Case Report

Gastrointestinal bleeding from gangliocytic paraganglioma treated with palliative radiotherapy: a case report

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Abstract: Gangliocytic paraganglioma (GP) is a rare neuroendocrine tumor typically found in the second part of the duodenum. The rarity of this tumor has not allowed development of treatment guidelines. The mainstay of treatment involves endoscopic or surgical resection. Adjuvant chemotherapy or radiation have been utilized in a few cases. Gastrointestinal bleeding from GP treated with radiotherapy has not been described in the literature. The case described is of a patient presenting with a 6-month history of hematochezia and a one week history of fatigue. An esophagogastroduodenoscopy (EGD) was performed demonstrating a 3-cm periampullary, non-obstructing mass with areas of ulceration and oozing. Pathology from biopsy samples showed trabeculae and cords of epithelioid cells bordered by S-100 positive spindled cells consistent with paraganglioma as well as scattered "large cells" without typical ganglion cell morphology. GP was favored versus other neuroendocrine carcinomas given its classic location in the second part of duodenum, presentation with bleeding, and the morphological pattern of paraganglioma. This patient was a poor surgical candidate and at high risk of perioperative mortality due to multiple chronic comorbidities and poor functional capacity. It was decided to administer fourteen courses of 35 Gray (Gy) palliative radiotherapy to control the patient's gastrointestinal (GI) bleeding. Surveillance EGD was performed after his tenth treatment which showed no further areas of oozing along the mass. From his first to his last radiotherapy session, his hemoglobin improved from 7.5 to 8.9 g/dL without further episodes of hematochezia. One week after his discharge, the patient died from cardiac arrest. Radiotherapy may be useful in controlling GI bleed secondary to GP in a palliative setting.

Keywords: Neuroendocrine tumor; paraganglioma; gastrointestinal hemorrhage; radiotherapy; case report

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Introduction

Gangliocytic paraganglioma (GP) is a rare neuroendocrine tumor typically found in the second part of the duodenum (1). It consists of epithelioid cells, spindle cells with Schwann cell-like differentiation, and ganglion cells (2). Endoscopic or local surgical resection, pancreaticoduodenectomy, radiotherapy and chemotherapy are treatment options. Endoscopic removal is safe and effective if the tumor is suspended by a stalk with absent local and regional disease. Surgical resection with duodenotomy also may be considered in this setting (3). Pancreaticoduodenectomy has been used for tumors with nuclear pleomorphism, high mitotic activity, and infiltrative margins (3). Chemotherapy was used in a patient with distant metastasis (mets), but without subsequent response (4). Radiotherapy (RT) has been used with mets to regional lymph nodes, the liver, and pelvic cavity

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with mixed results (4,5). The most common complication experienced with GP is gastrointestinal (GI) bleeding (1). To our knowledge, there are no cases of GI bleeding secondary to GP treated with palliative radiotherapy alone cited in the literature. We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/dmr-20-135).

Case presentation

A 78-year-old Caucasian male with a past medical history of systolic heart failure, sick sinus syndrome s/p pacemaker, hypertension, chronic kidney disease (CKD), and recently diagnosed multiple myeloma, not started on treatment, presented with a 6-month history of hematochezia and one week history of fatigue. Notably, the patient had a negative esophagogastroduodenoscopy (EGD) and colonoscopy 3 months prior at an outside hospital. He had no family history of GI cancer or other malignancy. His social history was significant for a 30-pack-year smoking history, an occasional glass of wine and no illicit drug use. On arrival, his vital signs included blood pressure of 99/77, heart rate 88, temperature 97.4 °F, respiratory rate 18, SpO_2 96%. Rectal examination was significant for frank red blood on gloved finger. His abdomen had normal bowel sounds and was soft, non-distended, and non-tender to palpation. There was no cervical, supraclavicular, axillary or inguinal lymphadenopathy appreciated on exam. His complete blood count was significant for a hemoglobin (Hgb) of 8.6 g/dL, from a baseline of 11.0 g/dL. His platelet count was 190 K/μL, prothrombin time was 11.3 seconds, international normalized ratio was 1.13 and partial thromboplastin time was 33.0 seconds. His blood urea nitrogen was 65 mg/dL and creatinine was 3.23 mg/dL, from a baseline of 20 and 1.4 mg/dL respectively. An EGD and colonoscopy were completed. Colonoscopy was limited due to bright red blood throughout the colon. The EGD showed a 3 cm periampullary, non-obstructing mass with areas of ulceration and oozing (*Figure 1*).

