Case Report

A fatal primary gastric melanoma treated by a double immunotherapy with ipilimumab/nivolumab: description of a case report

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Background: Primary gastric melanoma (GM) is a very uncommon tumor with a poor prognosis. Until now, only a few cases have been reported in the literature.

Case Description: A 70-year-old, Caucasian, ex-smoker man, presented with asthenia, anorexia, and weight loss of 5 kg during the last 2 months. Biological test showed high levels of transaminases and a microcytic, hypochromic anemia. Whole body CT-scan documented a gastric tumor lesion with concomitant loco-regional lymph node and hepatic metastases. Histology was consisted with the diagnosis of a primary GM. A double immunotherapy with nivolumab and ipilimumab was started but, 2 weeks later, the patient presented an acute hepatic failure quickly leading to his death despite a high dose corticotherapy.

Conclusions: The particularity of this case relies on the rarity of GM, its difficult diagnosis representing a clinical challenge, and the complexity of its management that is not validated by large clinical trials, data being extrapolated from the treatment protocols routinely used in cutaneous melanoma. In our case, the patient died 2 weeks after the first cycle of a nivolumab/ipilimumab combined treatment for an acute hepatic failure that could be related to a treatment toxicity or a tumor hyperprogression. The patient's survival was very short not allowing any accurate evaluation of the efficacy of this therapy.

Keywords: Melanoma; gastric cancer; immunotherapy; case report

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Introduction

Gastric melanoma (GM) is an uncommon tumor with a poor prognosis (1). Only a few cases have reported in the literature to date (1-6). The diagnosis is often a clinical challenge as the symptoms are aspecific (1-7). Its rarity and the lack of large clinical trials make difficult the management of GM as no validated treatments are available, data being extrapolated from cutaneous melanoma (1-6). In our case, we diagnosed a metastatic primary GM in a patient presenting with asthenia, anorexia, and weight loss of 5 kg during the last two months. He received a cycle of a double immunotherapy with nivolumab and ipilimumab, this later at a reduced dose because of his comorbidities and altered performance status (PS). Two weeks after, the patient was hospitalized for an acute, fatal hepatic failure that could be related to a treatment toxicity or a tumor hyperprogression. We present the following article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-79/rc).

