An Incidence of Distant Unexpected Metastases in Esophageal Adenocarcinoma

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Abstract

This case is a rare presentation of distant unexpected metastases in esophageal adenocarcinoma. A 65-year-old male presenting with dysphagia and breakthrough reflux symptoms was evaluated by gastroenterology and found to have esophageal adenocarcinoma on Esophago Gastroduo Denoscopy (EGD). Imaging was suspicious for locoregional disease and the patient underwent neoadjuvant chemotherapy. He developed a Deep Venous Thrombosis (DVT) of the left upper extremity and was treated with anticoagulation prior to operative intervention. Ultimately the DVT site became larger post-operatively and was re-evaluated with imaging and found to be a mass consistent with primary cancer. The mass was excised and there was a local recurrence shortly afterwards. The patient resumed adjuvant chemotherapy and immunotherapy and continues to be evaluated surpassing the average survival noted with distant unexpected metastases.

Background

Esophageal cancer is the 6th most common cause of cancer mortality globally. It is aggressive in nature and has the ability to spread through direct extension, lymphatic's, and hematogenous routes often presenting at later stages. Roughly 1% of all skin metastases originate from the esophagus, a rare finding of progressive disease with a dismal prognosis.

Case

A 65year-old male was referred for evaluation of biopsy-proven poorly differentiated esophageal adenocarcinoma. The patient underwent Endoscopic Ultrasound (EUS) and Positron Emission Tomography (PET) that were negative for distant metastases but demonstrated spread to regional lymph nodes. Treatment included neoadjuvant chemoradiation followed by esophagectomy. Six weeks after surgical resection, an enlarging left upper extremity mass was excised and found to be consistent with the primary tumour.

Conclusion

In this case report, we present an incidence of isolated cutaneous metastasis six weeks after esophagectomy and neoadjuvant chemoradiation. This case highlights the limitations of imaging and the importance of careful physical examination in the workup of potential metastatic disease. Additionally, cutaneous metastases from esophageal cancers are a rare finding, particularly esophageal adenocarcinoma. This case contributes to the reported increased incidence of distant unexpected metastases.

Keywords: Unexpected metastases • Esophagectomy • Esophago gastroduo denoscopy

Introduction

Esophageal Cancer (EC) is the 6th most common cause of cancer mortality globally [1-5]. There are two principal histologic types, Esophageal Squamous Cell Carcinoma (ESCC) and Esophageal Adenocarcinoma (EA), both of which are more common in men. ESCC is the most common EC worldwide but the incidence is decreasing in developed countries where EA comprises approximately two-thirds of new cases [6,7]. Key risk factors to EA include obesity, Gastroesophageal Reflux Disease (GERD), and Barrett's esophagus. These trends are expected to continue to grow in the future with EA surpassing ESCC [1]. The most common esophageal cancer [8,9]. There are minimal screening programs available for early detection of EC leaving diagnoses to ultimately be made late in the disease course with associated poor prognoses. National Comprehensive Cancer Network (NCCN) reports at the time of diagnosis 50% of patients have cancer that extends beyond the loco-regional confines of the primary, less than 60% of patients with locoregional cancer can undergo curative resection, and approximately 70% to 80% of resected specimens harbour metastases in the regional lymph nodes [10]. Metastases from esophageal carcinomas are frequently in the abdominal lymph nodes (45%), liver (35%), lungs (20%), cervical/supraclavicular lymph nodes (18%), bones (9%), adrenals (5%), peritoneum (2%), brain (2%), stomach (1%), pancreas (1%), pleura (1%), skin/ body wall (1%), pericardium (1%), and spleen (1%) [11]. Cutaneous metastases from esophageal adenocarcinoma are rare, comprising <1% of overall cutaneous metastases. This is likely under-reported as the incidence of distant unexpected metastases continues to increase. Recent literature has shown in the incidence of 7%-13% of esophageal metastases noted to extend to skin and muscle.

