CASE REPORT

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Multifocal Gastrointestinal Melanoma

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ABSTRACT

Primary mucosal melanoma is a rare disease, with a worse prognosis than cutaneous melanoma. We present a patient with primary melanoma of the stomach and small intestine, with good outcome after radical surgical excision and adjuvant ipilimumab therapy.

Key words: gastrointestinal tract – melanoma – multifocal.

Abbrevations: 18-FDG-PET-CT: 18-F-fluorodeoxyglucose positron emission tomography; HMB 45: Human Melanoma Black; MelanA/Mart-1: melanoma recognized by T cells-1.

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INTRODUCTION

Melanoma represents 1-3% of all malignant cancers [1]. Although it is most common in the skin, it can also involve the respiratory, gastrointestinal and urogenital mucosa [2]. Mucosal melanomas are more aggressive, compared to skin melanomas, with a 5-year survival of 25% [3]. They are found to be primary or secondary in nature. Primary mucosal melanomas are very rare and account for 1.4% of all melanomas [2]. The majority of mucosa lesions found along the gastrointestinal tract are metastatic; the most frequent locations of metastasis are the small intestine, colon and stomach [4, 5]. Primary mucosal melanoma arises in any site of the gastrointestinal tract, but it is most common in anorectal (31.4% in the anal canal and 22.2% in the rectum) and oropharyngeal region (32.8%), while esophagus (5.9%), stomach (2.7%), small intestine (2.3%), gallbladder (1.4%) and large intestine (0.9%) are rare sites of origin [2, 6]. According to these percentages, primary melanoma of the stomach is an extremely rare tumor, with approximately 20 cases reported in the literature [2]. We present a case of gastric melanoma with simultaneous small bowel lesions.

CASE REPORT

An 82-year-old female was referred for an episode of melena lasting for 48 hours. She had diabetes mellitus type II, treated with metformin. Physical examination revealed mild tachycardia and pale skin. Laboratory studies revealed hypochromic anemia that required two units of blood transfusion. Upper gastrointestinal endoscopy found multiple pigmented polypoid masses at the distal greater curvature of the stomach, measuring 1.5, 2 and 3.5 cm in diameter (Fig. 1) with stigmata of oozing bleeding.

Histological examination of the endoscopic biopsies revealed malignant epithelioid and spindle cells, immunohistochemically positive for melanoma markers: S100 (acidic melanocytic protein, 100% soluble in ammonium sulfate at neutral pH), HMB 45 (Human Melanoma Black-45, an antibody to a premelanosome glycoprotein) and MelanA/Mart-1 (melanoma antigen recognized by T cells-1, an antibody to a cytoplasmic protein of melanosomal differentiation). The dermatologic examination was normal and no history of regressed skin lesions was recollected. The ophthalmological and gynecological examinations were normal. The whole body 18-F-fluorodeoxyglucose positron emission tomography (18-FDG-PET-CT scan) revealed the gastric lesions, and small left pulmonary nodules, 1.3 cm in maximum diameter, compatible with metastases. There was also an increased uptake

of 18-FDG along the gastrointestinal tract, attributed to the use of metformin. The patient underwent partial distal gastrectomy with D1 lymph nodes dissection. Pathological examination of the surgical specimen revealed ulcerated polypoid masses of the greater curvature 3.2/2.5/1, 4.1/3.2/1.5 and 1.8/1.4/1cm in diameter. The histological examination revealed malignant melanoma (mixed type with epithelial and spindle cells) positive for HMB-45, melan A and S100, which invaded the

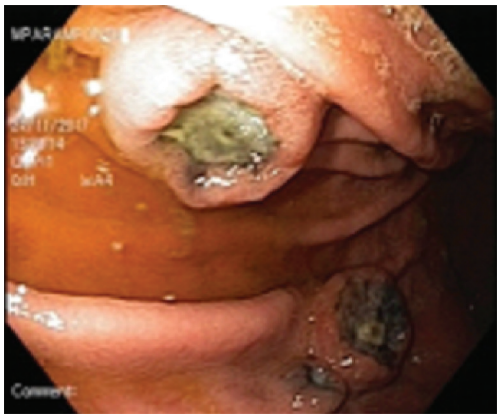

Fig. 1. Endoscopic images of gastric melanoma.

submucosa (Fig. 2). Lympho-vascular emboli were observed in the submucosa (Fig. 2). Ki 67 proliferative marker was positive in approximately 50% of tumor nuclei. The tumor cells invaded one of the lymph nodes. Molecular study was negative for BRAF mutation. The patient started therapy with pembrolizumab (200mg i.v. every three weeks) with good tolerance.

