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CASE REPORT

Metastatic multifocal melanoma of multiple organ systems: A case report

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Abstract

BACKGROUND

Malignant melanoma is becoming more common among middle-aged individuals all over the world. Melanoma metastasis can be found in various organs, although metastases to the spleen and stomach are rare. Herein we present a rare metastatic multifocal melanoma, clinically and histologically mimicking lymphoma, with metastases of multiple organs.

CASE SUMMARY

A 46-year-old Caucasian male with a history of nodular cutaneous malignant melanoma was presented with nausea, general weakness, shortness of breath, abdominal enlargement, and night sweating. The abdominal ultrasound revealed enlarged liver and spleen with multiple lesions. Computed tomography demonstrated multiple lesions in the lungs, liver, spleen, subcutaneous tissue, bones and a pathological lymphadenopathy of the neck. Trephine biopsy and the biopsy from the enlarged lymph node were taken. Tumor cells showed diffuse or partial positivity for melanocytic markers, such as microphthalmia - associated transcription factor, S100, HMB45 and Melan-A. The tumor harbored BRAF V600E mutation, demonstrated by immunohistochemical labelling for BRAF V600E and detected by real-time polymerase chain reaction test. Having combined all the findings, a diagnosis was made of a metastatic multifocal melanoma of the stomach, duodenum, liver, spleen, lungs, lymph nodes and bones. The patient refused treatment and died a week later.

CONCLUSION

This case report highlights the clinical relevance of rare metastatic multifocal melanoma of multiple organ systems.

Key Words: Metastatic melanoma; Gastrointestinal tract; Nodular; Multifocal; BRAF V600E; Case report

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Core Tip: Malignant melanoma is becoming more common among middle-aged individuals all over the world. Melanoma metastasis can be found in various organs, although multiple metastases to the spleen and stomach are rare. Herein we present a rare metastatic multifocal melanoma, clinically and histologically mimicking lymphoma, with metastases of multiple organs including spleen, stomach, bones, lungs, liver, lymph nodes. This case report highlights the clinical relevance of metastatic multifocal melanoma.

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INTRODUCTION

The incidence rate of melanoma is continuously increasing among middle-aged adults[1]. According to the American Cancer Society, approximately 106110 new cases of melanoma will be diagnosed in the United States for the 2021. Since metastatic melanoma is highly associated with increased mortality, the prognosis for metastatic disease is extremely poor. Approximately 90 percent of patients diagnosed with metastatic melanoma of 3 or more metastases die within one year[2]. The most common metastatic sites of the cutaneous malignant melanoma are lymph nodes, lungs, brain and liver[3]. Though melanoma metastases can be found in almost any part of the body, metastases found in the stomach or spleen are very uncommon[4]. In this case report, we present a patient suffering from malignant cutaneous melanoma with metastases to multiple organs, including stomach, spleen, duodenum, liver, lungs, bones, and lymph nodes.

CASE PRESENTATION

Chief complaints

A 46-year-old Caucasian male was referred to the Department of Hepatology and Gastroenterology complaining of nausea, general weakness, shortness of breath, abdominal enlargement, and night sweating.

History of present illness

Patient's symptoms started about a month ago.

History of past illness

He had a history of localized cutaneous malignant melanoma of the right ear auricle, status after excision with surgery carried out 1 year ago. The excision of the tumor and histological examination was performed in other institution. The primary tumor was nodular melanoma with ulceration and a Breslow thickness of 3.55 mm. High mitotic activity (58 mitosis per square millimeter) was also mentioned in the pathological report. The sentinel lymph node was negative for metastatic melanoma.

Personal and family history

He had no family health history of cancer.

Physical examination

The enlarged and painless lymph node of the neck was found upon physical examination. No other abnormal findings were found.

Laboratory examinations

The initial laboratory tests performed in the Emergency Department showed the increased aspartate transaminase 110 U/L, alanine transaminase 55 U/L (< 40 U/L), alkaline phosphatase 451 U/L (< 40 U/L), lactate dehydrogenase (LDH) 1200 U/L (125-243 U/L), gamma- glutamyl transferase 802 U/L (< 36 U/L), C-reactive protein 168.8 mg/L (0-5 mg/L).

