Case Report

A REPORT OF THREE CASES WITH THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) SECONDARY TO AN OCCULT GASTRIC ADENOCARCINOMA

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a disseminated form of thrombotic microangiopathy with clinical findings consisting of fever, microangiopathic hemolytic anemia (MAHA), thrombocytopenia, fluctuating neurologic impairment and renal dysfunction. However, Microangiopathic hemolytic anemia has been described in association with disseminated malignancies, most commonly adenocarcinoma of the breast or stomach. We present three patients with microangiopathic anemia in whom metastatic cancer was finally diagnosed; however, they died of refractory hemolytic anemia in the end.

The occurrence of microangiopathic hemolytic anemia and thrombocytopenia in patients with disseminated malignant in gastric adenocarsinoma is well documented. Therefore, the diagnosis of tumor-associated TTP should be considered in unresponsive TTP patient treated with plasmapheresis.

KEY WORDS: Thrombotic thrombocytopenic purpura, Gastric carcinoma, Microangiopathic hemolytic anemia.

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a classic disease of hematology. Because of the lack of a gold standard-defining test, the diagnosis of TTP rests on the signs and symptoms. The presence of the clinical dyad, acute and severe thrombocytopenia and MAHA, is widely accepted as being sufficient to establish an initial diagnosis of TTP to introduce plasma exchange as an effective treatment modality, given the high mortality rate without urgent treatment.[1] Thrombotic thrombocytopenic purpura (TTP) is a disseminated form of thrombotic microangiopathy. The classic pentad of clinical findings consists of fever, microangiopathic hemolytic anemia (MAHA), thrombocytopenia, fluctuating neurologic

impairment and renal dysfunction.[1]

Recently a syndrome resembling thrombotic thrombocytopenic purpura, manifested by microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency, has been reported in patients with adenocarcinomas, particularly of the stomach, and in patients with epidermoid carcinoma and colon carcinoma; however, it is an unusual form.[2]

Only a few cases of TTP secondary to metastatic adenocarcinoma are known in the literature.[2-7] The mechanism of secondary TTP is different from the idiopathic mechanism.[3]

About 50% of malignancy-associated TTP pertain to gastric carcinoma. It usually occurs at the terminal stage of cancer and is extremely rare as an initial presentation in patients with cancer.[1] Usually TTP associated with cancer might have responded poorly to due to delayed diagnosis of TTP and advanced cancer, both Plasma Exchange (PE) and chemotherapy seem to be effective for treatment in patients.[4]

CASE REPORT

Report-1: A 19 year-old man had a low back pain with radiation to lower limbs, CT scan and MRI revealed tumor at the surface of one lumbar vertebra. He immediately underwent surgery and several biopsies were taken which showed signet ring cells and the patient after medical therapy was discharged. However, after one month, he came back to hospital with a history of hemorrhage. Sinus and nose CT scan revealed no abnormality but laboratory findings showed a platelet count of 29000 mm^3,WBC=11100/ mm^3, Hb=11.8g/dl, PLT=mm3, HCT=33.7, MCV=98.6 fl, BS=108 mg/dl, BUN=31 mg/dl, Cr=0.8 mg/dl, ESR=60 1h ,Pt =11 s, PTT =32 s, Bili Tot =2.4mg/dl, Bili Dir = 0.3mg/dl, LDH = 774 IU/l.

Bp: 120/80 mg, PR =80, T=37, RR=17, direct and indirect Coomb's tests were negative. Ultrasound examination of the liver reported multiple masses, suggesting metastatic malignancy according to the history of vertebra tumor. Endoscopy was done which showed a gastric mass, then the diagnosis was confirmed to be signet ring adenocarsinoma by biopsy and as chemotherapy started for the patient, PLT count began to rise to 101000 within 14 days. At discharge, the patient was in good general condition. However, at the second round of chemotherapy, PLT decreased to 32000 again. Laboratory findings were: LDH=1265 IU/l, PLT=32000 mm^3, WBC=12800/mm^3, Hb =6.9g/dl, HCT=21.6.

Findings such as direct bilirubin rising, due to liver metastatic(previous Direct billirobine was 0.1mg/dl), peripheral blood smear (PBS) study showing a retic count of 17% and many fragmented cells were compatible with the diagnosis of microangiopathic hemolytic anemia. Plasmapheresis was added to treatment six months later, although the first responses were good, he died of refractory TTP.

