Hemolytic Anemia of Malignancy: A Case Study Involving Signet Ring Cell Metastatic Breast Cancer with Severe Microangiopathic Hemolytic Anemia

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Abstract
Hemolytic anemia in the setting of malignancy is a rare manifestation of paraneoplastic syndrome with significant morbidity. Here we discuss a case involving metastatic breast cancer presenting with severe hemolytic anemia and renal failure secondary to thrombotic microangiopathy of malignancy. This case discusses the workup for secondary hemolytic anemia, a possible role for therapeutic plasma exchange in this setting, as well the current understanding of the management of microangiopathic hemolytic anemia of malignancy.

Introduction
Microangiopathic hemolytic anemia was first characterized by Brain and colleagues based on the finding of fragmented red blood cells in peripheral blood smears [1]. While there
are many potential causes for hemolytic anemia, one uncommon cause is due to the presence of cancer with likely origin in gastric, breast and lung [2–5]. Here we discuss a case involving metastatic breast cancer presenting with severe hemolytic anemia and renal failure secondary to thrombotic microangiopathy from underlying malignancy.

Case Report

A 52 year old female was emergently transferred from an outside hospital for higher level of care for suspected thrombotic thrombocytopenic purpura (TTP). Her past medical history is significant for Stage 3 estrogen receptor positive/progesterone receptor positive/HER2-neu negative left breast infiltrating lobular carcinoma diagnosed in Dec 2014. She received four cycles neoadjuvant chemotherapy with docetaxel and cyclophosphamide followed by bilateral mastectomy with 15/15 left sided lymph nodes positive for disease, with pathologic staging IIIC of the left breast. She then completed 7 cycles of adjuvant chemotherapy gemcitabine and cisplatin followed by adjuvant postmastectomy radiation and subsequently started adjuvant anastrozole. She was closely followed with imaging and labs by her primary oncologist given her high risk of recurrence. She was noted to have stable imaging findings through October 2015, when it was noted that she had elevated CEA of 1,570 and mild transaminases with jaundice. Anastrozole was stopped, and PET performed in October 2015 showed increase uptake in the porta hepatis, with follow up CT abdomen/pelvis concerning for new but poorly defined liver lesions. She subsequently developed gross hematuria after the CT scan and was sent to a community hospital where she was found to have hemoglobin 6.0 g/dL and hematocrit 22%, with normal platelet count. She was then transferred to a second hospital for higher level of care, where her hemoglobin was found to be 5.3 g/dL and platelets 103 bil/L on presentation. On day 2 at the second outside hospital, she developed severe thrombocytopenia (platelets 23 bil/L) with worsening renal function, and lactase dehydrogenase (LDH) elevation to 3,565 U/L. She underwent esophagoduodenoscopy (EGD) for evaluation of anemia which showed extrinsic compression at the gastroesophageal junction and documented linitis plastica appearance of the gastric wall with biopsy showing signet ring adenocarcinoma, diffuse type with pathology signed out as consistent with gastric adenocarcinoma. Patient’s renal function subsequently declined with creatinine elevation to 2.6 mg/dL and peripheral smear revealed schistocytes, prompting initiation of plasma exchange at outside hospital due to concern for TTP.

It was at this point that the patient was transferred for further higher level of care to our center. At the time of presentation to our institution, patient was noted to have hemoglobin of 7.5 g/dL, hematocrit of 22.1%, platelets of 57 bil/L, creatinine of 2.3 mg/dL, normal fibrinogen level, total bilirubin of 12.7 mg/dL with direct bilirubin of 2.0 mg/dL, and LDH of 2,540 U/L. Peripheral smear revealed increased schistocytes >10 per high powered field. She was continued on therapeutic plasma exchange and supportive transfusions. Records from the outside hospital showed a normal ADAMTS13 levels, but it was unclear whether this was drawn before or after plasma exchange was begun. Comprehensive review of records from the patient’s outside oncologist and hospitalization revealed both her medical history and recent gastric pathology results. After nine days of plasma exchange, there was correction of creatinine (2.3 mg/dL to 1.3 mg/dL), transient improvement of LDH to 877 U/L and total bilirubin down trending from 12.7 to 7.4 mg/dL, but without significant improvement in platelet count (range 30–57 bil/L). Based on clinical course so far, microangiopathic hemolytic anemia of malignancy (also referred to as cancer-associated microangiopathic hemolytic anemia [CA-MAHA])
presented as the most possible underlying cause for the patient’s persistent hemolysis. Plasma exchange was stopped, and ADAMTS13 level rechecked 48 hours after last plasma exchange came back normal, arguing against TTP.

