

Case Report

Primary gastric malignant melanoma might originate from amine precursor uptake and decarboxylation cells

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Abstract: Primary gastric malignant melanoma is a rare malignant tumor. The purpose of this study is to determine the origination of primary gastric malignant melanoma. We report a case of a 63-year-old male with a history of right limb movement disorder for one month. The patient underwent microscopic supratentorial mass resection and proximal stomach resection. Hematoxylin-eosin and immunohistochemical staining, amplification refractory mutation system analysis and transmission electron microscopy test were performed. Hematoxylin-eosin staining showed diffuse patchy distribution of tumor cells, the pleomorphism, epithelioid or fusiform, abundant cytoplasm, increased mitotic figures, and obvious melanin particles. Immunohistochemical results indicated positive expression for S-100, HMB45, Melan-A, CD56, NSE, Syn, CgA, Vimentin and bcl-2, and negative expression for CK-Pan, CD117, Dog-1, CD34, Desmin, Actin-ping, HHF35, MBP. BRAF V600E mutation was detected in primary gastric malignant melanoma. The neurosecretory granules were observed in the cytoplasm of melanoma cells. Pathological examination finally made a definite diagnosis of primary malignant melanoma, serosa layer and perigastric lymph nodes involved (1/20), with the left parietal lobe metastasis. Immunohistochemical and transmission electron microscopy test results indicated that primary gastric malignant melanoma might originate from amine precursor uptake and decarboxylation cells.

Keywords: Stomach, primary, malignant melanoma, amine precursor uptake and decarboxylation cells

Introduction

Malignant melanoma is a malignance, originated in melanocytes, which are commonly found in the skin, eyes, meninges, and anal region, including the rectum and sigmoid colon. Primary gastric malignant melanoma (PGMM) is rare [1, 2]. The clinical manifestation is not specific and usually similar with other common malignancies at this site, such as gastric cancer and lymphoma. Most melanomas identified in the stomach represent metastases from cutaneous sources. Here we report a case of PGMM, and review related literature for further understanding and management of this disease.

Case report

A 63-year-old male was referred to Xiangya Hospital with a history of right limb movement

disorder for one month. On admission, he was chronically ill-looking. His blood pressure was 129/79 mmHg, pulse 78/min, respiration 17/min, and body temperature 36.8°C. Lungs were clear to auscultation and heart examination was normal, without murmur or rubs. Liver and spleen were non-palpable. Color of skin and mucous membrane were normal, without melanin spots and tumor. Laboratory test results showed WBC $10.3 \times 10^9/L$, RBC $4.89 \times 10^{12}/L$, hemoglobin 99 g/L. Tumor markers showed CA19-9 8.72 KU/L (0~35 KU/L), CEA 1.22 ng/mL (0~5 ng/mL), CA125 7.61 KU/L (0~35 KU/L).

Head Magnetic Resonance Imaging (MRI) brain scan enhancements showed the abnormal signal and spectrum of the left parietal lobe: hemangioblastoma? Glioma (**Figure 1**). Admit-

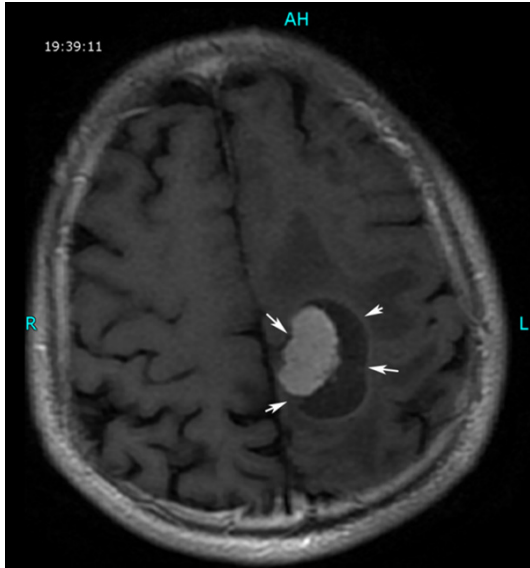


Figure 1. Head MRI brain scan enhancements revealed the abnormal signal and spectrum of the left parietal lobe: hemangioblastoma? Glioma?

ting diagnosis was intracranial mass (the left parietal lobe): hemangioblastoma? Glioma? During hospitalization, the patient underwent microscopic supratentorial neoplasm resection.

