Pseudoprogression of liver metastases and mixed response in primary gastric melanoma treated with nivolumab: A case report

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Abstract. Primary gastric melanoma (PGM) is an extremely rare malignancy with a poor prognosis, and evidence regarding the efficacy of immune checkpoint inhibitors remains limited. The present report describes the case of a 70-year-old male patient with metastatic PGM who was treated with nivolumab monotherapy. Histopathological examination of a gastric tumor confirmed malignant melanoma, and staging studies revealed lymph node, lung and subsequent liver metastases. After nivolumab initiation, computed tomography demonstrated shrinkage of the primary gastric lesion but enlargement of metastatic lesions with the appearance of new liver and pleural metastases, resulting in a mixed response and progressive disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). However, based on Immune RECIST (iRECIST), treatment was continued because pseudoprogression was suspected. Follow-up imaging revealed regression of liver metastases after initial enlargement, consistent with site-specific pseudoprogression, while disease control of the primary lesion, lymph node metastases and lung metastases was maintained for ~5 months. Although the disease eventually progressed because of pleural metastases, the present case demonstrated the potential clinical benefit of nivolumab in metastatic PGM. To the best of our knowledge, the present case may represent one of the few reported instances of site-specific pseudoprogression and mixed response in PGM, and highlights the importance of iRECIST-guided assessment to avoid premature discontinuation of immunotherapy.

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Abbreviations: PGM, primary gastric melanoma; RECIST, Response Evaluation Criteria in Solid Tumors; iRECIST, Immune Response Evaluation Criteria in Solid Tumors; GI, gastrointestinal; ICIs, immune checkpoint inhibitors; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; PET/CT, positron emission tomography/computed tomography; FDG, fluorodeoxyglucose; PD-L1, programmed death-ligand 1; CPS, Combined Positive Score; iCPD, immune-confirmed progressive disease

Key words: PGM, nivolumab, pseudoprogression, mixed response

Introduction

Primary gastric melanoma (PGM) is an extremely rare malignancy, representing only a small portion of all gastrointestinal (GI) melanomas. Owing to its rarity, its clinical features are not well-defined, and the prognosis is particularly poor in cases that are unresectable or metastatic. At present, no established clinical guidelines for managing PGM exist. While surgical resection is the main treatment for localized disease, systemic therapy is commonly employed for advanced cases. Current treatment strategies for advanced melanoma prioritize immune checkpoint inhibitors (ICIs), including antibodies targeting programmed death-1, cytotoxic T-lymphocyte-associated antigen 4, or lymphocyte-activation gene 3, with molecularly targeted therapy considered for patients harboring actionable alterations such as *BRAF* V600 mutations (1,2). However, evidence regarding the optimal systemic treatment of PGM remains extremely limited given its rarity, and reports describing durable disease control in patients with metastatic PGM are scarce. Furthermore, response assessment during ICI therapy can be challenging because atypical patterns of response, including pseudoprogression and mixed responses, may occur. Distinguishing true progression from pseudoprogression is crucial to prevent premature discontinuation of effective treatment.

In this study, we report a case of metastatic PGM treated with nivolumab, which exhibited a mixed response including site-specific pseudoprogression, leading to temporary yet clinically significant disease control. To our knowledge, this represents a distinctive observation offering clinical insights into the management of this uncommon condition.

Case report

A 70-year-old man with a medical history of atrial fibrillation and psoriasis was prescribed rivaroxaban for anticoagulation

at a local clinic. He first sought medical attention at a different hospital due to melena. Subsequent esophagogastroduodenoscopy identified a stomach mass. Despite a biopsy, a conclusive diagnosis could not be established. He was therefore referred to Ibaraki Prefectural Central Hospital for additional evaluation and treatment and was admitted in July 2025.

