

Rare Metastasis of Esophago-Gastric Cancers: Case series with review of literature

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Abstract

Purpose: in this case series we aim to highlight rare metastasis of gastric and esophageal cancers metastasizing to unusual locations causing a diagnostic challenge on presentation. We also review pertinent literature of rare locations of metastasis of gastro-esophageal cancer (GEC).

Materials and methods: this is a retrospective analysis of four patients managed at our institution with one year follow up between 2020-2021. We include baseline patient characteristics, presenting symptoms, diagnostic work up and management of each individual case.

Results: Out of the 4 cases with GEC; two had gastric adenocarcinoma, one esophageal adenocarcinoma and one gastro-esophageal junction adenocarcinoma which metastasized to various locations throughout the body. Among the rarest locations of metastasis of gastric cancer is skeletal muscles. The locations of metastases were: ovaries and peritoneum from gastric adenocarcinoma, brain and liver from gastric adenocarcinoma, skeletal muscles from esophageal adenocarcinoma,

and skeletal muscles and breast from GEC adenocarcinoma. The main diagnostic tool to identify these rare sites metastasis was Positron emission tomography scan (PET/CT).

Conclusion: Studies have shown that not all gastroesophageal malignancies present with these alarm symptoms and up to 40% of patient can present without alarming symptoms. In our study; we shed the light on the possible rare metastatic sites that could have been missed with the regular presentation. Some of the rarest location of metastasis is to the skeletal muscles, which was present in two of our patients with an origin of gastric and esophageal cancer, which was identified with PET/CT. This study clarifies the importance of including whole body PET/CT scan in the staging process for patients with esophageal and gastric cancers to identify such rare sites metastasis that will alter the stage and clinical management of GEC patients.

Introduction

Gastric cancers (GC) are the fifth most commonly diagnosed tumor and fourth leading cause of cancer related deaths worldwide.^{1,2} The incidence of metastatic gastric cancer remains high; as it is considered one of the leading causes of cancer death worldwide. It is very common for gastric cancer to present at a very late stage with metastases being identified at the time of diagnosis in up to 40% of patients. The peritoneum and liver are the most common sites of metastases in the gastric cancer population.³ The incidence and mortality has declined over the last century, however, the survival rates for gastric cancer is poor. Metastatic gastric cancers remain a challenging entity to approach. If the diagnosis of metastatic disease is made on presentation; patients may have about 6 months survival combined with the limited role of surgery in stage IV patients.^{4,5} Multimodality treatment options are available and are being investigated for metastatic disease including various chemotherapeutic agents and cytoreductive surgery for patients with peritoneal metastasis with improved overall survival up to 15 months compared to population based studies.^{6,7}

Similarly, metastatic esophageal cancer, has a poor survival

as well of a median of around one year. Distant metastatic disease is also common with up to 40% of patients diagnosed with esophageal cancer present with metastasis. Esophageal cancer represents similar treatment challenges as gastric cancer.⁸ Metastatic sites most commonly involve the liver, bone and lungs.⁹

Gastric cancer metastasizing to the breast is rare. In fact, metastatic breast disease from extra-mammary neoplasm is not common with a reported incidence of 0.5 to 1.2%.¹⁰ Less than 60 cases reported in the literature of gastrointestinal cancer metastasizing to the breast.¹¹ Skeletal muscle metastasis from a gastric origin is even a rarer entity with a poor prognosis; and as of recent literature there is no established incidence rate for it.^{12,13}

Our objective is to highlight rare presentations of stomach and esophageal metastasizing to unusual locations causing a diagnostic challenge on presentation. We are also including a literature review of rare locations of metastasis of gastric and esophageal cancer.

Case Presentations

We present a total of four patients who presented to our institution over the course of one year with unusual presentations of tumors involving the stomach. This took place in the main tertiary hospital, Hamad General Hospital, Hamad Medical Corporation, in Doha, Qatar from 2020-2021. The patients are presented in chronological order of presentation to our unit. Baseline demographic data, clinical presentation and primary diagnoses are outlined in table 1. A summary of biomarkers and treatment course is summarized in table 2.

