Case Report

Thrombotic Microangiopathy and Leukoerythroblastosis Associated with Metastatic Infiltrating Lobular Carcinoma

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Abstract.

A 56-year-old female presenting with vaginal bleeding and exertional dyspnea for 2 weeks was admitted to hospital. The clinical course and blood analysis revealed several uncommon signs of thrombotic microangiopathy: microangiopathic hemolytic anemia (schistocytes, decreased haptoglobin, and a negative direct Coombs’ test), thrombocytopenia, leukoerythroblastic blood film, creatinine, lactate dehydrogenase, and alkaline phosphatase were also elevated. Bone marrow biopsy revealed metastatic infiltrating lobular carcinoma and focal bone marrow necrosis; and the primary lesion was subsequently identified in the right breast. We concluded that microangiopathic hemolytic anemia, thrombocytopenia, leukoerythroblastic blood film, lactate dehydrogenase, and alkaline phosphatase strongly indicated a disseminated malignancy with bone marrow involvement rather than thrombotic thrombocytopenic purpura or disseminated intravascular coagulation, which are also common in a disseminated malignancy. In breast cancer cases with hematological signs, prompt the bone marrow examination is more important than traditional systemic hormone or systemic chemotherapy or ineffective supportive treatment such as plasma exchange in order to obtain hematological response.

Keywords: infiltrating lobular carcinoma, thrombotic microangiopathy, microangiopathic hemolytic anemia, leukoerythroblastosis, breast cancer
INTRODUCTION

Thrombotic microangiopathy (TMA) is a rare but serious disease characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and microvascular thrombotic lesions and end organ damage. TMA can be present among numerous syndromes, such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremia syndrome, neoplastic disease, pregnancy-associated and malignant hypertension, and also in medication-related effects. The association of cancer with TMA (CA-TMA), though not frequent, is either chemotherapy-related or due to some other cause such as bone marrow infiltration [1]. Bone marrow infiltration (i.e., myelofibrosis, myelophthisis), as well as severe bone marrow stress (i.e., severe sepsis, necrosis), are associated with a leukoerythroblastic blood film (nucleated red blood cells and the development of left-shifted granulopoietic elements, sometimes including immature cells) in bones [2]. Although the hematological symptoms of CA-TMA may respond to anti-neoplastic agents, the overall prognosis remains poor. In this report, we describe a 56-year-old female who presented with TMA and a leukoerythroblastic blood film caused by breast cancer with bone marrow involvement.

