

Beyond the Surface: A Case Report of a Patient with Small Bowel Metastasis and Melanoma History. Diagnosis and Management.

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Rezumat

Dincolo de aparențe: raport de caz privind un pacient cu metastază la intestinul subțire și istoric de Melanom. Diagnostic și abordare terapeutică

Context: Melanomul malign (MM) este una dintre cele mai prevalente și letale forme de cancer de piele, rezultând din transformarea malignă a melanocitelor. Acesta reprezintă aproximativ 1,7% din totalul diagnosticărilor de cancer la nivel global și este al cincilea cel mai comun cancer în SUA. MM poate metastaza în aproape orice parte a corpului, iar detectarea timpurie îmbunătățește semnificativ prognosticul.

Case report: Prezentăm cazul unei femei în vârstă de 81 de ani cu istoric de melanom malign (leziune primară pe gamba stângă) și diverse comorbidități. Pacienta s-a prezentat cu o anemie severă de origine necunoscută. O scanare CT a fost efectuată datorită istoricului său medical, dezvăluind o îngroșare parietală circumferențială, asimetrică la nivelul unei anse ileale hipogastrice. Leziunea sugera un substrat tumoral. Colonoscopia ulterioară nu a arătat leziuni metastatice, dar intervenția chirurgicală a confirmat o metastază ileală a melanomului malign. Pacienta a suferit o rezecție segmentală laparoscopică, cu rezultate postoperatorii favorabile. Examinarea histopatologică a țesutului rezecat a confirmat diagnosticul de leziuni secundare ale intestinului subțire provenite de la melanomul malign.

Concluzie: Acest caz subliniază necesitatea de a lua în considerare melanomul metastatic la pacienții cu istoric de MM și simptome gastrointestinale vagi. Diagnosticarea timpurie și precisă prin tehnici avansate de imagistică și endoscopie poate îmbunătăți semnificativ rezultatele pacientului.

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Cuvinte cheie: melanom malign, metastaza intestinală, imunoterapie, microbiom intestinal, anemie

Abstract

Background: Malignant melanoma (MM) is one of the most prevalent and deadliest forms of skin cancer, resulting from the malignant transformation of melanocytes. It accounts for approximately 1.7% of global cancer diagnoses and is the fifth most common cancer in the US. MM can metastasize to almost any part of the body, with early detection significantly improving prognosis.

Case presentation: We report the case of an 81-year-old female with a history of malignant melanoma (primary lesion on the left calf) and various comorbidities. She presented with severe anemia of unknown origin. A CT scan was performed due to her medical history, revealing a circumferential, asymmetrical parietal thickening at the level of a hypogastric ileal loop. The lesion suggested a tumoral substrate. Subsequent colonoscopy showed no metastatic lesions, but surgical intervention confirmed a malignant melanoma ileal metastasis. The patient underwent laparoscopic segmental resection with favorable post-surgery outcomes. Histopathological examination of the resected tissue confirmed the diagnosis of small intestine secondary lesions from the malignant melanoma.

Conclusion: This case underscores the necessity of considering metastatic melanoma in patients with a history of MM and vague gastrointestinal symptoms. Early and accurate diagnosis through advanced imaging and endoscopic techniques can significantly improve patient outcomes.

Key words: malignant melanoma, small bowel metastasis, immunotherapy, intestinal microbiome, anemia

Introduction

Malignant melanoma (MM) stands out as one of the most prevalent and deadliest forms of skin cancer and represents the malignant transformation of melanocytes. Globally, it accounts for about 1,7% of the cancer diagnoses worldwide and ranks as the fifth most common cancer in the US. Malignant melanoma cells can spread from their original tumor site, skin or mucosa, and metastasize to almost any parts of the body. It is known that early detection plays an important role in prognosis; the five-year relative survival rate for stage zero melanoma is approximately 97 %, in contrast with 5-19 % for those with advanced stage malignant melanoma. Due to its poor prognosis, it is extremely important to detect the disease at its earliest form (1).