On the third day after the operation, massive hemorrhage in upper digestive tract was diagnosed and abdominal computed tomography (CT) scan which indicated: 1. The lesions between liver and stomach, gastrointestinal stromal tumor (GIST)? (**Figure 2A**) 2. The obvious thickening of gastric wall, gastric mucous membrane structure disappeared. 3. The mass properties between liver and stomach need to be determined: lymph node enlargement? GIST? (**Figure 2B**).

Gastroscopy showed a huge ulcer lump (5.0 cm×4.0 cm) at the bottom of stomach, with purplish-brown mucosa, considering melanoma or GIST? (**Figure 3A**). The patient underwent proximal stomach resection. Gross observation showed a 5.5 cm×4 cm×3 cm size ulcer lump in gastric mucous membrane, and a 3 cm×3 cm×2 cm size black lump in stomach bottom serosa, with clear boundaries (**Figure 3B**). The patient underwent proximal stomach resection.

Pathological examination showed diffuse patchy distribution of tumor cells, the pleomor-

phism, epithelioid or fusiform, abundant cytoplasm and vacuolated nuclei, and obvious nucleoli, increased mitotic figures, obvious melanin particles (**Figure 4A**). IHC results indicated positive expression for S-100 (**Figure 4B**), HMB45 (**Figure 4C**), Melan-A (**Figure 4D**), CD56 (**Figure 4E**), NSE (**Figure 4F**), Syn, CgA, Vimentin and bcl-2, and negative expression for CK-Pan, CD117, Dog-1, CD34, Desmin, Actin-ping, HHF-35 and MBP. The final diagnosis was (the bottom of stomach) primary malignant melanoma (ulcer type of neoplasm, 5.5 cm×4 cm×3 cm), serosa layer and perigastric lymph nodes involved (1/20), with the left parietal lobe metastasis.

BRAF V600E mutation was detected in PGMM by the fluorescent signal curves and the threshold line (**Figure 5**).

To elucidate the origination of PGMM, we examined the Cellular ultrastructure by use of TEM. As shown in the electron micrographs, the neurosecretory granules were observed in the cytoplasm of melanoma cells at low magnification (**Figure 6A**) (10000×) and at high magnification (**Figure 6B**) (20000×) (arrow).

Discussion

Malignant melanoma is derived from the partial malignant transformation of melanocytes. It is a kind of highly invasive malignance, with metastasis about 20% [3]. It can occur in the skin, eye, vulva, the next sites are rectum, anus, genital tract, esophagus, etc in the adults [4]. Literature review found that PGMM was rare, mainly in adults with male predominance. Epigastric discomfort, abdominal pain, hemorrhage of upper gastrointestinal tract were common symptoms [5, 6], and the upper gastric body was the common site.

Diagnosis of PGMM relied mainly on clinic, image, histopathology [7] and IHC. Pathological characteristics including: 1. Diffuse patchy distribution of tumor cells, the pleomorphism, epithelioid or fusiform, abundant cytoplasm and vacuolated nuclei, and obvious nucleoli, increased mitotic figures, obvious melanin particles [8]; 2. IHC showed HMB45, Melan-A, S-100 and Vimentin were positive, and CK-pan, EMA, CD45RO, CD20, and CD79a were negative; 3. Electron microscopy displayed tight melanoma particles in tumor cells; 4. BRAF V600E muta-

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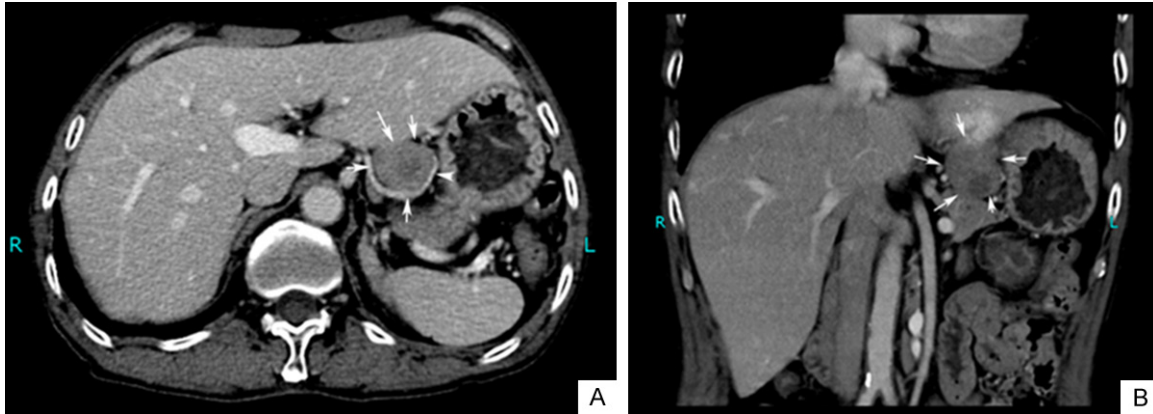


