



Case Report

Primary Gastric Melanoma of Unknown Origin: a Case Report and Short Literature Review

Athena Myrou¹, Theodoros Aslanidis², Andreas Protopapas¹, Elisavet Psoma³, Andreas Kontosis⁴, Triantafyllia Koletsa⁴

¹ First Propedeutic Internal Medicine Department, AHEPA University Hospital, Thessaloniki, Greece

² Intensive Care Unit, St Paul General Hospital, Thessaloniki, Greece

³ Computed Tomography Unit, Radiology Department, AHEPA University Hospital, Thessaloniki, Greece

⁴ Pathology Department, Faculty of Medicine, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece

Corresponding author: Theodoros Aslanidis, Intensive Care Unit, St Paul General Hospital, Thessaloniki, Greece; E-mail: thaslan@hotmail.com

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Abstract

Though being usually a cutaneous tumor, melanomas can occur in several extracutaneous sites. Primary mucosal melanomas are rare, and primary gastric mucosal melanomas are considered extremely rare. Compared with cutaneous and ocular melanoma, mucosal melanomas have the lowest five-year survival. High level of suspicion of such rare condition may be the only way for early detection, diagnosis and chance for successful management of similar cases. In the present report, a case of a primary gastric melanoma in a 73-year-old man is described, along with a short review of the literature.

Keyword

primary gastric melanoma

INTRODUCTION

Melanoma is a highly malignant neoplasm that commonly arises in skin from pigment cells (melanocytes). Extracutaneous melanomas include ocular melanomas, mucosal and leptomeningeal melanomas, and rare cases of melanoma originating in some internal organs. Mucosal melanomas arise from melanocytes located in mucosal membranes lining respiratory, gastrointestinal and urogenital tract.¹⁻²

However, gastrointestinal melanomas can occur anywhere along gastrointestinal tract (GIT); they are more commonly found in the oropharynx (32.8%), anal canal (31.4%), and rectum (22.2%).²⁻³ In case of GIT metastasis originating from a cutaneous melanoma, the most common sites are jejunum and ileum, followed by the colon, rectum, and then stomach.²

Primary gastric melanoma (PGM) is a rare clinical phenomenon.¹ It can present, similarly to other upper gastroin-

testinal lesions, with weight loss, abdominal pain, melena, and anaemia.⁴ However, due to the high occurrence of metastatic melanoma, PGM is often a diagnosis of exclusion.

Herein, we report an extremely rare case of PGM of unknown origin.

CASE REPORT

A 73-year-old white male presented to us with a one-month history of fatigue. He denied any fevers, chills, weight loss/gain, or change in bowel habits. General physical exam did not reveal any significant abnormalities. Both the patient's past medical and family history were unremarkable. He denied a history of smoking, alcohol intake and substance abuse.

However, full blood count indicated profound hypochromic microcytic anaemia, with a haemoglobin level of 7.8 g/dL

for which the patient received a transfusion, and was referred for further examinations.

Subsequent upper endoscopic gastrointestinal (GI) examination showed multiple hyperplastic gastric polyps less than 1 cm in size (0.5 cm) at the fundus of the stomach as well as in the body of the stomach. More gastric lesions were suspected. The histological examination of the polyps revealed extensive infiltration by a population of indifferent malignant cells. The histopathological examination of the gastric polyp biopsy revealed diffuse infiltration of the gastric mucosa by medium-sized malignant cells, mostly epithelioid, with lightly eosinophilic cytoplasm and round nuclei with distinct central nucleoli (Figs 1A, 1B). No pigment was observed. Immunohistochemically, the neoplastic cells showed strong positivity for vimentin, S100 (nuclear and cytoplasmic) and Melan-A (Fig. 1C), whereas antigen HMB45 expression was only focal. Quite a few cells were positive for CD117 but staining for antigens DOG1 and CD34 was negative. Immunostains for keratin CK8/18, EMA, chromogranin, synaptophysin, CD138, CD20, and CD3 were negative. The Ki67 proliferation index was 40%. Colonoscopy found no lesions.