Procalcitonin 7.76 ug/L (< 0.05 L ug/L) levels. Complete blood count revealed anemia with hemoglobin count of 115 g/L and leukocytosis with white blood cells count of 34.87 × 109 per L (4-9.8 × 10⁹ per L) (Table 1).

Imaging examinations

The abdominal ultrasound revealed enlarged liver (308 mm length) and spleen (157 mm length), with multiple hyperechogenic lesions with hypoechogenic shell, the largest with a diameter of 24 mm in the liver. A small amount of ascites was seen in the abdominal cavity.

The patient was referred to the Department of Hepatology and Gastroenterology with a suspected diagnosis of metastatic liver disease, and additional tests were performed.

Computed tomography (CT) was performed and demonstrated multiple lesions in the lungs, liver, spleen, subcutaneous tissue, and bones. CT also showed a pathological lymphadenopathy of the neck and the right lung. Fluid was present in both abdominal and pleural cavity (Figure 1).

Due to anemia and unknown primary cancer site, an upper endoscopy was performed. Gastroscopy revealed atypical ulcers of the duodenum (Figure 2A). It also showed several 0.5 cm red polyps in gastric body and fundus, also in the descending part of the duodenum (Figure 2B and C). Biopsies were taken and sent for histological evaluation.

Histological findings

Considering the typical symptoms (night sweats, fatigue), high leukocyte count and lesions in multiple organs, lymphoma was suspected. Trephine biopsy and the biopsy from the enlarged lymph node in the neck were taken.

Microscopically biopsies from stomach and duodenum lesions showed focally ulcerated, dense infiltrate in lamina propria, composed of discohesive medium-sized cells with pale or clear cytoplasm and hyperchromatic, oval, or irregularly shaped nuclei with small nucleoli (Figure 3A and B). Due to the lack of clinical information about prior melanoma, the suspicion of hematologic malignancy and histological features, such as multifocality and cell discohesion, our initial differential diagnosis was between myeloid leukemia or enteropathy-associated T- cell lymphoma.

However, staining for myeloid and lymphoid markers, such as LCA, CD34, CD117, MPO, CD68, CD123, CD7, CD4, CD3, CD20, CD30 were all negative. On the contrary, tumor cells showed diffuse positivity for CD99 - a non-specific immunohistochemical marker, expressed in a wide variety of malignancies, including melanoma. All the subsequently stained melanocytic markers showed diffuse or focal positivity (Figure 4).

The following bone marrow trephine biopsy revealed metastatic lesion with focal necrosis, composed of densely arranged tumor cells (Figure 5), analogous to previously seen in duodenal and gastric mucosa. Similar diffuse infiltrate with interspersed melanophages was seen in a subsequent core biopsy of the enlarged cervical lymph node.

Tumor cells showed diffuse immunohistochemical labelling for BRAF V600E (Figure 6). Moreover, BRAF V600E mutation was confirmed by real-time polymerase chain reaction test.

FINAL DIAGNOSIS

The final diagnosis of the presented case is a metastatic multifocal melanoma of the stomach, duodenum, liver, spleen, lungs, lymph nodes and bones.

TREATMENT

The patient was referred to the Oncology Clinic for chemotherapy admission.

OUTCOME AND FOLLOW-UP

Having combined all the findings a metastatic multifocal melanoma of the stomach, duodenum, liver, spleen, lungs, lymph nodes and bones was diagnosed.

As the disease was too advanced the surgical treatment was not applicable. After the diagnosis, the patient was referred to the Oncology Clinic for chemotherapy admission, but unfortunately, the patient



Table 1 Laboratory test results			
Characteristics	Result	Units	Normal value
ALT	110	U/L	< 40
AST	55	U/L	< 40
ALP	451	U/L	< 40
LDH	1200	U/L	125-243
GGT	802	U/l	< 36
CRP	168.8	mg/L	0-5
PCT	7.76	ug/L	< 0.051
Hgb	115	g/L	138-172
WBC	34.87	× 10 ⁹ /L	4-9.8

 $ALT: Aspartate\ transaminase;\ ALT:\ Alanine\ transaminase;\ ALP:\ Alkaline\ phosphatase\ LDH:\ Lactate\ dehydrogenase;\ GGT:\ Gamma-\ glutamyl\ transferase;$ CRP: C-reactive protein; PCT: Procalcitonin; Hgb: Hemoglobin; WBC: White blood cells.

