

Amelanotic metastatic gastric malignant melanoma: a case report

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Melanoma is a malignant form of cutaneous cancer with an increasing incidence since 1970s, accounting for nearly 75% of the death related to skin cancer especially in western countries. Highest recurrence and mortality were observed for the subtype with distal metastasis, demonstrating poor outcomes. However, high incidence of gastrointestinal metastasis of malignant melanoma is frequently misdiagnosed due to lack of specific clinical manifestations, especially for the rare observed cases presented amelanotic appearance, accounting for about 2% of all metastatic cases. In the present study, we reported a 36-year-old male patient, who was firstly diagnosed as gastric cancer, and then was confirmed as amelanotic melanoma metastasis by pathological examination, demonstrating positive for melanoma markers including Melan A, S-100, Hmb45 and CD79a. In conclusion, for the amelanotic neoplasm observed during gastroscopy in patients with melanoma history,

pathological examination should be carried out to confirm the possibility of melanoma metastasis, providing evidences for the following treatment. *Anti-Cancer Drugs* 33: e808–e812 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Established Facts and Novel Insights

Established Facts

- Melanoma is a malignant form of cutaneous disease with high metastasis and mortality.
- High incidence of gastrointestinal metastasis of malignant melanoma is frequently misdiagnosed due to lack of specific clinical manifestations.

Novel Insights

- For the amelanotic neoplasm found during gastroscopy in patient with a history of melanoma, detailed pathological examination should be carried out in combination with previous medical history to determine the nature of the tumor and treatment regime.

Introduction

Incidence of melanoma has kept rising since 1970s, with more than 232 100 cases diagnosed in 2017, accounting for

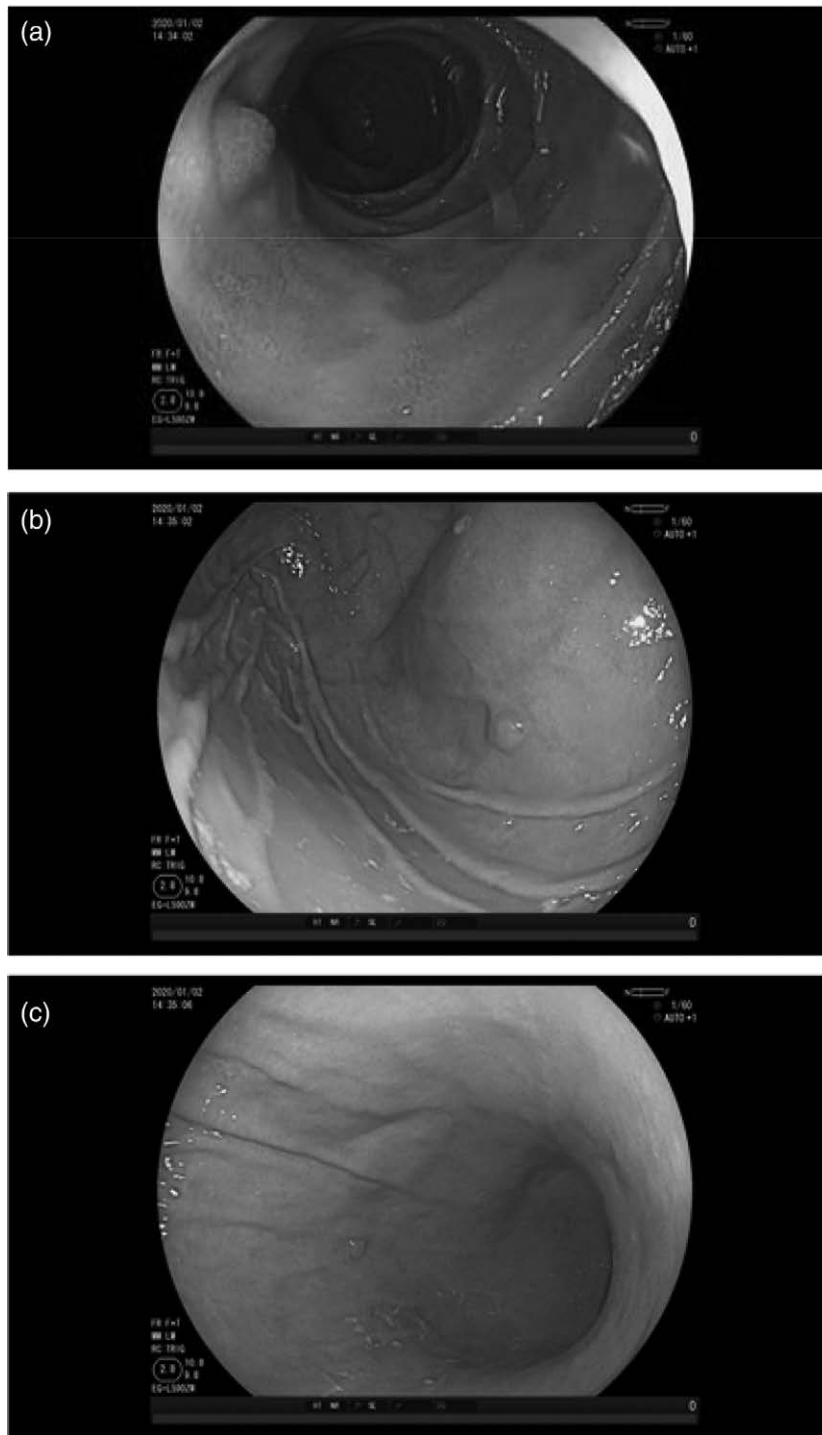
about 1.7% of all new cancer cases worldwide and causing about 55 500 deaths [1]. However, both the incidence and mortality differ widely among species, ranging from 0.2 of 100 000 in Asian population to 7.7 of 100 000 in Americans [1]. Risking factors for melanoma have been established as ultraviolet radiation, presence of dysplastic naevi, family or personal history of cutaneous melanoma [2]. Moreover, genetic alterations such like BRAF, the telomerase reverse transcriptase (TERT), the cyclin-dependent kinase inhibitor (CDKN2A), tumor protein 53 (TP53), phosphatase and tensin homology (PTEN) have been well documented [2,3]. Of note, BRAF^{V600E} has been observed in nearly 50% of all the melanoma cases, and inhibitors targeting this mutation demonstrated promising benefits in clinical practice. Compared with localized disease, mortality for patient with distal metastasis remains disappointing, which due to insufficient understanding of the underlying molecular mechanism. Moreover, clinical diagnosis of the distal metastasis sites is easy to be ignored in clinical practice, especially for the amelanotic melanoma. Taken together, thoroughly inspection should be warranted for patients with history of melanoma.