The patient had dermatological and ophthalmological consultations, as well as imaging examinations that excluded the presence of melanoma outside the gastrointestinal tract.

Computed tomography (CT) scan of the chest revealed a soft mass (diameter 1.7 cm) in the upper left lung lobe and multiple small nodules in both lungs and mediastinal lymph nodes. CT of the abdominal cavity showed enlargement of liver without infiltration of adjacent organs or enlarged lymph nodes. (Fig. 2)

Further molecular genetic testing did not reveal a V600R mutation in the BRAF gene.

The patient underwent thoracic biopsy. Sections from the lung specimen showed neoplastic nodules amid normal lung parenchyma. The nodules comprised epithelioid and spindle cells, with abundant eosinophilic or clear cytoplasm and prominent nucleoli, arranged in clusters (Figs 3A, 3B). The mitotic activity was moderate and the Ki67 proliferation index was up to 70%. The neoplastic cells were immunoreactive to vimentin, S100 (strong nuclear and cytoplasmic), Melan-A (Fig. 3C), and the majority of them to HMB45 antibody.

No staining was observed to keratins AE1/AE3, CK8/18, TTF1, NapsinA, P63, synaptophysin, CD56, CD117, CD34, SMA and desmin.

Subsequent Positron Emission Tomography (PET) scan showed a high uptake of 18F-FDG multiorgan involvement (metastases) in liver, lungs, small bowel and axial skeleton, implying disease progression.

A decision for repetition of GIT examination was taken; capsule endoscopy was performed, and further metastatic lesions were spotted in the lower intestine due to malignant melanoma. The patient was referred for oncological consultation and further chemotherapy and immunotherapy. Fourteen months after diagnosis the patient is still under oncological surveillance.

DISCUSSION

While melanoma is predominantly considered a cutaneous cancer, extracutaneous melanoma does occur. Bishop et al. identified the rate of extracutaneous melanoma to be 1/100,000 in Western countries⁵, or approximately 1.4% of the total number of melanoma cases.⁶

Malignant melanoma of the GIT is usually a metastasis from a cutaneous source. It is often a result of advanced disease at time of diagnosis and is associated with poor outcome. GIT primary melanomas are rare, with an estimated prevalence of 0.5 to 1 case per million, while PGM is an extremely rare clinical entity, with only 19 reported cases worldwide.⁷

Yet, even GIT metastases may not be clinically detected until after removal and potential cure of primary melanoma, mostly affecting the small bowel, the stomach and the colon.⁸ There is also a portion of GIT melanomas without any documented evidence of a primary lesion in the skin or elsewhere, even after thorough examination.^{9,10}

Allen and Spitz⁹ defined the main criteria for diagnosis of primitive nature of gastric melanoma: lack of concurrent or previous removal of a melanoma or atypical melanotic lesion from the skin, lack of other organ involvement and in-situ change in the overlying or adjacent GI epithelium.