The first patient (patient 1) is a 44-year-old female, with a history of diabetes and iron deficiency anemia, who presented with epigastric pain, melena and vomiting ten days after a routine cholecystectomy for symptomatic cholelithiasis. Her hemoglobin was 7.3gm/dl. During the cholecystectomy, the right ovary appeared bulky and multiple peritoneal nodules were encountered which were biopsied. The biopsy was negative for malignancy which was misleading initially. She was worked up with esophago-gastro-duodenoscopy (EGD) which showed a gastric ulcer with a necrotic center in the greater curvature and biopsies were obtained; which is displayed in (Figure 1A). CT and MRI scan showed peritoneal nodule and bilateral ovarian lesions measuring the largest on the right side at around 10 cm suggestive of metastatic gastric cancer as shown in (Figure 1B). Biopsy revealed gastric invasive ad-

enocarcinoma both mixed intestinal and diffuse type, HER2 negative, PD-L1 positive. The patient was started on palliative chemotherapy targeted for gastric cancer.

The second patient (patient 2) is a 45-year-old male, with a history of gastroesophageal reflux disease, that was brought to the emergency department after he experienced right sided weakness and muscle twitches that then progressed to tonic clonic seizure. His GERD symptoms had been investigated four years prior to presentation with an EGD, biopsies showed Pylori and chronic gastritis. Work up showed a left frontal precentral mass, WBC 27.1x10³/uL, hemoglobin of 9.8gm/dL and the patient underwent an urgent decompressive craniotomy with excision of the mass; his CT scan is shown in (image 2B). Histopathological examination of the resected brain mass showed metastatic adenocarcinoma with foci of neuroendocrine cells suspicious for an upper gastrointestinal tumor or pancreatico-biliary tumor. This represented a diagnostic dilemma so initial work up included an EGD that showed a gastroesophageal junction (GEJ) ulceroproliferative lesion involving the esophagus, cardia and lesser curvature which was biopsied in (Figure 2A) and a CA19-9 of 68 U/mL. Positron emission tomography (PET/CT) scan showed fluorodeoxyglucose (FDG) uptake activity in the GEJ, FDG avid nodes in the posterior mediastinum and peri gastric stations and multiple intense focal uptakes in the liver suspicious for metastases as well. Biopsy result showed moderately differentiated adenocarcinoma, HER2 negative, PD-L1 positive. One month after his EGD, his dysphagia progressed, and he required endoscopic stenting of the malignancy. Palliative chemotherapy was initiated targeting gastric cancer (using docetaxel, oxaliplatin, 5-fluorouracil and leucovorin (FLOT) protocol). A follow up MRI showed a new enhancing nodule adjacent to the resection site of the brain metastatic mass concerning for recurrence. Follow up PET/CT scan showed similar findings as the initial scan in addition to progressive liver metastases.

The third patient (patient 3) is a 45-year-old male that presented with a four-month history of chest pain and dysphagia progressive to solids then liquids. He also reported 9kg of unintentional weight loss and occasional episodes of nausea and belching/eructation. Initially when his symptoms started, he was diagnosed with GERD and discharged on a proton pump inhibitor with no response. He was eventually referred to our institution where his work up led to an EGD which showed a mid-esophageal lesion which proved to be poorly differentiated adenocarcinoma, HER2 negative, PD-L1 positive; that is shown in (figure 3C). The patient was started

on neoadjuvant chemotherapy with curative intent with an eventual aim for curative resection. A follow up PET/CT scan after the patient completed his 4 cycles of FLOT; showed significant regression of the hypermetabolic esophageal lesion, a hypermetabolic focus in the mid abdomen suspicious for a metastatic lymph node, and a hypermetabolic focus around the left femoral vessels with a mass as shown (in Figures 3A&3B). A multidisciplinary team decision was to obtain a biopsy and proceed accordingly. The patient was electively admitted, and he had exploration of the left inguinal and femoral area. The mass was biopsied and was found to be adeno-squamous carcinoma within the skeletal soft tissue of the thigh. His primary tumor was deemed inoperable due to metastatic disease and he was switched to a palliative chemotherapy regimen.