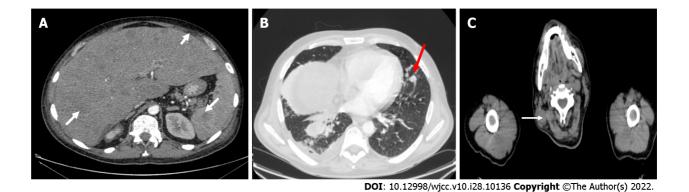


Figure 1 Computed tomography scan. A: Lesions in the liver, spleen, subcutaneous tissue (arrows); B: Lesions in the lungs (arrow); C: Pathological lymphadenopathy of the neck (arrow).



Figure 2 Upper endoscopy. A: Atypical ulcers of the duodenum; B: Atypical polyps in gastric fundus (arrow); C: Atypical polyp in descending part of the duodenum.

refused treatment for personal reasons and died a week later at the hospital, due to malignancy (Figure 7).

Figure 3 Stomach lesion and duodenal biopsy. A: Stomach lesion biopsy. Ulcerated diffuse infiltrate in body-type mucosa; B: Duodenal biopsy. Subtle focal infiltrate in lamina propria, composed of medium-sized dyscohesive cells.

DISCUSSION

Cutaneous melanoma is a malignant tumor arising from melanocytes usually due to effusive ultraviolet exposure[5]. The very first case of melanoma in European literature can be found in the publication of Dr. Highmore and Dr. Bonet, published in 1651. They portrayed melanoma as fatal dark lesions on their patients' bodies[6].

Nodular melanoma is an aggressive, rapidly growing type of cutaneous melanoma, that lacks radial growth phase[7]. Nodular melanoma is repeatedly associated with worse outcome in comparison to other types of cutaneous melanoma[8-10]. Even then adjusted for tumor thickness, nodular melanoma vs superficial spreading melanoma demonstrate higher rate of regional metastasis[10] and substantially worse disease-free survival (DFS)[8]. Ulceration status for cutaneous melanoma is not only a determinant of T classification, but also a predictor of aggressive behavior. Faut et al[11] found that ulcerated nodular melanoma with negative sentinel lymph node biopsy (SLNB) had significantly worse melanoma specific survival (MSS) and DFS in comparison to overall melanoma group with negative SLNB. In fact, ulcerated nodular melanoma with negative SLNB group had similar MSS and DFS as an overall melanoma group with positive SLNB[11].

Although mitotic rate is no longer used as a one of the determinants of T classification[12], it should still be evaluated and noted in pathological report, due to its predictive value [13,14]. The presence of any mitoses in the dermis is associated with positive sentinel lymph node and poorer survival [15]. Interestingly, sentinel lymph node of the primary cutaneous tumor in the current case was negative for metastatic melanoma, despite high tumor thickness and a brisk mitotic activity.

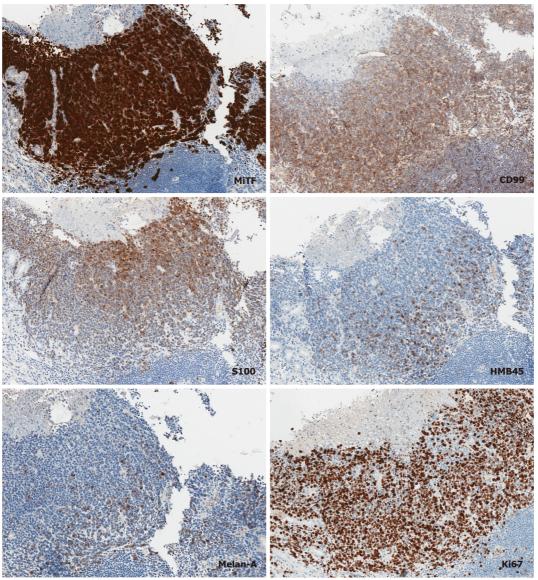
Consistent with study of Hugdahl et al[16], the metastatic melanoma of the current case report demonstrated high BRAF V600E expression, associated with aggressive features in nodular type melanoma group, such as increased thickness, ulceration and higher mitotic count.