Upon admission, his Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score was 1, indicating that he remained ambulatory and capable of light or sedentary activity despite some restriction in strenuous physical activity (3). Physical examination findings were unremarkable, except for skin lesions related to comorbid psoriasis. Laboratory tests showed only anemia, with a hemoglobin level of 9.6 g/dl. Esophagogastroduodenoscopy identified a solitary 70-mm mass in the upper gastric body with no other synchronous lesions (Fig. 1), and a biopsy was performed for pathological examination. Hematoxylin and eosin staining showed a dense proliferation of atypical cells (Fig. 2A). Immunohistochemical analysis indicated positivity for S-100 and human melanoma black-45, weak positivity for c-kit, and negativity for cytokeratin AE1/AE3, CD34, and DOG1, leading to the diagnosis of malignant melanoma (Figs. 2B and C, and S1A-D). Detailed information on the reagents used for the immunohistochemical analyses, including reagent names, dilutions, catalog numbers, and manufacturers, is provided in Table SI. Whole-body positron emission tomography/computed tomography (PET/CT) showed significant fluorodeoxyglucose (FDG) uptake in the gastric lesion and hepatoduodenal ligament lymph nodes. Although no evident FDG uptake was observed, lymph node enlargement measuring several millimeters was detected in the lesser curvature of the stomach and the para-aortic region. Additionally, micronodules were identified in the left lung, indicative of metastasis of the malignant melanoma. Physical examination-including full-body skin examination-as well as esophagogastroduodenoscopy (Fig. 1), nasal endoscopy (Fig. S2), and imaging studies such as FDG-PET/CT revealed no findings suggestive of an alternative primary lesion (Fig. S3A-E), and the tumor was therefore diagnosed as primary gastric malignant melanoma. Programmed death-ligand 1 (PD-L1) expression was assessed by immunohistochemistry using the PD-L1 IHC 28-8 pharmDx 'Dako' kit (Agilent Technologies, Inc., Santa Clara, CA, USA; Code No. SK005; approval number 22800EZX00077000), which contains a rabbit monoclonal anti-PD-L1 antibody (clone 28-8), and the Combined Positive Score was 10-20 (Fig. 2D). The BRAF V600E mutation was absent, as assessed using the MEBGEN™ BRAF 3 Kit (Medical & Biological Laboratories Co., Ltd., Nagoya, Japan; Code No. GS-D0651) based on the polymerase chain reaction-reverse sequence-specific oligonucleotide (PCR-rSSO) method. Subsequently, nivolumab monotherapy (240 mg every two weeks) was initiated within the approved indication for malignant melanoma in Japan, which is not restricted to cutaneous origin (4). The date of the first nivolumab administration was defined as Day 0. Rivaroxaban was discontinued before treatment because of tumor-related bleeding. At the initiation of treatment, the ECOG PS was 1, the patient was asymptomatic, and the serum LDH level was 213 U/l (reference range 124-222 U/l).

Following the start of treatment, exacerbation of psoriasis and transient fever occurred. Psoriasis flares were limited to skin involvement and were managed with topical corticosteroids and calcipotriol ointment; systemic corticosteroids were not used. Consequently, the second nivolumab administration was postponed until one month after the initial treatment, but the subsequent biweekly administration schedule was maintained. A contrast-enhanced CT scan conducted on Day 71 revealed a decrease in the primary lesion, indicating disease control. However, the lymph node and lung metastases showed enlargement, and new liver and pleural metastases emerged. A mixed response with varying treatment effects by site was observed, leading to a diagnosis of progressive disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) (Fig. 3A and B). However, given the shrinkage of the primary tumor, the absence of a marked increase in serum LDH levels, and the classification of the lesions as immune unconfirmed progressive disease according to immune Response Evaluation Criteria in Solid Tumors (iRECIST)-which leaves open the possibility of pseudoprogression-we made a comprehensive assessment and decided to continue treatment (5). At the time of the decision to continue treatment, the ECOG PS was 1, the patient was asymptomatic, and the serum LDH level was 284 U/l. A follow-up contrast-enhanced CT scan was performed on Day 139 (Fig. 3C). The primary lesion, lymph node metastases, and lung metastases remained stable without enlargement. Liver metastases, which had initially increased in size, subsequently regressed by 34% (from 23.2 to 15.4 mm, orange arrows in Fig. 3B and C), consistent with pseudoprogression. Although pleural metastases exhibited over 20% enlargement and were classified as immune-confirmed progressive disease (iCPD) by iRECIST, overall disease control was deemed successful. The ECOG PS remained 1, the patient remained asymptomatic, and the serum LDH level remained stable at 342 U/l; treatment was therefore continued with the anticipation of pseudoprogression in the pleural lesion. However, the serum LDH level rose sharply, and on Day 165, the patient developed dyspnea and presented to the emergency department (Fig. 4). A plain CT scan revealed new lung metastases, pleural effusion, and enlargement of