Four months later she was referred again to our clinic for melena and severe anemia. Upper gastrointestinal endoscopy revealed two pigmented polypoid lesions at the gastric remnant (Fig. 3). During surgery, another four ulcerated masses were found at the small intestine (two at the jejunum and two at the ileum). She underwent total gastrectomy with Roux-en-Y anastomosis and segmental excision of the jejunum and ileum. The histological examination of the excised lesions revealed malignant melanoma (mixed type with epithelioid and spindle cells), positive for HMB 45, melan A and S100 with Ki 67 positive in more than 50% of tumor nuclei. The excised lymph nodes were negative for malignant cells. The gastric lesions invaded the submucosa (Fig. 4A), while the small intestine melanoma invaded the muscularis propria (Fig 4B). Lympho-vascular emboli were also noted. The patient's postoperative course was unremarkable. Due to recurrent disease, she started therapy with ipilimumab 3mg/kg (4 courses every 21 days). She completed treatment with good tolerance. Re-staging scans at 4 weeks after treatment showed stable disease, without radiologic recurrence in the abdomen, while the pulmonary lesions remained stable.

Clinical re-evaluation at 6 and 12 months after second surgery revealed the patient in good clinical condition.

DISCUSSION

The patients with primary gastric melanoma can present symptoms similar to other upper gastrointestinal lesions:

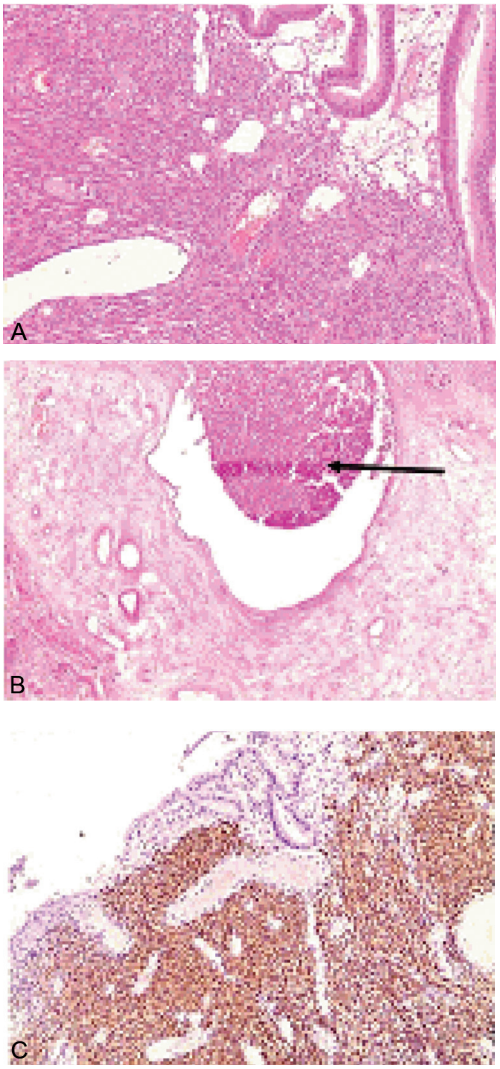

Fig. 2. Malignant melanoma in the gastric mucosa (A, H&E x100) extending into the submucosa where a vascular embolus is recognized (B, H&E x40, arrow). Immunohistochemistry showed positive MelanA (C, x100), i.e. acidic melanocytic protein, 100% Soluble in ammonium sulfate at neutral pH.

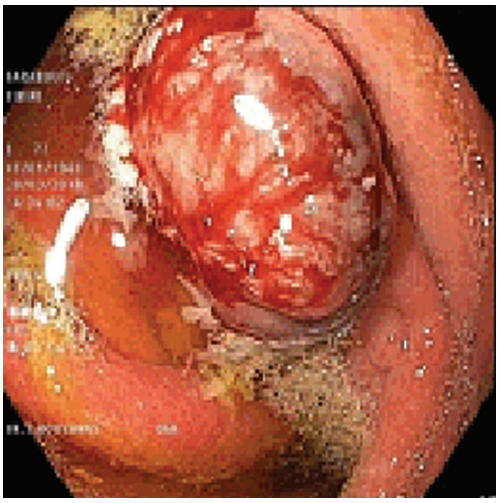

Fig. 3. Endoscopic images of melanoma at the gastric remnant.

