



Rare Recurrence of Esophageal Cancer as Bone Marrow Carcinomatosis Leading to Bone Marrow Failure and DIC

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Abstract

Introduction: Esophageal cancer portends a poor prognosis due to high risk of recurrence, even following treatment with curative intent. Recurrence often occurs as distant metastasis, commonly in liver, lung, bone and brain with bone marrow metastasis being infrequently cited in medical literature. Herein we describe a case of bone marrow metastasis of an esophageal primary following resection.

Case presentation: A 78 year-old male with locally advanced GEJ cancer who underwent chemotherapy followed by surgical resection with complete pathological response presented 6 weeks later with right lower quadrant pain. He was found to have hemorrhage in right perinephric space secondary to a ruptured kidney cyst with labs suggestive of DIC and hemolytic anemia. Patient was transfused multiple units of FFP, cryoprecipitate, and blood and ultimately required coil embolization of the right renal artery. The patient was discharged home after prolonged hospital course, and was found to have persistent pancytopenia with hypofibrinogenemia. Bone marrow aspirate and biopsy were performed, which revealed a necrotic marrow replaced with signet ring adenocarcinoma consistent with his esophageal primary. Patient requested hospice care and died six weeks later.

Conclusion: Recurrence of esophageal cancer is common and can occur locoregionally or as distant metastasis, however bone marrow as a site of metastatic spread occurs infrequently. Esophageal cancer recurs typically within two years of resection, therefore follow up and surveillance is a vital component of management, keeping in mind that bone marrow is a possible though atypical site of recurrence.

Keywords: Bone marrow carcinomatosis; metastatic esophageal cancer; adenocarcinoma; DIC

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Consent: Consent was taken from the patient for publication of this case report.

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Introduction

Esophageal cancer is known to have high rates of recurrence and distant metastasis, even following resection with common sites including liver, lung, bone, and brain. Cases of metastatic spread of esophageal cancer to bone marrow are rare and infrequently cited in medical literature. We report one such case, which presented as persistent DIC prompting a bone marrow biopsy.

Case Report

We present a case of a 78 year-old male patient who initially was diagnosed with a locally advanced GEJ cancer in April of 2017. He underwent chemotherapy with carboplatin and Taxol for four doses with suboptimal response, which was followed by modified FOLFOX with proton therapy, which he completed in July of 2017. He underwent surgical resection in September of 2017 with a complete pathological response in the primary and 1 out of 21 positive lymph nodes. He presented 6 weeks later to a local hospital with severe right lower quadrant pain and was found to have hemorrhage in right perinephric space. This was thought to be secondary to a ruptured kidney cyst as the patient had a history of multiple large kidney cysts. He was also found to have laboratory evidence of DIC with decreased fibrinogen levels of 55 mg/dL, increased PT of 19.9 s, increased D-dimer of 3700 $\mu\text{g/mL}$ and increased fibrin split products $>40 \mu\text{g/mL}$. Hemolytic anemia was also suspected due to increased LDH levels, decreased haptoglobin levels and persistent anemia. The patient was admitted to the ICU for further monitoring and was transfused multiple units of FFP and cryoprecipitate as well as blood. He ultimately required a coil embolization of the right renal artery due to persistent anemia and blood product requirement. Additional imaging revealed a giant hemangioma in the liver, which was chronic with no evidence of metastatic disease on imaging.

The patient had a prolonged hospital course, which was complicated by an acute CVA, which was medically managed. TPA could not be administered due to ongoing intra-abdominal hemorrhage and DIC. The etiology was thought to be related to either DIC with prothrombotic condition despite INR in the 2-range or lone atrial fibrillation. Patient had persistent pancytopenia with hypofibrinogenemia although the exact cause of his low grade DIC remained unclear. He ultimately was stabilized and discharged home. Due to persistent and worsening pancytopenia and persistent evidence of DIC a bone marrow aspirate and biopsy was performed. The histologic sections revealed extensive replacement of the marrow space by a poorly differentiated adenocarcinoma, which was confirmed by immunohistochemical analysis for AE1/3, with signet ring cell features. Morphological comparison with the initial tumor revealed cytomorphologic features in keeping with the previously established esophageal adenocarcinoma primary. The patient requested hospice care and died six weeks later.

