Microangiopathic Hemolytic Anemia in Metastasized Signet Ring Cell Carcinoma: A Report of Three Cases

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Abstract

Systemic manifestations of gastric cancer related to paraneoplastic phenomena are rarely seen at initial presentation. We report three patients who presented with microangiopathic hemolytic anemia (MAHA) with initial symptoms of metastatic signet ring cell adenocarcinoma.

Key words: Gastric carcinoma; Microangiopathic hemolytic anemia; Plasma exchange; Paraneoplastic syndrome; Signet ring carcinoma; Bone marrow metastasis; Osteoblastic metastasis

INTRODUCTION

Microangiopathic hemolytic anemia (MAHA), which results in the production of fragmented erythrocytes (schistocytes), may be caused by defective prosthetic cardiac valves, disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), malignant hypertension, and advanced carcinoma. MAHA also occurs as a paraneoplastic syndrome in different solid tumors. It is a serious, often fatal complication of malignancy. Tumor-derived factors, procoagulants, immune complexes, some chemotherapy drugs, fibrinoid necrosis of bone marrow, and tumor cell emboli of arteries, arterioles, and capillaries are the causes of cancer-associated MAHA (CA-MAHA). Chemotherapy is the only effective therapy.

CASE REPORT

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CASE 1

A woman aged 29 years was referred for back pain experienced over a six-month period. In the physical exam, the patient was tender to palpation in the lower thoracic and lumbar spine. The patient had no saddle anesthesia or focal neurologic deficits. She was pale and had no evidence of icterus or lymphadenopathy. There was no organomegaly.

The initial laboratory evaluation revealed a white blood cell (WBC) count of 11.4 K/UL, hemoglobin of 9.9 g/dL with an mean corpuscular volume (MCV) of 103 fL, and a platelet count of 95 K/UL. Haptoglobin decreased to a level less than 10 mg/dL. Creatinine was elevated to 1.9 mg/dL and serum calcium was 15.5 mg/dL. Liver function tests (LFT) were significant for alkaline phosphatase at 523 U/L; all other LFTs were normal. A peripheral blood film showed anisocytosis, polychromasia, nucleated red blood cells, and fragmented red blood cells. Computed tomography imaging of the chest, abdomen, and pelvis revealed a compression fracture of the T10 vertebral body as well as lytic lucencies in all vertebral bodies, a small amount of free fluid lateral to the liver and minimal peritoneal and pleural effusions. No monoclonal band was detected in serum and urine immunoelectrophoresis. Tumour markers were as follows; CA19-9:140, CA72-4:143, CEA:4.1 and CA15-3: 21. A subsequent bone marrow evaluation yielded no aspirate (“dry tap”), but a biopsy specimen was obtained. Bone marrow biopsy showed infiltration by signet atypical ring-shaped large cells thus the pathologist advised to search for the primary site. Mammography revealed heterogeneously dense breast with no evidence of mass lesions, architectural distortion or microcalcifications. Ultrasonography of the breast was normal.
Endoscopy of the upper gastrointestinal tract revealed pangastritis and bulbitis. In the axial and appendicular skeletal system, lytic/sclerotic, and heterogeneous diffuse/local hypermetabolic changes were detected on 18F-fluorodeoxyglucose (18F-FDG) positron-emission tomography (FDG PET). No primary site was found except for the presence of an endometrial mass. The patient was subsequently discharged and was seen in the oncology clinic to begin chemotherapy for metastatic signet ring cell adenocarcinoma. Her coagulation profile was suggestive of DIC because of the raised levels of FDP and low fibrinogen. The patient continued to deteriorate despite repeated blood transfusions and was transferred to reanimation service; she died one week later.

**CASE 2**

A man aged 34 years presented to the emergency department with progressively increasing back pain, icterus, intermittent mild abdominal pain, and weight loss. The physical examination showed global pallor, icteric sclera, and mild abdominal tenderness.