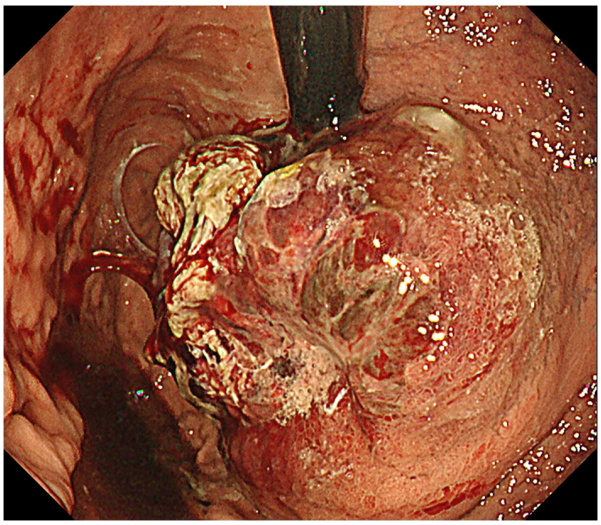


Figure 1. Esophagogastroduodenoscopy findings. A 70-mm mass was identified in the anterior wall of the upper body of the stomach. The tumor was soft, bled easily and showed black discoloration.

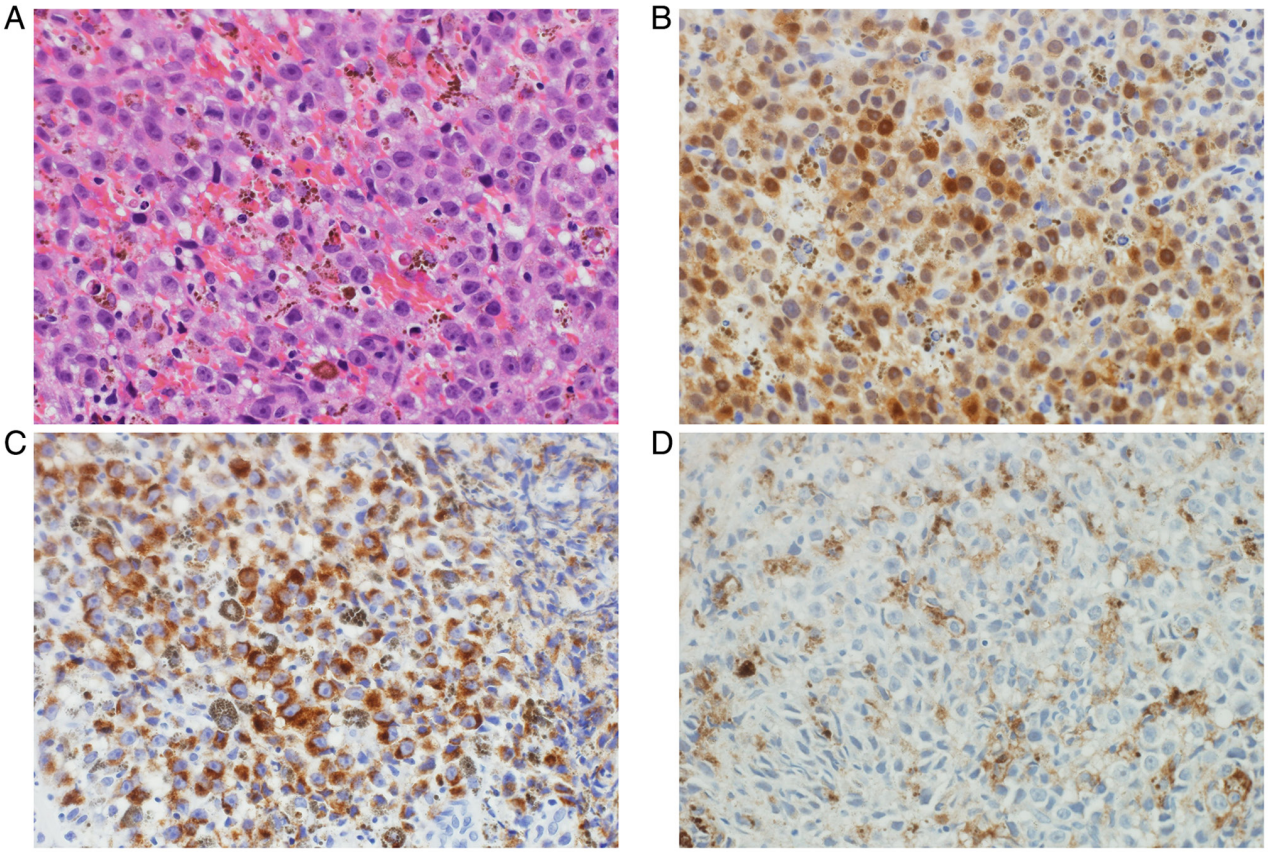


Figure 2. Pathological examination of gastric biopsy specimens. (A) Hematoxylin and eosin-stained sections exhibited dense proliferation of melanoma cells characterized by nuclear enlargement, pleomorphic nuclei, prominent nucleoli and melanin pigment accumulation. Immunohistochemically, tumor cells showed diffuse positivity for (B) S-100 and (C) human melanoma black-45. (D) The expression of PD-L1, as assessed by immunohistochemistry using the PD-L1 IHC 28-8 pharmDx 'Dako' kit, ranged from 10 to 20 based on the combined positivity score. (A-D) Magnification, x400. PD-L1, programmed cell death ligand 1.

the pleural metastases (Fig. 3D). At this point, the ECOG PS had deteriorated to 2, indicating that the patient remained ambulatory and capable of self-care but was unable to perform work activities. His dyspnea subsequently improved, and the serum LDH level had decreased from a recent peak of 821 U/l to 467 U/l, allowing outpatient management. Because no alternative treatment options were available, nivolumab was administered on Day 174. Despite no enlargement of the primary tumor observed during EGD (Fig. 5), the pleural effusion subsequently increased, and the patient was hospitalized on Day 179 because of worsening dyspnea. Based on the diagnosis of malignant pleural effusion, atypical cells were detected via thoracentesis. With further deterioration of his general condition, the ECOG PS had worsened to 3, indicating that he was capable of only limited self-care and was confined to a bed or chair for more than 50% of waking hours; nivolumab treatment was therefore discontinued. The patient was referred to a hospital near his home for palliative care and passed away on Day 216.

