


# A Fatal Case of Metastatic Primary Gastric Melanoma: Diagnostic Challenges and Therapeutic Dilemmas

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**Background:** Primary gastric malignant melanoma (PGMM) is an exceedingly rare non-epithelial tumor. Only a limited number of cases have been documented, posing significant diagnostic and therapeutic challenges.

**Case Presentation:** A 75-year-old man presented with cough and sputum. Computed tomography (CT) suggested a malignant tumor with multiorgan metastasis. Gastroscopy revealed multiple polypoid lesions, and histopathology confirmed melanoma. After multi-disciplinary discussion, primary gastric melanoma was diagnosed. Despite aggressive treatment, the disease progressed rapidly, and the patient died six months after diagnosis.

**Conclusion:** This case highlights the importance of early endoscopy in patients with metastatic tumors of unknown origin. Although outcomes remain poor, this report contributes to the understanding of PGMM diagnosis and management.

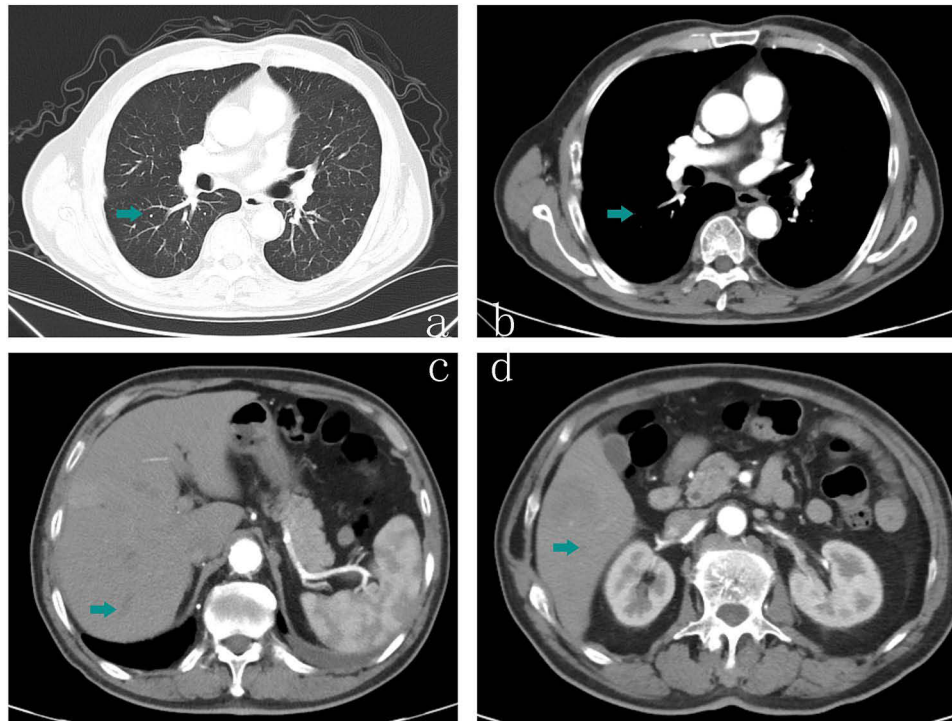
**Keywords:** primary gastric malignant melanoma, PGMM, diagnosis, treatment

## Introduction

Malignant melanoma (MM) is a highly aggressive tumor derived from melanocytes. It can occur in the skin, mucosa (eg, head and neck, digestive tract, urogenital tract), and other sites, and is associated with a generally poor prognosis.<sup>1</sup> Due to the scarcity of melanocytes in the gastrointestinal tract, both primary and metastatic gastrointestinal melanomas are uncommon.<sup>2</sup> Primary gastric melanoma (PGMM) is particularly rare, accounting for only about 1% of all extracutaneous melanomas.<sup>3</sup> Its unclear pathogenesis, nonspecific symptoms, high malignancy, tendency for distant spread, and lack of specific management guidelines make PGMM a considerable clinical challenge.<sup>4</sup> A systematic review of 25 PGMM cases<sup>3</sup> found that the tumor occurs mainly in the gastric body, with a mean age of onset of  $63.4 \pm 8.97$  years. Patients often present with nonspecific gastrointestinal symptoms such as abdominal pain, weight loss, and anorexia. At diagnosis, 62.5% of patients have local lymph node infiltration, and 25% have distant metastases, contributing to a poor overall prognosis. We report an elderly male patient who initially presented with respiratory symptoms and experienced rapid disease progression. Gastroscopy showed multiple polypoid elevations in the gastric body, and biopsy confirmed malignant melanoma. Comprehensive examination and multidisciplinary consultation led to a final diagnosis of primary gastric malignant melanoma with multiple organ metastases. This report details the diagnostic and therapeutic course of this case to improve clinical recognition and reduce misdiagnosis.