Case presentation

A 36-year-old man presented with progressive anorexia, intermittent nausea and vomiting without significant medical causes. On 2 January 2020, gastroscopy

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Fig. 1

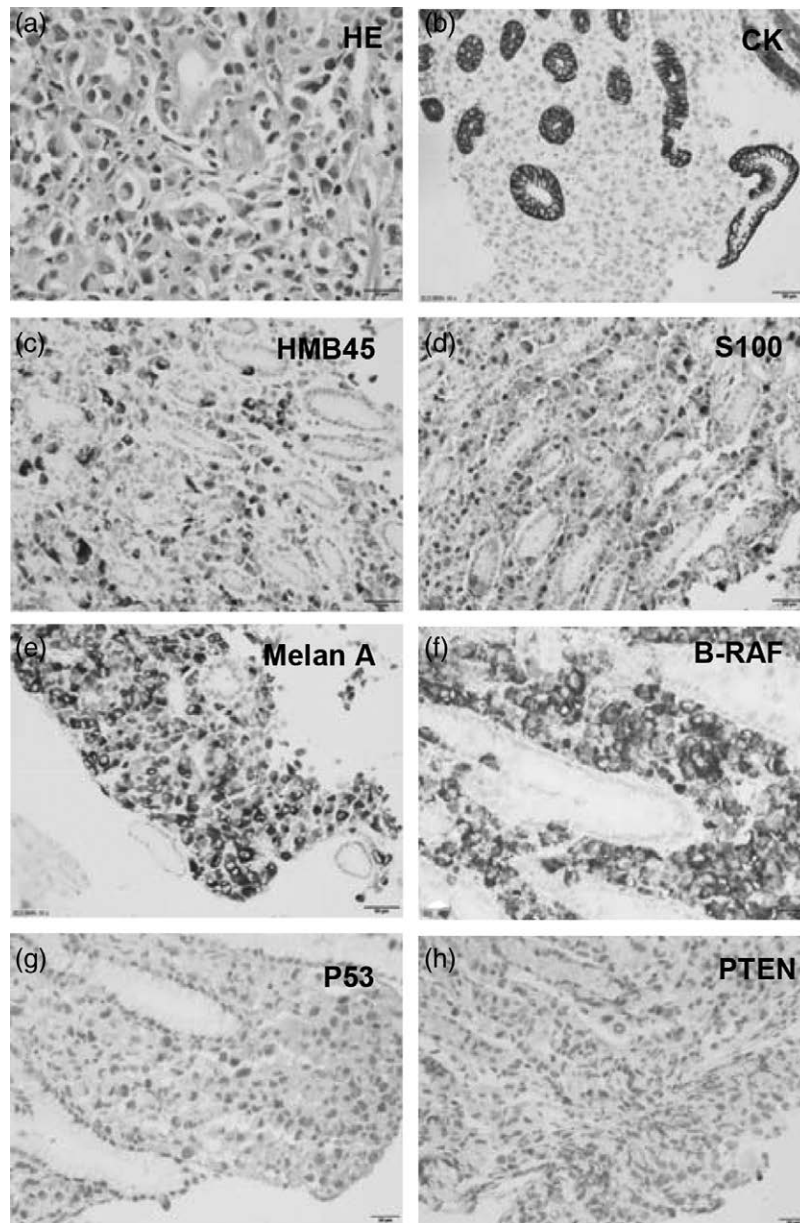


The endoscopic images of amelanotic metastatic gastric malignant melanoma. Hemispherical protuberance of about 0.4 cm gastric metastatic sites without pigmentation that found in the lower curvature of the body and the fundus of the stomach.

examination revealed (Fig. 1) two hemispherical protuberance (0.4 cm) at the lower part of the body and the fundus of the stomach, respectively. Subsequently, both elastic lesions were removed and were then sent

