

Melanoma metastasis mimicking gastric cancer: a challenge that starts from diagnosis

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Abstract: The gastrointestinal tract is an uncommon site of metastasis in melanoma. However, when the primary melanoma cannot be found, the diagnosis of gastric melanoma by endoscopic biopsy is problematic mainly because some tumors are amelanotic and do not contain melanin granules detectable by microscopy. A 56-year-old Caucasian man with melanoma was referred to us following an initial histopathological diagnosis *via* gastroscopy of poorly differentiated primary gastric carcinoma. A computerized tomography (CT) scan showed metastatic disease and on the basis of this information we started palliative chemotherapy. However, the atypical presentation of the disease with subcutaneous metastases prompted us to make a more in-depth evaluation. Immunohistochemical evaluation modified the diagnosis to melanoma. After only one cycle of chemotherapy, treatment was changed to dabrafenib + trametinib, which was better tolerated and initially induced a partial response. The patient is currently in good clinical condition 20 months after diagnosis. Our case report highlights the difficulty in diagnosing melanoma of the gastrointestinal tract and indicates the need for pathologists and clinicians to consider such a possibility when they are faced with a diagnosis of poorly differentiated gastric cancer and unusual sites of metastasis.

Keywords: gastric cancer, gastric melanoma, gastrointestinal metastasis, misdiagnosis, poorly differentiated gastric cancer

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Introduction

Non-cutaneous melanoma represents a rare form of melanoma. In a review of 84,836 cases of melanoma diagnosed between 1985 and 1994, 91.2% were cutaneous, 5.2% ocular, 1.3% mucosal and 2.2% of unknown primary origin.¹ There are very few case reports of confirmed primary esophageal, stomach, small bowel or anorectal melanoma in the literature.² Melanocytes, the cells from which melanoma is believed to originate, have been found in oral, esophageal and anorectal mucus,³ but it is still controversial whether primary melanoma can arise from the stomach, small intestine or colon as there are no melanocytes in these regions. One hypothesis put forward to explain

the potential mechanism by which this would be possible is that multipotential neural crest cells may migrate to these regions and develop into melanoma after differentiation. Another hypothesis suggests that amine precursor uptake and decarboxylation (APUD) cells in the gastrointestinal tract may be capable of differentiating into melanocytes.⁴

Diagnosis is difficult, especially when the biopsied tumor tissue contains no melanin pigmentation. Amelanotic melanoma is extremely rare and is often misdiagnosed at biopsy as poorly differentiated carcinoma, undifferentiated carcinoma, leiomyosarcoma or neurofibroma.⁵ Although there

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Figure 1. Image taken during gastroscopy showing protruding/ulcerated lesion in the subcardia.

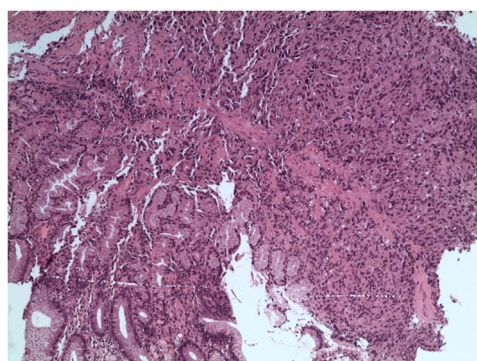


Figure 2. Histological section of gastric biopsy showing gastric mucosa with neoplastic infiltration.

are very few reported cases of melanoma mimicking gastric carcinoma,^{6,7} the extremely low incidence and lack of awareness about this disease may also contribute to misdiagnosis by endoscopists, physicians and pathologists. Herein we report a rare case of gastric melanoma that was misdiagnosed as gastric cancer, and provide a review of the literature on other similar misdiagnosed cases.

Case presentation

A 56-year-old Caucasian man with fair skin and an unremarkable past medical history underwent gastroscopy at the end of February 2019 because of severe dyspepsia. He had also lost (7 kg) in the previous 6 weeks. At the time he was not taking any prescription drugs. The gastroscopy showed



Figure 3. Endoscopic ultrasound revealed several sessile umbilicated plaques/papules in the gastric body.

an ulcerated lesion of the gastric fundus (Figure 1) with erythematous mucosa of the antrum and pyloric stenosis. The lesion was biopsied and a histological diagnosis of poorly differentiated gastric cancer with signet-ring cell features was made (Figure 2). The gastroenterologist thus referred the patient to our cancer institute for a consultation. Pulmonary and abdominal examination was negative and no enlarged superficial lymph nodes were found. Blood tests were within limits apart from moderate anemia, with hemoglobin 10.8 g/dL (range 12–15.5).