The fourth case (patient 4) is a 51-year-old diabetic, hypertensive, female who was diagnosed with breast cancer. She received neoadjuvant chemotherapy, underwent surgical excision, and started on adjuvant chemotherapy. Her post-operative pathology deemed her to have advanced metastatic breast cancer due to positive axillary lymph nodes, and she was switched to the palliative pathway. During her palliative treatment protocol, she presented to the emergency department with complaints of dysphagia, vomiting and back pain. She had complained of dysphagia a week before being diagnosed with breast cancer and was evaluated with laryngoscopy that was unremarkable. After her admission with dysphagia, an EGD showed a GEJ infiltrating ulcerative lesion. A CT scan showed a large enhancing mass related to the lesser curvature of the stomach and the distal esophagus, suspected metastatic lymph nodes in the splenic hilum, retro pancreatic and ischio-rectal fossa, and hypodense focus in the L4 vertebral body suspicious for metastatic disease. The scan also showed soft tissue enhancing nodules related to the gluteus muscle. An ultrasound revealed a new breast lesion on the ipsilateral side as the previously diagnosed malignancy. These nodules around the gluteus muscle represented a diagnostic conundrum. Further workup included a PET/CT scan showed extensive skeletal muscle involvement including abdominal wall, gluteal muscles and psoas muscle (Image 4A&4B); metastatic retroperitoneal nodes and L4 metastatic lesion. Biopsy results showed GEJ showed poorly differentiated adenocarcinoma, HER2 negative, PD-L1 negative and immunohistochemistry for mismatch repair (MMR) proteins showed loss of nuclear expression of MLH1 and PMS2 proteins. The gastric tumor metastasized to bilateral breasts and thigh skeletal soft tissue which was proven with biopsies. She was started on palliative chemotherapy. As of the date of submission of the article, all patients are alive.

Table 1: Demographics of the study population

Patient	Age	Sex	Comorbidities	Clinical presentation	Primary diagnosis
1	44	F	DM, IDA	Persistent epigastric pain post cholecystectomy	Gastric cancer
2	45	M	None	Chest pain with upper thigh swelling	Gastric cancer
3	45	M	GERD	Seizures, right sided twitches, weakness and anaemia	Oesophageal cancer
4	51	F	Breast cancer	Dysphagia, shoulder/leg pain	GE junction cancer

DM: diabetes mellitus; HTN: hypertension; IDA: iron deficiency anemia; GERD: gastroesophageal reflux disease; GE: gastroesophageal.

Table 2: Biomarkers and chemotherapy for the study population

Patient	Primary location	Metastasis site 1	Metastasis site 2	HER-2	PDL-1	MMR	Primary HPE	Treatment
1	Stomach	Ovaries	Peritoneum	Negative	Positive	Negative	Invasive adenocarcinoma	Palliative chemotherapy
2	Stomach	Brain	Liver	Negative	Positive	Negative	Moderately to poorly differentiated adenocarcinoma	Craniotomy and metastectomy followed by palliative chemotherapy
3	Esophagus	Thigh	NA	Negative	Positive	Negative	Moderately to poorly differentiated adenocarcinoma	Neoadjuvant chemotherapy
4	GEJ	Thigh	Breast	Negative	Negative	Deficient repair	Poorly differentiated adenocarcinoma of gastric origin	Palliative chemotherapy

NA: not applicable; GEJ: gastroesophageal junction; HER-2: human epidermal growth factor receptor 2; PDL-1: programmed death-ligand 1; MMR: mismatch repair; HPE: histopathological examination