Clinical workup for EA includes laboratory studies, imaging studies, and comprehensive endoscopy. After a complete history, physical exam, Complete Blood Count (CBC) and chemistry, endoscopy will allow direct visualization of the Gastrointestinal (GI) tract and primary means for tumour biopsy. If the mass is above the carina, bronchoscopy can rule out tracheal involvement. Computed Tomography (CT) imaging can assess for lung and liver metastases. Patients without M1 disease use combined Endoscopic Ultrasonography (EUS) and (CT) Positron Emission Tomography (PET) for initial staging, they are mainstays of the clinical work-up [9,12]. HER2/new testing is recommended if metastatic disease is documented or suspected [13,14]. Tumour markers are not statistically significant in detecting disease at this time. There have been cases of esophageal adenocarcinoma producing CA 19-9, and some evidence that CEA, Cyfra21-1, p53, SCC-Ag and VEGF-C may have diagnostic value but they are without threshold effect making early detection difficult. Laparoscopy and thoracoscopy can be used for staging regional nodes [15-17].

Surgery is the cornerstone of treatment for respectable EA in the appropriate patient population. Early stages allow for increased options including endoscopic resection if the tumour is limited to mucosa or submucosa with low-risk features. Survival has been noted to decrease with increasing depth of tumour invasion, presence of regional lymph node metastases, and distant metastases, as we would expect [18]. For those with locally advanced disease, pre-operative chemotherapy and/or radiation is offered prior to surgical resection [19]. Preoperative chemoradiation plus surgery reduced the 3-year mortality and locoregional recurrence compared with either modality alone [9,10]. If distant metastases are noted on clinical work-up, palliative chemoradiation and stenting are options.

Case Report

A 65year-old former smoker with 80 pack year smoking history and medical history of gastroesophageal reflux disease, coronary artery disease with coronary artery bypass grafting, hypertension, and hyperlipidemia was referred by GI for treatment of biopsy-proven esophageal adenocarcinoma. The patient presented with dysphagia and breakthrough reflux symptoms despite medications. EGD revealed esophagitis, gastritis, H. pylori, erythema, and irregular stricture of GE junction. Biopsy results demonstrated poorly differentiated adenocarcinoma. Additional staging included EUS and PET scan. During EUS the tumour was noted to be partially circumferential with irregular borders and suspected invasion into the muscular is propriety with one malignant-appearing lymph node at level 8L. PET scan agreeably demonstrated hypermetabolic activity of the distal esophagus and mildly prominent hypermetabolic gastrohepatic lymph nodes suspicious for local nodal metastatic disease. No evidence of distant metastatic disease was identified in the neck, chest, abdomen, or pelvis. The EC was determined to be clinical stage III: T3N1M0 adenocarcinoma of distal esophagus/GEJ. A stent and port were placed and medical oncology began 3 weeks of chemo-radiation with a good response. Repeat PET/CT demonstrated continued hypermetabolic activity of the esophageal mass with a resolution of previously hypermetabolic gastrohepatic lymph nodes. During his course of chemotherapy, the patient was admitted for nausea and vomiting with associated hematemesis and placed on TPN for nutritional support, he also suffered pneumonia after aspiration during which he required bilateral thoracentesis for persistent effusions, cytological fluid analysis was negative. Lastly, during his course of chemotherapy, he developed a DVT to the left upper extremity that was noted on ultrasound and treated with Eliquis. Robotic Ivor Lewis esophagectomy with mediastina lymph node dissection and jejunostomy tube placement was uneventful and the patient was discharged within a week. Pathology demonstrated negative margins, CK7, MOC31, and adenocarcinoma markers positive, 1/15 LN positive, the metastatic deposit noted isolated tumour cells within the lymph node and associated necrosis. Six weeks after surgery during follow up the patient complained of an enlarging LUE mass at the previous DVT site, it was noted to be erythematous and tender. Repeat US demonstrated enlargement of the mass and resolution of the supposed DVT. MRI demonstrated a 3.4 cmx2.6 cmx3.3 cm irregular, mildly enhancing subcutaneous mass, intermediately T2 hyperintense with stippled foci of T2 hypointensity and isochoric to underlying muscle on T1-weighted nonfat saturated. The mass was excised 2 weeks later and found to be consistent with the primary tumour, metastatic poorly differentiated adenocarcinoma with negative margins. On subsequent imaging four months after initial PET/CT and esophagectomy, progression of disease was noted. New adenopathy was present in the right lower cervical nodes, left sub-pectoral, left upper medial arm, mediastina involvement, as well as bilateral pleural disease, with right hila adenopathy more significant than left. No FDG avid disease was noted in the abdomen or pelvis. A second ultrasound of the left upper extremity was done and noted an additional two complex solid nodules distal to the surgical site of the previously excised cutaneous met as well as a sermon at the previous operative site (Figure. 1-4). The patient who was completing his second course of adjuvant Option (immunotherapy) as initially planned, was transitioned back to chemotherapy and a short course of radiation was recommended. Patient is currently continuing to undergo treatment [20] (Figure. 5-8).