## Case Presentation

A 75-year-old man was admitted to the Respiratory Department on March 4, 2024, with a two-year history of intermittent cough, expectoration, and dyspnea that had worsened over the previous four months. He also reported upper abdominal fullness, anorexia, acid reflux, and fatigue. His medical history included well-controlled hypertension. Contrast-enhanced chest computed tomography (CT) (Figure 1) revealed: ①. A nodular lesion in the right lower lobe, highly suggestive of metastasis; ②. Enlarged metastatic axillary lymph nodes; ③. Multiple liver metastases; bilateral adrenal gland thickening; and

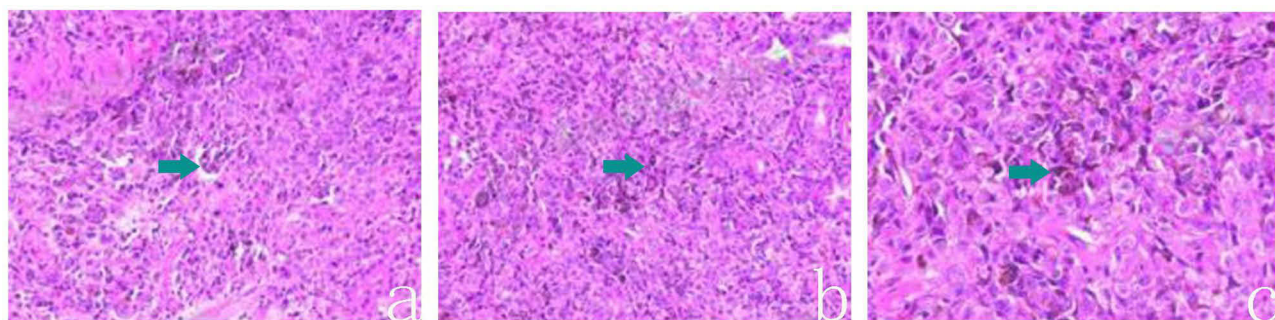


**Figure 1** Chest CT scan shows (as indicated by the blue arrows in the figure) nodular lesions in the right lower lobe, suggestive of metastases; these lesions are visible on the lung window (a) and the mediastinal window (b). Additionally, multiple hepatic metastases are demonstrated (c and d).