Figures

Figures of the cancer cases during the work up stages

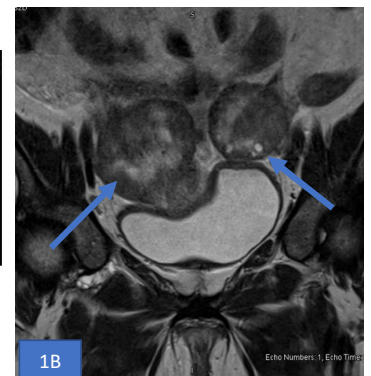
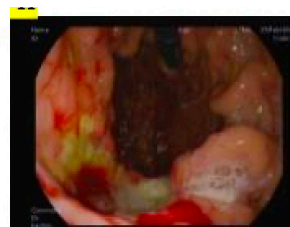
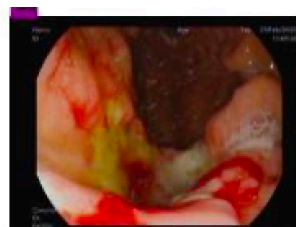
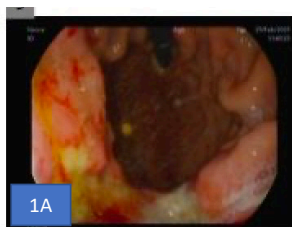


Figure 1A: Patient 1: MRI pelvis showing ascites and enlarged ovaries with cysts (blue arrows).

Figure 1B: shows the OGD with the gastric outgrowth.

Figure 2A: Patient 3: PET CT scan showing the avid uptake of contrast in the GE junction.

Figure 2B: CT head taken showing the mass (blue arrow).

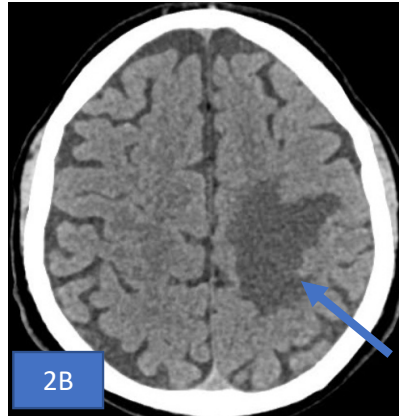
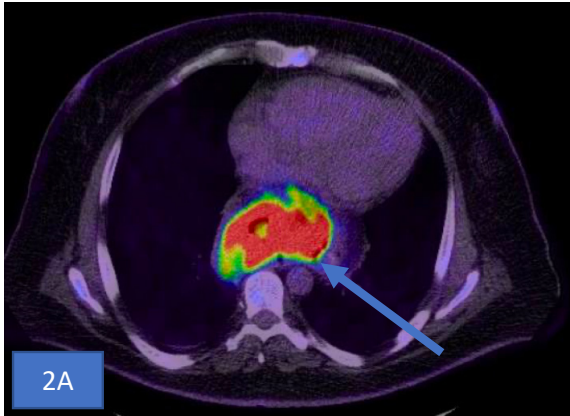


Figure 3A and 3B: Patient 2: PET CT scan showing avid uptake in the skeletal muscles of the thigh (green circle).

Figure 3C: OGD showing the oesophageal growth.