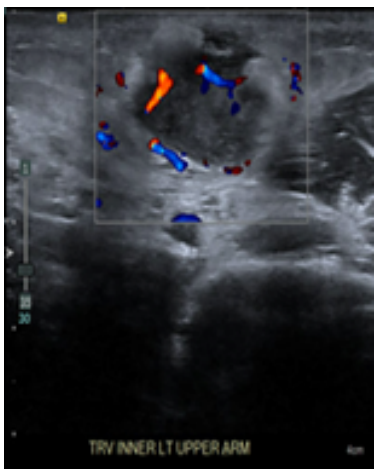
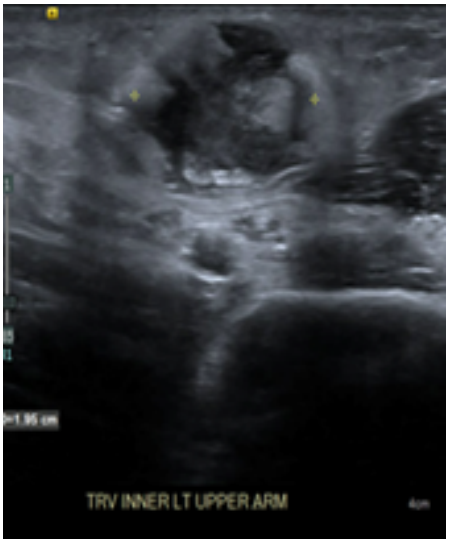


Figure 1. Initial Ultrasound of Left Upper Extremity (1/18/22).



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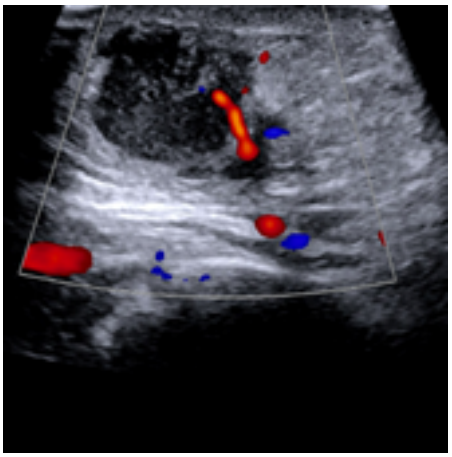

Figure 3. Ultrasound of Left Upper Extremity.

