Primary Gastric Melanoma – Is an Aggressive Strategy Worthwhile?

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Abstract

**Background:** Primary gastric melanoma (PGM) is a rare malignancy. Unlike skin melanoma which carries a definitive correlation to sun exposure, the pathogenesis of gastric melanoma is not well defined. It appears in the older age with median of 70 years and has no known risk factors. The diagnosis may be challenging due to non-specific symptoms, and endoscopy with tissue biopsy along with detailed physical examination ruling out skin and ocular lesions, and PET-CT, are the tools for establishing diagnosis. The prognosis for PGM is poor mainly due to late diagnosis. No detailed staging algorithm nor treatment protocols for PGM exists.

**Methods:** A case series of all patients with PGM that were evaluated and managed by our surgical oncology service between 2011 and 2016. Data regarding diagnosis, imaging, pathologic evaluation and treatment protocols were collected and analyzed.

**Results:** During study acquisition period, 3 cases with the diagnoses of PGM were identified. One patient was treated with aggressive surgery upfront, one patient was treated with more conservative surgical approach with delay from diagnosis to surgery, and one patient was not eligible for surgery due to age, medical and general condition. In 5 years of follow-up only the patient that had aggressive surgery survived.

**Conclusion:** PGM carry very bad prognosis. We believe that aggressive surgery should be considered as the main component of the therapy plan without delay, for better clinical outcome and survival.

Introduction

Malignant melanoma is an aggressive type of cancer with common cutaneous expression and minor extra cutaneous sites. Primary mucosal melanoma including Gastro-intestinal (GI) melanoma is rare, with ano-rectal being the most common site in the GI group [1]. Mucosal melanoma's properties are markedly different from cutaneous melanoma. The incidence increases with older age, median of 70 years old, with a stable incidence over the years, it is often diagnosed in an advanced stage and associated with poor outcome [2]. According to the WHO classification, based on clinical, histological, epidemiological and genomic characteristics, primary mucosal melanoma is defined as type 6, has no race predominance, no risk factors, and is unrelated to sun exposure. It exhibits lentiginous pathological pattern, usually with no precursor nevus [3] [4].

GI melanoma usually appears as metastasis from a previously diagnosed cutaneous lesion rather than primary. On autopsy, up to 60% of patients with malignant melanoma have GI metastases, however only 1–4% of melanoma patients will have clinical manifestations of GI tract involvement during their lifetime [5]. Primary gastro-intestinal melanoma is uncommon, furthermore Primary Gastric Melanoma (PGM) is an extremely rare entity represented in the literature by few case reports. No detailed staging algorithm nor treatment protocols for PGM exists, due to its rarity.
The pathogenesis of PGM is unclear since normal stomach epithelium lack melanocytes. The theories of Ectopic migration of melanocyte precursors or differentiation of the APUD cells to melanocytes have been suggested for GIT melanoma however there is no consensus available [6] [7].

The diagnosis of PGM is challenging as symptoms may be non-specific. The clinical manifestation is varied and patients can exhibit any of the following symptoms: fatigue, weight loss, abdominal pain, hematemesis, melena, nausea or abdominal mass. Less common clinical manifestations are GI obstruction or perforation and massive hemorrhage.

The Criteria for primary GIT melanoma includes:

1. Absence of any primary lesion.
2. No history of removal of melanoma or atypical melanocytic lesion from the skin or other organs.
3. Absence of extra-intestinal metastatic spread of melanoma.
4. Presence of intra mucosal lesions in the overlying or adjacent epithelium [8].

Endoscopy and tissue diagnosis are essential for diagnosis. Some of the lesions are pigmented while others are amelanotic. The lesions may be reported as undifferentiated carcinoma, thus specific Immunohistochemically stains for melanoma must be performed in order to achieve a proper diagnosis, including S-100 protein, HMB45, and Melan A [9]. The final diagnosis is sometimes made only after surgical intervention (with en block resection).

Detailed physical examination for skin lesions coupled by comprehensive ocular testing must be done for the diagnosis of PGM, and PET-CT serves for detection of metastatic spread.

A genetic testing of melanoma is mandatory in the era of successful innovating immunotherapy and targeted therapies for specific mutations. KIT tyrosine kinase receptor mutations can be found in mucosal melanoma, whereas BRAF mutations that are more common in cutaneous melanoma, are less expresses in PGM [4] [10].

The prognosis for PGM is poor with median survival of 5 months [11], Mainly due to late diagnosis. Recently better results are reported following aggressive surgical approach accompanied by adjuvant oncological and immunotherapy.

