma is an extremely rare entity and, in most cases, the diagnosis is difficult to make [1].

However, researchers believe that all melanomas of the small bowel are metastases from unknown primary cutaneous melanoma, and consequently, primary melanomas of the small intestine are generally not separate entities [2].

Cutaneous, anal, or ocular melanomas can metastasize in different sites of the digestive tract and the most common one is the small bowel. Therefore, metastatic melanoma from the small intestine is very common and it can occur in 35% to 70% of the patients [3-6].

In most patients, the disease is undetectable in the early stages, and diagnosis being made late, when complications

have already occurred. In some cases, the diagnosis is missed throughout lifetime [7,8].

This article reports the case of small bowel metastatic melanoma, where surgery and immunotherapy were effective treatments, offering the best chance for long-term survival. A brief discussion of the pertinent literature data was also made.

## Case Presentation

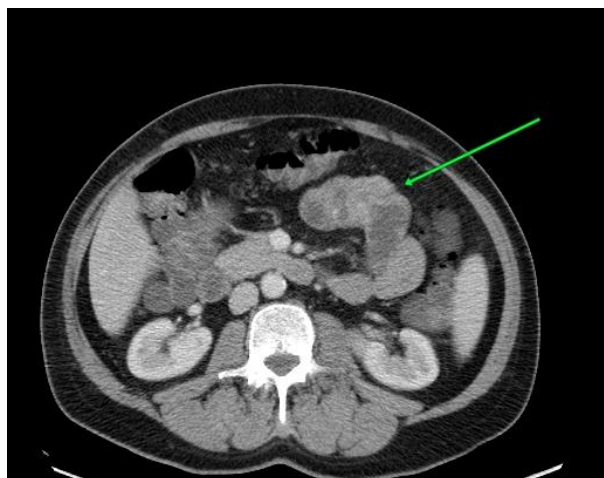
A 52-year-old male patient was evaluated in December 2020 for severe anemia of unknown etiology. His medical background revealed an oncological history of left temporal ulcerated cutaneous melanoma dating from 2018, which was removed by means of wide surgical excision with sentinel lymph node biopsy (SLNB). The histopathology revealed a stage IIIC melanoma. The tumor infiltrated the subcutaneous fat (Clark's Level V), with ulceration, positive sentinel lymph node (pT4b, pN1 (SNL)), BRAF negative.

After the surgical intervention, taking into consideration the patient's request, it was decided to keep the patient under clinical observation. Six months later, on the imaging evaluation, the PET-CT revealed multiple hepatic, skin and lung metastases.

Thus, the tumor board decided to initiate Nivolumab (1 mg/kg) + Ipilimumab (3 mg/kg) every three weeks for 4 administrations and then Nivolumab 240 mg twice a month, as a maintenance treatment.

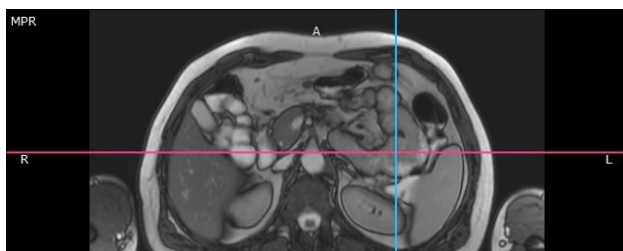
In December 2020, the laboratory examinations revealed that his hemoglobin level was 6.6 g/dL. Additional tests were performed to diagnose the specific cause of the patient's anemia. The lab values indicate iron deficiency anemia. We further examined the relationships between iron deficiency anemia and positive immunochemical fecal occult blood test (FOBT).

Neither upper nor lower gastrointestinal endoscopy revealed an actively bleeding source. Subsequently, a CT enterography was performed. The results showed a diffuse parietal thickening at the jejunal loops.



**Figure 1.** Computed tomography revealed parietal thickening located in the middle and distal jejunum.

To complete the diagnosis, the patient underwent an entero-MRI which showed an intraluminal jejunal tumor and concentric wall thickening of the middle and distal jejunal loops.



**Figure 2.** Magnetic resonance imaging reveals jejunal tumor.

The  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography revealed areas of increased uptake of fludeoxyglucose near the angle of Treitz. The lesion was poorly described due to enteric intussusception.



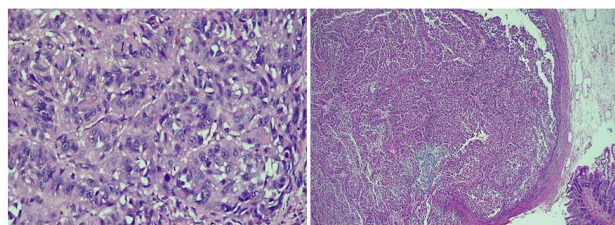
**Figure 3.** A whole-body PET imaging with fluorodeoxyglucose revealed the intussusception of the small bowel caused by the jejunal metastasis.

Therefore, surgery with a biopsy of the lesion was mandatory to make an accurate diagnosis. The patient underwent successful laparotomy and extensive jejunal resection with end-to-end anastomosis and regional mesenteric lymphadenectomy. The recovery was successful after the major surgery without any complications.



**Figure 4.** Intraoperative imaging of multiple jejunal masses.

On the histopathological examination, the resected jejunal segment showed mixed epithelioid and spindle cell melanoma, revealing the diagnosis of metastatic malignant melanoma.