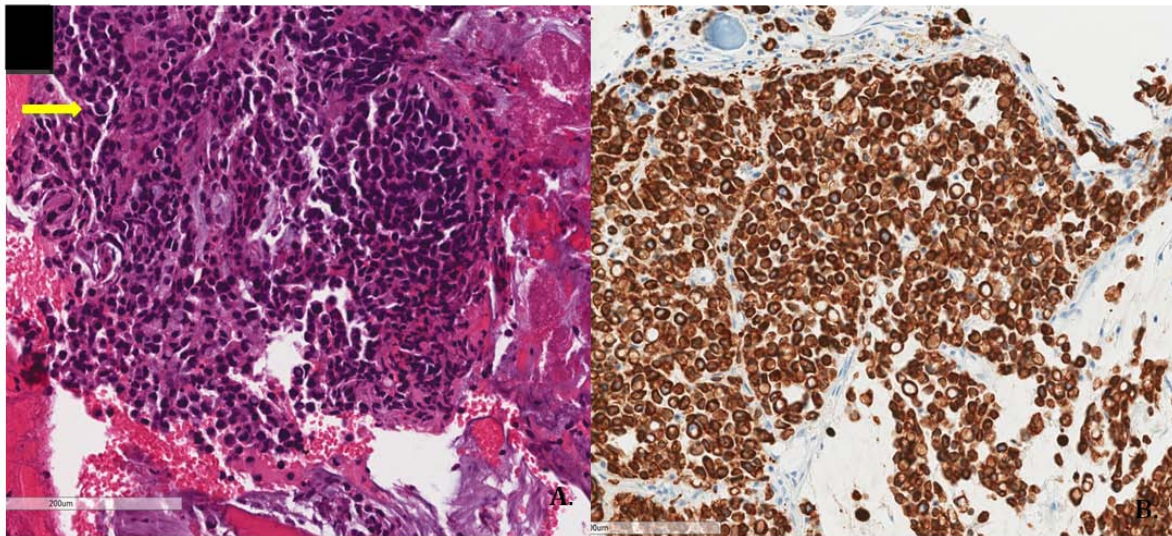


Figure 1 A. H&E staining of marrow reveals metastatic adenocarcinoma, poorly differentiated, with mucinous and signet ring morphology (arrow) with tumor necrosis and markedly decreased marrow reserve. B. Immunoperoxidase stains reveal that almost entire marrow is diffusely positive for cytokeratin AE1/AE3 including areas of necrosis indicating extensive involvement by metastatic adenocarcinoma.

Discussion

Esophageal cancer is the 11th leading cause of cancer death with a 5-year survival rate of 18.8%, however in patients with distant metastasis, this number decreases to 4.6% [1]. The poor prognosis of this malignancy can be attributed to the high rates of recurrence and metastatic spread. One study noted that 38% of cases experience recurrent disease with distant metastasis occurring in 55% of recurrences, locoregional spread in 28% of cases, and 17% of cases with both [2]. In this case of early recurrence with distant metastases to bone marrow, survival was less than six months following surgical resection.

Recurrence is estimated to occur in approximately 38% of cases of esophageal cancer, including squamous cell carcinoma or adenocarcinoma. The median time to recurrence of esophageal cancer is 5.5 years, however among these cases 75% of recurrences occurred within the first two years after surgery, which is consistent with our case of rapid recurrence only 6 weeks following surgical resection with complete pathological response.² Most common sites of metastatic spread include liver, lymph nodes, lung, bone, and brain, with metastatic spread to bone offering the poorest prognosis [3]. Esophageal adenocarcinoma, as in our case, is noted to be almost twice as likely to have metastasized at time of diagnosis than esophageal squamous cell carcinoma [4].

Though bone marrow involvement has been reported as micrometastasis, no known cases of metastatic invasion of bone marrow by esophageal cancer have been reported in medical literature. Micrometastases are small collections of tumor cells that have spread from the primary tumor and are able to evade detection with imaging studies. Presence of micrometastasis has been associated with tumors of poorer histological grade [5], lymphovascular invasion, and advanced T-stage [6], though reports on the effect of bone marrow micrometastasis vary with regard to overall survival [6-8].

Several case reports documenting metastatic spread of gastric cancer to bone marrow exist in medical literature, including the ones mentioned in the table below [9-11]. One such case had a

remarkably similar presentation to our case, in which the patient presented with a clinically significant bleed (epistaxis) and was subsequently found to have DIC. However only one case has been found describing esophageal cancer as a primary source of bone marrow carcinomatosis, in which case the primary neoplasm was an esophageal squamous cell carcinoma ^[12]. In these cases that have been previously reported, survival was limited to a few weeks at best.

Table 1 Existing reports of gastric and esophageal cancer with bone marrow metastasis

Author	Primary neoplasm	Previous treatment	Presenting symptoms	Other
Seki, Y. et al 2016 [9]	Mucin-producing gastric adenocarcinoma at GE junction, previously undiagnosed	None	Epistaxis, found to have DIC	Patient expired on hospital day 3
Fonocho, E. et al 2017 [10]	Non-metastatic gastric adenocarcinoma in antrum of stomach	Roux-en-Y gastrojejunostomy two years prior	Pancytopenia	Also had bone metastases. Underwent palliative chemotherapy
Chen, Y. et al 2014 [12]	Esophageal squamous cell carcinoma with metastatic disease to liver and bone	Chemoradiotherapy with cisplatin/5-fluorouracil	Headache, diplopia, hearing impairment	Found to have dural metastasis on MRI in addition to BM metastasis on BM biopsy
Ekinci, A.S. et al 2014 [11]	5 cases of gastric adenocarcinoma, 4 in the corpus, 1 in the cardia	One patient had previous curative surgery with adjuvant chemoradiotherapy. Others had no previous treatment	Various cytopenias	Range of survival 20-53 days in 4/5 patients deceased at time of publication

Many case reports exist documenting DIC as a complication of bone marrow carcinomatosis. DIC is also a common complication of malignancy, specifically solid tumors. DIC in cancer has, in general, a less fulminant presentation than the types of DIC complicating sepsis and trauma ^[13]. This process is mediated by tissue factor expression by tumor cells in addition to other procoagulant molecules, a process which is promoted by pro-inflammatory cytokines. Additionally, most tumors induce a hypofibrinolytic state promoting DIC. Chemotherapy can also increase risk of developing thrombosis due to damaging effects to endothelium ^[13]. DIC is more commonly associated with adenocarcinoma than other tumor types, and the tumors typically originate in the GI tract, pancreas, lung, breast, or prostate ^[14].

In conclusion, no existing literature exists to our knowledge of metastatic esophageal adenocarcinoma leading to bone marrow carcinomatosis, though rare reports exist of this pattern of metastasis in gastric cancer. Both gastric and esophageal cancer have high rates of recurrence and require enhanced surveillance following treatment.

Consent

Written informed consent was obtained from the patient's wife for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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