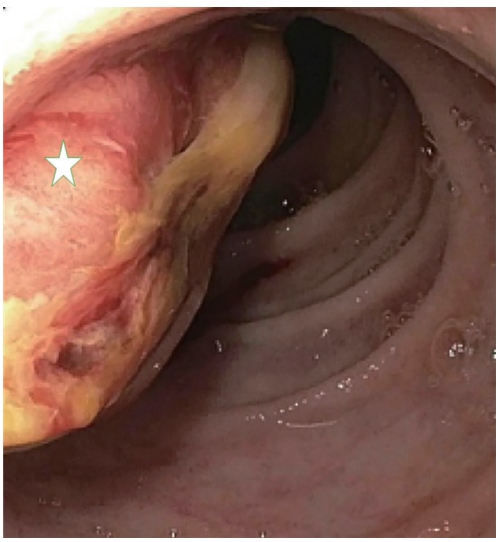

Figure 1 First esophagogastroduodenoscopy, pre-radiotherapy, demonstrated a 3-cm, friable, non-obstructing mass (white star) with areas of ulceration and oozing in the second portion of the duodenum.

Biopsy samples from the mass demonstrated trabeculae (*Figure 2A*) and cords of epithelioid cells (*Figure 2B*) bordered by S-100 positive spindled cells (*Figure 2C*) consistent with paraganglioma. There were scattered "large cells" (*Figure 2B*)

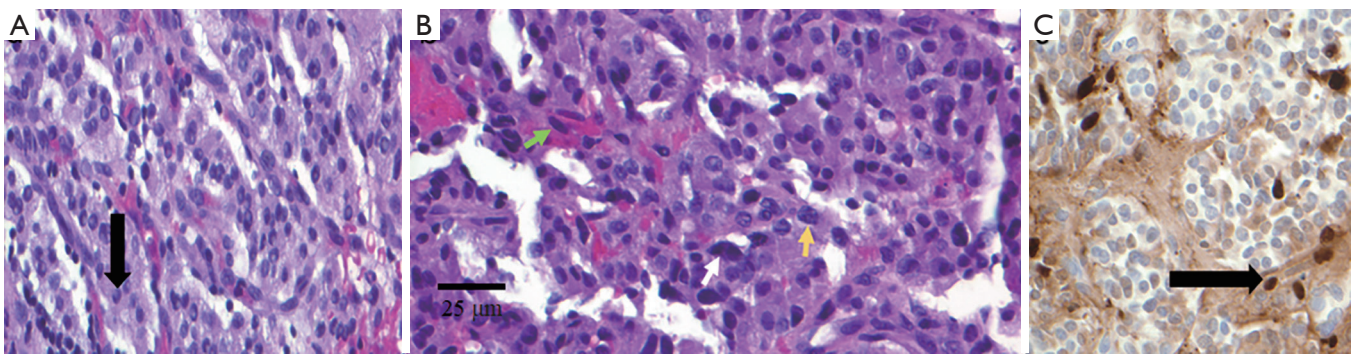

Figure 2 Histological and immunohistochemical images of gangliocytic paraganglioma. (A) Trabeculae with epithelioid cells (black arrow) (hematoxylin-eosin staining). (B) Tumor consisting of epithelioid cells (yellow arrow), spindle cells (green arrow) and "large cells" (white arrow) (hematoxylin-eosin staining). (C) Spindle cells (black arrow) immunoreactive to S-100 protein.