CASE REPORT

A 56-year-old woman was admitted to our hospital presenting with vaginal bleeding and dyspnea for 2 weeks. She had an indurated mass in the right breast, but did not want further diagnosis and treatment for it. Before we our physical examination, she didn't even mention of the breast mass. The physical examination showed pallor, fever, icteric sclera, and an indurated mass of the right breast with axillary lymphadenopathy on the same side. The patient was diagnosed to have MAHA on the basis of laboratory findings, which included anemia (hemoglobin: 6.1 mg/dL, normal range: 12-14 mg/dl); with schistocytosis, polychromasia, and thrombocytopenia, as well as a leukoerythroblastic blood film (LEB; nucleated red blood cells and left shifted granulocytic elements). The differential white blood cell count (WBC) was 19700/μL (normal range: 3600-10000/μL); seg, 56%; lymphocytes, 20%; band, 13%; myelocyte, 3%; promyelocyte, 3%; meyloblast, 1%. Additional hematological findings were platelets, 9000/μL (normal range: 14000-380000/μL); decreased haptoglobin (<6.6 mg/dL, normal range: 30-200 mg/dl), a negative direct Coombs’ test, and elevated serum total bilirubin (4.56 mg/dL, normal range: 0.3-1.2 mg/dL), mildly elevated creatinine (1.3 mg/dl, normal range: 0.4-1.0 mg/dl) and proteinuria (protein in urine analysis: 100 mg/dL, normal range: negative), lactate dehydrogenase (LDH) (1802 IU/L, normal range: 98-192 IU/L), and alkaline phosphatase ALK-P (462 IU/L, normal range: 32-91 IU/L). The tumor markers levels including Ca-125 (2292.1 U/mL, normal range: <35 U/ml), carcinoembryonic antigen (CEA) (134.3 ng/mL, normal range:
<5 ng/ml), and Ca15-3 (1178.6 U/mL, normal range<31.3 U/ml) were all elevated. Prothrombin, partial thromboplastin, and fibrinogen levels were all within the normal range. Chest CT revealed an infiltrative mass in the subareolar region of the right breast and multiple reticular nodules with skin thickening and multiple enlarged lymph nodes in the right axilla. Abdominal CT revealed diffuse osteoblastic lesion, but without lung or liver metastasis, and prominent enhancement over uterine endometrium. A bone scan showed diffusely increased activity in most of the skeleton, suggesting bone metastasis. A bone marrow biopsy revealed nests or cords of infiltrating tumor cells with hyperchromatic or vesicular nuclei and clear or eosinophilic cytoplasm in desmoplastic stroma (Figure 1). Marrow necrosis was also evident. Immunostaining was positive for cytokeratin and the estrogen receptor but negative for E-cadherin. A core needle biopsy of the previously palpable right breast mass showed similar morphology (Figure 2) and immunostaining. The pathological finding of hysteroscopic myomectomy from the uterus also revealed metastatic infiltrating lobular carcinoma. An infiltrating lobular carcinoma of the right breast with bone marrow metastasis associated with TMA, bone marrow necrosis (BMN) and LEB was therefore diagnosed. We prescribed letrozole (2.5 mg OD), capecitabine (850 mg/m² bid), and oral vinorelbine (80 mg/m² every week), and blood-component treatment (Figure 3). The tumor marker levels markedly decreased and hemoglobin level and platelet count gradually improved. She was discharged 30 days after the initial presentation. We arranged chest CT scan three months later, which revealed a partial response in the breast mass as compared with the previous scan (tumor response definition according to RSCIST criteria version 1.1). We kept oral chemotherapy until new liver metastasis occurred one year later. We changed the regimen to doxorubicin liposome (50 mg/m² every month) monotherapy after the disease progress.
DISCUSSION

Cancer is only rarely associated with thrombotic microangiopathy; the most common such tumors are gastric cancer (55%), breast cancer (13%), and lung cancer (10%), and the remainder are malignancies of unknown origin [3]. The pathogenesis of CA-TMA is complex and not well understood: endothelial injury, intraluminal tumor emboli, tumor-derived factors, DIC due to cancer-derived procoagulants, and chemotherapy agents have all been proposed as contributory factors [1]. CA-TMA patients respond to anti-tumor chemotherapy and have higher survival rates than patients without chemotherapy [4], and therefore early detection of disseminated malignancy and initiation of appropriate chemotherapy are very important [5]. Interestingly, CA-TMA is commonly accompanied by bone marrow infiltration [1,6]. Abnormal angiogenesis in the marrow, aggressive growth of tumor and secondary myelofibrosis were mentioned and discussed in a previous study [6]. But in a study of 25 patients with bone marrow infiltration, only half had the typical TMA presentation [7]. Thus whether bone marrow infiltration is a cause of TMA needs to be further investigated.