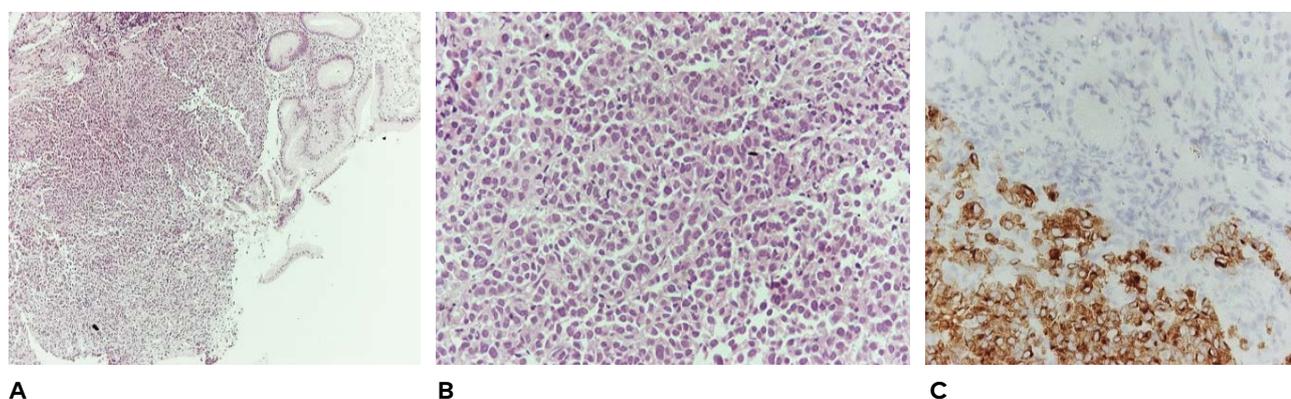


Figure 1. Histopathological examination images of gastric polyp biopsy. Gastric mucosa infiltrated by medium-sized neoplastic cells (A) with mild pleomorphism (B) and immunoreactivity to Melan-A antibody (C). Nodular infiltration of lung parenchyma.