Melanoma can metastasize to almost every human organ. The most frequent sites of metastasis are nearby skin, lymph nodes and subcutaneous tissue. Also, melanoma can metastasize to distant organs, most commonly to the brain, liver, lungs, bones, and intestines [2,17]. The most common sites of metastases in the gastrointestinal tract include small intestine, large intestine and the anorectal part of the colon[18]. When progressing, metastatic gastrointestinal tract melanoma can cause intestinal obstruction or bleeding[19]. In the presented case report, melanoma metastasized to multiple organs including stomach, spleen, and bones.

It should be mentioned that metastases of melanoma to the stomach are rare. According to the literature, the typical location of melanoma metastases in the stomach is the body and fundus of the stomach, and metastases are usually arranged as single derivatives rather than multiple ones[20]. Clinically gastric metastases can be silent for a long time or mimic the symptoms of gastritis and are often detected in the end stages of the disease. The prognosis of patients with melanoma metastasis in the gastrointestinal tract (GI) is poor and the median survival time is 4 to 6 mo[21].

As well as to the stomach, metastases to the spleen are rare, especially solitary metastasis. In our case report CT demonstrated multiple lesions in the spleen. Splenic metastases are usually asymptomatic and incidentally found[22]. If isolated and suitable for resection, surgery is the most effective treatment for metastatic spleen melanoma [23]. However multiple metastases like in this case report, are a sign of aggressive disease with a dismal prognosis.

Ultrasound, CT, magnetic resonance imaging and positron emission tomography are used to determine the location of melanoma metastasis, but they are not specific enough to identify the disease [24]. Endoscopy is the "gold standard" for diagnosing GI melanoma. Blecker et al [25] described three forms of endoscopic melanoma metastases presentation: ulcerated melanotic nodules growing on normal rugae, mass lesions with necrosis and melanosis as well as submucosal masses with ulcerations.



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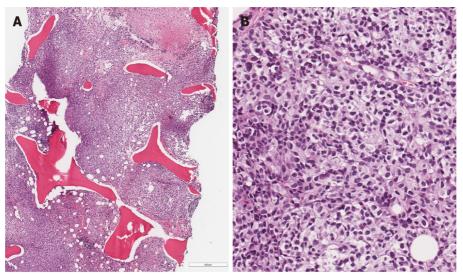
Figure 4 Immunohistochemistry. Tumor cells diffusely and intensely positive for microphthalmia-associated transcription factor, diffusely positive for CD99, partially positive for S100 and focally faintly positive for HMB45 and Melan-A. Ki-67 proliferation index was up to 80%. MiTF: Microphthalmia-associated transcription factor.

In our presented case, gastric melanoma metastases were atypical and were presented as nonspecific red polyps. It is important to note that GI melanoma metastases can look like primary gastric tumors, metastases from other sites as solid tumors or even hematologic malignancies, as in the current case. Therefore, the immunohistochemical stains, such as S100 and HMB45, must be applied to make a final

Treatment of the metastatic melanoma relies on the site and the number of metastases. According to literature, when possible, surgery is the best treatment option and can prolong patients' lives[27]. Radiotherapy is not a method of choice because melanoma is known as radio resistant. Systemic chemotherapy is now used as palliative treatment option for relapsing and resistant to other treatments melanomas[28].

The new studies focus on immunotherapy and target - therapy. Either alone or in combination with chemotherapy, immunotherapy has revolutionized how this malignancy is treated. The most usually applied medications in clinical practice are Nivolumab, Ipilimumab and Pembrolizumab[29]. In the longest follow - up study - Keynote - 001 (phase Ib) study, 655 patients with advanced melanoma received Pembrolizumab. This study showed that for patients, who were treated with Pembrolizumab overall survival rate is higher than those who received treatment with Ipilimumab (28.4% and 12.3%)

In a study by De Luca et al[31], nivolumab showed to be effective and tolerated treatment for metastatic melanoma in patients with BRAF V600E mutation. In our case, BRAF V600E mutation was verified for the patient, but unfortunately the patient declined the proposed treatment. According to



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Figure 5 Bone marrow trephine biopsy. A: Metastatic melanoma with focal necrosis replacing hematopoietic tissue; B: Diffuse compact infiltrate of epithelioid cells with clear or pale cytoplasm and oval, indented or elongated nuclei.