Endoscopic ultrasound confirmed the presence of a 2-cm ulcerated lesion in the subcardia region. Several sessile umbilicated plaques/papules covered with ulcerated mucosa (max diameter 10 mm) present in the gastric body and antrum (Figure 3) were initially hypothesized as secondary lesions and were thus biopsied. These last lesions were negative for cancer at immunohistochemical (IHC) evaluation and were also assessed for cytokeratin AE1/AE3, which confirmed their negativity.

The scan also revealed subversion of the normal gastric wall with serosal invasion and perigastric lymphadenopathies (T4N+ according to the AJCC (American Joint Committee on Cancer) Staging Manual, 8th Edition).⁸ A chest and abdominal computerized tomography (CT) scan revealed the presence of at least 20 lung lesions ranging in size from a few millimeters to a few centimeters, and an esophageal lymph node (station 8) of 22 mm. A number of solid subcutaneous lesions (max diameter 14 mm) were found

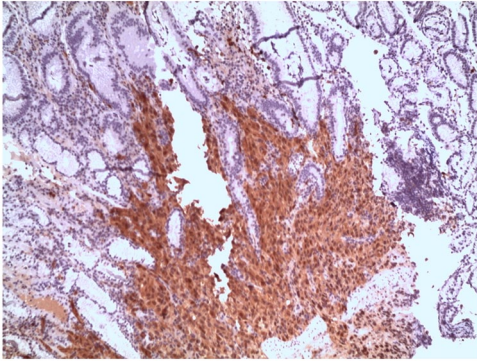


Figure 4. Immunohistochemistry staining showing S100 positivity.

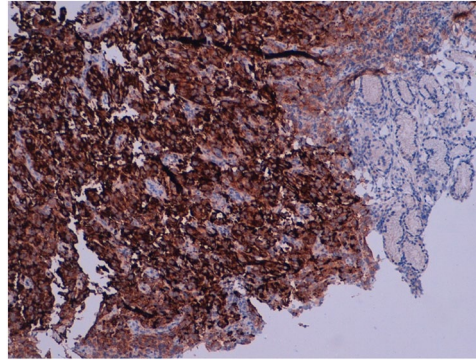


Figure 6. Immunohistochemistry staining showing B-RAF positivity in tumor cells.

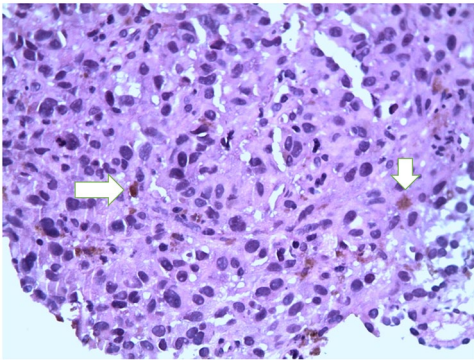


Figure 5. Isolated deposits of melanic pigment in tumor cells, marked with arrows.

near the dorsal vertebra and in the gluteal region bilaterally (max diameter 15 mm). There were also numerous nodular lesions compatible with peritoneal carcinosis. A large lesion invading the parietal wall (65 × 47 mm) was detected in the gastric fundus, and some lesions of undetermined significance were found in the adrenal glands.

Before starting palliative chemotherapy for gastric cancer, we evaluated the HER2 status by IHC (score of 0) and assessed dihydropyrimidine dehydrogenase activity (1129–5923 CG (DPYD-rs75017182)), the results indicating the need to begin with a lower dose of fluoropyrimidine.⁹ In March 2019, the patient received a first cycle of chemotherapy comprising oxaliplatin 85 mg/m² administered intravenously (i.v.) over 2 h (day 1) plus calcium levofofolinate 200 mg/m² i.v. over 2 h (day 1), 5-fluorouracil (5-FU) 2400 mg/m² i.v. over 48 h (days 1–2) and 5-FU 400 mg/m² i.v. over 3–4 min (day 1) with the

fluoropyrimidine reduced to 75% (FOLFOX6). Side-effects were grade (G) 1 diarrhea and G2 anal mucositis, lasting for 7 days.