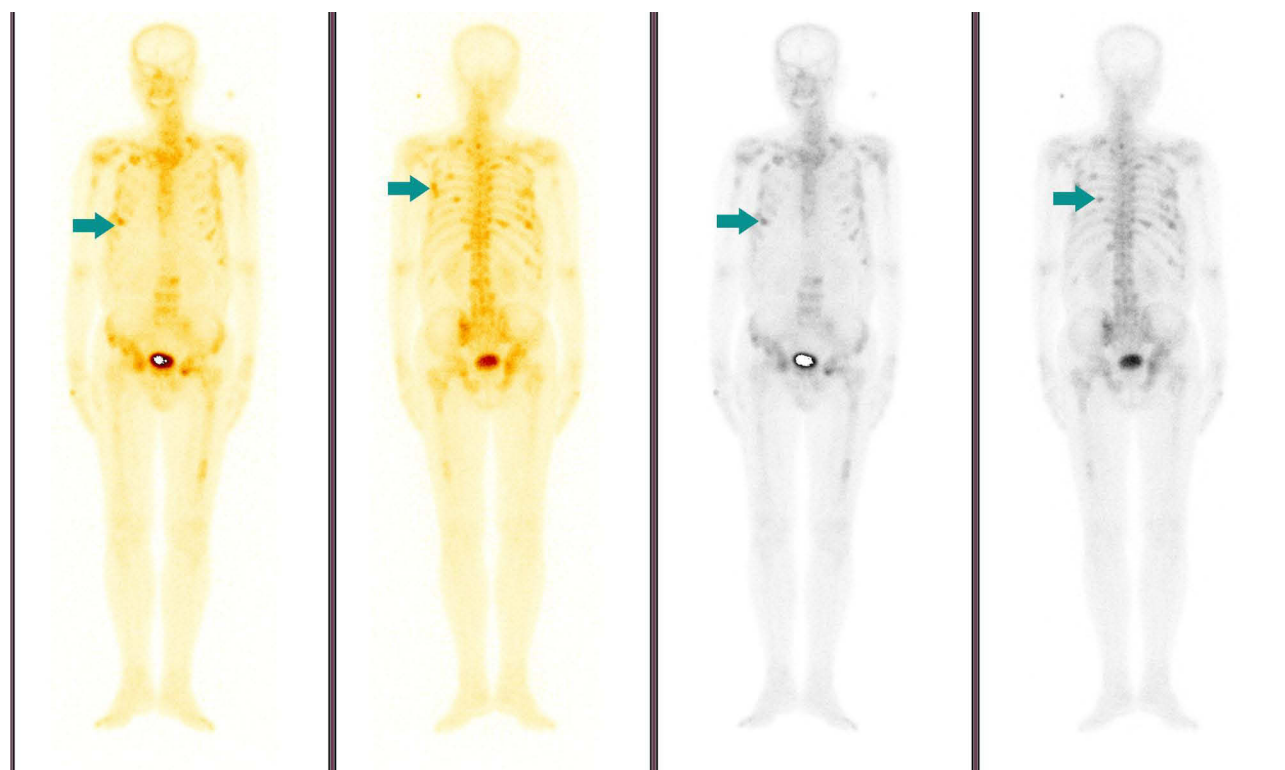
scattered perirenal soft tissue nodules, all suggesting metastasis; ④. Patchy osteolytic lesions in multiple vertebrae, appendages, and ribs, consistent with metastasis. Whole-body PET-CT showed: ①. Multiple liver and extensive bone metastases; ②. Small bilateral lung nodules with minimal fluorine-18-labeled deoxyglucose (FDG) uptake, some suspicious for metastasis; ③. A slightly enlarged left axillary lymph node with negligible FDG uptake, possibly metastatic; ④. Bilateral adrenal thickening and scattered small perirenal nodules with minimal FDG uptake, also suspicious for metastasis; ⑤. No clear primary tumor site was identified. Segmental FDG uptake in the right colon warranted colonoscopy. Subsequent endoscopic examinations were performed. Gastroscopy (Figure 2) showed six polypoid elevations (0.4–0.8 cm in diameter) with rough surfaces on the greater curvature of the lower gastric body. Endoscopic polypectomy was performed. After obtaining informed consent from the patient's family, endoscopic high-frequency electrocoagulation and snare polypectomy were performed, and the resected tissue was submitted for pathological examination. Pathology (Figure 3) indicated malignant melanoma.



**Figure 2** Gastroscopy reveals multiple polypoid protrusions (a–c) on the greater curvature of the lower gastric body (as indicated by the blue arrows in the figure), with a rough surface and visible melanin deposition.



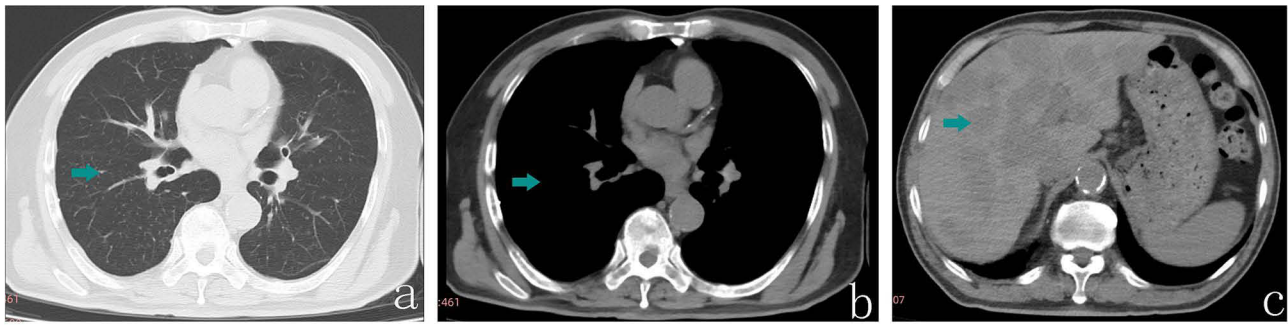
**Figure 3** The pathological section (HE staining, 20×10 magnification) reveals melanoma cells with irregular morphology, melanin granules within the cytoplasm, and nuclear pleomorphism and atypia (a and b). The pathological section (HE staining, 40×10 magnification) reveals infiltration of melanocytes within the lesion accompanied by melanin deposition (c).



**Figure 4** Multiple foci of abnormally increased bone metabolic activity.

Immunohistochemistry (IHC) results were as follows: HMB45(+), Melan-A(+), S-100(+), CKP(-), Vimentin(-), Cyclin-D1 (+), p16(+), CD117(-), KI-67 (proliferation index approximately 70%), CK8/18(-). Colonoscopy revealed a 0.6 cm sigmoid polyp, which was resected; pathology showed an adenomatous polyp. A whole-body bone scan (Figure 4) confirmed multiple bone metastases. Following multidisciplinary discussions, the final diagnosis of primary gastric malignant melanoma with systemic multiple metastases was confirmed.