Discussion

This case presents a significant clinical course, with disease control maintained for approximately five months using nivolumab in unresectable PGM. A mixed response was observed, including features consistent with site-specific pseudoprogression. To the best of our knowledge, this case may represent one of the few reports of unresectable PGM demonstrating the efficacy of nivolumab, with a response pattern of site-specific pseudoprogression resembling that observed in cutaneous melanoma.

More than 95% of malignant melanomas are of cutaneous origin, with mucosal melanomas, particularly those originating from the GI tract, being exceedingly rare (6). Among GI melanoma sites, the oropharyngeal region (32.8%), anal canal (31.4%), and rectum (22.2%) are the most common, while the stomach (2.7%) exhibits a lower incidence (7). Consequently, only approximately 50 cases of PGM have been documented globally, with no established standard treatment guidelines. The prognosis for PGM is notably grim; a review of 34 cases revealed a mean survival of 21.05 months in the surgical group compared to 4.5 months in the nonsurgical group, with no one-year survivors in the nonsurgical group (8).

The diagnosis of primary gastrointestinal melanoma remains challenging because universally accepted diagnostic criteria have not been established. Blecker *et al* (9) proposed criteria including the absence of a concurrent or previous cutaneous melanoma or atypical melanocytic lesion, the absence of other organ involvement, and the presence of an *in situ* change in the overlying or adjacent gastrointestinal epithelium. In the present case, these criteria could not be strictly applied because the patient had synchronous distant