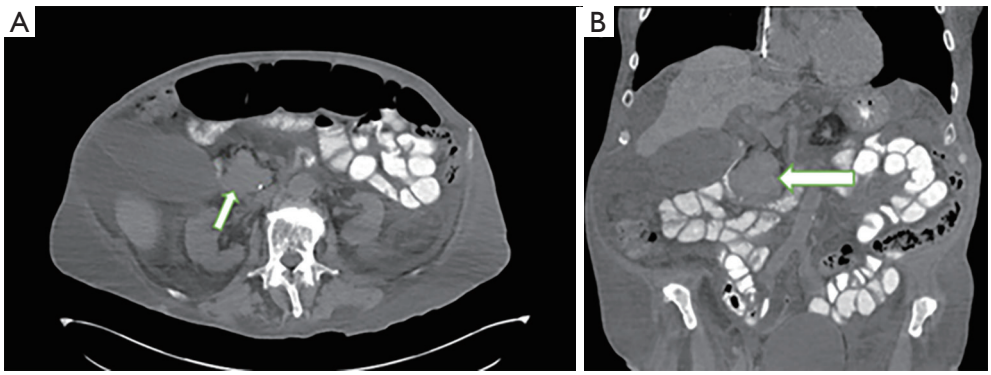

Figure 3 Radiological images of gangliocytic paraganglioma. (A,B) Computed Tomography of the abdomen/pelvis with oral and without intravenous contrast demonstrating a soft tissue density (white arrow) measuring 5.1 cm × 4.5 cm × 4.1 cm, unclear origin from the duodenum or pancreatic head. (A) Axial view. (B) Coronal view.

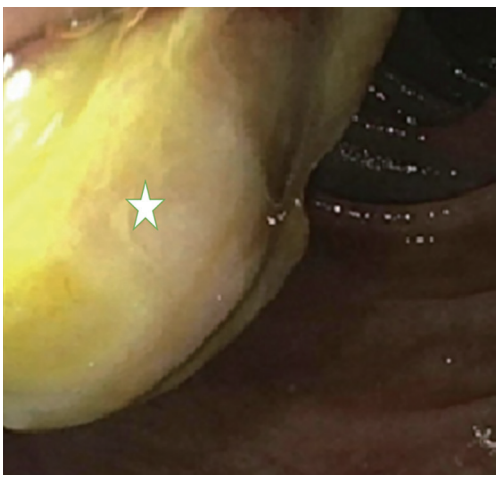

Figure 4 Second Esophagogastroduodenoscopy, after ten courses of radiotherapy, demonstrated the same mass (white star), but with decreased vascular markings and no evidence of oozing.

noted as well without typical ganglion cell morphology. A computed tomography (CT) chest, abdomen and pelvis (CAP) with oral and without intravenous contrast (*Figure 3*) was performed and showed a 5.1 cm × 4.5 cm × 4.1 cm mass in the second portion of the duodenum involving the pancreatic head. There were no local or distant mets revealed. In a multidisciplinary conference, GP was favored versus other neuroendocrine carcinomas given its classic location in the second part of duodenum, presentation with bleeding, and the morphological pattern of paraganglioma. Also, small biopsies were taken from a large mass, which ultimately was not removed. With GP, which is known to have a heterogenous distribution of cell types, ganglion cells may have been missed with biopsy.

This patient was a poor surgical candidate and at high risk of perioperative mortality due to multiple chronic comorbidities and poor functional capacity. Thus, preoperative staging with endoscopic ultrasound (EUS) was deferred. CT Angiography and embolization were not undertaken due to acute kidney injury on CKD. In the multidisciplinary conference, it was decided to administer fourteen courses of 35 Gray (Gy) palliative RT to control the GI bleeding.

Prior to his first RT session, his Hgb was 7.5 g/dL. Surveillance EGD was performed after his tenth treatment which showed decreased vascular markings and no areas of oozing on the mass (*Figure 4*). He received all fourteen days of radiation and after his final treatment, his Hgb was 8.9 g/dL. From his ninth treatment to his discharge one week later, he did not require packed red blood cell (PRBC) transfusions. The patient was transferred out to a rehabilitation facility and unfortunately died one week later from cardiac arrest.

All procedures performed in studies involving human participants 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.