for pathological examination. Hematoxylin-eosin (HE) staining images strongly suggested the lesion as neoplasm as shown in Fig. 2a. Considering the medical history of melanoma resection in June 2019,

Fig. 2



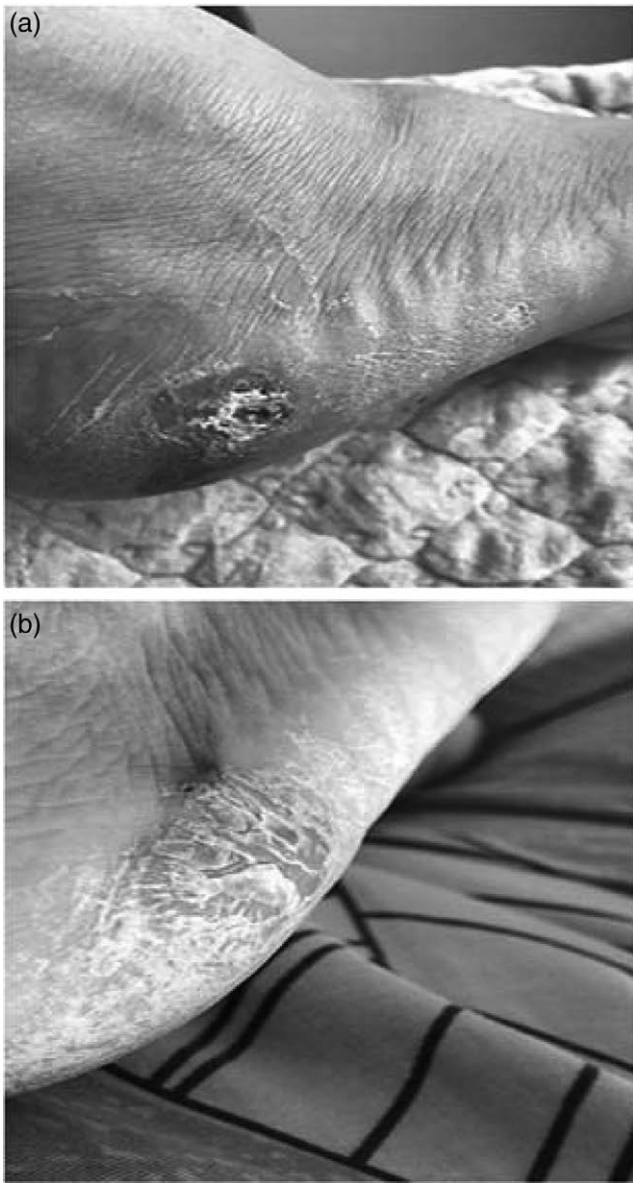
Immunohistochemistry of cancer biomarkers in specimen from stomach biopsy. Metastatic melanoma stained with hematoxylin-eosin, original magnification 200 X. Immunohistochemistry examination of cancer-related marker including: CK (–), B; HMB45 (+), C; S-100 (+), D; MelanA (+), E; B-RAF (+), F; P53 (+), G; PTEN (–), H.