Diagnosis was challenging before the final pathological report demonstrating malignancy in our patient, particularly in distinguishing her condition from TTP, DIC, or even hematological malignancy (based on the LEB). We presume that CA-TMA may exhibit some of the same characteristics as TTP. In most cases, TTP arises from deficiency of the enzyme ADAMTS13, a metalloprotease responsible for cleaving large multimers of the von Willebrand factor. Plasmapheresis has become the treatment of choice for TTP. But our patient had clinical improvement after the anti-cancer regimen without plasmapheresis. Prothrombin, partial
<table>
<thead>
<tr>
<th>No</th>
<th>Age/sex</th>
<th>Symptom</th>
<th>Hematological examination of peripheral blood</th>
<th>Pathological biopsy of bone marrow</th>
<th>Treatment after bone marrow metastasis</th>
<th>Hematological response</th>
<th>Bone marrow diagnosis to death (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54/ female</td>
<td>Dizziness, Fever, Bruising</td>
<td>LEB, MAHA, Thrombocytopenia</td>
<td>Clusters or strands of carcinoma cells infiltrating in the fibrotic stroma ER(+), PR(+), HER2(-)</td>
<td>Supportive treatment</td>
<td>Not evaluated</td>
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</tr>
<tr>
<td>2</td>
<td>53/ female</td>
<td>Bone pain</td>
<td>N</td>
<td>Metastatic adenocarcinoma in the marrow space ER(+), PR(+), HER2(-)</td>
<td>Palliative radiotherapy, AI</td>
<td>Not evaluated</td>
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</tr>
<tr>
<td>3</td>
<td>64/ female</td>
<td>Headache, dizziness</td>
<td>LEB, MAHA, Thrombocytopenia</td>
<td>Tumor cells arranged in single file or nest infiltrating in the fibrotic marrow cavity. ER(+), PR(+), HER2(+)</td>
<td>Vinorelbine, Palliative radiotherapy</td>
<td>CR</td>
<td>28.9</td>
</tr>
<tr>
<td>4</td>
<td>31/ female</td>
<td>Headache, dizziness</td>
<td>LEB</td>
<td>Metastatic carcinoma with solid tumor nests infiltrating in the desmoplastic marrow. ER(+), PR(+), HER2(-)</td>
<td>AI, Capcitabine</td>
<td>Not evaluated</td>
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<td>5</td>
<td>38/ female</td>
<td>Bone pain</td>
<td>LEB</td>
<td>A small cluster of metastatic infiltrating duct carcinoma ER(-), PR(-)</td>
<td>Capcitabine, Palliative radiotherapy</td>
<td>Not evaluated</td>
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</tr>
<tr>
<td>6</td>
<td>56/ female</td>
<td>Bleeding</td>
<td>LEB, MAHA, Thrombocytopenia</td>
<td>Infiltrating lobular carcinoma consisting of infiltrating tumor cells in single file pattern to small nests to cords architecture in the desmoplastic stroma. ER(+), PR(+), HER2(-)</td>
<td>Capcitabine, Navelbine, AI</td>
<td>CR</td>
<td>Alive</td>
</tr>
</tbody>
</table>

LEB: leukoerythroblastosis, MAHA: microangiopathic hemolytic anemia, Aromatase inhibitor (AI)
ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2
Hematological response: Complete response (CR): Hb>10 g/dl , PLT>100*10^3/L, transfusion independent, persist 4 weeks
Partial response : Hb increase>2 g/dl, PLT increase>20*10^3/L, persist 4 weeks
No response (NR)
No need to evaluation (N)
Tumor response: RECIST criteria version 1.1
thromboplastin, and fibrinogen levels were all within the normal range in this patient. So we made the diagnosis of CA-TMA rather than of TTP or DIC.

TMA and LEB were the first presenting symptoms in our patient, without a tumor source identified prior to the pathological diagnosis of lobular breast cancer. Leukoerythroblastic reactions have been attributed to “crowding out” of marrow elements by tumor cells because of their interaction with hematopoietic cytokines, and it occurs in 30-35% of non-hematological malignancies with bone marrow metastases [8]. Furthermore, the combination of leukoerythroblastosis and TMA is highly suggestive of metastatic malignancy in the bone marrow [2,9]. Other confirmatory biochemistry findings were elevated LDH and high ALK-P [5,9]. Patients with disseminated malignancy involving the bone marrow typically have a very poor prognosis and survive for only a few days or weeks because of bone marrow failure induced bleeding tendency, infection, and high tumor burden according to previous case reports. Treatment must be focused on primary tumors but a majority of patients receive supportive treatment only. Survival also can be affected by the tumor origin, but no studies have ever discussed discrepancy in outcomes among different tumors.

