

Primary malignant melanoma of the gastroesophageal junction with KIT gene exon 11 mutation

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Abstract

Mucosal melanoma (MM) represents an uncommon form of melanoma. Primary gastrointestinal tract (GIT) melanoma is even rarer. A 70-year-old male visited the Liaoning Cancer Hospital and Institute, China, due to upper abdominal discomfort for the past two months. His endoscopy revealed a prominent, 6-cm ulcerated neoplasm in the gastroesophageal junction (GEJ). Lesion endoscopic biopsy showed diffusely distributed tumour cells. He underwent subtotal gastrectomy with lymph node dissection (LND). Postoperative histopathology revealed a diffuse distribution of tumour cells with numerous tumour-infiltrating lymphocytes (TILs) and pigment granules. Immunohistochemical (IHC) results were positive for both S-100 and HMB-45. Molecular analysis showed KIT gene exon 11 mutations. Although the clinicians emphasised the necessity of systemic chemotherapy and immunotherapy with the patient and his family, the patient did not receive any adjuvant therapy and died 36 months after surgery. Primary malignant melanoma of GEJ should be considered in a differential diagnosis for gastrointestinal malignancies, especially after excluding the source of metastasis through a systemic examination.

Keywords: Gastroesophageal junction, KIT gene, Malignant melanoma.

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Introduction

Melanoma often occurs within the melanocyte-located tissues, such as the eyes, skin, mouth, anus, nasopharynx, vagina, and the urinary tract. Skin is the major site.¹ Mucosal melanoma (MM) represents an uncommon form of melanoma. MM reveals a poor prognostic outcome relative to cutaneous melanoma (CM) and has no efficient therapeutic approach presently. Highly uncommon gastrointestinal malignant melanoma usually appears as

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metastatic lesions in advanced skin lesions.² An even rarer type is primary gastrointestinal tract melanoma. The present case report documents a case of extremely rare primary GEJ malignant melanoma.

Case Report

A 70-year-old male patient visited the Liaoning Cancer Hospital and Institute, China, on November 2, 2019, with complaints of upper abdominal discomfort for two months. He had developed epigastric discomfort two months ago, which was relieved by oral acid suppressants. Physical examination and laboratory tests revealed normal levels of tumour markers, AFP, AFU, CA199, CA724 and CEA. He had hypertension for 10 years, and denied any other special medical history. Endoscopy revealed a prominent, 6-cm ulcerated mass at the GEJ (Figure 1A) and his CT scan showed a thickened gastric wall with ulceration at the GEJ

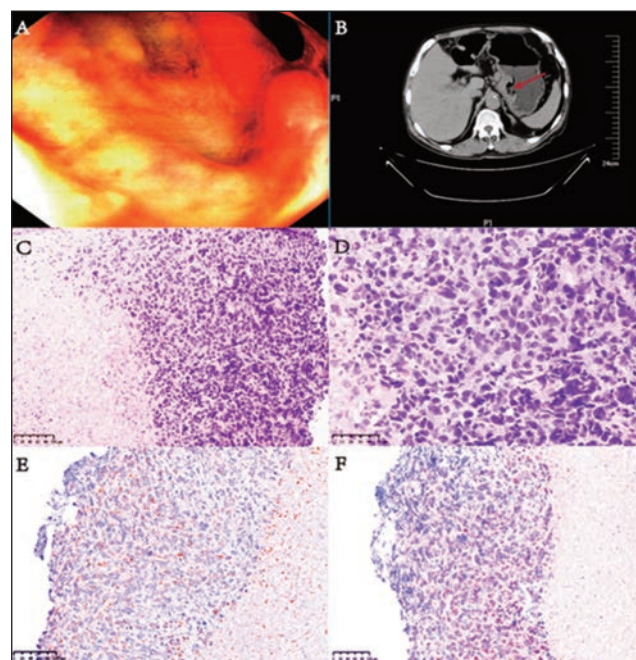


Figure-1: Endoscopy and CT images. (A) Endoscopy reveals a prominent, 6-cm ulcerated mass at the gastroesophageal junction; (B) CT scan shows a thickened gastric wall with ulceration at the gastroesophageal junction; (C) Endoscopic biopsy pathology images. Sheet necrosis and diffuse tumour cell distribution (HE x200); (D) Significant cellular atypia, with nucleoli in some cells (HE x400); (E) Immunohistochemical staining remains positive for HMB45 (IHCx200); (F) Immunohistochemical staining remains positive for S-100 (IHCx200).

