Malignancy Associated Microangiopathic Hemolytic Anemia and Thrombocytopenia

Abstract
Disseminated malignancy can rarely present with microangiopathic hemolytic anemia and thrombocytopenia clinically similar to thrombotic thrombocytopenic purpura (TTP), but does not respond to plasma exchange. TTP carries a grave prognosis if plasma exchange is delayed. Evaluating patients presenting with microangiopathic hemolytic anemia and thrombocytopenia is challenging for clinicians. Thrombotic thrombocytopenic purpura (TTP) should be considered in such patients and emergency plasma exchange is to be initiated. But all the clinical features seen in TTP can be caused by a disseminated malignancy. The awareness of such a rare presentation of disseminated malignancy helps clinicians to avoid unnecessary delay in appropriate treatment and the complications due to plasma exchange. We report two patients who presented with microangiopathic hemolytic anemia and thrombocytopenia due to disseminated malignancy.

Keywords: Disseminated malignancy, microangiopathic hemolytic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura

Introduction
Disseminated malignancy can rarely present with microangiopathic hemolytic anemia and thrombocytopenia clinically similar to TTP, but does not respond to plasma exchange. TTP carries a grave prognosis if plasma exchange is delayed. In patients presenting with microangiopathic hemolytic anemia and thrombocytopenia, if the malignancy is not clinically apparent plasma exchange may be started thinking as TTP. So, early recognition of cancer-associated microangiopathic hemolytic anemia with thrombocytopenia is important to avoid inappropriate plasma exchange and delay in cancer-specific chemotherapy.¹

Case Reports
Case 1
A 56-year-old man was admitted with high-grade fever, myalgia, and generalized body ache for 20 days. He was on medications for diabetes since 20 years. He had pallor, was icteric and had no other signs. His hemoglobin was 6.9 g/dl (normocytic, normochromic), total white blood cell (WBC) count 6900/μl, platelet count 0.11 × 10⁹/L, erythrocyte sedimentation rate (ESR) 65 mm in 1 h. Peripheral smear showed normocytic normochromic anemia with evidence of microangiopathic hemolysis and severe thrombocytopenia [Figure 1a]. His corrected reticulocyte count was 5%, serum lactate dehydrogenase (LDH) 1594 U/L and the direct and indirect Coombs tests were negative. Prothrombin time and partial thromboplastin time were normal. Urinalysis showed no albuminuria with 6–8 leukocytes/high power fields. Chest X-ray and electrocardiogram were normal. Biochemical parameters revealed normal blood sugars, renal function tests, and serum electrolytes. Liver function tests showed indirect hyperbilirubinemia with normal enzymes. Ultrasonography of abdomen showed mild prostatomegaly, minimal right pleural effusion, and mild ascites. He was started on plasma exchange therapy since according to the revised diagnostic criteria thrombotic thrombocytopenic purpura (TTP) must be considered in the presence of thrombocytopenia and microangiopathic hemolytic anemia alone. Etiological work up including dengue, leptospira, Rickettsia, Epstein Barr virus, HIV, hepatitis B and C serologies, and antinuclear antibody were negative. Test for malarial parasite was negative and blood cultures did not reveal any growth. Since the platelet count showed no improvement...
after few cycles of plasma exchange a bone marrow study was done which showed metastasis from poorly differentiated adenocarcinoma [Figure 1b]. The workup for primary did not reveal anything, and despite all efforts, he succumbed to his illness few days later.