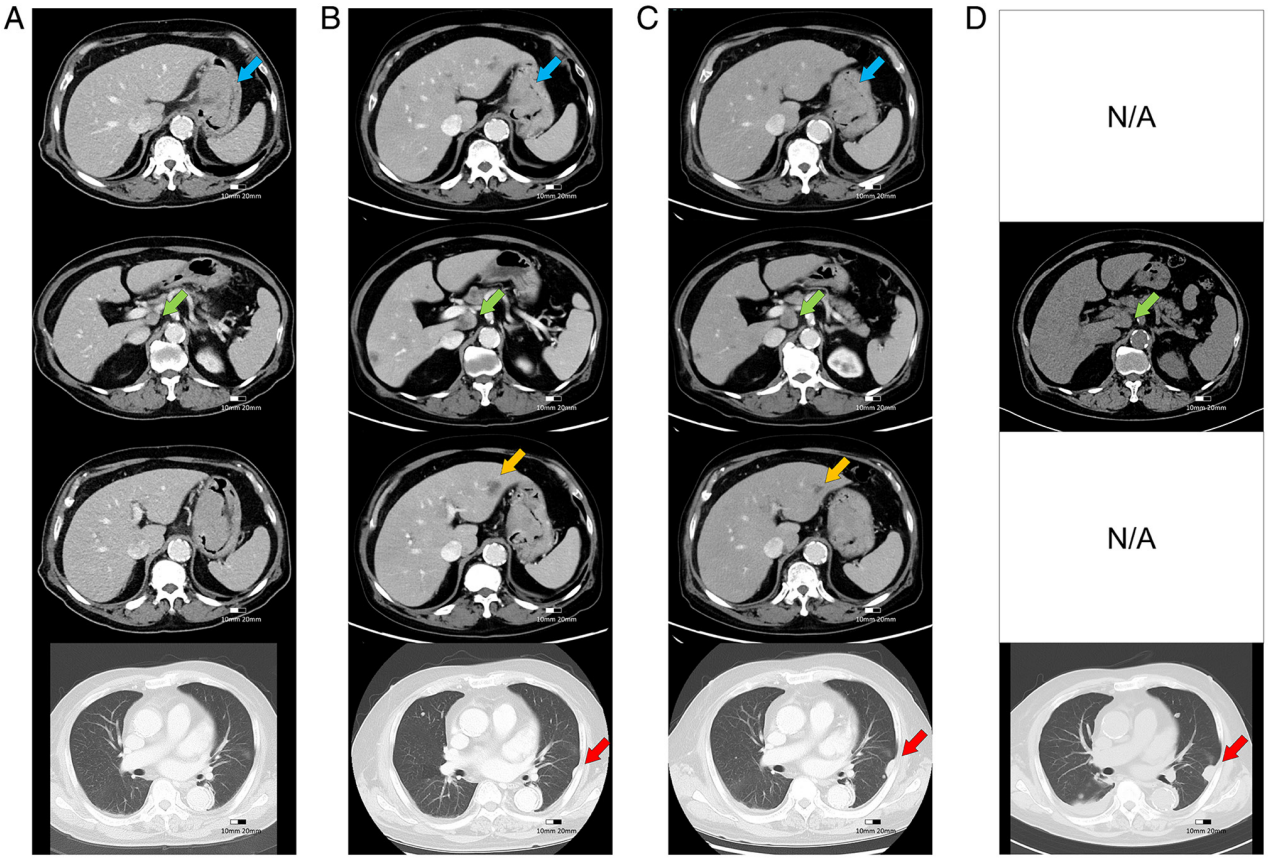


Figure 3. CT scans of the primary site (blue arrows), lymph node metastases (green arrows), liver metastases (orange arrows) and pleural metastases (red arrows). The primary tumor remained unchanged after shrinking, the lymph nodes remained unchanged, the liver metastases shrank after initial enlargement, and the pleural metastases showed enlargement. (A) Enhanced CT images before treatment initiation. (B) Enhanced CT images obtained 71 days after the initial treatment. (C) Enhanced CT images obtained 139 days after initial treatment. (D) Plain CT images obtained 165 days after initial treatment. CT, computed tomography; N/A, not available.