The patient's family initially declined antitumor therapy. After symptomatic treatment, he was discharged. Two months later, he developed severe lower back and leg pain and became unable to walk. Re-evaluation (Figure 5) showed disease progression: increased size and number of lung, liver, perirenal, vertebral, and rib metastases. The patient then received immunotherapy with toripalimab (240 mg every 21 days) and denosumab (120 mg) for three cycles. During treatment, he developed thrombocytopenia and abnormal liver and kidney function.



**Figure 5** Follow-up CT indicated metastatic progression of lesions in the lungs (a and b) and liver (c).



**Figure 6** Repeat follow-up CT showed multiple pulmonary metastases with an increased number and larger size compared to prior imaging (a); and multiple hepatic metastases, also showing an increased number and larger size than before (b and c).

A follow-up CT on August 7, 2024 (Figure 6) showed significant progression: increased pulmonary nodules; pleural thickening and effusion; progression of hepatic, adrenal, peritoneal, and retroperitoneal metastases; large-volume ascites; and increased osteolytic lesions. The patient was determined to be terminal, with a poor general condition, and no further antitumor treatment was feasible. After family consultation, he was discharged against medical advice. Telephone follow-up revealed that his condition deteriorated rapidly, and he died approximately 40 days later.

## Discussion

Melanoma is a highly malignant tumor derived from neural crest melanocytes, known for its aggressiveness, rapid progression, and poor prognosis.<sup>5</sup> An estimated 5–10% of metastatic melanomas have an unknown primary site, possibly due to occult primary lesions or regression of ectopic melanocytes before metastasis.<sup>6,7</sup> Melanoma metastasizes via three main pathways:<sup>8</sup> ① Lymphatic spread, the most common route, where tumor cells enter the bloodstream via lymphatics and lymph nodes and then disseminate hematogenously to organs such as bone, liver, and lungs; ② Hematogenous spread directly from the primary site without involving lymph nodes; ③ Direct invasion of adjacent organs or tissues. According to the latest Chinese cancer epidemiological survey, the annual incidence of melanoma is only 0.88 per 100,000 people,<sup>9</sup> making PGMM an exceptionally rare subtype of mucosal melanoma.<sup>10</sup> Mucosal melanomas are more aggressive and have higher rates of recurrence and metastasis, likely due to the rich lymphatic and vascular supply of mucosal tissue.<sup>11</sup> The pathogenesis of PGMM remains unclear. One theory suggests that melanocytes migrate to the stomach during embryonic development and later undergo malignant transformation.<sup>12</sup> Another proposes that gastric APUD (amine precursor uptake and decarboxylation) cells may transform into melanocytes.<sup>13</sup> In terms of diagnosis, early detection of PGMM is extremely challenging due to its non-specific clinical symptoms and endoscopic appearances.<sup>14</sup> Gastric melanoma typically appears as scattered black patches and can be classified into three subtypes: pigmented nodules on gastric folds, ulcerated submucosal tumors, and mucosal elevations with black patches and ulcers.<sup>15</sup> Therefore, the presence of gastric melanosis during endoscopy should prompt suspicion of this tumor. Definitive diagnosis relies on

endoscopic biopsy and immunohistochemical staining.<sup>4</sup> Imaging (CT, MRI, PET-CT) is valuable for staging and prognosis. Microscopically, melanoma cells often appear irregular, contain melanin granules, and show nuclear pleomorphism. Characteristic IHC markers include S-100, Melan-A, HMB-45, Tyrosinase, and MITF. S-100 is highly sensitive, while Melan-A, HMB-45, and Tyrosinase are highly specific.<sup>16</sup> Given the extremely low incidence of PGMM, a comprehensive examination of other body sites is essential to rule out metastatic disease when gastric melanoma is detected. Furthermore, the early diagnosis of primary gastric melanoma is exceedingly challenging; however, heightened clinical vigilance may create opportunities for timely intervention. Potential diagnostic triggers include: ① For patients with unexplained gastrointestinal bleeding (particularly melena or chronic anemia) accompanied by weight loss, this etiology should be included in the differential diagnosis even if endoscopic findings are atypical; ② Any gastric lesion observed endoscopically that exhibits deep black, blue, or mottled pigmentation should raise strong suspicion for this condition, and multiple deep biopsies are recommended; ③ In patients with confirmed metastatic lesions (eg, in the liver or adrenal glands) but no identified primary tumor, the possibility of primary gastric melanoma should be considered after excluding common primary sites, and proactive gastroscopic evaluation should be pursued. In this case, the patient presented with respiratory symptoms. The presence of accompanying digestive symptoms led to gastrointestinal endoscopy. Timely endoscopic biopsy upon lesion discovery was crucial, and the subsequent IHC results were pivotal in confirming the diagnosis. The positivity of HMB45, Melan-A, S-100, Cyclin-D1, p16, a high Ki-67 index of 70%, and negativity of CKP, Vimentin, CD117, and CK8/18 strongly supported the diagnosis of primary gastric malignant melanoma. Comprehensive examinations and multidisciplinary discussions ultimately confirmed the diagnosis of primary gastric malignant melanoma with systemic multiple metastases.