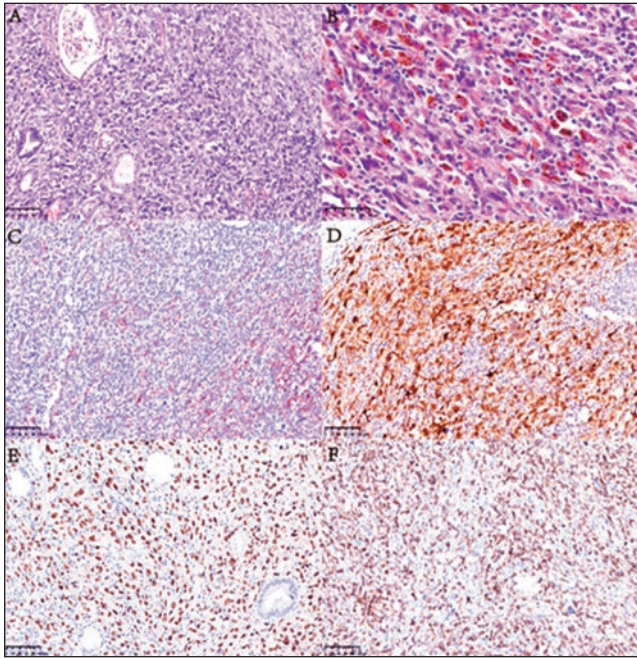


Figure-2: Postoperative histopathology images. (A) Diffuse distribution of tumour cells, easily confused with hypodifferentiated carcinoma or lymphoma (HE x200); (B) Pigment granules are visible in a few tumour cells (HE x400); (C) Immunohistochemical staining remains positive for HMB45 (IHCx200); (D) Immunohistochemical staining remains positive for S100 (IHCx200); (E) Immunohistochemical staining remains positive for SOX10 (IHCx200); (F) Immunohistochemical staining result of LCA suggests numerous TILs.

(Figure 1B). Pathological diagnosis of endoscopic biopsy confirmed a malignant tumour. Subsequently, he was subjected to subtotal gastrectomy with lymph node dissection (LND). Macro pathologically, the tumour was an ulcerative lesion, 6cm in diameter and located at the GEJ. The distance from the epicentre of this tumour to GEJ was less than 2cm and the tumour corresponded with Siewert II.³ Histopathology and immunohistochemistry suggested malignant melanoma of GEJ. No tumour tissue was observed at the resection margins. The possibility of metastatic malignant melanoma from skin, eye, and other extra-gastrointestinal organs to the GEJ was excluded by a thorough examination, including visual examination of the skin, enteroscopy, PET-CT, fundus angiography, ocular ultrasound and ocular magnetic resonance imaging. The patient was finally diagnosed with primary GEJ malignant melanoma. Endoscopic biopsy of the lesion revealed diffusely distributed tumour cells (Figure 1C-D) and IHC positivity for HMB-45 (a melanoma-specific antigen) (Figure 1E), S-100 (Figure 1F), negativity for cytokeratin (CK), and high expression (40%) for Ki-67 proliferation index. Pathological diagnosis of endoscopic biopsy confirmed a malignant tumour. Postoperative histopathology showed a diffuse distribution of tumour cells that were epithelioid, partially spindle-shaped, and had large and visible nucleoli,

which can be easily confused with hypo differentiated carcinoma or lymphoma (Figure 2A). Few tumour cells showed pigment granules (Figure 2B). IHC staining was positive for HMB-45 (Figure 2C), S-100 (Figure 2D), SOX10 (Figure 2E), MelanA, but negative for CK, synaptophysin (Syn), leukocyte common antigen (LCA), CD117, and DOG1. Further, immunohistochemical staining of LCA showed numerous TILs between tumour cells (Figure 2F). Negative expression of CK and Syn could rule out poorly differentiated adenocarcinoma and neuroendocrine carcinoma. Negative expression of LCA in tumour cells confirmed the absence of lymphoma, CD117 and DOG1, ruling out a stromal tumour. Molecular analyses showed the exon 11 mutation in the KIT gene with no abnormalities within BRAF, KRAS, NRAS, and PIK3CA genes. Although the clinicians emphasised the necessity of systemic chemotherapy and immunotherapy with the patient and his family, the patient did not receive any adjuvant therapy and died 36 months after surgery.

Discussion

Mucosal melanoma (MM) represents an uncommon tumour subtype, accounting for <2% of overall diagnoses of melanoma.⁴ Common sites of primary MM are the oropharyngeal region (32.8%), the anal canal (31.4%), and rectum (22.2%), whereas the oesophagus (5.9%) and stomach (2.7%) are the less commonly seen sites.⁴ The present case report documents an extremely rare primary GEJ malignant melanoma.

Primary malignant gastric melanoma exhibits no specific clinical presentations, including abdominal pain, loss of appetite, and weight loss, which are indistinguishable from gastric cancer, as observed in this patient, who presented with symptoms of abdominal discomfort only.