**Methods**

This is a case series of all patients with PGM that were evaluated and managed by our surgical oncology service at our institute between 2011 and 2016. Data regarding diagnosis, imaging, pathologic evaluation and treatment protocols were collected and analyzed retrospectively. The study was approved by the local institutional review board, IRB approval: WOMC-0241-20.

This case series has been reported in line with the PROCESS Guideline [12]
Results

During the study period 3 patients who were diagnosed with PGM were treated in our center.

Case 1

57 years old male, admitted with anemia and rectal bleeding. Abdominal CT scan and gastroscopy revealed a proximal gastric tumor diagnosed as PGM. Multi-disciplinary evaluation recommended PET-CT however due to continuous bleeding the patient underwent total gastrectomy with Roux & Y reconstruction with curative intent (Fig. 1). Pathology indicated a 15 cm PGM with 1 LN involvement and no BRAF mutation. No adjuvant therapy was prescribed. Six months later, focal disease adjacent to the anastomosis was diagnosed after PET-CT, treatment with immunotherapy (anti PDI/Keytruda) was started. The patients have no evidence of disease (NED) clinically and radiologically after 5 years of follow up.

Case 2

A 72 years old male, was admitted with melena. Gastroscopy revealed an ulcerated 3.5 cm antral tumor proven to be PGM. Detailed physical examination was normal, and PET CT ruled out metastatic disease. With 2 months’ delay because of different therapeutic approaches, Distal subtotal gastrectomy with Roux & Y reconstruction was performed. Post-operative period was complicated with GI fistula and 3 months later PET-CT diagnosed metastatic spread. Immunotherapy was started with disease progression and the patient deceased 20 months after diagnosis with brain and colonic metastases.

Case 3

An 89 years old female, with history of dementia, anemia and end stage renal failure was admitted to the hospital due to melena and anemia. Gastroscopy revealed an antral lesion proved to be PGM. Detailed physical examination was normal, and PET CT ruled out metastatic disease. Due to her age and general status (cognitive and medical) she wasn't eligible for surgical or oncological treatment and received only supportive care. The patient deceased 6 months after diagnosis.

Discussion

Primary Gastric Melanoma is a rare entity; it has no recognized staging system nor established treatment protocols our small series emphasized that early aggressive surgery improves survival.

Cheung et al [11] demonstrated in the largest Gastrointestinal melanoma study in 2007, that surgery was beneficial regarding to survival rates at all sites, stage, tumor grade and differentiation of all GI melanoma. Factors related to worse outcome were positive lymph node status, older age, and PGM having the worst prognosis of 5 months. Radiation therapy did not influence overall survival in this article. The benefits of surgery were emphasized even in metastatic disease by Patel et al and Holmberg
et al [13] [14] showing that gastro-intestinal metastasis resection relieves symptoms and allows continuation of oncological treatment. Patel showed better survival rates whereas Holmberg did not.

Primary gastric melanoma is represented in the literature by few case reports. Vast majority of cases reported were treated surgically [8] [9] [10] [15] [16] [17] [18] [19]. Survival was better, with less recurrence, whenever a more aggressive strategy was adopted [15] [16] [19].

There is no report on the benefit of Adjuvant or neo adjuvant therapy in PGM mainly because of the rarity of the disease. As in cutaneous melanoma, in which aggressive surgery and lymph node assessment is the preferred treatment, in our opinion, upfront surgical resection should be the protocol for PGM, in an attempt to reduce disease spreading.

This strategy is opposed to Gastric adenocarcinoma in which during the last 5 years there has been a shift towards neo adjuvant chemotherapy in eligible patients. The FLOT study have emphasize the benefits of RT0 resection and less lymph nodes involved after neo adjuvant chemotherapy compared to surgery alone [20]. However, patients that carry the MSI mutation were found to have no benefits from neoadjuvant chemotherapy.

Until approval and defined positive predictive value, the exact protocol of PGM should be step wise, taking into account aggressive R0 resection with or without adjuvant immunotherapy. Treatment should not be delayed. Furthermore, we suggest a genetic test to encourage oncologic treatment when possible (a main treatment in some cutaneous melanoma patients). Our patient who was treated using this concept demonstrated Disease Free Survival of more than 5 years.

Our case series have some limitations. The 3 cases reported, though all admitted due to UGI bleeding, are different in treatment strategy and rhythm. This heterogeneity along with no current staging and guidelines for treatment, make it difficult to evaluate and reach a ”gold standard” recommendation for treatment and managing the patient with PGM.

**Conclusion**

Primary gastric melanoma is a rare entity and should be suspected whenever patient complains are concurrent with a gastric lesion. Tissue biopsy coupled by specific Immunohistochemical Stains as S100, HMB-45, should be done alongside complete physical examination (dermatologist and ocular) and FDG PET CT for the definitive accurate diagnosis of PGM.