The unusual presentation of the disease with subcutaneous metastases and numerous lung nodules prompted us to request a more in-depth evaluation of the biopsy. IHC evaluation revealed that the cancer was negative for pan-keratin, CD-34, LCA and DOG-1, but positive for S-100 (Figure 4) and CD-117. Accordingly, the pathologist revised the initial diagnosis of gastric cancer to a secondary localization of melanoma.

Given the important change in diagnosis, we requested a second opinion from another pathologist. The pathologist described gastric mucosa infiltrated by epitheliomorphic neoplasia with discrete atypical cells. Some deposits of intracytoplasmic melanin pigment (Figure 5) were also observed. IHC characterization showed positivity for S100, Melan A, B-RAF (Figure 6) and MART-1, thus confirming the gastric location of melanoma. Subsequent mutational analysis revealed V600E mutation of the BRAF gene. Although at this point the diagnosis of melanoma was confirmed, further investigation was needed to determine whether the stomach was a metastatic site or the primary site of disease. A thorough re-assessment of the patient's medical history confirmed no history of melanoma or regression of cutaneous pigmented lesions. The only event worthy of note was cryotherapy for keratosis of the trunk performed several years before. In March 2019 the patient underwent a series of clinical evaluations. A dermatological examination visit revealed a purple nodular lesion of about 5 mm on the glans and a small subcutaneous lesion on the left side of the

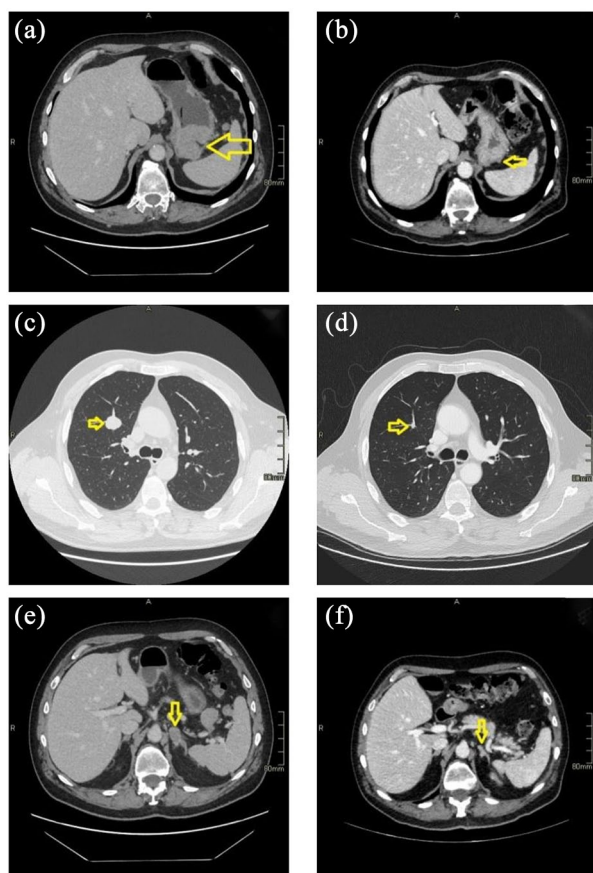


Figure 7. CT scan showing gastric wall, lung metastasis and left adrenal gland at diagnosis (A, C and E, respectively) and after dabrafenib + trametinib (B, D and F, respectively). CT, computerized tomography.

scalp. Although the dermatologist advised the removal of both lesions, it was decided with the patient to postpone the biopsies for the moment. The ophthalmology consultation was negative.

The otolaryngologist's visit, including digital fibroscopy, was negative for cancer. We also scheduled a proctological evaluation but the patient, psychologically and emotionally drained after so many medical examinations, refused. Given that there was sufficient information to plan treatment, in April 2019, after the single cycle of FOLFOX6, the patient began specific therapy for melanoma; oral therapy was started with dabrafenib 150 mg twice a day + trametinib 2 mg/day every 30 days for melanoma.

A rapid, objective response was observed after one month of dabrafenib + trametinib consisting in the disappearance of the scalp and glans lesions. Treatment was well tolerated and 4 months later,

tumor assessment with a total body CT scan showed a partial response of disease (Figure 7A–F). The patient received 12 cycles of dabrafenib + trametinib up to March 2020, when a total body CT scan showed stable disease in the chest and abdomen but suspected brain lesions, subsequently confirmed by brain MRI. The patient has been scheduled for panencephalic radiotherapy and is continuing with dabrafenib + trametinib.