Chemotherapy for bone marrow metastases poses a treatment challenge because the various cytotoxic agents also have a suppressive effect on the bone marrow. Letrozole, capecitabine, and vinorelbine are now widely used to treat metastatic breast cancer. In our patient, we prescribed chemoendocrine therapy and achieved a good partial response. We initiated empiric hormone treatment (letrozole) for possible breast cancer prior to definitive tissue evidence. After the definitive diagnosis was made, we shifted to capecitabine and vinorelbine in an effort to avoid further severe bone marrow suppression. Vinorelbine has significant activity against breast carcinoma and oral vinorelbine is generally well tolerated [10]. Capecitabine for metastatic breast cancer has a favorable safety profile, lacking myelosuppressive activity [11]. Ghons et al. reported that Navcap (vinorelbine and capecitabine) followed by Docetaxel regimens were tolerated with manageable toxicity, offering consistent activity in terms of the response rate [12]. Our patient did not require transfusion of blood components after chemotherapy and there was no ongoing anemia or bleeding tendency. The relatively long survival in our patient was probably attributable to the favorable hematological responses to chemotherapy.

Six patients of breast cancer with bone marrow metastasis treated at our hospital between 2002 and 2011 were analyzed (Table 1). The hematological signs in our patients indicated microangiopathic ane-

<p>| Table 2. Hematological parameters of the patients at the time of diagnosis (case 6: present case) |</p>
<table>
<thead>
<tr>
<th>No</th>
<th>WBC(×10³/μL)</th>
<th>Hb (g/dL)</th>
<th>PLT (×10³/μL)</th>
<th>RDW (%)</th>
<th>Reticulocyte (μL)</th>
<th>ESR (mm/hr)</th>
<th>Coagulation (PT/APTT sec)</th>
<th>LDH (U/L)</th>
<th>ALK-P (U/L)</th>
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<td>193</td>
<td>15</td>
<td>16350</td>
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<td>6.1</td>
<td>9</td>
<td>20.2</td>
<td>130788</td>
<td>381</td>
<td>11.3/27.8</td>
<td>1802</td>
<td>462</td>
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<td>Normal range</td>
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<td>12-14</td>
<td>14.9-70000</td>
<td>&lt;25</td>
<td>28.6-38.6</td>
<td>192</td>
<td>91</td>
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</table>

NA: not available
mia and thrombocytopenia (3 out of 6 patients), LEB (5 out of 6 patients). Other confirmatory biochemistry findings were elevated LDH, elevated red cell distribution (RDW), and high ALK-P (Table 2). All the patients had bone metastasis. One patient received supportive treatment with short survival (2.1 months). Other patients received aggressive combination treatment such as palliative radiotherapy, hormone therapy, oral chemotherapy, systemic chemotherapy. Two patients achieved complete hematological response (Definition: Hemoglobin>10 mg/dl, platelet> 100000 μL, Transfusion independent for four weeks). The estimated median overall survival after the date of bone marrow metastasis diagnosed was 32.3 months (95% confidence level: 15.4-49.2 months), and 2 patients are still alive. Even with severe bone marrow failure due to bone marrow metastasis, aggressive combination treatment as improved marrow function is possible in 5 of our 6 patients.

CONCLUSIONS

We highlighted that aggressive treatment in breast cancer with bone marrow metastasis and received hematological response rather than traditional supportive treatment alone. Early detection of bone marrow metastasis is mandatory in breast cancer, especially for such patients who present with unknown etiology of anemia, thrombocytopenia, leukoerythroblastosis, elevated RDW, ALK-P, LDH.

REFERENCES