Figure 2. Computed tomography (CT) scan enhanced three-dimensional imaging. A: Liver and spleen CT scan enhanced three-dimensional imaging indicated the lesions between liver and stomach, GIST? B: Abdominal pelvic CT scan enhanced three-dimensional imaging manifested the obvious thickening of gastric wall, gastric mucous membrane structure disappeared, and the mass properties between liver and stomach need to be determined: lymph node enlargement? GIST?

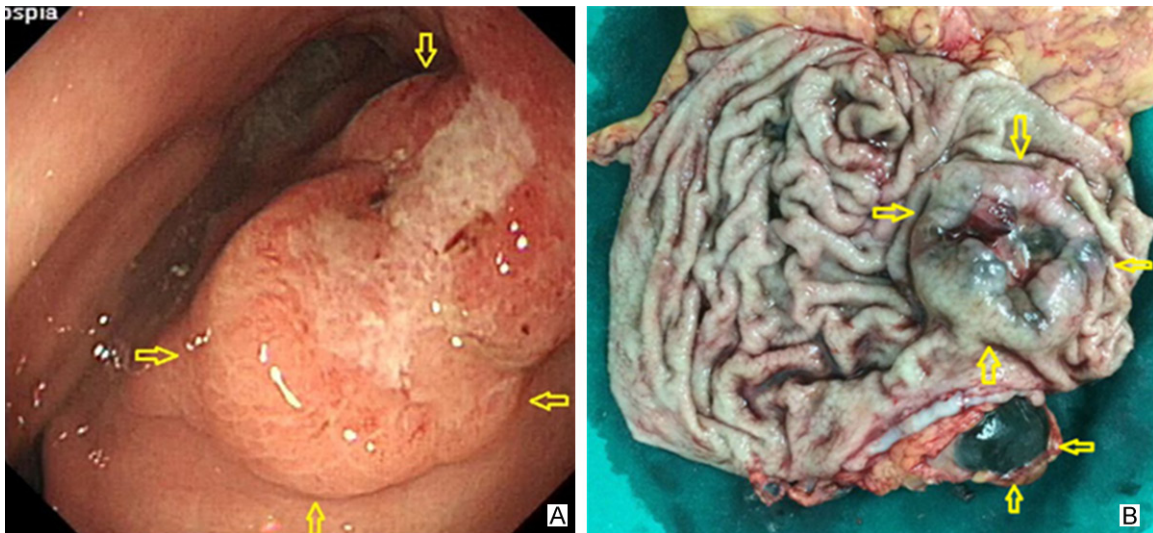


Figure 3. Characteristics of the tumor. A: Gastroscopy showed a huge ulcer lump (5.0×4.0 cm) at the bottom of stomach, with purplish-brown mucosa, considering melanoma or GIST? B: Gross observation showed a 5.5×4×3 cm size ulcer lump in gastric mucous membrane, a 3×3×2 cm size black lump in stomach bottom serosa, with clear boundaries.

tion rate was positive in 70-80% malignant melanoma [9-11].

In this patient, the diagnosing criteria for primary gastric melanoma were based on: 1. Histopathology and image supported primary gastric tumor. Tumor located in the mucosa layer of stomach. 2. The morphology was consistent with typical features of malignant melanoma. 3. IHC results showed HMB45, S-100, Melan-A and Vimentin were positive, and EMA, CEA were negative. 4. No potential lesions were

found on the skin, eye, vulva, rectum, anus, genital tract, esophagus, etc, suggesting the diagnosis of primary gastric melanoma was correct.