Discussion

We report the case of a patient with metastatic gastric melanoma referred to us with an initial histopathological diagnosis of primary gastric carcinoma. Our case raises some interesting considerations. First, the diagnosis of melanoma of the stomach is often difficult, and differentiating metastatic from primary melanoma may be impossible. The prognosis of patients with metastatic melanoma is also very poor. Our patient is possibly only the third case of melanoma with gastric involvement treated with BRAF inhibitor immunotherapy.

A more in-depth explanation follows. The diagnosis of gastric melanoma by endoscopic biopsy is extremely problematic: some tumors are amelanotic and do not contain melanin granules detectable by microscopy; melanocytes normally concentrate in foci or nodules covered by normal mucosa and thus may be missed by endoscopic biopsy.¹⁰ Taking into account the solitary lesions, ulceration and the presence of some signet-ring elements in our patient, a diagnosis of carcinoma was made. When we formulated the hypothesis of metastasis, IHC analysis was performed and the diagnosis was modified. Only a few intracytoplasmic melanin granules were found.

The most sensitive markers in melanoma are S100 protein and HMB-45,¹¹ that of S-100 varying between 33% and 100% and that of HMB-45 ranging from 80% to 97%, with a high specificity (100%).^{12,13} Melanocytes contain vimentin, an intermediate filament usually expressed in primary and metastatic melanoma cells. Vimentin positivity can differentiate melanoma from undifferentiated carcinoma, but not from lymphoma or sarcoma.¹⁴ The Melan A protein is a melanocytic differentiation antigen produced by the MART-1 gene and is believed to be specific to melanocytic cells.¹⁵ In our case, S100 positivity and the presence of Melan A enabled us to abandon the diagnosis of gastric cancer in favor of melanoma.

Table 1. Cases of misdiagnosis of melanoma in gastric cancer.

Reference	Characteristics of gastric lesion at gastroscopy	Pathological characteristics of gastric biopsy at IHC		Diagnosis by gastroscopy	Primary versus metastatic gastric melanoma
Bahat <i>et al.</i> ⁶	Ulcerated mass protruding into the lumen in the corpus	CD-30 (n) CD-38 (n) LCA (n) Pancytokeratin (n)*	HMB-45 (p) S-100 (p)*	First: diffuse infiltrating signet-ring cell gastric carcinoma Second: melanoma	Metastatic gastric melanoma
Cho <i>et al.</i> ⁷	Polypoid lesion with central ulceration in the body	Not evaluated		Poorly differentiated adenocarcinoma	Primary gastric melanoma
Callaghan <i>et al.</i> ²⁴	Large ulcerated lesion of the upper stomach	–	HMB-45 (p) Melan A (p) S-100 (p) B-RAF (p) (V600E)*	First: poorly differentiated adenocarcinoma Second: melanoma	Primary gastric melanoma
Grilliot <i>et al.</i> ²⁵	Large lesion of the gastroesophageal junction	AE1/AE3 (n) CK7 (n) CK20 (n)*	HMB-45 (p) Melan A (p) S-100 (p)*	First: poorly differentiated carcinoma Second: signet-ring melanoma	Primary gastric melanoma
Song <i>et al.</i> ²⁶	Bleeding mass in the upper stomach	CK5/6 (n) CD-3 (n) CD-20 (n) CGA (n)	Ki67 (p) SYN (p) HMB-45 (p) Melan A (p) S-100 (p)	Poorly differentiated adenocarcinoma plus neuroendocrine tumor	Primary gastric melanoma
Wang <i>et al.</i> ²⁷	Bulky black tumor in the gastroesophageal junction	Not evaluated		Poorly differentiated adenocarcinoma	Primary gastric melanoma
This report	Polypoid ulcerated lesion (positive at biopsy) in the subcardia plus several sessile umbilicated plaques/papules (max. about 10 mm (negative at biopsy) in the gastric body and antrum	AE1/AE3 (n) HER2 (n) CD-34 (n) LCA (n) DOG-1 (n)*	S-100 (p) CD-117 (p) Melan A (p) MART-1 (p) B-RAF (p) (V600E)*	First: poorly differentiated signet-ring cell gastric cancer Second: melanoma	Metastatic gastric melanoma
*Revision of first report with immunohistochemistry (IHC). n, negative; p, positive.					