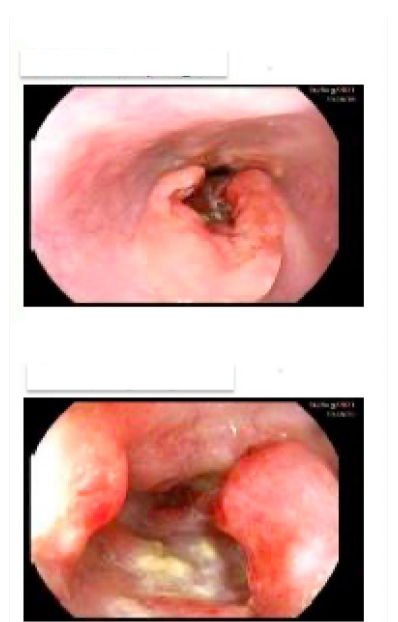
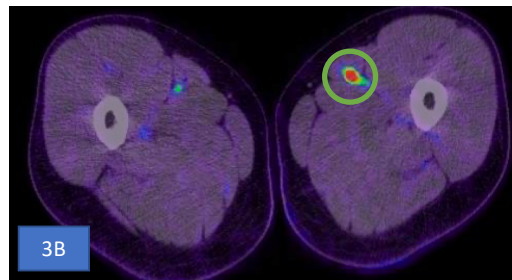
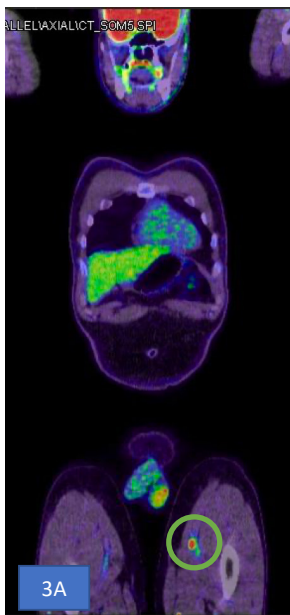
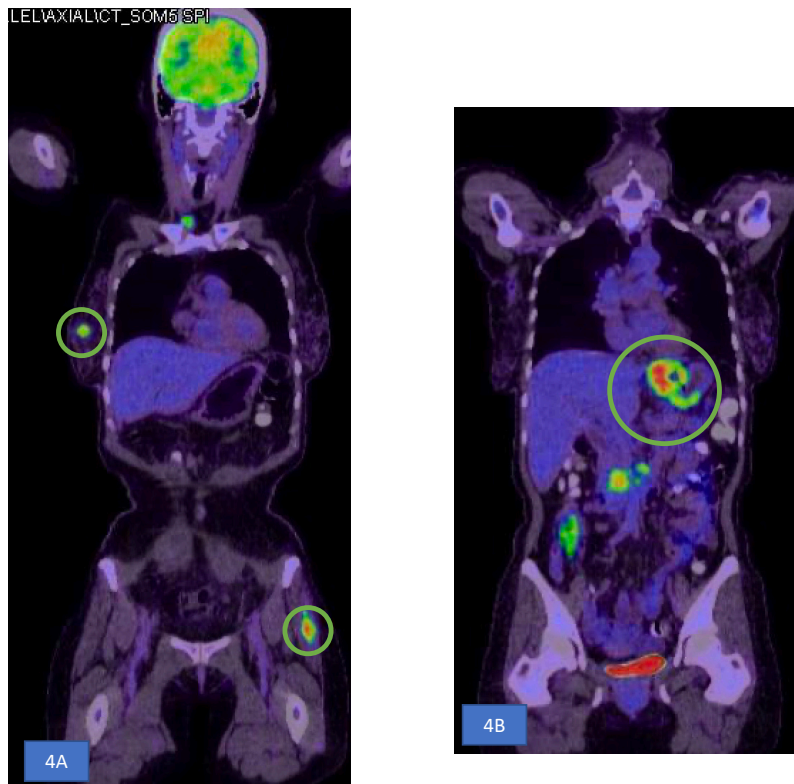


Figure 4A and 4B: Patient 4: PET CT scan showing avid uptake in the right breast and the skeletal muscles in the left side (green circle).



Discussion

Diagnosing gastric cancer, particularly more advanced tumors does not usually present a diagnostic dilemma. Dyspeptic symptoms can be a warning sign for underlying malignancy or identify a patient as high risk.¹⁴ Knowing well that gastroesophageal reflux, peptic ulcer and functional dyspepsia are usually the culprit for these symptoms and a minority will be caused by an esophageal or gastric tumor.¹⁵ This is when symptoms such as dysphagia, weight loss, gastrointestinal bleeding, anorexia and persisting vomiting should sound an alarm necessitating an urgent endoscopy.¹⁶⁻¹⁸ However, we can not only depend on such symptoms to develop before initiating the diagnostic cascade. As we have shown above with patient 2 and 3, these symptoms can start earlier on and should not be taken lightly. Studies have shown that a large majority of patient with a gastroesophageal tumor present with these concerning symptoms at the time of endoscopy.¹⁹⁻²¹ By the same token, studies have shown that not all gastroesophageal malignancies present with these alarm symptoms and up to 40% of patient can present without alarming symptoms.^{22,23}

Combine vague symptomatology with a myriad of risk factors such as H. pylori, dietary intake, some of which are directly linked to gastric cancer and some of which have conflicting supportive data, the question of screening comes into play.²⁴ Gastric cancer screening has been established in Japan since 1983 as well as South Korea.²⁵ Results from Japan, show an increase in overall survival as a result of early gastric cancer detection due to the endoscopic screening program.²⁶ Worldwide standardization of a gastric cancer screening programs remains an issue of debate due to epidemiological and cost effectiveness reasons and we at our institution, like many others, depend on symptoms for initiation of a diagnostic work up.¹⁴