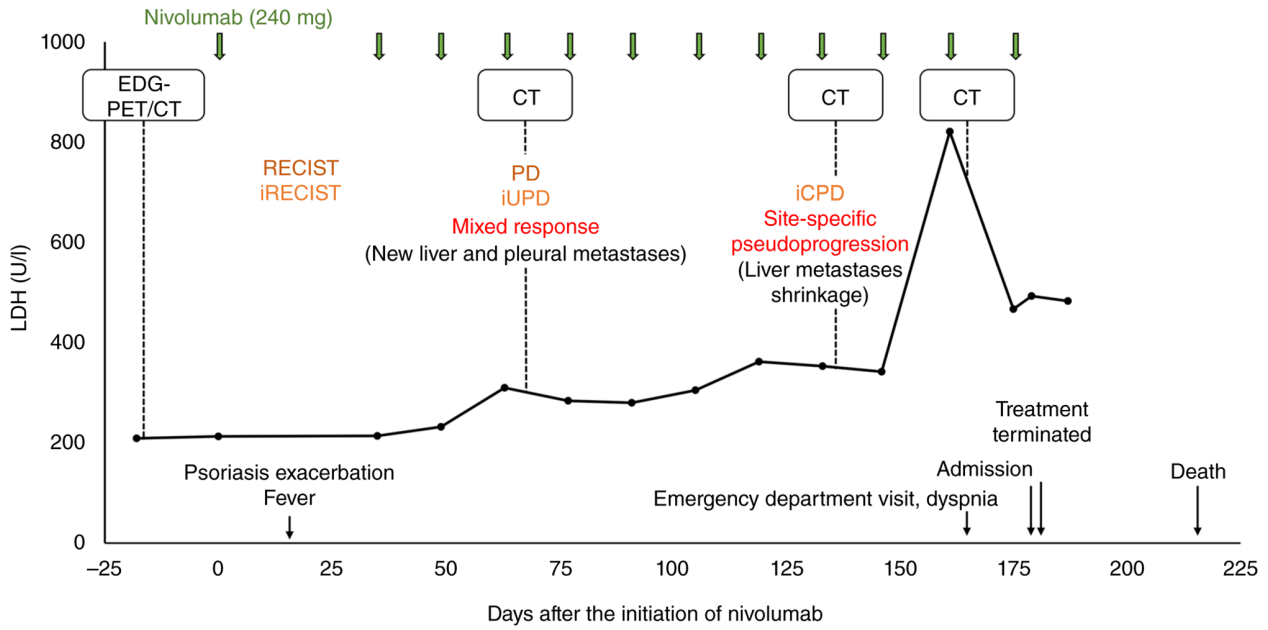


Figure 4. Clinical course and changes in serum LDH levels. The patient was treated with nivolumab (240 mg every 2 weeks), although the second administration was delayed due to an exacerbation of psoriasis and transient fever. Day 0 was defined as the date of the first nivolumab administration. On day 71, contrast-enhanced CT revealed a mixed response. Treatment was continued under the suspicion of pseudoprogression, and regression of the liver metastases was confirmed on day 139. However, pleural and lung metastases subsequently progressed, accompanied by clinical deterioration. LDH, lactate dehydrogenase; FDG-PET, fluorodeoxyglucose-positron emission tomography; CT, computed tomography; RECIST, Response Evaluation Criteria in Solid Tumors; iRECIST, Immune Response Evaluation Criteria in Solid Tumors; PD, progressive disease; iUPD, immune-unconfirmed progressive disease; iCPD, immune-confirmed progressive disease.

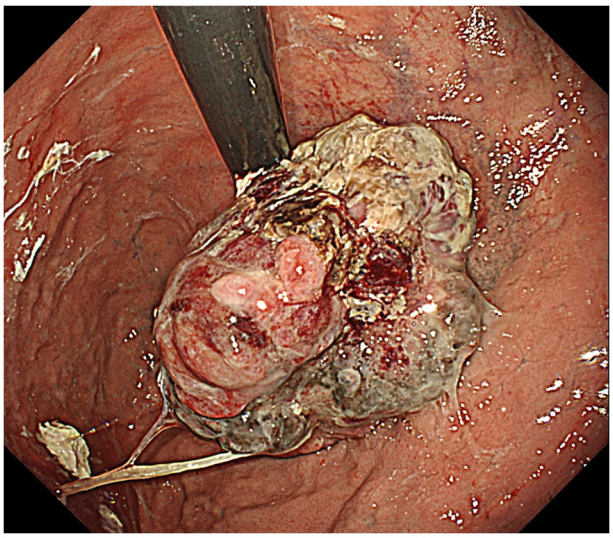


Figure 5. Esophagogastroduodenoscopy findings on day 173 after the initial treatment. The tumor in the upper stomach had shrunk compared with pre-treatment.

metastases at diagnosis and extensive invasion of the gastric lesion precluded reliable assessment of an *in situ* component. Nevertheless, comprehensive clinical evaluation, including a full-body dermatological examination, esophagogastroduodenoscopy, nasal endoscopy, and FDG-PET/CT, revealed no alternative primary lesion. Therefore, considering the solitary gastric lesion and the overall clinical findings, the tumor was clinically diagnosed as PGM.