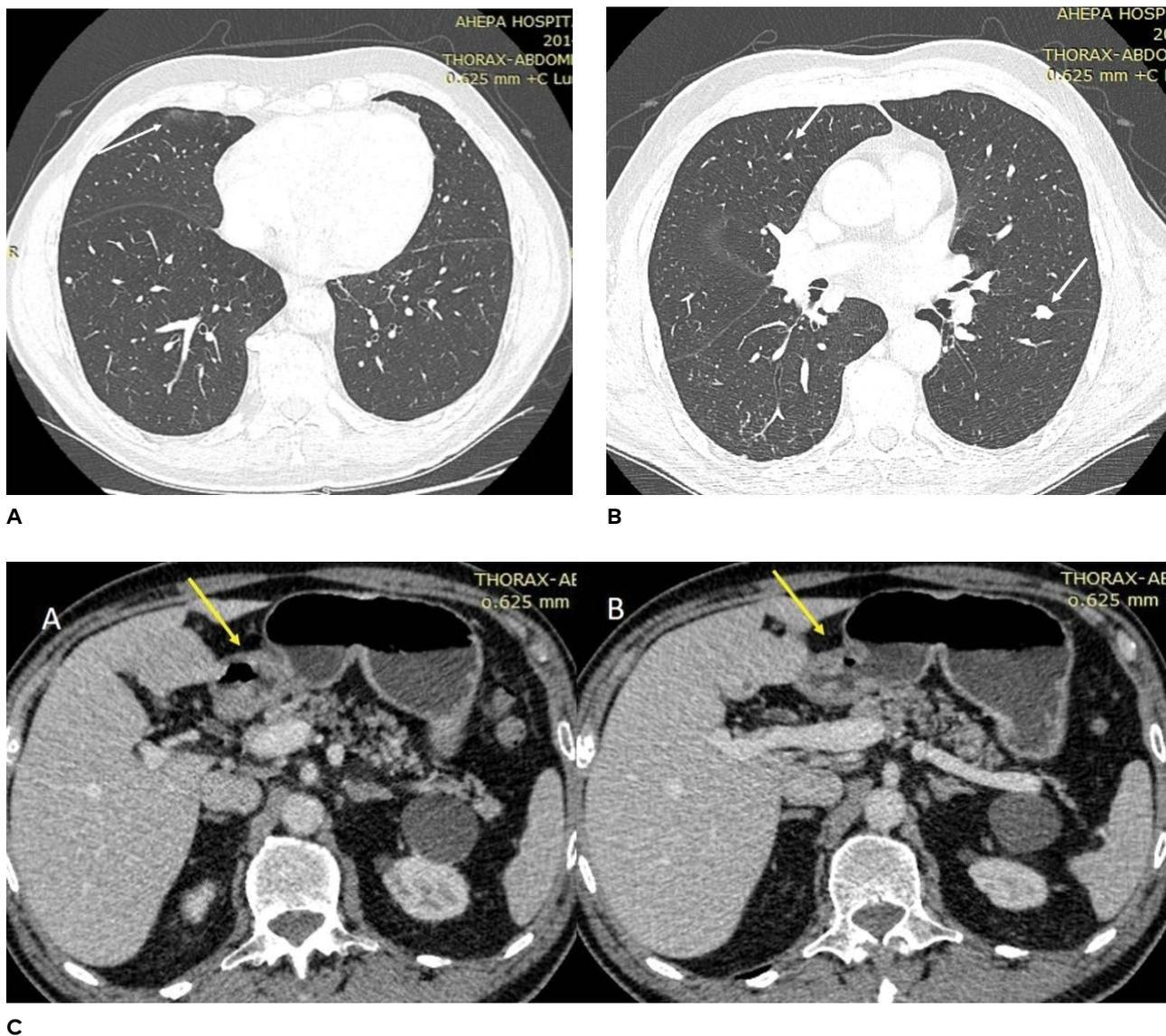


Figure 2. A, B, C: Snapshots of CT scan where small soft masses are revealed (arrows). (A: HE $\times 100$; B: HE $\times 400$; C: IHC $\times 100$)

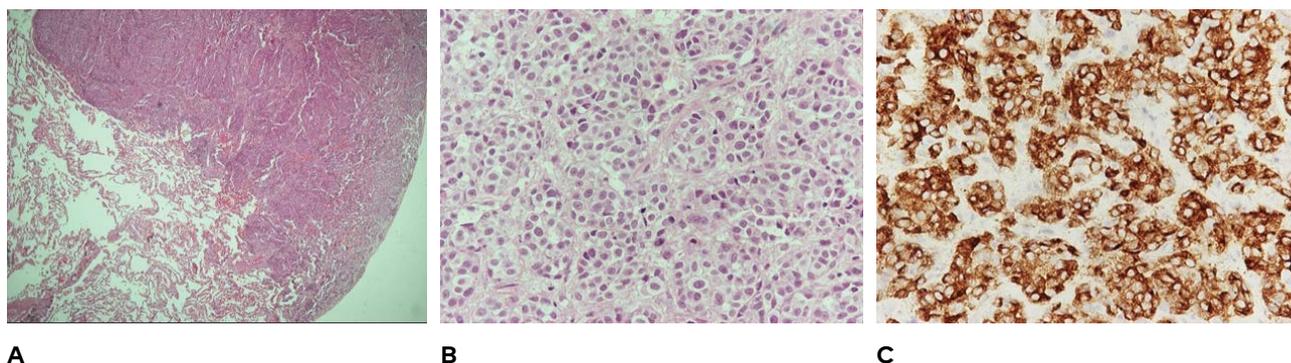


Figure 3. Nodular infiltration of lung parenchyma (A) by large cells with abundant cytoplasm and prominent nucleoli (B) exhibiting Melan-A positivity (C). (A: HE $\times 40$; B: HE $\times 400$; C: IHC $\times 400$).

The last criterion is not easy to assess, since diagnosis of mucosal melanomas is usually delayed, because of hidden location and lack of early symptoms.

Lagoudianakis et al. established specific diagnostic

criteria for primary malignant melanoma of the gastrointestinal tract.¹⁰ The criteria consist of a lack of concurrent or previous removal of a melanoma or atypical melanotic lesion from the skin, lack of other organ involvement, in

situ change in the overlying or adjacent GI epithelium and disease free survival of 12 months after diagnosis.¹¹⁻¹³ The latter is of critical importance in order to clearly distinguish between primary and metastatic lesions since “50% of patients with stage IV melanoma or visceral disease from unknown primary will have died at 12 months from diagnosis”.¹⁴ This is valid for our case, too, since in our patient there have passed already 14 months from diagnosis.

GI melanomas – primary or secondary in nature is often difficult to establish, giving rise to much controversies.⁸ Arguments in support of the idea that GI melanomas are metastatic lesions, even in the absence of a primary metastasis, are based on the natural history of melanoma. The fact that the GIT is the most common site of metastases of cutaneous melanoma¹⁵ and since the presence of melanocytes in the epithelium of the stomach and intestines has not been demonstrated, the origin of melanoma in these sites remains obscure.