The aggressive nature of GEC and late presentation has led to advancement in treatment strategies including trials on therapeutic efficacy of immunotherapeutic drugs.²⁷⁻³⁰ We observed in our patient in our patient population, that three of the patients tested positive for PD-L1. Some recent trials have shown that monoclonal antibodies lead to favorable outcomes in patients with various cancers.^{31,32} A meta-analysis by Gu et al, showed PD-L1 expression linked related to depth of tumor infiltration,

lymph node metastasis, Epstein-Barr virus and microsatellite instability.³³ Janjigian et al, showed in a recent randomized phase 3 trial, chemotherapy combined with PD-1 inhibitor, Nivolumab, showed superior overall survival compared with chemotherapy alone in patients with advanced gastroesophageal tumors.³⁴ Although not observed in our patient population, targeted monoclonal antibody against HER2 in combination with chemotherapy has shown some survival benefit.³⁵

Our aim of presenting these cases is: a) highlight the possible presentation of an advanced gastric cancer, b) shed light on gastroesophageal reflux symptoms can be the hint we need as care providers to go down the diagnostic route, c) define the values of whole-body PET/CT scan in identifying metastasis. Patient 4 complained of dysphagia, but she was also diagnosed with breast cancer with nodal metastases at the same time. It took her healthcare providers down the route of treating her malignancy when in fact there was another underlying pathology in the GEJ as well. Her newly discovered primary metastasized to the breast. Her tumor was negative for expression of Her2. The management and treatment of such patient can be tricky due to their rare incidence.^{10,36}

We have shown in three of four of our presented patients, the diagnostic value of ¹⁸F FDG PET/CT scans in the initial work up and follow up of this patient population. Findlay et al, showed the benefit of routine PET/CT for staging their patients including identifying unsuspected metastases, aiding with staging of lymph nodes and risk stratifying patients with FDG-avid nodes. They also show cost effectiveness of staging PET/CT albeit on a small population in a limited model with a final recommendation that PET/CT should be placed in guidelines for its role in staging.³⁷ Some studies have shown that patients with FDG-avid nodes have worse overall survival (OS) and/or disease free survival.³⁷ Coupe et al, showed that FDG uptake in both tumor and lymph nodes were related to poor overall survival.³⁸ Namikawa et al, on a study of 90 patients reported 78.9% sensitivity of PET/CT detecting a primary gastric cancer.³⁹ PET/CT scans arguably have a valuable role in initial diagnostic workup and can be useful in detecting distant metastasis possibly saving the patient a futile treatment approach.

Skeletal muscle metastasis is an even rarer occurrence and represents a diagnostic challenge when a patient present and is diagnosed with gastric tumor with a concomitant thigh swelling. According to our search, a total 16 cases have re-

ported including our two above mentioned patients of gastric tumors metastasizing to skeletal muscle (patient 3 &4).^{12,40,41}

Limitations to this study include the retrospective nature of the data presented and a small sized cohort of patients. Furthermore, observational information can be extrapolated from the patient information however, further studies and larger patient cohorts are required, in particular, for screening program advocacy on a local or international level.

Gastric cancers are known to present at advanced stages and have poor survival. It is imperative to diagnose this patient population timely and initiate treatment to prolong their survival. In the absence of a screening program, clinicians must actively look for common, alarming and/or uncommon symptoms that points them to adequate diagnostic work up.

Conclusion

Studies have shown that not all gastroesophageal malignancies present with these alarm symptoms and up to 40% of patient can present without alarming symptoms. In our study; we aimed to shed the light on the possible rare metastatic sites that could have been missed with the regular presentation. Some of the rarest location of metastasis is to the skeletal muscles, which was present in two of our patients with an origin of gastric and esophageal cancer. This study will also clarify the importance of including whole body PET/CT scan in the staging process for patients with esophageal and gastric cancers to identify such rare sites metastasis that will alter the stage and clinical management of patients.

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