Evidence of unresectable PGM is limited, and current treatment approaches align with those for cutaneous melanomas. However, it is essential to recognize that mucosal melanomas differ from cutaneous melanomas in their biological background. Specifically, compared with cutaneous melanoma, mucosal melanoma exhibits a higher frequency of *KIT* and *SF3B1* mutations (10), a lower frequency of *BRAF* and *NRAS* mutations (10), a lower tumor mutational burden (11), and reduced expression of tumor-infiltrating lymphocytes and PD-L1 (12,13). Although these factors may decrease sensitivity to ICIs, clinical trial data have demonstrated clinically meaningful activity of ICIs in mucosal melanomas. A pooled analysis of clinical trials reported objective response rates of 23.3% with nivolumab monotherapy and 37.1% with nivolumab plus ipilimumab (2). Similarly, a post-hoc analysis of the KEYNOTE-001, -002, and -006 trials demonstrated a 19% objective response rate with pembrolizumab, with a median duration of response of 27.6 months (14). These findings are further supported by a multicenter phase II trial of nivolumab monotherapy in patients with unresectable or metastatic mucosal melanoma (15). However, evidence specific to PGM remains scarce and is limited to individual case reports. Reported ICI regimens include ipilimumab, nivolumab, toripalimab, toripalimab plus paclitaxel, and nivolumab plus ipilimumab (16-20). Molecular and PD-L1 status were inconsistently reported across these cases. Bolzacchini *et al* (16) described a *BRAF* V600-mutated tumor initially treated with vemurafenib, which achieved disease control for approximately 6 months before progression and subsequent treatment with ipilimumab; the patient died approximately 11 months after diagnosis. Long *et al* (19) reported radiological disease stabilization after four cycles of toripalimab plus paclitaxel, although treatment was discontinued because of gastrointestinal bleeding. In contrast, Sohail *et al* (17) and Zhu *et al* (18) reported disease progression or clinical deterioration during nivolumab or toripalimab therapy, respectively. In the case reported by Longo *et al* (20), only one cycle of nivolumab plus ipilimumab was administered before the patient developed acute hepatic failure and died 2 weeks later, precluding reliable assessment of treatment response. Overall, progression-free survival, treatment duration, and overall survival were incompletely reported in several cases, and formal response criteria such as RECIST or iRECIST were generally not specified.

Compared with these previous reports, the present case was characterized by a heterogeneous, site-specific response to nivolumab, with regression of the primary gastric lesion and liver metastases despite continued progression of pleural disease. Treatment response was serially evaluated using both RECIST and iRECIST, and the transient enlargement followed by regression of the liver metastases was interpreted as site-specific pseudoprogression. In addition, PD-L1 CPS was 10-20, whereas PD-L1 status was not reported in most previous cases (16-20).

The interpretation of PD-L1 expression in the present case requires caution because the reported value was assessed using the CPS, whereas most previous studies of melanoma evaluated the proportion of PD-L1-positive tumor cells using tumor cell-based scoring methods. PD-L1 expression in melanoma is highly heterogeneous; using the 28-8 assay, a study of 104 melanoma specimens demonstrated PD-L1 expression ranging from 0 to 100% of tumor cells, with 52 and 36% of cases showing expression in ≥1 and ≥5% of tumor cells, respectively (21). In another study using the 28-8 antibody, PD-L1 positivity was observed in 25.0% of melanoma specimens overall, with a lower positivity rate in mucosal melanoma (12.5%) than in cutaneous melanoma (55.6%) (13). However, these studies used tumor cell-based scoring rather than CPS, and their values therefore cannot be directly compared with the CPS of 10-20 observed in our patient. One possible explanation for the relatively high CPS in the present case is an immune-active tumor microenvironment. Previous studies have demonstrated an association between PD-L1-positive melanoma cells and $CD4^+$ and $CD8^+$ tumor-infiltrating lymphocytes (13), and PD-L1 expression may be adaptively induced by inflammatory signaling, including interferon-γ produced by tumor-infiltrating lymphocytes (22). However, because the tumor-infiltrating lymphocyte profile and interferon-γ signaling were not directly evaluated in our patient, this explanation remains hypothetical.

Nivolumab monotherapy was selected over combination immunotherapy for two primary reasons. First, we considered patients' social circumstances and safety. Although combination therapy with nivolumab and ipilimumab demonstrates high response rates, mucosal melanoma carries a risk of grade 3 or higher immune-related adverse events in approximately 40% of cases (2). Given the patient's difficulties with frequent hospital visits and emergency care, safety was prioritized. Second, therapeutic efficacy was predicted based on PD-L1 expression. A subgroup analysis of the CheckMate 067 trial for metastatic melanoma demonstrated the advantages of

ICI combination therapy in PD-L1-negative cases (23). Since this case showed PD-L1 CPS of 10-20, indicating positive expression, we determined that monotherapy might achieve a certain degree of efficacy. The patient experienced psoriasis exacerbation as an immune-related adverse event. According to multicenter studies, ICI therapy increases the frequency of psoriasis exacerbation; however, these are manageable. Although a few patients required discontinuation of ICI, treatment outcomes in patients with psoriasis exacerbations were equivalent or superior. Therefore, preexisting psoriasis should not preclude ICI administration for malignant tumor treatment (24).