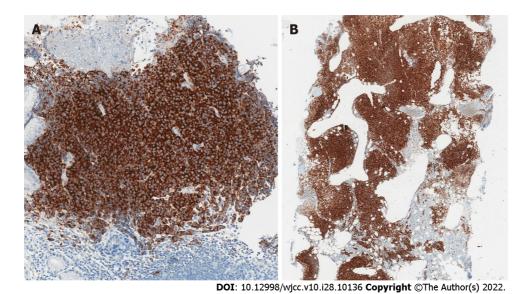


Figure 6 Strong diffuse tumor positivity for BRAF. A: Gastric biopsy, B: Bone marrow trephine biopsy.

clinical studies, BRAF mutation detection is also seen elevated in patients with melanoma. Since 50% of cutaneous melanomas have mutation in BRAF immunotherapy alone or immunotherapy in combination can prolong patients' lives[31,32].

Since melanoma has a poor prognosis for late stages, there are several biomarkers for the diagnosis and prognosis to help determine which patients are at risk of melanoma and what type of treatment do they need. Unfortunately, majority of melanoma diagnostic indicators rely on melanocyte detection rather than melanoma identification.

Serum LDH was the first serological marker to be included in the American Joint Committee on Cancer (AJCC) staging system. In metastatic melanoma, increased serum LDH is amongst the most significant independent prognostic markers[33]. A high blood LDH level has also been demonstrated to be a poor predictor of treatment response[33]. In recent studies, increased baseline LDH has also been consistently linked to low survival and response to immunotherapy rates [34]. However, an elevation in serum LDH is not specific only to melanoma[33]. S100B, a tumor marker, is more specific to melanoma even if its levels can be elevated in other diseases[35]. In a study by Mocellin et al[36], higher S100B levels in the blood were linked to a worse chance of survival in melanoma patients. In a study by Wagner et al[34], when compared to individuals with normal S100B and LDH, patients with high initial S100B and LDH had considerably worse survival rates. Furthermore, the biggest systematic review yet discovered that serum \$100B has a higher accuracy than LDH in predicting melanoma recurrence [37].

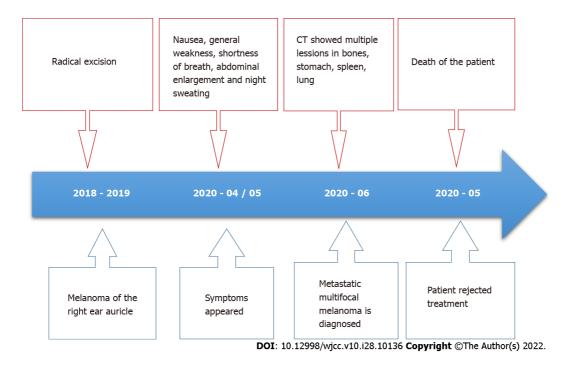


Figure 7 Case history timeline. CT: Computed tomography.

However, to this day there is no agreement on the use of blood testing to detect disease relapse in individuals who have had their melanoma excised.

Nowadays, there are several clinical trials that are about circulating melanoma cells detection and new strategies of screening for early detection of melanoma in population[38]. However, current evidence is limited; therefore, further longitudinal studies looking for early melanoma detection are needed.

CONCLUSION

In this case report, we present a rare case of melanoma metastasizing to multiple organs: GI tract, bones, spleen, lungs, and lymph nodes. This case highlights the importance of suspicion for metastatic melanoma in patients with a history of melanoma in the past. When the diagnosis is confirmed via immunohistochemical staining, combination treatment of surgical resection, chemotherapy or immunotherapy should be considered as it may prolong survival rate.

FOOTNOTES

Author contributions: Maksimaityte V, Reivytyte R, Milaknyte G performed patient's data extraction and literature analysis; Stundiene I was the gastroenterologist who followed up the patient; Maksimaityte V, Reivytyte R, Stundys D, wrote the manuscript; Mickys U, Razanskiene G Kazenaite E, Valantinas J, Stundiene I revised the manuscript for important intellectual content; all authors approved the final version of the manuscript to be submitted.

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