**Case 2**

A 58-year-old housewife was admitted with altered sensorium and yellowish discoloration of eyes for 10 days. She had infiltrative ductal carcinoma of the right breast treated with modified radical mastectomy followed by 10 cycles of chemotherapy with docetaxel and radiotherapy, following which she was on daily tamoxifen. She was known to have diabetes for 4 years and hypothyroidism for 1 year on thyroxine supplementation. She was drowsy, had pallor, jaundice, and had no other signs. Her hemoglobin was 7.9 g/dl (normocytic, normochromic), total WBC count 14,000/μL, platelet count 0.6 × 10^9/L, ESR 44 mm in 1 h. Peripheral smear showed evidence of microangiopathic hemolysis and thrombocytopenia [Figure 2a]. Her corrected reticulocyte count was 3%, serum LDH 794 U/L and the direct and indirect Coombs tests were negative. Prothrombin time and partial thromboplastin time were normal. Urinalysis showed no albuminuria with 4–6 leukocytes/high power fields. Urine culture grew *E. coli*. Chest X-ray and electrocardiogram was normal. Biochemical parameters revealed normal blood sugars, thyroid, and renal function tests with mild hyponatremia. Liver function tests showed indirect hyperbilirubinemia with normal enzymes. Computed tomography of the head was normal. A bone marrow study was done which showed infiltration with malignant cells [Figure 2b]. Tamoxifen was discontinued and she was given piperacillin and tazobactam for urinary tract infection. She became conscious few days later but was not willing for further management and got discharged.

Figure 2: (a) Peripheral smear showing microangiopathic hemolysis in case 2 (Leishman stain, ×100). (b) Bone marrow showing sheets of large tumor cells in case 1 (H and E, ×40)

Microangiopathic hemolytic anemia can be associated with a variety of diseases including thrombotic TTP, hemolytic uremic syndrome, disseminated intravascular coagulation (DIC), preeclampsia, eclampsia, malignant hypertension, drugs and autoimmune disorders. Clinical, hematologic, biochemical parameters helps to differentiate between them. TTP carries very high mortality rate if inappropriately treated.[3] Patients presenting with microangiopathic hemolytic anemia and thrombocytopenia are likely to suffer from TTP; hence, they are treated with plasma exchange immediately. Early plasma exchange allows more than 80% of patients with idiopathic TTP to achieve remission. Rarely, microangiopathic hemolytic anemia and thrombocytopenia can be the predominant presenting clinical features in patients whose systemic malignancy is not initially apparent causing diagnostic dilemmas. Hence, clinicians must be aware that patients with clinically diagnosed TTP may have an occult systemic malignant disorder.[3]

Patients presenting with microangiopathic hemolytic anemia and thrombocytopenia due to malignancy often have widely disseminated cancer. Even though treatment success may be limited, prompt diagnosis is important for appropriate management. The risks of plasma exchange can be avoided if the malignancy is recognized promptly.

Differentiating acute disseminated cancer from acute TTP using baseline clinical and laboratory characteristics is challenging.[4] Certain features may suggest the presence of an occult systemic malignancy including; presenting symptoms of dyspnea, cough, and pain other than abdominal pain.[1] Extremely elevated serum LDH may suggest tumor lysis, even if increased levels are seen in TTP patients. The presence of many nucleated red cells and immature granulocytes in the marrow may also suggest metastatic malignancy. Many patients with systemic malignancy causing microangiopathic hemolytic anemia and thrombocytopenia may have DIC, but the absence of evidence for DIC does not exclude the possibility of malignancy. Case 1 did not show any of aforementioned features, and a bone marrow study clinched the diagnosis. Patients who have a history of malignancy favor the possibility of disseminated malignancy.[1] One of our patients (case 2) had a history of malignancy which helped us in the diagnosis and avoiding the risks of plasma exchange. Failure to respond to plasma exchange in patients with a diagnosis of TTP also favors disseminated
malignancy. Case 1 described above did not show any improvement after few cycles of plasma exchange which made us think of an occult malignancy.

Even though the optimal therapy for malignancy causing microangiopathic hemolytic anemia and thrombocytopenia is unknown, immediate initiation of an effective antineoplastic treatment is of utmost importance. Plasma exchange therapy is the treatment of first choice for TTP, but its benefit in disseminated malignancy remains highly controversial.\[^{4-6}\] We hope the cases described here may help readers to be aware of disseminated malignancy when evaluating patients presenting with microangiopathic hemolytic anemia and thrombocytopenia.

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**Conflicts of interest**

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**References**