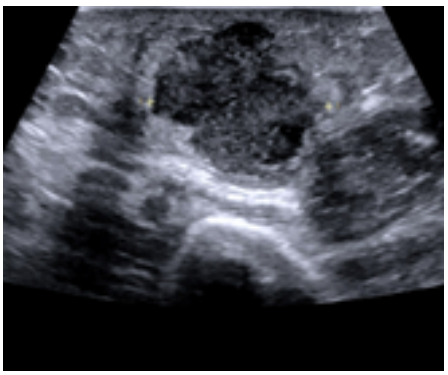

Figure 4. Ultrasound of Left Upper Extremity.

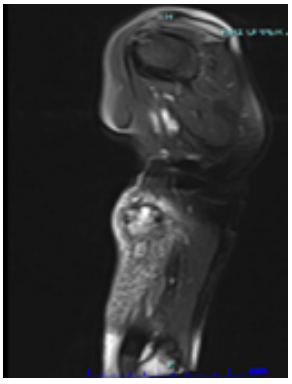

Figure 5. MRI of Left Upper Extremity W/WO.

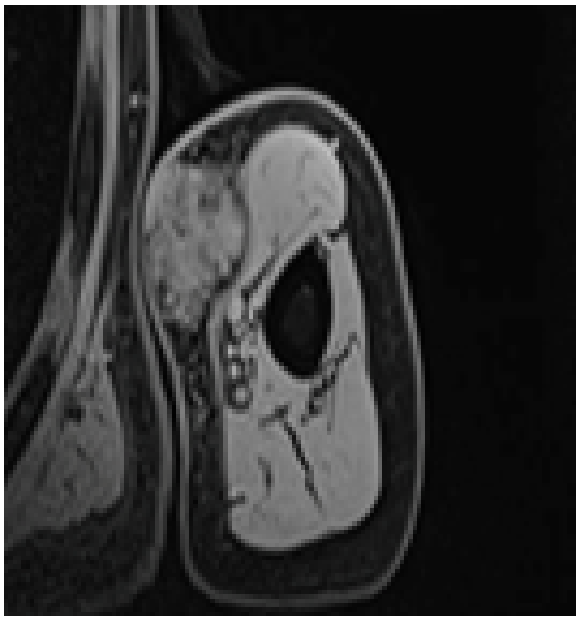

Figure 6. MRI of Left Upper Extremity W/WO.

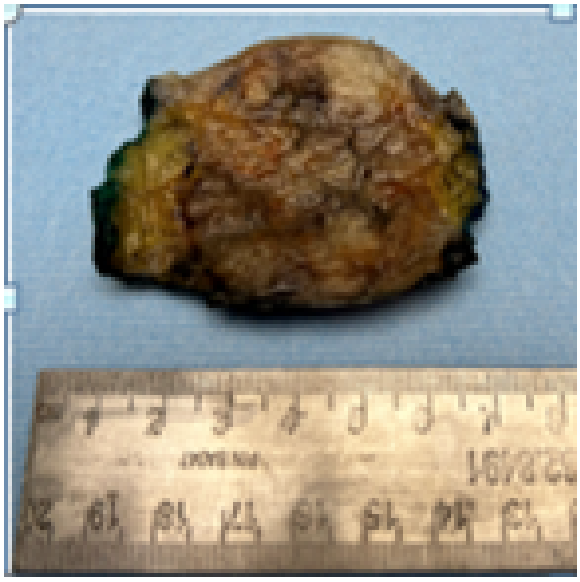

Figure 7. Left Upper Extremity Soft tissue mass after excision (4/7/22).

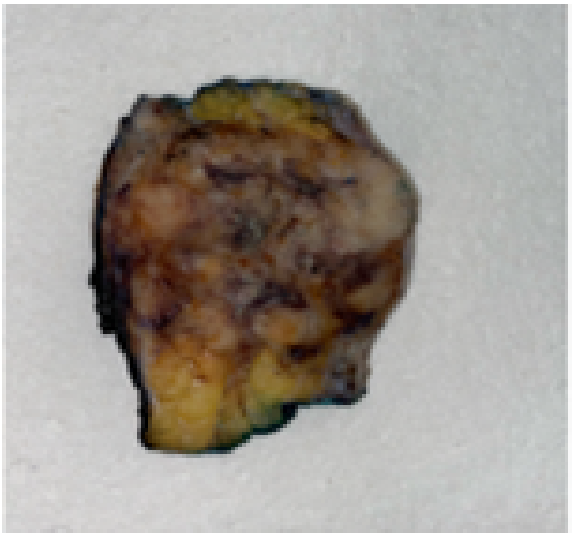

Figure 8. Left Upper Extremity Soft tissue mass after excision (4/7/22).