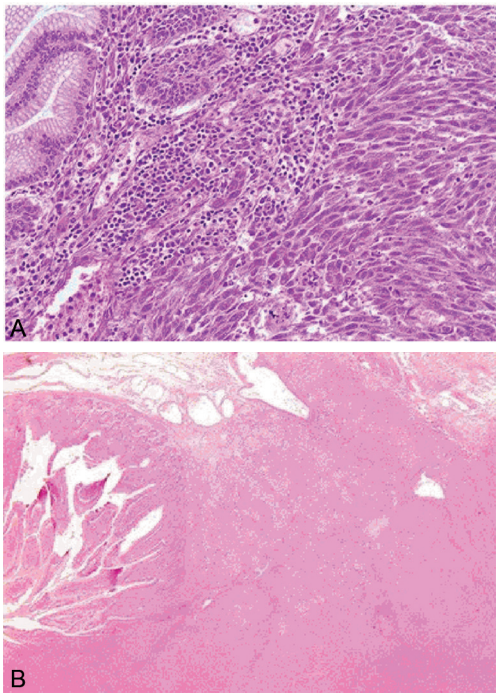

Fig. 4. Malignant melanoma at the gastric remnant infiltrating mucosa (A: H&E x 200) and melanoma infiltrating small intestine wall (B: H&E x20).

weight loss, abdominal pain, melena and anemia [7]. Ahn et al. [8] proposed three endoscopic patterns: a mass-forming, a nodular, and flat-pigmented pattern. According to the histological type, there are the epithelioid (found in 63% in primary lesions and 90% in metastatic) and the mixed type (found in 37% in primary lesions and 10% in metastatic) [8]. Our patient had the mass-forming pattern, with mixed histological type.

Multifocal gastrointestinal mucosal melanoma is usually of metastatic origin. However, in up to 9% of cases, the primary site is unidentifiable [9]. The development and pathogenesis of mucosal melanoma is unknown and two mechanisms have been proposed [1]. Firstly, primary APUD cells (originating from neural crest) may gain or retain the ability to differentiate into melanocytes and subsequently undergo malignant transformation [1, 10]. Secondly, migration of melanocytes into the gastrointestinal tract is supposed; this hypothesis was suggested by the observation that benign melanosis of the esophagus could be mutated and transformed into malignant melanocytes [11]. The criteria for the diagnosis of primary mucosal melanoma are: (1) lack of concurrent or previous removal of a melanoma or atypical melanotic lesion from the skin, (2) no involvement of other organs upon presentation, (3) documented disease–free survival of at least 12 months after radical resection, as less than 50% of patients with metastatic melanoma survive longer than one year and carry a median survival of 10 months [11, 12]. According to the mentioned criteria, our case was diagnosed initially as gastric melanoma with pulmonary and small bowel metastases. However, the diagnosis of mass-forming pattern melanoma in the small intestine, invading the muscularis propria, 4 months after the first operation, raised the possibility that these lesions could have preexisted. The initial uptake of 18-FDG along the gastrointestinal tract, attributed initially to metformin use, could not exclude the possibility of a small focus of malignant melanocytes in the small intestine [13]. Also, the recurrence of the melanoma at the gastric remnant four months after the first operation supported the hypothesis of a multifocal gastrointestinal melanoma with pulmonary metastases. Mucosal melanomas are more aggressive, being associated with a worse prognosis than cutaneous melanoma, probably because of the delay in diagnosis and rich lymphatic and vascular supply of the gastrointestinal tract mucosa [14, 15]. However, early detection with curative surgical excision provides a long-term disease free interval [15].

CONCLUSION

Despite the poor prognosis of primary mucosal multifocal gastrointestinal melanoma, the early diagnosis and radical surgical excision followed by adjuvant chemotherapy resulted in a good clinical outcome at least 12 months after the diagnosis in our patient.

Conflicts of interest: None to declare.

Authors' contributions: S.K. and T.R. collected the data and wrote the manuscript. H. Goga, H. Gakiopoulou, P.A, G.H and D.M were responsible for patient diagnosis and treatment. All the authors approved the final version of the manuscript.

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