Discussion

GP is a rare tumor typically found in patients between the ages of 15 to 84 with a slight male predominance (1). This tumor was first described by Dahl *et al.* in 1957 as a "duodenal ganglioneuroma", with Kepes *et al.* in

1971 recognizing features of both ganglioneuroma and paraganglioma, thus coining the term "gangliocytic paraganglioma" (2,6). Two theories have been proposed to explain its development. The first proposes an ectodermal origin from pluripotent cells in the neural crest. The second proposes that it originates from endodermally derived epithelial cells in the ventral primordium of the pancreas and neuroectodermal ganglion or spindle cells (7). It is unclear whether this patient's GP originated in the duodenum or pancreatic head despite endoscopy and CT imaging. Regardless of the tumor origin, tumor behavior is usually benign with regional lymph node mets occurring in about 5–7% of cases and rare invasion of nearby structures (1,5,8). To investigate for local spread of the tumor and detect metastatic lymph nodes, pre procedural imaging studies such as CT CAP and EUS should be performed (8,9). Per our patient's CT CAP, there were no signs of regional lymphadenopathy or distant mets. EUS was not performed as he was at high risk of perioperative mortality with resection. After imaging is completed, then a treatment plan needs to be decided.

As the origin of the GP in this case was unknown between the duodenum and pancreas, the best treatment would have been pancreaticoduodenectomy, but there was a high perioperative mortality risk. Pancreaticoduodenectomy with lymph node dissection has been proposed to be used for most cases of GP given possible mets or recurrence not visualized by preoperative and postoperative imaging (3-5). This procedure though has a perioperative mortality risk of 4% and complications include biliary leakage and delayed gastric emptying (3-5).

Local surgical resection by duodenotomy is the most common treatment, but endoscopic resection has lower morbidity and mortality risk (10). Some authors argue that endoscopic resection should happen when the tumor is <2 cm in size (3). Some authors confirmed that endoscopic resection for tumors >2 cm can be performed without complication (11). In a report by Park *et al.*, there was successful endoscopic resection of tumors up to 3 cm in size. But when tumors are too large, such as one case that was 4.3 cm, it may be difficult to fit a snare over the stalk (10). Our patient's tumor would have been difficult to endoscopically resect.

To our knowledge, there has been one case of GP managed with chemotherapy. Li *et al.* report a patient who underwent pancreaticoduodenectomy and was found to have mets in the liver and pelvic cavity 4 months later. Adjuvant chemotherapy was used with cyclophosphamide, vincristine, and dacarbazine. Also, adjuvant RT was used over a span of 30 days with a total dose of 50 Gy. Unfortunately, the masses did not regress (4).

In a report by Wong *et al.*, a patient with GP underwent pancreaticoduodenectomy but was found to have periduodenal and peripancreatic lymphadenopathy. Adjuvant RT was used over 37 days with a total dose of 50 Gy. There was no recurrent disease on surveillance CT imaging and endoscopy (5). To our knowledge, there are no other cases of GP treated successfully with radiation in the post-surgical bed.

There have been multiple studies, most retrospective and related to inoperable gastric or rectal cancer, that show favorable rates of GI bleed hemostasis with palliative RT (12-15). In a study completed in 2015 with advanced gastric cancer patients, 17 out of 313 patients received RT to treat GI bleeding with 73% achieving hemostasis and a median time to hemostasis of two days. The median Hgb level 30 days after RT elevated from 6 to 9 g/dL ($P<0.001$) and median volume of PRBC per month decreased from 1,120 to 280 mL ($P=0.007$). Only one patient died from GI hemorrhage in this sample (15). This study like many completed with RT induced hemostasis of GI bleed is limited by sample size, standard RT dosing regimens, as well as prognostic criteria to assess whom would benefit most from treatment (13,16). The study as described above may add context to our patient with GP who had no further hematochezia, a rising hemoglobin and decreased PRBC requirements with RT. It also may have taken more sessions to achieve hemostasis in our patient in the setting of platelet dysfunction secondary to acute renal failure. The mechanism of RT induced hemostasis is still not fully known. Damage to vascular endothelial cells, platelet aggregation, induction of tissue factor, and induction of embolism within vessels are all thought to play a role (15-17).