PGMM should be distinguished with other gastric tumors, including poorly differentiated adenocarcinoma, metastatic malignant melanoma, GIST, and so on [12-14]. 1. Metastatic gastric malignant melanoma: the main difference between primary and metastatic malignant melanoma was that if there had lesions other

Primary gastric malignant melanoma

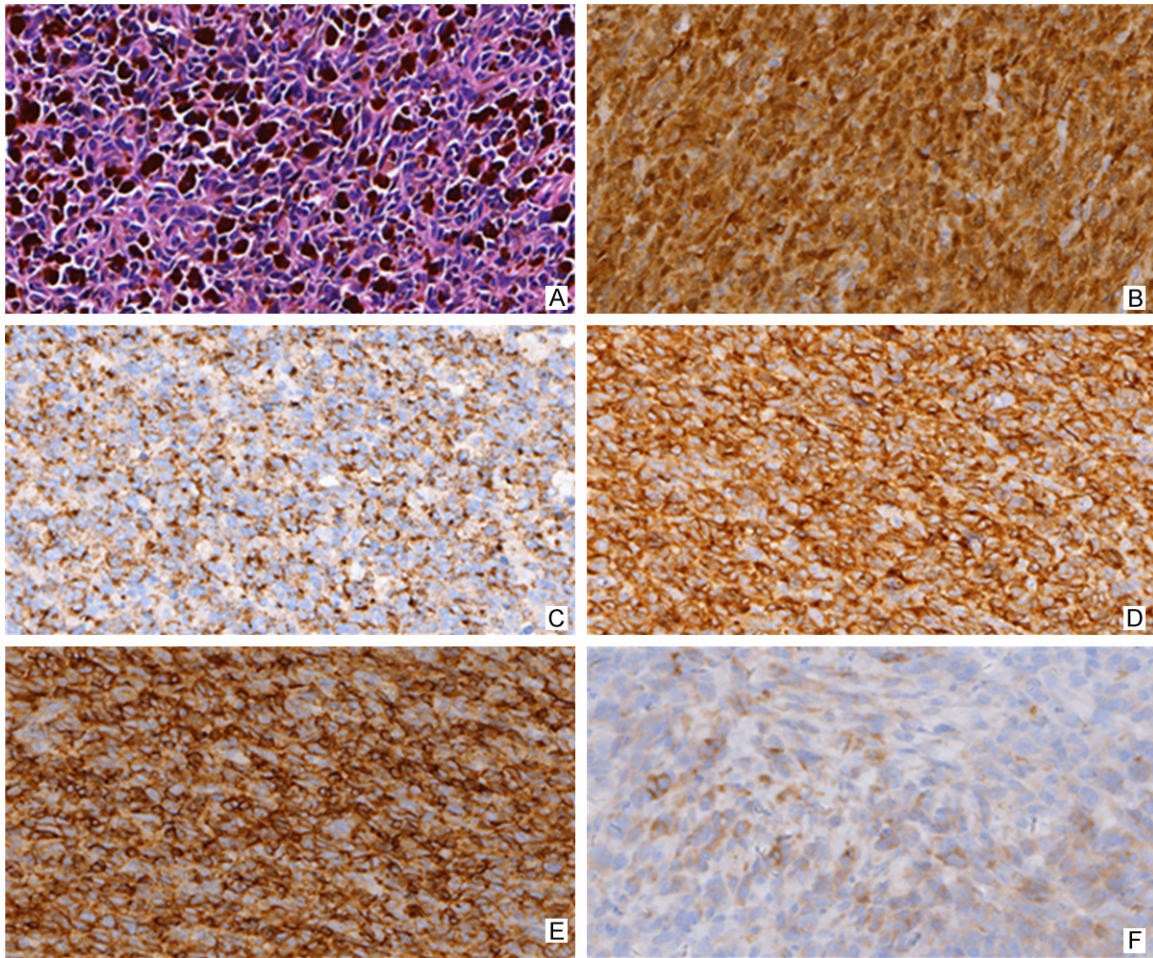


Figure 4. Hematoxylin-eosin and Immunohistochemical staining of Primary gastric malignant melanoma. A: Primary gastric malignant melanoma showed diffuse patchy distribution of tumor cells, the pleomorphism, obvious melanin particles (400×) (HE); B: The tumor cells were positive for S-100 protein in both nucleus and cytoplasm (400×); C: The tumor cells were positive for HMB45 protein in cytoplasm (400×); D: The tumor cells were positive for Melan-A protein in cytoplasm (400×); E: The tumor cells were positive for CD56 protein in membrane (400×); F: The tumor cells were positive for NSE protein in cytoplasm (400×).