Given prior diagnosis of invasive lobular carcinoma which can present with signet ring features, we requested outside pathology slides and tissue block for confirmation. There was delay in obtaining outside pathology tissue, hence patient underwent repeat EGD at our institution, with endoscopist reporting normal appearing stomach wall without thickening or obvious mass. However, biopsies of gastric antral nodules and body polyps revealed adenocarcinoma with weak to moderate staining of ER and PR and immunohistochemical profile consistent with gastric mucosal involvement by lobular carcinoma of breast origin. The patient was then started on chemotherapy with doxorubicin and paclitaxel (fractionated into weekly dosing instead of q3 weeks due to poor functional status). The choice of chemotherapy was partly determined by her prior exposure to chemotherapy. After her first dose of chemotherapy, patient’s status declined, with worsening of hemolysis (peripheral smear with >50% schistocytes per high powered field), increased transfusion requirements (Hgb as low as 3.6 g/dL), worsening creatinine from 1.3 to 1.7 mg/dL, uptrending bilirubin from 7.4 to 14.6 mg/dL, uptrending LDH from 877 to 5,015 U/L, and persistent thrombocytopenia (PLT range 22–48 bil/L). Due to worsening status on day 6 of chemotherapy, plasma exchange was reinitiated as patient had shown prior response. From day 6 to day 11 after first dose of chemotherapy, patient’s transfusion requirement declined, she became responsive to platelet transfusion, and her creatinine stabilized back to baseline of 1.3 mg/dL. She was able to tolerate 2nd and 3rd doses of chemotherapy on days 11 and 19, respectively, with subsequent normalization of bilirubin and no further schistocytes seen on peripheral smear. Plasma exchange was subsequently stopped on day 19 of chemotherapy following response to systemic treatment. Patient was discharged home on day 34 after she was clinically stable and was subsequently able to follow up in clinic for continuation of weekly chemotherapy. Approximately one month following her hospital discharge, she was hospitalized for and treated with endoscopic retrograde cholangiopancreatography (ERCP) due to choledocolithiasis, likely secondary to pigment gallstones which may have developed over the course of her hemolytic episodes. Prior to her third round of chemotherapy, the patient unfortunately presented to the ED in PEA arrest, and resuscitation efforts were held due to advanced directive for do-not-resuscitate status. Per family, patient had grown progressively fatigued with jaundiced appearance one day prior, prompting suspicion for relapse of hemolytic episode.

Discussion

The pathophysiology behind microangiopathic hemolytic anemia of malignancy is not well understood. It is thought to be a paraneoplastic syndrome related to the underlying malignancy and not an independent condition that co-exists with known cancer. Several mechanisms have been proposed. First, it has been speculated that metastatic cancer with bone involvement may lead to secondary myelofibrosis that lead to direct release of prothrombotic ultra large von Willenbrand factor multimers, which promote coagulation through binding of glycoprotein 1b-IX complex and platelet aggregation. A second mechanism proposed involves red cell fragmentation due to direct contact with tumor emboli within blood vessels or intraluminal fibrin thrombi [1, 2, 6, 7].

It is well known that under normal conditions, the metalloprotease ADAMTS13 (a VWF-cleaving protease) rapidly degrades ultra large VWF multimers to prevent catastrophic
thrombosis and microvascular damage. Prior studies have had conflicting results between hemolytic anemia of malignancy and ADAMTS13 deficiency; in one study surveying patients with metastatic disease, large VWF multimers were found to be present due to ADAMTS13 deficiency, whereas a smaller study was unable to match this result [8, 9]. However, the larger study did not correlate ADAMTS13 deficiency with clinically significant hemolytic anemia. Therefore, traditional methods of managing hemolytic anemia secondary to ADAMTS13 deficiency or antibodies to VWF-cleaving factor, such as therapeutic plasma exchange or immunosuppression (glucocorticoids, cyclophosphamide, or rituximab), are generally not effective in the setting of hemolytic anemia of malignancy [10, 11]. Nonetheless, in our case study above, the patient had normal ADAMTS13 level and did appear to have partial response from therapeutic plasma exchange with marked decline in both LDH and bilirubin while on exchange therapy along with decrease in transfusion requirements indicating improvement in the underlying hemolytic process. While there is no clear role for eculizumab in hemolysis of malignancy due to lack of demonstrated association between CA-MAHA and complement antibody treatment in two patients for whom hemolytic anemia was diagnosed prior to diagnosis of malignancy [12]. Management for microangiopathic hemolytic anemia of malignancy primary involves control of the underlying malignant process. Unlike other paraneoplastic syndromes, hemolytic anemia of malignancy tends to occur in the setting of cancer recurrence, possibly due to cancer clonal selection of a therapy-resistant population after chemotherapy. Therefore, in patients presenting with idiopathic hemolysis for whom immune mediated hemolysis (including atypical HUS), vasculitis, TTP, consumption coagulopathy such as DIC, and infection related HUS have been ruled out, workup to include mammography, EGD/colonoscopy, and other age appropriate screenings should be considered to rule out underlying gastric, breast, lung, renal and prostate cancer. Furthermore, in patients currently on chemotherapy, there is a well-known association between hemolytic anemia and drugs such as carboplatin, gemcitabine [13], and paclitaxel [14].

Hemolytic anemia of malignancy has a very poor prognosis, with a nearly 50% mortality rate within 1 month of diagnosis [3, 12, 15]. Response to chemotherapy may induce a complete remission after just one cycle, but relapse is frequent due to the presence of metastatic disease. In conclusion, based on our case study presented above, aggressive supportive care and a thorough workup to rule out other acquired causes of hemolytic anemia is an essential component of management in addition to systemic therapy to control the underlying malignancy. Even with resolution of hemolysis, we recommend close follow up for long term sequelae such as development of pigment stones which may further complicate or delay chemotherapy course.

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Statement of Ethics

The authors have no ethical conflicts to disclose.
Disclosure Statement

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Author Contributions

EHL drafted the manuscript. EHL, SO, and GN are medical oncologists and AA is the nephrologist involved in the patient’s care.

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