In an effort to reduce the risk of misinterpreting a metastasis to the gastric wall as a primary lesion, criteria to guide the diagnosis of primary melanoma have been published: (a) single lesion of melanoma in the stomach proved by pathology;^{1,16} (b) no concurrent lesions in other sites of the body; (c) no history of melanoma; (d) disease-free survival of at least 12 months after curative surgery. From an endoscopic point of view, gastric metastasis from melanoma may appear as black-pigmented ulcers, diffuse black pigment in the mucosa, multiple small-size nodules of the mucosa or submucosa, polypoid lesions, or extrinsic masses.¹⁷ Although these lesions are often pigmented, they may also be non-pigmented, mimicking other forms of neoplastic epithelial

lesions or MALT (mucosa-associated lymphoid tissue) lymphomas.^{18–22} In our patient the subcardia gastric lesion was non-pigmented and extended into the gastric wall, and there were also some umbilicated lesions. Although this may indicate a gastric origin of disease, the presence of other umbilicated gastric lesions (albeit negative to biopsy) and a small lesion on the glans suggested that the stomach was a metastatic site. It must be underlined that the primary site of disease is unknown in a considerable proportion of melanoma patients.²³

In the literature there at least six cases of gastric melanoma misdiagnosed as gastric cancer (Table 1).^{6,7,24–27} Three authors^{6,24,25} were able

spontaneously to correct the first diagnosis of gastric cancer to gastric melanoma before making any therapeutic decisions. Bahat *et al.*⁶ explained that the correct diagnosis was facilitated by taking into consideration the presence of lung metastasis and negative markers, and by the fact that the patient had recently undergone surgery to remove a pigmented nevus which, however, had not been examined by a pathologist. Cho *et al.*⁷ and Song *et al.*²⁶ only made a correct diagnosis after gastrectomy. Cho *et al.*⁷ hypothesized that the initial diagnosis of gastric cancer may have been due to an insufficient number of tumor cells in the biopsy material. Song *et al.*²⁶ concluded that the misdiagnosis was linked to the presence/absence of melanin: gastric melanoma with visible pigmentation is easy to diagnose, whereas lesions with little or no melanin may be misleading. The authors commented that, during gastroscopy, the pigmentation of the tumor may have been covered by blood, leading to a less than adequate biopsy sample. Wang *et al.*²⁷ described a primary advanced esophago-gastric melanoma, choosing not to focus on the misdiagnosis at gastroscopy and biopsy but rather on the rarity of the case. In the cases described by Cho *et al.*,⁷ Song *et al.*²⁶ and Wang *et al.*,²⁷ the absence of metastatic disease may have made the diagnosis more difficult, whereas an atypical metastatic site would probably have prompted clinicians to make a more in-depth evaluation of the case.

According to the literature, about half of all patients with gastric metastasis concomitantly show metastatic lesions in other organs, and the mean time from the diagnosis of gastric metastasis to death is around 4.75 months.²⁸ Our patient is still alive 20 months after diagnosis.

To the best of our knowledge this is the third case of melanoma with gastric involvement treated with BRAF inhibitors.^{24,29} BRAF is one of the most significant gene mutations in cutaneous melanoma (approximately 50%) but is rare in mucosal forms of the disease.³⁰ The presence of skin lesions and substantial disease burden in a case of poorly differentiated gastric cancer must raise the suspicion of an incorrect histological diagnosis. Gastric melanomas with unusual phenotypes may thus represent a diagnostic challenge for the endoscopist, pathologist and oncologist.

Conclusion

There are a number of reasons for the misdiagnosis of gastric melanoma at biopsy. First, melanomas are known for their wide range of microscopic appearances that may resemble other tumor types. Scant clinical information and details of the patient's medical history can also hinder the diagnosis of the pathologist. Our experience highlights that clinicians should take into account the possibility of melanoma in cases of poorly differentiated gastric cancer with uncommon metastatic sites.

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Author contributions

MM and MG conceived the idea for and designed the study. FP made the diagnosis of melanoma. DO performed the CT scans. GB, SR, AP, LR, FDR, FGS and GLF carried out the literature search. MM wrote the first draft of the article and other authors contributed to finalizing the present version of the paper. All the authors approved the article for publication.

Conflict of interest

The authors declare that there is no conflict of interest.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical statement

The study was carried out in accordance with the principles laid down in the Declaration of Helsinki. Ethics approval was not necessary for this work due to its design (case report). Written informed consent was obtained from the patient.

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