For ICI treatment, evaluation using RECIST alone may underestimate treatment efficacy. A retrospective study of 292 patients with unresectable cutaneous melanoma reported a mixed response in 22% of patients, of whom 56% subsequently achieved a response, indicating that mixed response does not necessarily represent treatment failure (25). A separate study of advanced melanoma further demonstrated that dissociated responses, characterized by simultaneous regression and progression of different tumor lesions, may reflect interlesional biological heterogeneity and differences in the tumor microenvironment between metastatic sites (26). In addition, a recent study of mucosal melanoma demonstrated heterogeneity in the tumor immune microenvironment, with more immune-infiltrated tumors showing a higher, although not significant, response rate to ICI therapy (27). Compared with the previously reported cases of PGM treated with ICIs, in which the clinical courses were predominantly characterized by disease progression, radiological stabilization, or unevaluable treatment response (16-20), the present case demonstrated a distinct site-specific heterogeneous response. Regression of the primary gastric lesion and liver metastases occurred despite continued progression of the pleural lesions. In particular, the liver metastases initially enlarged and subsequently regressed, consistent with pseudoprogression, whereas the progressive pleural lesions accompanied by malignant pleural effusion and clinical deterioration were more consistent with true progression. Thus, pseudoprogression and true progression may occur concurrently at different metastatic sites, highlighting the interlesional heterogeneity of ICI responses in PGM (16-20). Although the disease eventually progressed, regression of the primary lesion and liver metastases, together with temporary control of lymph node and lung metastases, resulted in approximately 5 months of disease control. These findings suggest that nivolumab may have provided clinically meaningful antitumor activity in this patient with PGM despite eventual disease progression.

This case has some limitations. First, although no other primary lesion was identified by physical examination, esophagogastroduodenoscopy, nasal endoscopy, imaging studies, or FDG-PET/CT, dedicated ophthalmologic and anogenital examinations were not performed. Therefore, an occult primary melanoma of the eye or anogenital region could not be completely excluded. Second, histopathological confirmation of the progressive lesions was not performed, and the diagnosis of site-specific pseudoprogression was based solely on radiological findings. Third, tumor mutational burden and comprehensive genomic profiling by next-generation sequencing were not assessed, limiting evaluation of potentially actionable or prognostic alterations. Fourth, the relatively short follow-up period-death occurred 216 days after nivolumab initiation-limited assessment of the long-term durability of the treatment response. Finally, although treatment beyond progression may benefit selected patients with melanoma (28), the supporting evidence is largely retrospective, and continued treatment risks delaying subsequent therapy or prolonging exposure to immune-related adverse events. In addition, given the subsequent clinical deterioration associated with pleural progression, it is possible that the continuation of nivolumab beyond iCPD represented treatment beyond true progression rather than appropriate management of pseudoprogression. Thus, the clinical benefit of continuing nivolumab beyond iCPD in this patient remains uncertain.

In summary, we observed a case of extremely rare PGM that displayed a mixed response with site-specific pseudoprogression while undergoing nivolumab treatment. Even in PGM, radiographic enlargement in the initial stage of ICI administration does not always signify actual progression. To prevent overlooking treatment possibilities, we propose that meticulous serial imaging assessments following iRECIST guidelines are crucial instead of promptly halting treatment.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

YS and AS conceived and designed the present case report, and collected and reviewed the clinical data. YS and AS confirm the authenticity of all the raw data. AS evaluated treatment outcomes. MF, HA, NY, HSu, HH, HI, MY, MO, MA, MG and KA participated in the clinical management of the patient and discussions regarding treatment strategies. They also contributed to the interpretation of the clinical course and treatment response. HSa performed the pathological evaluation and contributed to the interpretation of the pathological findings. All authors contributed to drafting or critically revising the manuscript for important intellectual content, and read and approved the final version of the manuscript.

Ethics approval and consent to participate

In accordance with institutional policy, case reports intended for academic presentation or publication require review and approval by the institutional ethics committee. Accordingly, the present case report was approved by the Ethics Committee of Ibaraki Prefectural Central Hospital (approval no. 1777; date of approval, January 27, 2026; Kasama, Japan).

Patient consent for publication

Written informed consent for publication of the present case report was obtained from the wife of the patient.

Competing interests

The authors declare that they have no competing interests.

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