Strengths of this report include demonstrating GI bleed cessation with RT that has been described in previous studies of inoperable GI tumors and surveillance endoscopy confirming no further oozing from the lesion. The limitations of this report include the lack of follow up after treatment to assess for longer term efficacy, rebleeding or toxic effects from radiation and being the first report described in this patient population.

Unfortunately, our patient died ten days after his final RT treatment from reported cardiac arrest. He did not have outpatient follow up scheduled until the following week after his death. Nausea, vomiting, dyspepsia and abdominal pain, from GI mucosal erosion and ulceration, can occur

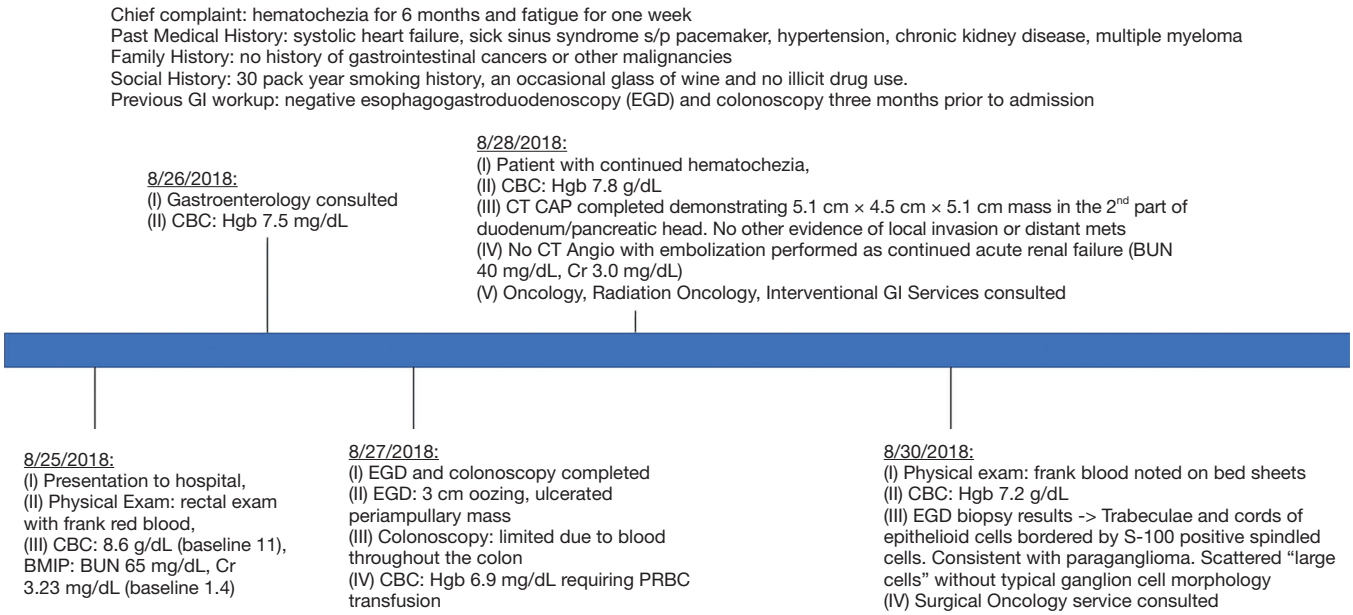

Figure 5 A timeline of the patient's original presentation, clinical course, and diagnosis of GP. GP, gangliocytic paraganglioma.