Metastatic spread from a tumor originating outside the peritoneal cavity which involves

the small intestine is rarely seen. However, in malignant melanoma, the small bowel is relatively frequently affected. While most of the cases are secondary lesions, there are a few primary cases where an initial site cannot be found. Notably, small bowel metastatic melanomas are generally clinically undetectable in their early stages. Diagnosis is therefore often delayed and is made only when complications occur (2). Gastrointestinal metastases are frequently detected during autopsy, with only a small proportion (2-5%) of the patients diagnosed while living (3).

Case Report

We present the case of an 81-year-old female with a medical history of malignant melanoma, characterized by primary lesions on the left calf and metastases in the lungs, lymph nodes, and skin. She underwent

surgery on November 15, 2022, and has also been treated for venous thrombosis and perineal rupture. The patient also had a history of cholecystectomy 30 years ago. The patient was admitted into the hospital for a severe anaemia (Hb level 5,8 g/dl) due to unknown reasons. Because of this suspicion and including the history of melanoma, a CT was done.

A short review of the history of melanoma for this case: in November 2022, the patient undergoes a surgical intervention for a lesion localized on the left calf. In December 2022, a histopathology exam was performed using the resected piece. The result was malignant melanoma with hypoderm invasions, Breslow index 8,8 mm, mitotic index 11 mitosis/mm², Clark V with moderate lymphocytic infiltrate. No ulceration, sentinel lymph nodes, perineural or perivascular invasion were found. The oncology board's decision was to initiate the treatment with Nivolumab and to undergo the testing for BRAF mutation.

The patient started the treatment and after four months the oncology team was reunited for the reevaluation of the case. Also, a cerebral, thoracic, abdominal, and pelvic CT was performed. This investigation showed no cerebral, pulmonary, and abdominal secondary lesions, only a small (10/6 mm) focal hypodense hepatic lesions on the IV segment with cystic substrate. The BRAF testing was performed, and it appeared negative. The patient did seven series of treatments, well tolerated, with no secondary effects. The oncology team decided to continue the treatment and to make another evaluation after six months, by performing a CT scan, blood tests and protein S100 analysis.

On 28/12/2023, a third oncology committee was done; a new CT was performed (with no changes compared with the previous one). The patient continued the treatment. In total she received 18 Nivolumab doses, the last one being administrated on 12/12/2023. The team's decision was to continue the therapy and reevaluate the patient after six months by doing a PET-CT, computer tomography of the thorax, abdomen, and pelvis and blood tests. During this time, the patient developed a



Figure 1. Parietal thickening of an ileal segment, in close contact with the anterior peritoneum, with arterial hyperenhancement, with densification of peri-ileal fat tissue. Arterial phase.

severe anaemia, with no evident cause. Hospitalization was the best option to resolve this issue.

Between 23/03/2024 and 04/04/2024, the patient was hospitalized. She performed an abdominal-pelvic CT which showed a circumferential, asymmetrical parietal thickening at the level of a hypogastric ileal loop (about 10 cm long and 13 mm thickness). The lesion was spread to the anterior parietal peritoneum wall which had a discrete thickening aspect with a local area of fat densification and a few loco-regional lymph nodes (approximately 26/23 mm). The CT aspect was suggestive for a tumoral substrate (*Figs. 1, 2, 3*). The patient also performed a colonoscopy, which showed no evidence of metastatic lesions.

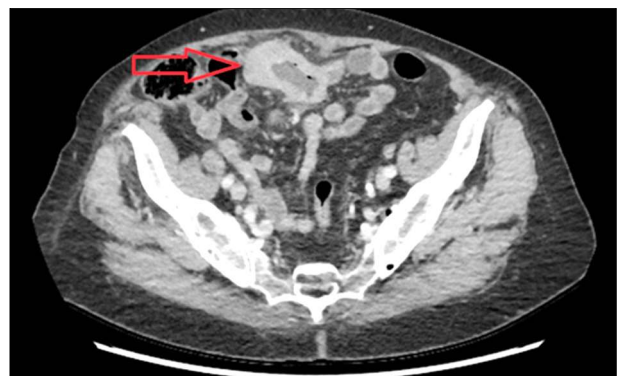


Figure 2. Parietal thickening of an ileal segment, in close contact with the anterior peritoneum, with arterial hyperenhancement, with densification of peri-ileal fat tissue. Venous phase.



