Hemolytic Anemia and Metastatic Carcinoma: Case Report and Literature Review

Avani A. Pendse, MBBS, PhD, Claire H. Edgerly, MD, Yuri Fedoriw, MD

ABSTRACT

Hemolytic anemia can complicate the development of a variety of solid tumors and hematologic malignancies. Although patients may have an established diagnosis with documented metastases, microangiopathic hemolytic anemia (MAHA) can be a presenting feature of an occult malignancy. Prompt diagnosis is essential because conditions that mimic the symptoms of MAHA, including thrombotic thrombocytopenic purpura, have different prognoses and therapeutic options. Although the exact pathogenesis is not yet delineated, we present herein a case of cancer-associated MAHA and discuss the known pathways that can contribute to the initiation and propagation of hemolytic anemia in patients with cancer. The patient is a 69-year-old woman with breast carcinoma that had metastasized to her rectum, urinary bladder, and brain. She eventually developed progressive decline in her functional status, with intermittent epistaxis and melena. The results of laboratory studies revealed hemolytic anemia and thrombocytopenia; results of a bone-marrow biopsy confirmed the involvement by metastatic carcinoma. The patient received red blood cell and platelet transfusions and was discharged to hospice care after clinical stabilization. She died soon thereafter.

Keywords: Microangiopathic hemolytic anemia, metastatic carcinoma, thrombotic thrombocytopenic purpura, ADAMTS13, thrombocytopenia

Case Report

The patient is a 69-year-old woman with infiltrating lobular carcinoma of the breast, as diagnosed via core biopsy in 2002. Later that year, the patient had undergone a modified radical mastectomy with a final histopathologic diagnosis of infiltrating lobular carcinoma, classic type, involving the upper-outer and lower-outer quadrants of the right breast. The metastatic carcinoma involved all 7 right axillary lymph nodes that were sampled, including a level III lymph node. Immunohistochemistry (IHC) staining analysis performed on the breast core biopsy specimen revealed positive results for estrogen receptor (ER) and progesterone receptor (PR).

Hemolytic anemia can manifest as a paraneoplastic phenomenon in patients with solid tumors and hematologic neoplasms; this manifestation often portends an unfavorable prognosis. In rare instances, it is a feature of an occult primary malignant neoplasm. As in the case we discuss in this article, hemolysis typically occurs late in the course of the disease and appears abruptly as severe anemia. Currently, no specific type of therapeutic treatment has been effective.

Abbreviations

MAHA, microangiopathic hemolytic anemia; IHC, immunohistochemistry; ER, estrogen receptor; PR, progesterone receptor; CK-7, cytokeratin 7; GCDFP, gross cystic disease fluid protein; CDX2, caudal-related homologue 2; CNS, central nervous system; ADAMTS13, a disintegrin and metalloprotease with thrombospondin type 1, repeats 13; TF, tissue factor; PT, prothrombin time; aPTT, activated partial thromboplastin time; HUS, hemolytic uremic syndrome; DIC, disseminated intravascular coagulation; vWF, von Willebrand factor; DDAVP, deamino-8-D-arginine vasopressin; ILs, interleukins; TNF-α, tumor necrosis factor–alpha; GPIb, glycoprotein Ib; FIX, Factor IX

1Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill

*To whom correspondence should be addressed.
E-mail: gfedoriw@med.unc.edu
results were consistent with metastatic disease from the primary breast tumor. The results of a subsequent biopsy of a bladder mass were also consistent with metastatic carcinoma. Results of rectal and bladder biopsies showed a signet-ring cell component that was not identified in the original tumor. A signet-ring cell variant of lobular carcinoma of the breast is a well-defined diagnostic entity; metastases arising from a non–signet-ring-cell primary can evolve into signet-ring cell carcinoma. In 2011, central nervous system (CNS) metastasis was confirmed by cytological evaluation of the cerebrospinal fluid.

A month later, the patient experienced progressive weakness in her lower extremities, dyspnea on exertion, and dizziness while standing. She had an episode of epistaxis but did not bruise easily. The anemia and thrombocytopenia raised concern for metastatic involvement of the bone marrow. In addition to bone marrow metastases, anemia and thrombocytopenia in a patient with cancer can result from malignancy–induced bone marrow fibrosis, myelotoxic effects of chemotherapeutic agents, and secondary infection. These entities were ruled out based on lack of diagnosed bone marrow fibrosis, normal and minimally reduced white blood cell counts, and the absence of other evidence of infection. The results of the peripheral blood smear were consistent with intravascular hemolysis (namely, decreased haptoglobin and elevated lactate dehydrogenase), with numerous schistocytes and red-cell fragments (Image 1A). Levels of a disintegrin and metalloprotease with thrombospondin type 1, motifs 13 (ADAMTS13) and tissue factor (TF) were unavailable. Fibrinogen levels were modestly decreased or normal; a single measurement revealed an elevation in the level of D-dimers. Prothrombin time (PT) showed modest elevation; however, the activated partial thromboplastin time (aPTT) was normal. Results of a subsequent bone-marrow biopsy demonstrated hypercellular marrow with involvement by metastatic carcinoma (Images 1B and 1C). The presence of hemolytic anemia, thrombocytopenia, and neurological involvement in the patient, which are important diagnostic criteria for thrombotic thrombocytopenic purpura (TTP) in addition to fever and renal impairment, raised concern for TTP. Although these findings were explained by the involvement of the bone marrow and central nervous system (CNS) by the metastatic disease of the patient, TTP remained an early diagnostic consideration. The patient received red blood cell and platelet transfusions and was discharged to hospice care after clinical stabilization. She died soon after discharge.