than gastric pattern from clinical and imageology data [15-17]. Therefore thorough physical examination, laboratory studies, and imaging are required to rule out this possibility. 2. Poorly differentiated adenocarcinoma: IHC are helpful to confirm: HMB45 (+), S-100 (+), Melan-A (+), Vimentin (+), AE1/AE3 (-). 3. Gastric lymphoma: barium meal examination showed irregular diffuse thickening in gastric mucosa plica, with irregular multiple ulcer, and ulcer edge mucosa forming large fold, single or multiple circular filling defect, a cobblestone appearance change. Gastroscopy showed huge gastric mucosa plica, with single or multiple polypoid. Stomach biopsy can be used to identify. 4. Other primary gastric tumor: GIST, malignant schwannoma,

leiomyosarcoma, and so on. IHC (HMB45, CD-117, S-100, SMA, Desmin, etc) can effectively help to diagnose.

The precise mechanism of the occurrence and development of this malignance had not been clarified. Due to its scarcity, some scholars postulated that the PGMM might originate from squamous intraepithelial melanocytes of cardia [18]. Another possible explanation of its origin according to the amine precursor uptake and decarboxylation (APUD) cell concept is suggested [19-21]. This concept may lessen the doubts and confusion whenever a gastric melanoma is discovered and a primary tumor at one of the more common sites can reasonably be excluded.

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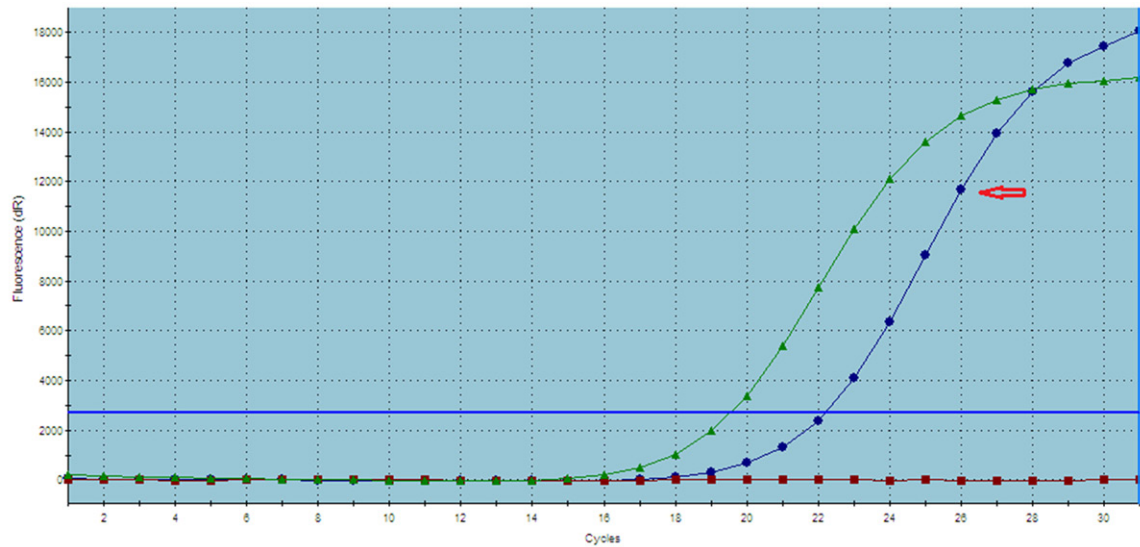


Figure 5. BRAF V600E mutation test via ARMS analysis. BRAF V600E mutation was detected in primary gastric malignant melanoma (red arrow).