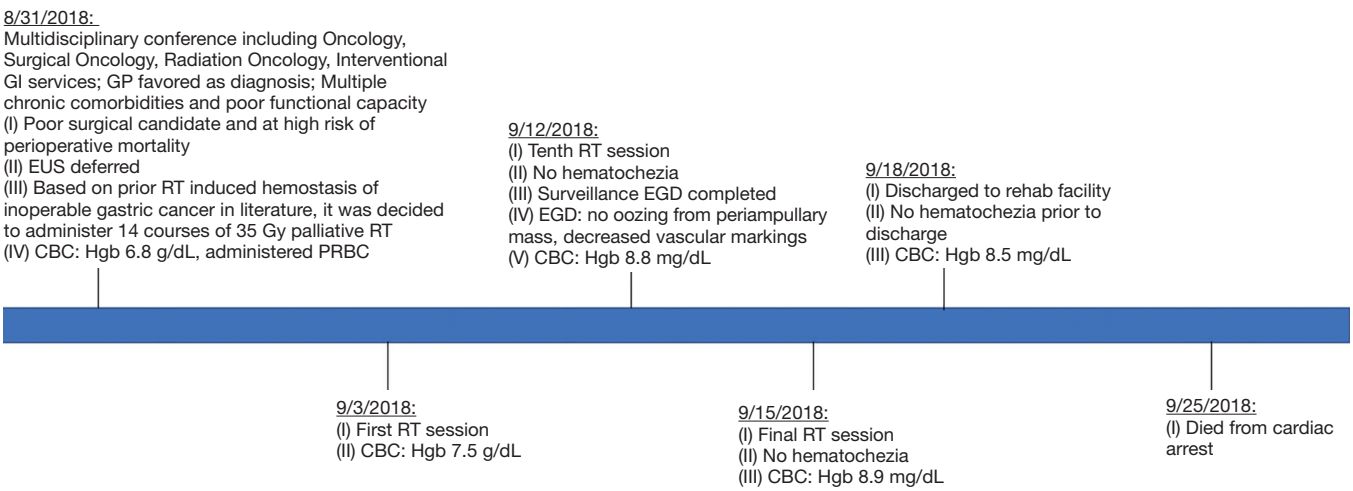

Figure 6 A continuation of the timeline from *Figure 5*. Depicting the rest of the patient's clinical course, treatment, and death.

early after RT to the upper abdomen in 50% of patients (18). Given our patient's findings on surveillance EGD, lack of further hematochezia or melena, lack of abdominal pain, and stable Hgb prior to discharge, he appeared to tolerate the treatment well (*Figures 5*,*6*). External beam three-dimensional (3D) conformal RT was performed and localized to the area of this patient's GP in the duodenum. 3D simulation RT is associated with a decreased risk in normal tissue toxicity (18). Cardiac toxicities such as arrhythmia, pericarditis, tamponade, cardiomyopathy, and myocardial infarction typically occur with RT localized to the chest (19). Over the course of treatment, he displayed no signs of GI or cardiac toxicity. RT likely did not contribute to his demise. It is possible he had delayed signs and symptoms of GI toxicity after discharge with either rebleed from his tumor or perforation that led him to cardiac arrest. This patient also had multiple other comorbidities that may have played a role including systolic heart failure, sick sinus syndrome, acute kidney injury on CKD, hypertension, and recently diagnosed multiple myeloma.

Given his multiple comorbidities, high perioperative mortality risk, large tumor size, and unclear tumor origin, neither endoscopic nor surgical resection were performed. For 6 months prior to and during his admission, the patient had GI bleeding, the most common complication of GP. As there was previous success with hemostasis using RT in patients with symptomatic locally advanced or recurrent gastric cancer and better response using treatment fractions less than 39 Gy, it was decided in a multidisciplinary conference to use 14 fractions of 35 Gy RT to treat his GI bleeding (20). RT may have utility in treating GP complicated by GI bleeding but there should be a risk *vs.* benefit discussion as there may be delayed radiation toxicity.

Conclusions

GP is a rare tumor with a multitude of treatment options. There have only been a few cases described of GP patients receiving RT but none treating GI bleeding as in this case. On follow up endoscopy after 10 days of treatment, the tumor showed no sign of active bleeding and decreased vascular markings. It appears RT may be useful in controlling GI bleed secondary to GP in a palliative setting, but further studies need to be completed to evaluate its short and long term efficacy, the proper dosing regimen and duration of treatment, and impact on quality of life and survival in this patient population.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/dmr-20-135

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr-20-135). 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 studies involving human participants 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.

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