Laboratory findings were hemoglobin level 9.7 g/dL, platelet count 82 100 /mm$^3$, and WBC 9700 /mm$^3$, creatinine 0.8 mg/dL, serum calcium 9.1, total bilirubin 3.2 mg/dL (direct 1.2 mg/dL), lactate dehydrogenase (LDH) 774 IU/L, and alkaline phosphates (ALP) 1010 IU/L; the direct and indirect Coombs tests were negative. Routine coagulation tests were normal but fibrinogen degradation products were slightly increased. Peripheral blood smear test showed fragmented erythrocytes, anisocytosis, poikilocytosis, and polychromatosis. Under the impression of TTP, we started daily plasmapheresis urgently. After several sessions of plasmapheresis he showed relative improvement in his general condition but the platelet count and hemoglobin increased very little. ADAMTS13 activity and inhibitor level was measured before beginning plasma exchange treatment and the result was normal. Advanced studies were performed to rule out malignancy. Thoracoabdominal CT scans demonstrated multiple enlarged abdominal lymph nodes, vertebral lytic lesions, and peritoneal effusions. A whole body scan using technetium 99 m showed increased uptake in the areas of the sternum, ribs, thoracolumbar spine, shoulders, and pelvis. The positron-emission tomography - computerized tomography (PET-CT) scan revealed increased 18F-FDG accumulation in abdominal lymph nodes and vertebral lytic lesions. Endoscopy of the upper gastrointestinal tract revealed a malignant-appearing mass in the gastric antrum. Biopsy was positive for signet ring cell carcinoma. The final diagnosis revealed advanced gastric cancer with osteoblastic bone metastasis.

**CASE 3**

A man aged 49 years was admitted to the hospital because of back pain and jaundice. A physical examination was essentially normal except for the presence of moderate pallor and icteric sclera. The remarkable laboratory findings were hemoglobin level 6.4 g/dL with MCV 85 fL, platelet count 10 000 /mm$^3$, and WBC 11 200 /mm$^3$. Serum creatinine 0.7 mg/dL, total bilirubin 2.3 mg/dL (direct, 0.6 mg/dL), LDH 1904 IU/L, and ALP 847 IU/L. Direct and indirect Coombs tests were negative. A peripheral blood smear contained schistocytes and spherocytes, which suggested hemolysis, and also showed leukoerythroblastosis, polychromasia, and nucleated red blood cells. With a suspicion of thrombotic thrombocytopenic purpura (TTP), we started daily plasmapheresis and exchange plasma transfusion, but the response was disappointing. Plasma ADAMTS13 metalloprotease activity, inhibitor level was normal. A CT scan of the abdomen revealed thickening of the gastric wall, abdominal lymph nodes, and lytic lesions with no liver metastasis or ascites. A bone marrow biopsy showed metastasis of a signet ring cell adenocarcinoma. An endoscopy was performed and we found infiltrative ulcerative lesions in the incisura angularis. The diagnosis was confirmed through a biopsy that revealed signet ring adenocarcinoma.

**DISCUSSION**

Microangiopathic hemolytic anemia (MAHA) is a typical feature of TTP and atypical hemolytic uremic syndrome. TTP is characterized by fever and central nervous system manifestations besides MAHA, but in atypical hemolytic uremic syndrome (aHUS), renal failure is the prominent abnormality. Collagen vascular disorders, infections, stem cell transplantation, HELLP syndrome, catastrophic antiphospholipid syndrome, surgery, drugs and malignancies are secondary causes of MAHA. Measuring ADAMTS13 activity is important while evaluating MAHA. TTP is usually associated with a severe deficiency in ADAMTS13 activity. By contrast, patients with aHUS or other secondary causes of MAHA usually display normal or at least detectable ADAMTS13 activity.

Systemic malignancy-related MAHA has been well described while systemic manifestations of cancer related to paraneoplastic phenomena are rarely seen at initial presentation. Paraneoplastic abnormalities that can occur in cancer include microangiopathic hemolytic anemia, diffuse seboroheic keratoses (sign of Leser-Trelat), acanthosis nigricans, membranous nephropathy, and hypercoagulable states (Trouseau’s syndrome). Immune thrombocytopenia, autoimmune hemolytic anemia, factor VIII antibodies, and anti-HU antibodies are some other rare immune-mediated paraneoplastic phenomena.

However, it is uncommon for microangiopathic hemolytic anemia and thrombocytopenia to be the predominant presenting clinical features in patients whose systemic malignancy is not initially apparent. Through several mechanisms, advanced malignancies may result MAHA. It may be due to thrombotic microangiopathy as a result of cancer-associated disseminated intravascular coagulation (DIC) or directly related to the carcinoma itself. Antineoplastic agents (mitomycin C, cisplatin, gemcitabine, VEGF inhibitors) may be related to MAHA by causing endothelial toxicity. Most of the pathogenesis is poorly understood. Exacerbation of the blood clotting process via stimulation of factor X due to mucus extracts derived from tumor cells is a possible way that DIC develops in adenocarcinomas. Damage to platelets and red blood cells on microvessel by direct contact with tumor cells is another possible pathology that leads to MAHA. The suspected pathogenesis of CA-MAHA, in the absence of DIC, may be because of microvascular tumor emboli or intraluminal fibrin thrombi. This phenomenon has been well described in the pulmonary microvasculature.