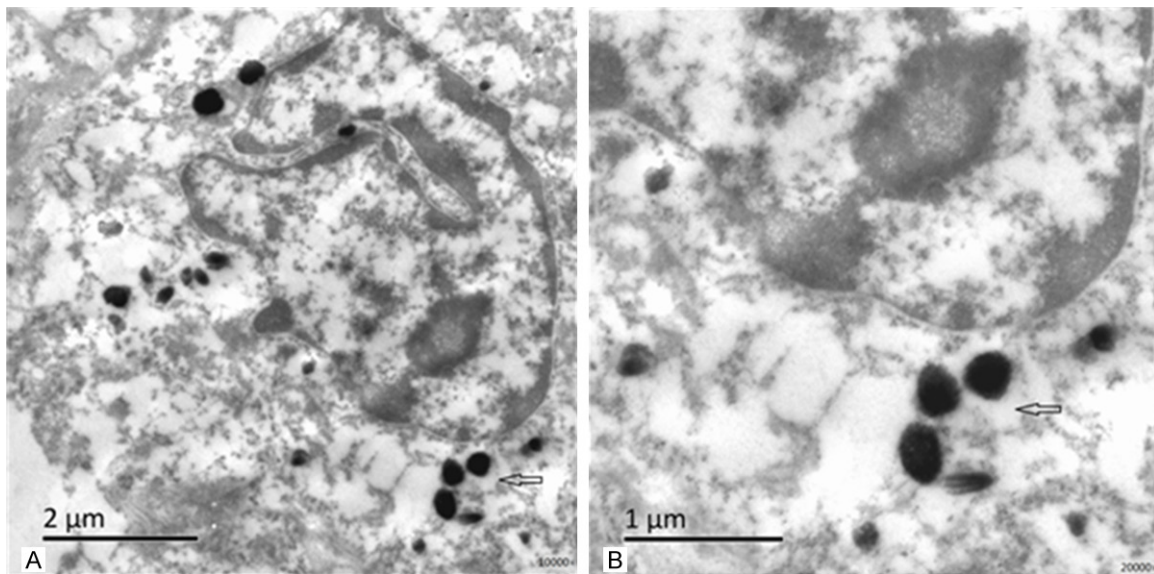


Figure 6. Transmission electron microscopy images. The neurosecretory granules were observed in the cytoplasm of melanoma cells (arrow). A: Low magnification (10000 \times); B: High magnification (20000 \times).

In this patient, neuroendocrine markers, such as CD56, NSE, Syn, CgA, were positive. TEM showed neurosecretory granules in the cytoplasm of melanoma cells. So the PGMM might originate from APUD cells.

Surgical resection is the main treatment for gastrointestinal melanoma. The patient underwent microscopic supratentorial mass resection and proximal stomach resection. He had 10 months relapse-free survival [22-26].

In conclusion, primary melanoma in gastrointestinal tract is rare tumor with poor prognosis. The diagnosis based primarily on clinic, image, histopathology and IHC results. PGMM might originate from APUD cells.

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Disclosure of conflict of interest

None.