immunohistochemical staining was performed for melanoma markers and the results demonstrated that the neoplastic cells of gastric body (Fig. 2) were positive for Melan A, S-100, Hmb45, CD79a, B-RAF and P53, focally positive for c-kit, and negative for AE1, CK, PTEN, CD56 and Syn, and the neoplastic cells of gastric fundus were positive for CD68 and negative for AE1 and CK. In addition, the B-RAF mutation of V600E was confirmed by the next-generation sequencing. Collectively, the patient was diagnosed with metastatic stomach melanoma. The patient was lately

diagnosed with multiple visceral and bone metastasis of melanoma by computed tomography (CT) scanning at the Beijing Cancer Hospital.

In 2014, a brown tough bulge firstly appeared on the right plantar of the patient and was left untreated until April 2019, when the lesion presented local ulceration and darkness, accompanied by local pain. The lesion was diagnosed as melanoma by pathological examination of biopsies on 27 May 2019 at the First Hospital of Peking University, and presence of black cells in the middle

Fig. 3



Picture of primary lesion of melanoma in patient's heel. The lesion before (upper image) resection and post-resection (lower image).

and lower layers of the epidermis were observed with hyperplastic, scattered and non-nested with obvious Atypia. The lesion was then removed by Mohs micro-surgery at the First Hospital of Peking University on 28 June 2019. Invasive nodular malignant melanoma was further confirmed by postoperative pathological examination, demonstrated as level 4 Clark grade, Breslow depth >2.175 mm, vertical growth, mitotic ratio <1 mm², no vascular involvement, no perineural invasion, no regression phenomenon, vertical growth, no microsatellite foci and no active infiltrating lymphocytes. The patient recovered well as shown in Fig. 3.

Discussion and conclusions

Malignant melanoma ranks as the most common cancer demonstrating gastrointestinal tract (GIT) metastasis. However, only 1–4% of patients with malignant melanoma are diagnosed with gastrointestinal metastases before death. On the contrary, GIT metastasis was observed in more than 60% of melanoma patients by autopsy. Furthermore, 23% of gastrointestinal metastases came from malignant melanoma [4]. The most common site of the gastrointestinal metastasis of malignant melanoma is the small intestine, followed by the stomach [5].

The low rate of diagnosis for gastrointestinal metastasis is mainly due to lack of distinguishable clinical manifestations, which are similar to those of gastritis, peptic ulcer and gastric cancer and the common symptoms are epigastric discomfort, poor receptivity, nausea and vomiting. In addition, the endoscopic results of melanoma are also atypical, so pathology and immunohistochemical are often required to confirm the diagnosis. The common endoscopic findings of melanoma are as follows [6]: (1) single protuberance with smooth local surface, with the top being pitted or ulcerated, similar to submucosal tumors; (2) multiple protuberances, whose endoscopic features are the same as those of single protuberance and (3) diffuse protuberances, similar to Bormann IV gastric cancer. The surface of most gastrointestinal melanomas often has varying degrees of pigmentation, which may be black, brown, gray or dark brown. In this case, the clinical manifestations were loss of appetite with nausea and vomiting, which were not specific, and there was no pigmentation on the skin of the whole body on physical examination. The gastroscopy showed the lesions were very small atypical multiple protuberances, with smooth, soft and elastic surface, no pigmentation and no obvious characteristics of malignant tumors. The biopsy specimen was devoid of melanin granules and the nuclei of the tumor cells were very similar to that of lymphoma, malignant melanoma and poorly differentiated adenocarcinoma. Therefore, the initial HE staining could not confirm the diagnosis of melanoma. After further immunohistochemical examination, the final diagnosis of gastric metastasis of malignant melanoma was confirmed.