MAHA is difficult to treat without reversing the basic underlying disease process; therefore, treatment of MAHA should center on the underlying cause. The possibility to provide potentially life-saving therapy is the most important point of rapidly diagnosing TTP and proceeding with PE.

The measurement of serum ADAMTS13 activity and inhibitor level can help distinguish idiopathic and secondary TTP, but it is not usually immediately available. Therefore, we recommend urgent initiation of plasma exchange for all suspected cases of MAHA and thrombocytopenia without an alternative explanation. Inadequate plasma exchange response should prompt an early
search for cancer-related microangiopathic hemolytic anemia[13]. Pulmonary symptoms at presentation, recent history of weight loss, dyspnea, wasting, bone pain, and massive erythromyeloa in are more frequent in CA-MAHA; platelet counts and serum lactate dehydrogenase levels tend to be higher and creatinine is usually lower in patients with CA-MAHA when compared with idiopathic TTP, according to a previous report[13]. Cases of CA-MAHA have normal to mildly reduced ADAMTS13 levels. However, reduced levels of ADAMTS13 have been described in disseminated malignancies, severe reduction of ADAMTS13 is mostly specific for immune-mediated TTP is generally not seen in CA-MAHA.

In our two patients with MAHA, who did not initially respond to plasma exchange, advanced investigations were performed to find the underlying etiology. In the case of CA-MAHA, PE has no proven benefit and may also be harmful. Potential complications and associated delays in diagnosis of an underlying disease may worsen overall prognosis[40].

In the majority of cases of CA-MAHA, the histologic type is adenocarcinoma. Gastric, breast, prostate, and lung carcinoma are the most common associated cancers. A relatively small number of patients with lymphoma or myeloma may have MAHA. Most patients have metastatic disease at diagnosis. MAHA is the presenting feature of the cancer or is concurrently diagnosed in most patients, but some patients may develop MAHA at the time of recurrence. In cancer-associated MAHA, the clinical and laboratory features of MAHA may be subtle, and these patients do not usually have signs of cerebral or renal dysfunction. Bone marrow involvement is probably an important pathologic feature for MAHA[1]. Bone marrow may even be the sole site of systemic involvement in malignant disease and this condition is called disseminated carcinomatosis of the bone marrow. Patients tend to be younger, usually with elevated ALP and/or LDH levels. There may be accompanying extensive bone metastases with osteolytic bone destruction, but hypercalcemia has a relatively low incidence. Gastric cancer with signet ring cell carcinoma or poorly-differentiated adenocarcinoma are the most diagnosed pathologic subtypes[27].

Many patients have documented bone marrow infiltration with concomitant necrosis or fibrosis; bone marrow tumor emboli have been found in some patients at autopsy[9]. Bone marrow metastasis may also be present with autoimmune hemolytic anemia or disseminated intravascular coagulation. Among our patients, DIC was highly associated with CA-MAHA in case one. In patients with bone marrow metastases from cancer, patients with MAHA have a worse prognosis than those without MAHA[1]. Tumors that commonly metastasize to the bone marrow are carcinomas of the prostate, breast, lung, and neuroblastoma[49]. If alkaline phosphatase, lactic dehydrogenase, and CRP is elevated, as it was in our three cases, a bone marrow biopsy should be performed to rule out metastasis. Liver involvement is often but not always associated with an elevation in the serum alkaline phosphatase concentration[30]. Bone marrow involvement is more common in patients with diffuse-type gastric adenocarcinoma and occurs in young patients in particular[32]. The second patient had osteoblastic bone lesions, which are more frequently associated with higher levels of serum ALP levels than osteolytic lesions[49]. Osteoblastic bone metabolism can be visualized with skeletal scintigraphy, and tumor metabolism through positron-emission tomography[19]. Initial bone metastasis, poor performance score, peritoneal metastasis, and hypercalcemia are associated with poor prognosis, which was seen in the first case[20].

CONCLUSIONS

Patients with signet ring adenocarcinoma who present with microangiopathic hemolytic anemia and thrombocytopenia may be misdiagnosed as having thrombotic thrombocytopenic purpura (TTP); we should search for possible underlying tumors because different malignant disorders can mimic TTP and effective chemotherapy may induce hematologic remission.

CONFLICT OF INTEREST

There are no conflicts of interest.

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