Additionally, several cases of spontaneous regression of a primary cutaneous melanoma with subsequent visceral and nodal metastases have been reported.¹⁶

Several pathogenetic theories have been proposed for primary visceral melanomas. One theory includes aberrant neural crest cell migration during development.¹⁷ Other theories explain the existence of primary visceral melanoma with metaplasia, for example amine precursor uptake and decarboxylation cells developing into primary gastrointestinal melanoma² and neuroendocrine system cells in the submucosal bronchial glands undergoing melanocytic differentiation to produce primary melanoma of the lung.¹⁶ A third and final theory regarding the development of primary visceral melanoma is regression of a primary cutaneous melanoma explaining the lack of cutaneous findings in the documented cases of primary visceral melanoma.⁷⁻¹⁸

Literature review of other cases of PGM and metastatic gastric melanoma reveals that the presentation is often vague with nonspecific symptoms of anorexia, dysphagia, nausea, vomiting, epigastric pain, fatigue, and weight loss.² The latter often lead to a delay in diagnosis.

Little is known about the exact etiology of gastric melanoma, and no definite risk factors have been identified. At the time of initial diagnosis, detectable metastases are present in 30%–40% of patients. The incidence of metastasis to regional lymph nodes is as high as 40%–80%, and the most common sites are periesophageal, mediastinal and celiac lymph nodes. Hematogenous dissemination is most prone to liver, lung and brain.¹⁹⁻²⁰

PGM prognosis is poor with a median survival of only 5 months, compared to 17 months for all primary gastrointestinal melanomas.^{2,20}

Early diagnosis is crucial for favourable evaluation of patients as possible surgical candidates. Due to the rarity of the disease, no standard treatment has been established so far. Treatment for metastatic melanoma includes surgical resection, immunotherapy and possibly radiation therapy. The choice of treatment should be individualized for each patient.

CONCLUSIONS

Clinical awareness and high level of suspicion of rare conditions like PGM are essential for early detection and diagnosis as this may be the only way that could possibly promise a successful management for these patients.

Authors Contribution

A.M. and A.P. managed the case and prepared the relevant clinical data, E.P., A.K., and T.K. prepared radiology and pathology data, T.A. and A.M. performed the bibliographic research, A.M. prepared the primary draft, T.A. reviewed and formed the final version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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Первичная меланома желудка неизвестного происхождения: клинический случай и краткий обзор литературы

Атина Миру¹, Теодорос Асланидис², Андреас Протопапас¹, Елисавет Псома³,
Андреас Контосис⁴, Триантафилия Колетса⁴

¹ Первая кафедра пропедевтики внутренних болезней, Университетская больница АНЕРА, Салоники, Греция

² Отделение интенсивной терапии, Больница Св. Павла, Салоники, Греция

³ Отделение компьютерной томографии, Клиника радиологии, Университетская больница АНЕРА, Салоники, Греция

⁴ Кафедра патологии, Медицинский факультет, Университет им. Аристотеля – Салоники, Университетская больница АНЕРА, Салоники, Греция

Адрес для корреспонденции: Теодорос Асланидис, Отделение интенсивной терапии, Больница Св. Павла, Салоники, Греция; E-mail: thaslan@hotmail.com

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Резюме

Хотя обычно это кожная опухоль, меланома может возникать в нескольких внекожных участках. Первичные меланомы слизистой оболочки встречаются редко, а первичные меланомы слизистой оболочки желудка считаются крайне редкими. По сравнению с меланомой кожи и глаза, меланома слизистой оболочки имеет наименьшую пятилетнюю выживаемость. Высокий уровень подозрения на такое редкое заболевание может быть единственным способом раннего обнаружения, диагностики и шансом на успешное ведение подобных случаев. В настоящем отчёте описан случай первичной меланомы желудка у 73-летнего мужчины, а также дан краткий обзор литературы.

Ключевые слова

первичная меланома желудка