**Figure 5.** The histopathological appearance of the jejunum [hematoxylin and eosin (H&E); 200 $\times$ ].

Considering these results, and the important clinical benefit of Nivolumab, the tumor board decided to continue the treatment with checkpoint inhibitors.

In May 2021, three months after the beginning of the treatment, the CT scan showed a stable disease, confirming that the combination therapy with Nivolumab and Ipilimumab, followed by Nivolumab for maintenance, can provide long-term benefits.

## Discussion

Improvement in the management of metastatic melanoma has led to improved overall survival, therefore, we experience a substantially increased number of uncommon metastatic sites. The melanoma is the tumor that metastasizes most frequently to the gastrointestinal tract, followed by breast carcinoma and lung carcinoma.

The small intestine, especially the jejunum, is the most common site of gastrointestinal melanoma metastases, followed by the large intestine and the stomach [9].

The most common melanoma metastases are placed at the level of gastrointestinal tract (20-60%), brain (10-40%), lung (18-40%), liver (10-20%) and bone (11-17%) [10-17].

Up to 2021, a number of 34 cases of jejunal metastases have been reported. There is a clear predisposition for the occurrence of intussusception upon diagnosis [18-24]. Less often, the patient is diagnosed with small bowel perforation [25-29], obstruction [30] occult gastrointestinal bleeding and anemia [31-35], or abdominal pain [36].

Three cases reported a primary malignant melanoma of the gallbladder with multiple gastrointestinal metastases including the jejunum [37-39], and one case presented jejunoileal metastases of malignant melanoma of the choroid [40].

The data support the idea that melanomas of the extremities are more likely to spread to the gastro-intestinal tract, more often than head and neck melanomas [41].

Most patients with metastatic intestinal melanoma are clinically non-diagnosed throughout lifetime. However, the autopsy reports described small bowel metastases in approximately 60% of the patients with melanoma [42].

In cancer patients, anemia should always be investigated to rule out intestinal metastases. This is not true only for melanoma patients, but also for patients with other primary tumor types [43,44].

However, despite the tremendous developments in the imaging techniques, the early diagnosis of intestinal melanomas remains a true challenge.

Traditionally, the tumor assessment by means of computed tomography is useful, but it may present limited sensitivity [45,46].

Therefore, modern imaging techniques – including magnetic resonance imaging, positron emission tomography, and capsule or double-balloon endoscopy [47,48] enhance the diagnostic performance in the detection of melanoma metastases from the small intestine.

In our case, the histopathological results confirmed the clinical suspicion of metastatic intestinal melanoma. The technique of extensive jejunal resection was discussed elsewhere [49,50].

Upon the diagnosis in 2018, the patient presented with locally advanced melanoma and positive sentinel lymph nodes pT4b, pN1, stage IIIC of disease.

According to international guidelines, patients with stage IIIC melanoma should undergo the complete excision of the primary tumor and therapeutic lymph node dissection [51]. Furthermore, adjuvant treatment is required to reduce the risk of recurrence. Unfortunately, in our country, Interferon was the only reimbursed treatment in the adjuvant therapy of advanced melanoma. After the efficacy and toxicity of this treatment were discussed with the patient, he decided to remain under observation.

The landmark phase 3 CheckMate 067 trial highlights the clinical benefit of Nivolumab and Ipilimumab in advanced and metastatic melanoma [52].

The sustained benefits demonstrated in this study accelerated in 2015 the approval of the combination of Nivolumab and Ipilimumab for the frontline therapy in this cancer site.

The 6.5-year outcomes from the global Checkmate 067 trial demonstrated long-term survival, with 81% of the patients being alive, and 27.6 months of median treatment-free in the Nivolumab plus Ipilimumab arm [53].

At the end of 2020, after the metastases were found, the patient initiated the treatment with Nivolumab and Ipilimumab, and currently the disease is under control after 30 months of immunotherapy.

### *When maintenance therapies are stopped*

International guidelines recommend continuing maintenance treatment with nivolumab until disease progression or unacceptable toxicity. However, some studies consider two years of maintenance therapy sufficient, provided that response, either partial or complete, is achieved [54].

In our case, the patient did not experience any immune-related toxicities, and we chose to continue the maintenance with nivolumab with the intent of achieving long-term control of the disease.

## Highlights

- ✓ The small intestine, especially the jejunum, is the most common site of gastrointestinal melanoma metastases.
- ✓ The diagnosis of intestinal metastases can be missed throughout lifetime, and it is essential to focus on the clinical examination, and any abnormal blood loss should be further evaluated.
- ✓ The development of immune checkpoint inhibitors has changed the way melanoma is treated, and the association of Nivolumab and Ipilimumab is one of the most effective options for advanced and metastatic melanoma.

## Conclusions

In conclusion, it seems that melanoma is more than a cutaneous cancer.

Melanoma can develop anywhere on the body and decision making in this cancer site should always be made in multidisciplinary teams. Moreover, it is essential to focus on clinical examination, and any abnormal blood loss to be further evaluated. If diagnosed in the early stages, melanoma can be successfully treated with surgery alone. But stage III melanoma has an increased risk of loco-regional recurrence and distant metastases. In these cases, the benefit of adjuvant immunotherapy is certain. However, even if patients have not had the opportunity of adjuvant treatment, combination therapy in the metastatic setting is also a valid and effective alternative.

## Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

## Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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