Figure 3. Parietal thickening of an ileal segment, in close contact with the anterior peritoneum, with arterial hyperenhancement, with densification of peri-ileal fat tissue. Late phase.

Due to this finding, the medical team decided to transfer the patient to a surgical department. On 29/04/2024 she undergoes a laparoscopic intervention (segmental resection) for a malignant melanoma ileal metastasis, complicated by intestinal stenosis and hemorrhage. The postoperative evolution was favorable, with no complication reported. Using the resected piece and a mesenteric lymph node a histopathology exam was performed and a final and complete diagnosis was given: small intestine secondary lesions caused by the malignant melanoma of the left calf.

Treatment

An important aspect of the melanoma treatment is represented by the immune checkpoint inhibitors. The main two classes are represented by: CTLA-4 inhibitors (Ipilimumab) and PD-1 inhibitors (Nivolumab and Pembrolizumab). Nivolumab is a completely human anti-PD-1 monoclonal antibody that blocks the interactions between PD-1 and its ligands, such as PD-L1 and PD-L2 by improving the response of the T cells (4). The patient received treatment with Nivolumab (18 doses in total) between December 2022 and December 2023. Nivolumab was administered intravenously every two weeks using the standard dosage of 240 mg. No side effects were reported during this time. The surgical treatment was represented by

end-to-end anastomosis after an elective laparoscopic resection of the affected area. None of the commonly seen complications, such as infections, fistulation, anastomotic leakage was found in this case (5).

Discussion

As one of the most aggressive malignancies, melanoma tends to invade locally and to disseminate (through lymph nodes or blood vessels) from the primary site to various parts of the body. The liver, lungs, bones, and skin are the most common sites of metastasis. Thus, the gastrointestinal tract (GIT) represents a less common location for secondary lesions (6).

Despite being a malignancy which frequently leads to GIT secondary lesions, the diagnosis remains challenging, approximately 2% of cases are clinically diagnosed (7) due to their subtle clinical presentation and vague appearance on imaging. CT serves as the standard method for detection with the MRI and PET-CT employed in specific circumstances (8). Even if the overall surveillance for this type of disease (MM with GIT metastases) is generally low, some patients may achieve a better prognosis after being treated surgically or using systemic therapies. Therefore, for optimizing both the quantity and quality of the patient's life it is mandatory to have an early diagnosis and treatment plan (9). Note that surgery is not considered a curative treatment, it can only be a palliative one. In an analysis, Wornom et al. reported that from a total of 65 patients which underwent surgery for MM, relief of symptoms were obtained in 77% of cases (10).

Among all the segments of the GIT, the small intestine is the most frequently involved (9). The diagnosis of gastric metastasis of MM is often made postmortem (11). Clinical antemortem detection represents about 1-5% (12). The small bowel lesions are diagnosed either at the time of MM diagnosis or several years later (an average time is seven years into the disease) (13). The pathogenesis of this event involves heightened expression of CCR9 (a

chemokine ligand) which promotes the migration of the malignant cells from the original site into the GIT, especially the small intestine which has a significant expression of the CCR9 receptor (9).

Clinical presentation typically features vague and non-specific symptoms, such as abdominal pain (17-64%), iron-deficiency anaemia, modifications of bowel habits, GI bleeding (26-84%), moderate jaundice and weight loss (10-47%) (9,11). An interesting aspect of this case is the correlation between the disturbance of the intestinal microbiome and the response to the immunotherapy. There are several studies that underline the inadequate response to immunotherapy (12). It was demonstrated that the gut microbiome can influence cancer development, progression and response to treatment, especially immunotherapy (14,15). That's an issue that deserves to be detailed in another analysis. In our patient's case, the intestinal metastasis is considered a high disturbance of the intestinal flora. So, we can ask the following question is there a connection between the poor response to therapy and the presence of the intestinal secondary lesion? A small number of patients can present acute abdomen due to tumor-induced obstruction or perforation. The diagnosis may be achieved by performing a CT scan (16), endoscopy, or a colonoscopy, or even a video-capsule endoscopy (a minimally invasive method used to visualize the entire small intestine) (17).