At present, the common immunohistochemical markers are S-100, MelanA, HMB45 and SOX-10 for the diagnosis of malignant melanoma. Novel molecular techniques can also assist in the diagnosis of melanoma [7], including comparative genomic hybridization, fluorescence in situ hybridization (FISH), tumor gene expression profiling [8], and adhesive patch genomic analysis [9]. FISH facilitates the assessment of melanoma-associated specific chromosomal abnormalities and is a direct diagnostic tool for ambiguous melanocytic lesions [10–12]. This patient was diagnosed with gastric melanoma by a combination of the above-mentioned immunohistochemical parameters.

The median survival time of malignant melanoma patients with gastrointestinal metastases is less than 1 year, and the

high mortality rate observed in these patients is associated with multiple metastases to other organs, such as the lung, liver, pancreas and brain [13]. Sun *et al.* [14] showed that radical surgery can effectively relieve symptoms in patients with malignant melanoma that initially metastasizes to the stomach, and may be helpful in extending survival.

Patients with gastric metastases from malignant melanoma have no typical clinical presentation and are often accompanied by a history of malignant melanoma of the skin and other sites. Therefore, clinicians need to ask for a detailed history to diagnose metastatic gastric melanoma. Recently there are few cases of gastrointestinal metastasis of malignant melanoma in the literature at home and abroad, most of which are case reports and there is a lack of understanding of this disease and treatment experience. It is easy to miss the diagnosis of gastric melanoma by gastroscopy and pathological biopsy without immunohistochemical staining, which leads to delayed treatments. Therefore, it is necessary to improve endoscopists' understanding of gastrointestinal malignant melanoma. During endoscopy, any suspicious lesions, especially protrusion lesions, whether single or multiple, with or without pigmentation, need to be carefully observed, actively sent for pathological tissue biopsy combined with immunohistochemical to achieve an early diagnosis to improve the prognosis of patients with melanoma. At the same time, for patients with a previous record of melanoma, regular physical examination is required and when gastrointestinal-related symptoms occur, abdominal-enhanced CT, gastrointestinal endoscopy and other examinations should be completed in time to determine whether there is metastasis of melanoma. Besides, pathology is still the gold standard for melanoma diagnosis. In our case, the patient was diagnosed with metastatic gastric malignant melanoma, relying on the relevant medical history of plantar melanoma, gastroscopic biopsy with special immunohistochemical staining. At present, the imaging results of the patient in January 2020 suggested that the melanoma had multiple organ metastases. For this patient, from the diagnosis of plantar melanoma to the multiple organ metastases of melanoma, the duration was only six months. For advanced patients with distant metastasis of plantar melanoma, systemic therapy including a complete resection of metastatic lesions, chemotherapy, targeted therapy and immunotherapy remain the most important treatment options. But specific treatment methods vary from person to person. We ultimately recommend that the patient visit a specialized hospital for melanoma.

In summary, for patients with a history of malignant melanoma, if they present nonspecific gastrointestinal symptoms, they should be alert to the possibility of gastrointestinal metastasis, and gastrointestinal endoscopy and gastroscopic biopsy with special immunohistochemical stains should be performed promptly. If necessary, novel molecular techniques can also be used for the diagnosis of melanoma. Patients with gastrointestinal metastasis of malignant

melanoma have a poor prognosis and their survival time is often no more than 1 year. Treatment includes surgical resection of solitary metastases, chemotherapy, immunosuppressive agents, biological chemotherapy and so on. Different patients need to be treated individually and precisely.

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M.Z. and D.-y.Z. design all the case design and data analysis; G.-j.Z. and Z.-b.W. collected the data; M.Z. and M.-y.L. wrote the article.

Ethical approval was obtained from Ethics Committee of General Hospital of the Chinese People's Liberation Army.

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

All the data and materials involved in the article are available upon request.

Conflicts of interest

There are no conflicts of interest.

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