## Discussion

Paraneoplastic syndromes are defined as “disorders caused by cancers, but not a direct result of cancer invasion of the affected organ or tissue.”2 Hemolytic anemia generally occurs as a rare and abruptly presenting paraneoplastic phenomenon. Patients with an occult primary malignancy may seek medical attention due to symptomatic hemolysis. Cancer-related hemolysis is most commonly characterized as MAHA, with fragmented red blood cells readily identified in the peripheral blood.3 Symptoms include weakness, fatigue, decreased exercise capacity, and fainting. Increased frequency of bone pain and respiratory symptoms has been reported4 in patients with cancer-associated MAHA. Common laboratory findings include reduced levels of hemoglobin and hematocrit, fragmented red cells or schistocytes in the peripheral blood, increased bilirubin and lactate dehydrogenase levels, and decreased haptoglobin levels. Most cancers associated with MAHA have been reported in patients with adenocarcinomas, particularly the mucin-producing variants. The most frequently implicated tumors are gastric, breast, and lung carcinomas.5 However, other epithelial tumors, including squamous cell carcinomas, have been associated with hemolysis.6

In addition to cancer, the clinical differential of MAHA includes TTP, hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC)/consumption coagulopathy, and vasculitides. TTP and HUS share certain important clinical features, such as hemolytic anemia, thrombocytopenia, renal impairment, and neurological symptoms. Also, patients with HUS have gastrointestinal symptoms and may have been infected with the shiga toxin Escherichia coli. In suspected cases of TTP, ADAMTS13 protein levels and/or the presence of an inhibitor antibody to ADAMTS13 can help to establish the diagnosis. Along with thrombocytopenia, patients with DIC/consumption coagulopathy have prolonged PT and aPTT, decreased fibrinogen concentration, and elevated levels of fibrin degradation products. Establishing a prompt diagnosis of cancer-associated MAHA is critically important because unlike in TTP-HUS, therapeutic plasma exchange has not been shown to improve outcome in these patients.7 The mechanisms underlying cancer-related hemolysis are not well understood. Hilgard and Gordon-Smith8 proposed that tumor emboli from disseminating carcinoma can activate platelets and promote fibrin deposition that lead to microangiopathic hemolysis. Consistent with this hypothesis, most cases...
of MAHA occur late in the course of disease, when metastases are typically present.

ADAMTS13, which has been implicated in the pathogenesis of TTP, is a metalloproteinase that cleaves the multimeric protein von Willebrand factor (vWF).\(^8,9\) vWF is produced in the vascular endothelial cells and is released into the circulation as a result of various stimuli, including epinephrine.\(^10\) Alternatively, vWF release can be stimulated by 1-desamino-8-D-arginine-vasopressin (DDAVP), hypoxia, and myriad cytokines, including interleukins (ILs) IL-2, IL-6, IL-8, and tumor necrosis factor–alpha (TNF-\(\alpha\)).\(^11\) With reduced ADAMTS13 function, the large multimers of vWF that are released from the vascular endothelial cells are not cleaved. These large forms of vWF can interact more intensively with platelet glycoprotein Ib (GPIb) and can lead to platelet activation.\(^8,9\) In a study using patients with disseminated tumors and control patients with corresponding, localized, nonmetastatic malignant neoplasms, Oleksowicz et al\(^12\) demonstrated that large vWF multimers are present in patients with disseminated cancers. The large vWF multimers result from deficient vWF-cleaving protease activity, due to a deficiency or functional aberration of this protein.\(^12\) However, the results of a smaller study by Fontana et al\(^13\) demonstrated that microangiopathic hemolytic anemia in the setting of metastasizing malignant tumors is not associated with a severe deficiency of the vWF-cleaving protease.\(^13\) Patients in the study by Oleksowicz et al\(^12\) did not have an ongoing clinical picture of MAHA. Also, the exposure of patients
with cancer in both studies to chemotherapeutic agents may complicate the pathogenesis of MAHA. Despite the conflicting data, we believe that the presence of high levels of vWF multimers and functional deficiency of the ADAMTS13/vWF-cleaving protease contributes to the pathogenesis of cancer-associated MAHA.

TF (thromboplastin) is a 47-kDa transmembrane glycoprotein found on the surface of many cells that initiates the extrinsic pathway of the coagulation cascade. TF also regulates the intrinsic pathway by triggering conversion of Factor IX (FIX) to FIXα and is a potent mediator of coagulation. Normally, TF is expressed in blood vessels in fibroblasts and smooth muscle cells. However, intravascular cells such as endothelial cells, platelets, and leukocytes express TF in response to injury. TF upregulation has been observed in tumor cells, which display procoagulant activity. TF is implicated in metastasis in glioma, breast carcinoma, and colon cancers. Expression of TF can potentially be increased via TNF-α, IL-1β, and other proinflammatory cytokines that are secreted by tumor cells. TNF-α and IL-1β also downregulate the expression of the thrombin surface receptor. As a result, a decrease occurs in the activation of the anticoagulant protein C system, thus contributing to the overall hypercoagulable state.

Hence, occurrence of MAHA in the setting of cancer is a complex pathophysiological process that is incompletely understood. Although there is some agreement among investigators regarding the pathways that can contribute to the initiation and propagation of hemolytic anemia in patients with cancer, early diagnosis and reliable clinical predictors are necessary to improve outcomes.

References