There are many articles that show the impact of video-capsule endoscopy into the diagnosis of small bowel pathologies, cancerous and non-cancerous (18). In addition, the capsule-endoscopy has demonstrated the effectiveness of detecting the "cold-black" lesions, connected with metastatic melanoma (19). Being a non-invasive technique, the video-capsule endoscopy is used frequently to diagnose occult GIT bleeding, when a classical superior/inferior endoscopy's result is negative (20). It is extremely important to keep in mind that, like any other investigation performed to a patient, video assessed endoscopy has its contraindications: history of stenosis by any

cause, intestinal obstruction, small bowel fistulae (18). Also, there are several limitations, the propulsion of the capsule depends on the peristaltic bowel's movement, which is variable (it can move the capsule quickly, so the pathological finding is poorly described). The biggest limitation is the impossibility of performing biopsies (21). There are several studies that recommend caution approach regarding the use of this technique in patients with different cardiac devices (cardiac pacemakers, autoimplantable cardiac defibrillators or left ventricular assist device). The reason for this the possible electromagnetic interference between the capsule and the cardiac device. This issue remains a strongly studied topic in the medical field (22-24).

Regarding the treatment, the immune-check point inhibitors, such as Nivolumab and Ipilimumab have improved the management of melanoma's treatment. These therapies improve the immune system's ability to target melanoma cells, leading to an elevated overall survival (OS). Also, the patient's quality of life was improved. Recent studies have shown the effectiveness of the combination between these therapies and surgery. This combination has demonstrated promising results by extending the survival rate and reducing the side effects, compared with the classical chemotherapy (25).

An important study, CheckMate 238, underlines that Nivolumab is one of the best options for this type of malignancy. In this study it was proved that Nivolumab can successfully be utilized as an adjuvant therapy for stage III/IV melanoma patients, compared to Ipilimumab. The study demonstrated long-term improvement in five-year recurrence-free survival (RFS) and also distant metastasis-free survival (DMFS) in Nivolumab branch than in Ipilimumab one. Some biomarkers, like INF γ , PD-L1, CD8 or low CRP level were correlated with a favorable OS and RFS. Despite these findings, it is important to identify new biomarkers that will predict more accurately the efficacy of immunotherapy and increase the patient's benefit (26).

Despite these advancements, it remains crucial to identify new biomarkers to predict immunotherapy efficacy more accurately, thus enhancing patient benefits. This need aligns with findings from the DREAMseq study, which evaluated the sequencing of immunotherapy with targeted therapy in advanced melanoma. DREAMseq revealed that starting treatment with immunotherapy, specifically the combination of nivolumab and ipilimumab, followed by targeted therapy, yielded better outcomes in terms of overall survival compared to the reverse sequence (27).

Our patient's case further illustrates the complex interplay between advanced imaging, early diagnosis, and the strategic application of immunotherapy. Her treatment with Nivolumab, without adverse effects, aligns with the therapeutic benefits highlighted in these studies. The continuation of her therapy, coupled with periodic comprehensive imaging (including PET-CT and CT scans of the thorax, abdomen, and pelvis) and blood tests, reflects a rigorous approach to monitoring and managing metastatic melanoma.

Conclusions

Correlating our case with those from specialized literature we can underline some significant aspects. It is important to always keep in mind a possible diagnosis of metastatic melanoma while dealing with a patient with vague gastrointestinal symptoms and a prior history of MM. Based on the information provided, it can be concluded that MM remains an aggressive condition, prone to local invasion and frequent metastasis, with a preference for the liver, lungs, bones and skin. Although GIT metastases are less common, their diagnosis is a challenge for medical teams due to vague clinical appearance. CT scanning is still the best option that we have to diagnose this malignancy, but the endoscopic approach needs to be intensively studied in order to develop a better tool for early diagnosis of MM metastasis. By improving our detection methods, we can improve the prognostic of this disease and the patient's life.

Conflict of Interest

The authors declare no conflict of interest regarding this case report.

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