As melanoma is an aggressive tumor, with a devastating metastatic potential, aggressive surgical excision with R0 resection and lymph nodes evaluation is the preferred treatment. Treatment must not be delayed due to PGM’s progressive nature, even without acceptable guidelines.

As immunotherapy made an extreme change in the multidisciplinary treatment of cutaneous melanoma, we believe it will also have an important role in GI melanoma and especially PGM.
Declarations

Conflict of interest statement: None declared

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References

1. Yde SS, Sjoegren P, Heje M, Stolle LB. Mucosal Melanoma: a Literature Review. Curr. Oncol. Rep. 2018.

2. Lerner BA, Stewart LA, Horowitz DP, Carvajal RD. Mucosal Melanoma: New Insights and Therapeutic Options for a Unique and Aggressive Disease. Oncology (Williston Park). 2017.

3. Elder DE, Bastian BC, Cree IA, Massi D, Scolyer RA. The 2018 World Health Organization classification of cutaneous, mucosal, and uveal melanoma detailed analysis of 9 distinct subtypes defined by their evolutionary pathway. Arch. Pathol. Lab. Med. 2020.

4. Merkel EA, Gerami P. Malignant melanoma of sun-protected sites: A review of clinical, histological, and molecular features. Lab Investig. 2017;97.

5. Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. Am J Surg. 1978;135.
6. Krausz MM, Ariel I, Behar AJ. Primary malignant melanoma of the small intestine and the APUD cell concept. J Surg Oncol. 1978;10.

7. Lagoudianakis EE, Genetzakis M, Tsekouras DK, Papadima A, Kafiri G, Toutouzas K, et al. Primary gastric melanoma: A case report. World J Gastroenterol. 2006;12.

8. Aggarwal R, Dhawan S, Chopra P. Primary Gastric Melanoma: a Diagnostic Challenge. J Gastrointest Cancer. 2014;45.

9. Rai MP, Nemakayala DR, Kandola SK, Sharma M. Primary gastric melanoma: A rare presentation. BMJ Case Rep. 2018;2018.

10. Callaghan G, Kelleher F, Ridgway P, Crowther S, Alakkari A, Ryan B. A Case of Primary Gastric Melanoma Exhibiting a Rare BRAF V600R Mutation. Eur J Case Reports Intern Med. 2018.

11. Cheung MC, Perez EA, Molina MA, Jin X, Gutierrez JC, Franceschi D, et al. Defining the role of surgery for primary gastrointestinal tract melanoma. J Gastrointest Surg. 2008;12.

12. Agha RA, Sohrabi C, Mathew G, Franchi T, Kerwan A, O'Neill N, et al. The PROCESS 2020 Guideline: Updating Consensus Preferred Reporting Of Case Series in Surgery (PROCESS) Guidelines. Int J Surg. 2020;84.

13. Patel K, Ward ST, Packer T, Brown S, Marsden J, Thomson M, et al. Malignant melanoma of the gastro-intestinal tract: A case series. Int J Surg. 2014;12.

14. Holmberg CJ, Alwan G, Ny L, Olofsson Bagge R, Katsarelias D. Surgery for gastrointestinal metastases of malignant melanoma - A retrospective exploratory study. World J Surg Oncol. 2019;17.

15. Wang J, Yang F, Ao WQ, Liu C, Zhang WM, Xu FY. Primary gastric melanoma: A case report with imaging findings and 5-year follow-up. World J Gastroenterol. 2019;25.

16. Cho JM, Lee CM, Jang YJ, Park SS, Park SH, Kim SJ, et al. Primary Gastric Malignant Melanoma Mimicking Adenocarcinoma. J Gastric Cancer. 2014;14.

17. Wang L, Zong L, Nakazato H, Wang WY, Li CF, Zhang GC, et al. Primary advanced esophago-gastric melanoma: A rare case. World J Gastroenterol. 2016;22.

18. Yamamura K, Kondo K, Moritani S. Primary malignant melanoma of the stomach: Report of a case. Surg Today. 2012;42.

19. Takahashi T, Sugita S, Kagaya H, Morita T. Surgically treated gastric melanoma of unknown primary: A case report from a 10-year survivor. Pathol Int. 2020;70.

20. Zhang S, Yan D, Sun Q, Du T, Cao D, Yang Y, et al. FLOT Neoadjuvant Chemotherapy Followed by Laparoscopic D2 Gastrectomy in the Treatment of Locally Resectable Advanced Gastric Cancer. Can J Gastroenterol Hepatol. 2020;2020.

Figures
Figure 1

En block total gastrectomy specimen showing primary gastric melanoma. Color should be used for figure in print.