Case description

In November 2021, a 70-year-old, Caucasian, ex-smoker

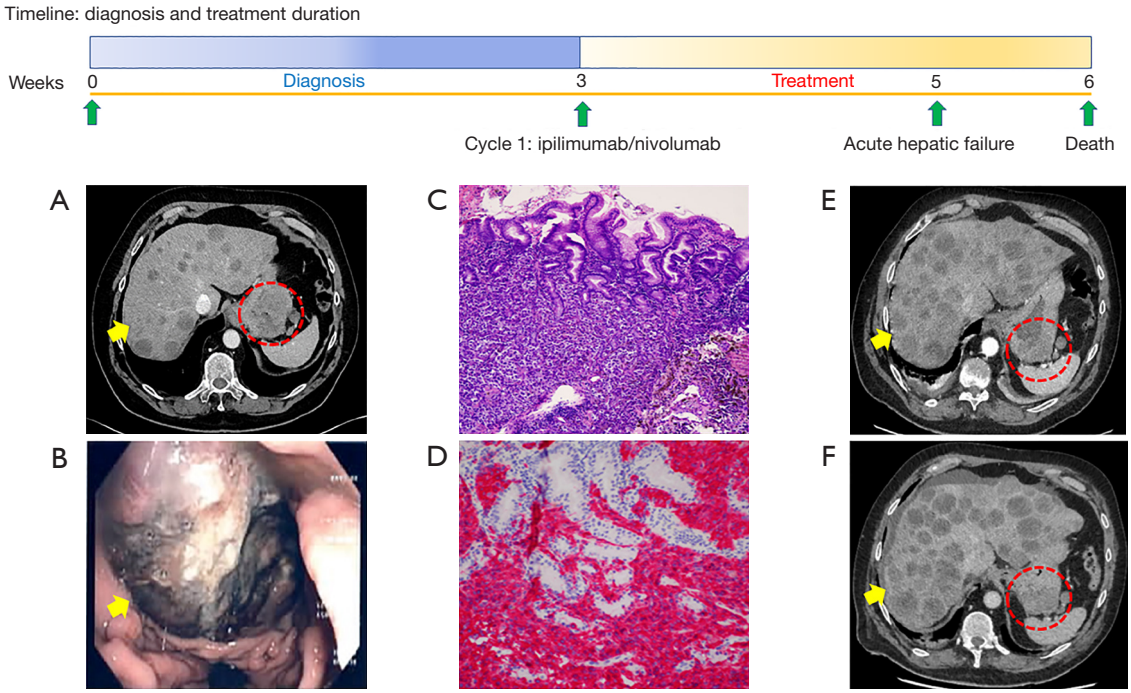

Figure 1 Timeline of tumor diagnosis and treatment. (A) Gastric contrast-enhanced tumor lesion (red circle) and concomitant, multiple, hepatic lesions (yellow arrow) (abdominal axial section CT scan at the diagnosis). (B) Oesophytic, ulcero-necrotic, black tumor lesion of the gastric great curvature (yellow arrow) (endoscopy). (C) Diffuse infiltration of gastric mucosa by pigmented, tumor cells arranged in a sheet-like pattern. Cancer cells presented a high pleomorphism with prominent eosinophylic nucleoli and a high proliferating index (histology; H&E stain, ×100). (D) Cancer cells are positive for Melan-A (H&E stain, ×200). (E) Tumor radiological evaluation before starting the double immunotherapy (abdominal axial section CT scan) documenting the multiple liver metastases (yellow arrow) and the gastric tumor (red circle). (F) Tumor radiological evaluation after the treatment (abdominal axial section CT scan) revealing a small size increase of the hepatic lesions presenting a large central necrosis (yellow arrow) and of the primary gastric tumor (red circle).

man consulted for asthenia, anorexia, and weight loss of 5 kg during the last 2 months. He had several relevant comorbidities, including an ankylosing spondylitis HLA-B*27-positive, a factor V Leiden thrombophilia, a bronchial asthma, a chronic atrial fibrillation, and a chronic glaucoma. His clinical history was characterized by an anterior uveitis, a herpes zoster keratitis, a leukocytoclastic vasculitis, and two episodes of acute cytomegalovirus and Epstein Barr virus-related hepatitis. The patient's PS Eastern Cooperative Oncology Group (ECOG) was 2. Clinical examination revealed an irregular hepatomegaly at 4 cm. No suspected cutaneous or ophthalmological lesions were observed. Biological tests showed high levels of transaminases and a microcytic, hypochromic anemia at 9 gr/dL. Whole-body CT scan documented the presence of a gastric tumor lesion (*Figure 1A*, red circle) and concomitant loco-regional lymph node and hepatic metastases (*Figure 1A*, yellow arrow). Gastroscopy revealed a voluminous, ulcero-necrotic, exophytic, black tumor lesion of the great curvature of 5 cm of diameter (*Figure 1B*, yellow arrow). Histology showed a diffuse infiltration of gastric mucosa by pigmented, tumor cells arranged in a sheet-like pattern (*Figure 1C*). Cancer cells presented a high pleomorphism with prominent eosinophylic nucleoli and a high proliferating index. At the immunohistochemistry, tumor cells were positive for Melan-A (*Figure 1D*), HMB-45 and PS100 and negative for cytokeratins confirming the diagnosis of a primary GM. No bRAF and NRAS gene mutations were observed. Before starting a systemic treatment, the patient underwent another whole-body CT-scan documenting a relevant tumor progression in the liver (*Figure 1E*, yellow arrow), as compared to the precedent radiologic evaluation performed only three weeks before, confirming the tumor aggressiveness. Based on these considerations and in the absence of validated data from the literature,

we administered a double immunotherapy with nivolumab (3 mg/kg: 275 mg, D1, every 3 weeks) and ipilimumab (1 mg/kg: 90 mg, D1, every 3 weeks), as for malignant cutaneous melanoma. The dose of ipilimumab was reduced because of patient's comorbidities and altered PS. This treatment was collegially discussed and validated and clearly explained to the patient who gave his informed consent. Two weeks later, the patient was hospitalized for confusion, asthenia and jaundice. Biological analyses revealed an acute hepatic failure. The whole-body CT scan documented a small size increase of the hepatic lesions presenting a large central necrosis (*Figure 1F*, yellow arrow). A high dose corticotherapy was administered suspecting a treatment toxicity but patient's clinical conditions quickly worsened leading to his death, 6 weeks after the endoscopic diagnosis of the primary GM.

Ethical statement

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In our case, the patient presenting a primary, metastatic GM received only one cycle of a double immunotherapy with nivolumab and ipilimumab. Two weeks later, he developed a fatal hepatic failure not responding to a high dose corticotherapy that should be related to an acute treatment toxicity or a tumor hyperprogression. The patient's overall survival from the endoscopic diagnosis was of 6 weeks attesting for the aggressiveness of this tumor and its very poor prognosis.

Primary melanoma of the gastrointestinal tract represents 1.4% of melanomas, the anorectal and esophageal being the most frequently reported location (1,7). A few cases of synchronous, multiple tumors have also been described (1-6).