Discussion

The report of cutaneous metastasis of oesophageal adenocarcinoma is significant as the prevalence of EA is increasing as well as the incidence of cutaneous metastases, although overall it continues to be a rare finding [21]. Cancers that are more notable for cutaneous metastases include breast cancer, melanoma, and colorectal cancer. Previously the life expectancy after cutaneous oesophageal metastases are discovered is about 4-6months [22]. According to the SEER database, the survival of patients with local, regional, and metastatic disease of the oesophagus and gastric cardiac is improving, averaging about 9 months, with individual reports of survival up to 37 months [23]. The increasing incidence and prevalence of EA is secondary to metaplasia and changes in gene structure and expression. Specifically, TP53 and HER2 [24]. Overexpression of HER2 has been found to be 2x more common in EA (15%-30%) vs ESCC (5%-13%), HER2 positivity having an increased propensity for lymph node spread and poorer prognosis. Immunohistological staining although understudied, demonstrates CK7 +/CK20+ are apparent in 1/3 of gastric adenocarcinomas, CK7−/CK20+ in another 1/3 of gastric adenocarcinomas, while CK7+/CK20− is reported in oesophageal adenocarcinomas which is consistent with our pathology. CK7 also is expressed in the Barrett oesophagus as well as oesophageal adenocarcinoma. Most primary tumours that develop at or near the GEJ are a complication of chronic GERD. Recently ESCC was the most common histologic subtype of oesophageal cancer, but in recent decades there has been an increase in the incidence of EA in developed countries. Histopathology reports are demonstrating the tumour subtype to be strongly connected to survival rate factor, in comparison to ESCC, it has been proven that the adenocarcinoma subtype is a longer survival rate factor.

Conclusion

Cutaneous metastases are a late-stage manifestation of the disease that occurs in fewer than 10% of patients with malignancy. Most commonly <1% can be attributed to oesophageal cancers. Current workup of EC includes imaging, endoscopy, and surgery pending tumour stage. There has been an increase in distant Unexpected Metastases (UM) acknowledging the limitations of PET/CT imaging and fostering suspicion that we are underdiagnosing UM while dealing with the distraction of advanced disease. EC was noted to have 7%-13% cutaneous metastases in recent studies, this growing tendency for expansion can occur during any cancer stage requiring continued careful physical examination and imaging during treatment. Our patient underwent neoadjuvant chemoradiation and subsequent esophagectomy with negative margins and 1/15 LN positive. The patient was diagnosed with DVT of the LUE during neoadjuvant therapy that was likely a missed distant unexpected metastatic lesion or an early recurrence of poorly differentiated cancer after completion of therapy. Despite therapy, the progression of the disease required a new chemotherapy regimen, in accordance with the well-known and aggressive nature of this disease. Survival and treatment options continue to improve alongside therapeutic modalities, hopefully, with continued progression of screening and treatment, the overall prognosis of esophageal cancers will continue to improve as well.

Acknowledgements

None.

Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Ethics Statement

The Piedmont Healthcare Institutional Review Board has determined this project does not meet the definition of human subject research under the purview of the IRB according to federal regulations.

Author Contributions

Elaine Lelli directed and worked on data curation, writing and forming the original draft. Evan Weitman and Eric Sceusi helped supervise the project and worked out the conceptualization, formal analysis and worked on the writing (original draft and review/editing).

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