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References

- [1] Augustyn A, de Leon ED, Yopp AC. Primary gastric melanoma: case report of a rare malignancy. *Rare Tumors* 2015; 7: 5683.
- [2] Lagoudianakis EE, Genetzakis M, Tsekouras DK, Papadima A, Kafiri G, Toutouzas K, Katergiannakis V, Manouras A. Primary gastric melanoma: a case report. *World J Gastroenterol* 2006; 12: 4425-4427.
- [3] Li ZY, Cai JQ, Cui XZ, Shao YF, Jin YB. Outcome of malignant melanoma in gastrointestinal tract: clinical analysis of 70 cases. *Zhonghua Wai Ke Za Zhi* 2008; 46: 574-576.
- [4] Jora C, Pankaj P, Verma R, Jain A, Belho ES. Primary malignant melanoma of the esophagus. *Indian J Nucl Med* 2015; 30: 162-164.
- [5] Mihajlovic M, Vlajkovic S, Jovanovic P, Stefanovic V. Primary mucosal melanomas: a comprehensive review. *Int J Clin Exp Pathol* 2012; 5: 739-753.
- [6] Tacastacas JD, Bray J, Cohen YK, Arbesman J, Kim J, Koon HB, Honda K, Cooper KD, Gerstenblith MR. Update on primary mucosal melanoma. *J Am Acad Dermatol* 2014; 71: 366-375.
- [7] Shan GD, Xu GQ, Chen LH, Wang ZM, Jin EY, Hu FL, Li YM. Diffuse liver infiltration by melanoma of unknown primary origin: one case report and literature review. *Intern Med* 2009; 48: 2093-2096.
- [8] Farnedi A, Magrini E, Betts CM, Cocchi R, Pession A, Foschini MP. Cytogenetic analysis of oral malignant melanoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 99: 655-656.
- [9] Zepeda-Lopez PD, Salas-Alanis JC, Toussaint-Caire S, Gutierrez-Mendoza D, Vega-Memije E, Silva SL, Fajardo-Ramírez OR, Alcazar G, Moreno-Treviño MG, Saldaña HA. BRAF mutation (V600E) prevalence in Mexican patients diagnosed with melanoma. *Case Rep Oncol* 2016; 9: 241-245.
- [10] Lyubchenko L, Emelyanova M, Shamanin V, Demidov L, Zasedatelev A, Nasedkina T. The \textit{BRAF} V600E mutation in single-institution study of Russian melanoma patients. *Cancer Biomark* 2016; 16: 153-160.
- [11] Sakaizawa K, Ashida A, Uchiyama A, Ito T, Fujisawa Y, Ogata D, Matsushita S, Fujii K, Fukushima S, Shibayama Y, Hatta N, Takenouchi T, Uehara J, Okuyama R, Yamazaki N, Uhara H. Clinical characteristics associated with BRAF, NRAS and KIT mutations in Japanese melanoma patients. *J Dermatol Sci* 2015; 80: 33-37.
- [12] Ozturk O, Basar O, Koklu S, Yuksel O, Purnak T, Sokmensuer C. An unusual presentation of malignant melanoma: amelanotic gastric metastasis. *Am J Gastroenterol* 2015; 110: 476.
- [13] Aggarwal R, Dhawan S, Chopra P. Primary gastric melanoma: a diagnostic challenge. *J Gastrointest Cancer* 2014; 45: 33-35.
- [14] Noraidah M, Jasmi AY. Malignant melanoma of the gastrointestinal tract presenting as a bleeding gastric ulcer. *Malays J Pathol* 2003; 25: 57-61.
- [15] Alghisi F, Crispino P, Cocco A, Richetta AG, Nardi F, Paoluzi P, Badiali D. Morphologically and immunohistochemically undifferentiated gastric neoplasia in a patient with multiple metastatic malignant melanomas: a case report. *J Med Case Rep* 2008; 2: 134.
- [16] Gabellini C, Trisciuglio D, Desideri M, Candiloro A, Ragazzoni Y, Orlandi A, Zupi G, Del Bufalo D. Functional activity of CXCL8 receptors, CXCR1 and CXCR2, on human malignant melanoma progression. *Eur J Cancer* 2009; 45: 2618-2627.
- [17] Bankar S, Patkar S, Desai S, Shrikhande SV. Unusual presentation of melanoma of unknown primary origin: a case report and review of literature. *J Cancer Res Ther* 2015; 11: 1025.
- [18] Ahn JY, Hwang HS, Park YS, Kim HR, Jung HY, Kim JH, Lee SE, Kim MA. Endoscopic and pathologic findings associated with clinical outcomes of melanoma in the upper gastrointestinal tract. *Ann Surg Oncol* 2014; 21: 2532-2539.
- [19] Krausz MM, Ariel I, Behar AJ. Primary malignant melanoma of the small intestine and the APUD cell concept. *J Surg Oncol* 1978; 10: 283-288.
- [20] Tabaie HA, Citta RJ, Gallo L, Biondi RJ, Meoli FG, Silverman D. Primary malignant melanoma of the small intestine: report of a case and discussion of the APUD cell concept. *J Am Osteopath Assoc* 1984; 83: 374-377.

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- [21] Khosrowshahi E, Horvath W. Primary malignant melanoma of the small intestine—a case report. *Rontgenpraxis* 2002; 54: 220-223.
- [22] El-Sourani N, Troja A, Raab HR, Antolovic D. Gastric metastasis of malignant melanoma: report of a case and review of available literature. *Viszeralmedizin* 2014; 30: 273-275.
- [23] Voss RK, Woods TN, Cromwell KD, Nelson KC, Cormier JN. Improving outcomes in patients with melanoma: strategies to ensure an early diagnosis. *Patient Relat Outcome Meas* 2015; 6: 229-242.
- [24] Cheung MC, Perez EA, Molina MA, Jin X, Gutierrez JC, Franceschi D, Livingstone AS, Koniaris LG. Defining the role of surgery for primary gastrointestinal tract melanoma. *J Gastrointest Surg* 2008; 12: 731-738.
- [25] Kim NR, Lee WK, Chung DH. Primary gastric melanoma with rhabdoid features: a case report. *Korean J Pathol* 2013; 47: 606-609.
- [26] Alazmi WM, Nehme OS, Regalado JJ, Rogers AI. Primary gastric melanoma presenting as a nonhealing ulcer. *Gastrointest Endosc* 2003; 57: 431-433.