The incidence of primary GM increases with age, and it is not correlated with ultraviolet (UV) exposure, race or other risk factors usually associated with cutaneous melanoma (1-7). No significant risk factors have been found to date, the correlation with tobacco smoking, oral melanosis and oropharyngeal mucosal melanoma being still controversial (7).

Clinically, primary GM presents with aspecific symptoms closely mimicking other gastric cancers or benign conditions, usually including abdominal pain, loss of appetite, weight loss, fatigue, dysphagia, hematemesis or melena, and a microcytic, hypochromic anemia. The acute upper gastrointestinal hemorrage is rarely described (1-7). Because of the rare possibility of a spontaneous regression of cutaneous melanoma reported in the literature, the clinical and radiological diagnosis of a primary GM is challenging and needs the exclusion of a gastric metastasis of an unknown primary melanoma (1). Consequently, it is imperative to examine other potential sites of primary disease, including a full body dermatological and ophthalmological examination and a colonoscopy (1-7). The ^{18}fluorodeoxyglucose PET scan may also be of value for assessing tumor extension (7).

Radiologically, GM appears as an aspecific thickening of the gastric wall or a contrast-enhanced soft-tissue lesion (1-6) because of its high vascularization. Melanotic lesions are hyperintense on T1 sequencing and hypointense on T2-weighted images at the MRI as melanin shows paramagnetic properties (1-6).

Most commonly, the endoscopy describes a large, friable, pigmented, ulcerated or polypoidal lesion (1-6). The presence of gastric melanosis and multiple synchronous lesions is not frequent (7). The endoscopic ultrasonography can be useful but it has not be routinely evaluated in GM (1-6).

There are no formal diagnostic criteria for the primary GM. Song *et al.* suggested several criteria including a single, pathology proven gastric lesion without other concurrent lesions or a history of melanoma (3).

As the Clark and Breslow staging system is not applicable for primary GM, the tumor, node, metastasis (TNM) staging is commonly used in the clinical practice (7).

Ultimately, the diagnosis of GM is based on a combination of histology and immunohistochemistry, which play a crucial role particularly in the presence of amelanotic lesions at the endoscopy (1-7). Histologically, mucosal melanoma cells often overexpress melanin, present a high pleomorphism with prominent nucleoli and are arranged in a sheet-like pattern (1-7). Immunohistochemistry shows a tumor expression of S100, Melan-A, HMB-45 and Sox10 (7). Mucosal melanoma is genetically different from cutaneous melanoma. *The BRAF V600E* and neuroblastoma *RAS*

mutation was reported in less than 10% and 5% of cases, respectively (7). The *KIT* kinase inhibitor is expressed in 15–21% (7). The cyclin-dependent kinase pathway, including the gain of *CK4* or *CK6* or the loss of *CDKN2A*, seems to play a role in certain patients. The *CCND1* is amplified in approximately 25% of patients (7). The PDGF receptor α-polypeptide is found in a relatively higher percentage of the reported cases (7).

The optimal management of mucosal melanoma is still unknown due to its rarity, the most current data being extrapolated from the primary cutaneous melanoma (1-6). For localized tumors, surgical resection with negative pathologic margin can be curative (1-6). Adjuvant radiotherapy can improve local disease control but no overall survival (OS) or disease-free survival (1-6). Adjuvant interferon was associated with an OS of 24 months in a case report (8). No data are available for immunotherapy or chemotherapy in this context. Surgery is not recommended in metastatic patients, as the prognosis of metastatic GM is very poor (1-6). Palliative radiation and endoscopy can be useful in symptoms and bleeding control (1-6). Prospective data of molecular treatment and immunotherapy are lacking, and they are extrapolated from cutaneous melanoma. A multicenter retrospective cohort analysis and, more recently, a larger pooled analysis confirmed the same activity of the immunotherapy in patients with mucosal and cutaneous melanoma (9,10).

The rarity of GM and the confounding data of the literature not exactly specifying the site of the mucosal melanoma make difficult to well define its prognosis. At the initial presentation, the patients usually present a metastatic disease because of a delayed diagnosis due to tumor aspecific symptoms leading to a poor prognosis (1-7).

Conclusions

The particularity of this case relies on the rarity of GM, its challenging diagnosis because of the aspecific symptoms and finally on its difficult management due to the absence of prospective and validated data. At our knowledge, this is the first published case report of a primary GM treated by a double immunotherapy. Nevertheless, the patient died 2 weeks after the first cycle of treatment for an acute hepatic failure. We do not know if it was related to an acute toxicity or a tumor hyperprogression attesting for the aggressiveness of GM. The patient's survival was very short not allowing any accurate evaluation of the efficacy of this therapy, which is particularly active in the treatment of metastatic cutaneous melanoma.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-79/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-79/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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