Regarding treatment, there is currently no unified guideline for mucosal melanoma, and most treatment strategies are extrapolated from the experience of primary cutaneous melanoma.<sup>14</sup> Surgery is considered the ideal curative approach, but due to anatomical variability, standardized protocols are lacking, and efficacy is often poor with high recurrence risk. Most PGMM cases are metastatic at diagnosis, precluding curative surgery and necessitating systemic therapy. In recent years, novel anti-tumor strategies,<sup>17</sup> such as molecular targeted therapy, immune checkpoint inhibitors,<sup>18,19</sup> cell therapy,<sup>20</sup> tumor vaccines,<sup>21</sup> and neoadjuvant therapy,<sup>22</sup> have been successfully applied in the adjuvant and advanced systemic treatment of melanoma, offering hope for improved outcomes. Among these, immunotherapy has emerged as a promising treatment strategy for MM, with a particular focus on immune checkpoint inhibitors such as PD-1 and CTLA-4 inhibitors. These agents leverage the body's immune response against tumors and have demonstrated significant efficacy. However, melanoma cells employ complex evasion mechanisms to escape immune surveillance, including the release of immunosuppressive factors and reduction of antigen-presenting capacity. These evasion strategies impair immune cell function, diminish their ability to recognize and eliminate tumor antigens, and thereby facilitate tumor immune escape.<sup>23</sup> Toripalimab, the first Chinese-made anti-PD-1 monoclonal antibody, was approved in 2018 for metastatic malignant melanoma.<sup>24</sup> In this case, the patient presented with extensive systemic metastases at diagnosis, indicating an advanced stage of the disease. After comprehensive evaluation, anti-tumor therapy with toripalimab combined with denosumab was initiated. Regrettably, the treatment failed to achieve a satisfactory response, and the tumor continued to progress until the patient's demise. The failure of immunotherapy may have resulted from a combination of factors: low tumor mutational burden and a "cold" immune microenvironment formed the intrinsic biological basis for resistance; delayed diagnosis led to high tumor burden, which limited the treatment window; and insufficient knowledge regarding this rare disease may have led to suboptimal treatment strategies. PGM is a rare disease characterized by an aggressive malignant behaviour. A study by Mellotte et al found a mean survival of 22 months; one-year survival was 56.5% with surgery and 66% with adjuvant therapy. Mean survival was 21.05 months ( $\pm 20.2$ ) in the surgical group versus only 4.5 months ( $\pm 3.61$ ) without surgery.<sup>14</sup> Our patient survived less than 6 months after diagnosis, consistent with these data.

## Conclusion

PGMM is a very rare and aggressive malignancy with nonspecific symptoms and a poor prognosis. Although imaging examinations are instrumental in its diagnosis, staging, and prognosis assessment, definitive diagnosis ultimately depends on endoscopic pathological examination and immunohistochemical staining. Currently, the absence of standardized diagnostic and therapeutic guidelines for PGMM poses significant challenges to early diagnosis. Therefore, clinicians

should maintain a high index of suspicion for melanoma in any atypical gastric lesion, and pursue early histological confirmation to avoid diagnostic delay and improve therapeutic outcomes. The accumulation of more clinical cases and continuous research hold the promise of expanding the diagnostic and therapeutic approaches for this disease. In the future, it is necessary to validate the biological characteristics of gastric polyp like PGMM in a multicenter retrospective cohort and explore targeted immune combination strategies. This case report contributes to a deeper understanding of the diagnosis and treatment of primary gastric malignant melanoma.

## Ethical Statement

The research does not require the approval of the ethics committee.

## Consent to Publish

Written informed consent was obtained from the patient's next of kin for publication of any potentially identifiable images or data included in this article.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

All authors declare no conflicts of interest in this work.

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