CT findings for gastric melanoma include soft-tissue masses and gastric wall thickening. They do not distinguish MM from other types of gastric tumours.⁵ Endoscopically, primary gastric malignant melanoma usually shows a large ulcerated or polypoid mass with superficial hyperpigmentation. However, non-pigmented malignant melanoma accounts for 10% to 25% of all primary gastric malignant melanomas. This makes it challenging to endoscopically differentiate gastric malignant melanomas from other types of tumours.⁵ Endoscopy revealed a prominent, 6-cm ulcerated mass at the GEJ junction with no melanin deposits on the mass surface. This is an important reason why a definitive diagnosis is impossible on endoscopy. There are three main theories related to the pathogenesis of primary GIT malignant melanoma.⁶ First, Melano blasts migrate into the gastrointestinal tract during embryogenesis. Second, uptake and decarboxylation of

amine precursors from neural crest cells can differentiate into melanocytes. Third, Schwann neuroblasts which also originate from the neural crest, cause tumorigenesis and may differentiate into primary melanoma. Therefore, malignant melanoma is more likely to occur where there are melanocytes. Primary malignant melanoma of gastrointestinal histopathology revealed a diffuse distribution of tumour cells, which could be easily confused with hypo differentiated carcinoma or lymphoma. Melanoma can be diagnosed according to IHC analysis that shows S-100 protein, Melan-A and HMB-45 positiveness, as demonstrated in the present case. Pigment granules were also observed within some tumour cell cytoplasm, which is an important indication for melanoma. After assisted diagnosis by immunohistochemical staining, lymphoma, poorly differentiated adenocarcinoma, stromal GIT and neuroendocrine carcinoma were excluded.

To diagnose a primary gastric malignant melanoma, Blecker et al.⁷ described the diagnostic criteria as a single, pathologically confirmed, intragastric melanoma lesion with the exclusion of metastases from other melanoma lesions. In the present case, after a thorough examination of the entire body, including visual examination of the skin, enteroscopy, PET-CT, fundus angiography, ocular ultrasound, and ocular magnetic resonance imaging, the possibility of malignant melanoma metastasising from the skin, eyes, and other organs was ruled out. It was confirmed that this case fully met the diagnostic criteria mentioned above. Gene alterations in primary MM and CM show a remarkable difference. About 50% of CM have BRAF mutations, which are not commonly seen within MM. Neuroblastoma RAS mutations are identified in the development of melanoma in 15% to 22% of CM and 5% of MM patients.⁸ The KIT gene is mutated in <20% of MM in Central Europe, with the majority of mutations located in exons 11 and 13.⁹ The prevalence of PIK3CA mutation in MM remains poorly documented. PIK3CA is reportedly susceptible to co-mutation with the BRAFV600E gene in non-small cell lung cancer.¹⁰ Molecular analysis showed KIT gene exon 11 mutation but no abnormalities in BRAF, KRAS, NRAS, and PIK3CA genes in our patient, suggesting the benefit of targeted therapy. Surgical resection is usually the preferred method to treat primary GIT melanoma. Timely diagnosis, curative surgery as well as aggressive LND contribute to precise stage classification and superior outcomes. Adjuvant therapies are chemotherapy, interferon-alpha, immunotherapy, targeted therapy, or their combinations.⁴ The median overall survival associated with primary malignant melanoma of the GI tract is reportedly 17 months. In the present case, a subtotal gastrectomy plus LND was performed. The patient survived for 36 months (died on December 8, 2022) without any

adjuvant treatment. It might be related to the abundance of TILs in the tumour.

Furthermore, it is worth exploring whether it is appropriate to diagnose primary malignant melanoma at the GEJ or to diagnose metastatic melanoma of unknown primary (MUP) in the absence of a primary lesion? The following points may provide hints: 1) This case was a single lesion at the GEJ, and the pathomorphology showed a close relationship between tumour cells and mucosa; 2) the gene detection results indicate a mutation in the 11th exon of the kit gene, which is more in line with the genotype change of MM; the MUP shows more BRAF mutations, similar to CM; 3) the overall survival of this case is 36 months, while the median survival of MUP patients is only 2-4 months for tumour cell metastasis. In summary, this case might be more inclined to be diagnosed as a primary malignancy at the GEJ.

Conclusion

This case report discusses an uncommon primary GEJ malignant melanoma case, which is difficult to diagnose through endoscopic biopsy. For poorly differentiated malignancies at GEJ, primary malignant melanoma should also be considered as one of the differential diagnoses. Immunohistochemical results facilitate a definite diagnosis. Surgery is the preferred therapeutic option to significantly improve the prognosis.

Ethical approval: This study was reviewed and approved by the ethics committee of the Liaoning Cancer Hospital and Institute, approval number [NO.20220306G]. This study was conducted in accordance with the Declaration of Helsinki of 1975.

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

Availability of data and materials: All data generated or analysed during this study are included in this article.

Disclaimer: None to declare.

Conflict of interest: None to declare.

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Abbreviations: MM: Mucosal melanoma; GIT: Gastrointestinal tract; GEJ: Gastroesophageal junction; LND: lymph node dissection; IHC: Immunohistochemistry; CT: Computed tomography; CM: Cutaneous melanoma; HE:

Haematoxylin and eosin staining; TILs: Tumour-infiltrating lymphocytes; AFP: Alpha-fetoprotein; AFU: Alpha-L-fucosidase; CEA: Carcinoembryonic antigen; CA724: Carbohydrate antigen 724; CA199: Carbohydrate antigen 199; MUP: Metastatic melanoma of unknown primary.

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Author Contribution:

XG: Drafting and writing.

ZZ: Acquisition of clinical information, analysis and organisation of data.

YZ: Concept, design, responsible for all aspects of the work, final approval.