Report-2: A 17-year-old girl with complaints of weakness, fever, and peripheral echimosis was referred to our clinic. Physical examination showed echimosis, pallor, petechia in legs, no family history was found, nor contact with drugs. She also had dysphasia. Primary laboratory findings were as follows:

WBC=12500mm^3, Hb=8.3 g/dl, PLT=15000 mm^3, BUN=52 mg/dl, Cr=1.7 mg/dl, Bili Tot=5.1mg/dl, Bili Dir=1.8 mg/dl, LDH =2150 IU/l, Retic =11%, Combs (D,I)=negative PT=12s, PTT=34s with no specific ultrasound findings compatible with the diagnosis of hemolysis. A peripheral blood smear was performed that showed schistocytes, few nucleated RBC and myeloid with no evidence of blast. Under the impression of TTP, we started daily plasmapheresis (2lit) urgently.

After several sessions of plasmapheresis she showed relative improvement in her general condition and the platelet count and hemoglobin did not increase much. Following the history of vague abdominal pain, epigastric tenderness and weigh loss, endoscopy was performed after TTP was subsided which showed infiltrative ulcerative lesions in the fundus to grater curvature and the diagnosis was confirmed by biopsy which revealed signet ring adenocarsinoma. Follow-up advanced evaluations showed metastatic foci in liver; there-

fore, chemotherapy was started but the response was disappointing and four months after the diagnosis, she died due to the extensive disease and severity of microangiopathic hemolytic anemia.

Report-3: A 19-year-old girl with no previous significant medical problems was referred with complaints of low back pain, pain in hip and knee and one month history of abdominal discomfort. She also complained of general weakness and sweating. Laboratory findings were hemoglobin level =10.2 g/dl, platelet count = 11000/mm^3 and WBC = 9000/mm^3, Creatinine = 3 mg/dl, total bilirubin =0.4 mg/dl (direct= 0 .1 mg/dl), lactate dehydrogenize (LDH) =3009 IU/ L (NL= 150–550) and alkaline phosphates (ALP) = 1237 IU/l, PTT = 48s, PT =12s, direct and indirect Coombs test were negative.

Lumbar and joint X-ray reported no specific findings. According to a peripheral blood smear which showed numerous schistocytes, nucleated RBC and normal coagulation test, diagnosis of TTP was confirmed and plasmapheresis started but the response was disappointing. Advanced studies were performed to rule out malignancy. Liver sonography reported several hypoecho masses suggesting liver metastases.

CT also showed hepatic hypodens lesions, hepatomegaly and small para-aourtic lymphadenopathies in the mid region of the abdomen. Bone marrow biopsy was performed which involved exactly, endoscopy was done which revealed malignancy in fondus, and biopsy showed signet ring adenocarsinoma. Other evaluations were aborted since the patient died due to severe hematemesis.

DISCUSSION

The initial diagnosis of thrombocytopenic purpura (TTP) may be uncertain because of the other disorders that can cause microangiopathic hemolytic anemia and thrombocytopenia and the principle diagnostic criteria may not be initially apparent.[5] Although in most patients, the disseminated malignancy that causes microangiopathic hemolytic anemia and thrombocytopenia is easily recognized, in some patients the malignancy is not clinically apparent, and therefore TTP is diagnosed and plasma exchange treatment begins. Failure in diagnosing disseminated malignancy exposes the patient to the major risks of plasma exchange[6] and causes delay of appropriate chemotherapy. However, failure to urgently initiate plasma exchange treatment in a patient with TTP may result in death.[5]

In our patients with TTP and anemia who did not initially respond to plasma exchange, advanced investigations were performed to find the underlying cause (malignancy), similar to a study by Pirrota et al.[3]

Clues that may suggest the presence of an occult systemic malignancy include presenting symptoms of dyspnea, cough, and pain other than abdominal pain. These symptoms were not common in our patients with idiopathic TTP but are common in patients with malignancies. Although increased serum LDH is characteristic of patients with TTP, extreme elevations are not typical and may suggest tumor lysis.[5] Since the increase of alkaline phosphates could be a sign of bone disease, whole body scintigraphy (99mTc) and bone marrow study were performed to rule out TTP secondary to cancer,[3] our third patient had increased alkaline phosphatase levels which was in accordance with Pirrotta et al.[3]

As seen in the metastasis to other organs, metastasis within the bone marrow may also be associated with increased angiogenesis for the growth of cancer. It is speculated that, in addition to abnormal angiogenesis in the marrow, aggressive growth of tumors and secondary myelofibrosis may injure endothelial cell of the vessels in the marrow by direct encroachment. These changes, it is speculated, could cause the release of uLvWF multimers, and with a possible decrease in the availability of the uLvWF-cleaving protease through undetermined mechanism ,such as decreased production or immune reaction, may contribute to the aggregation of platelets in advanced cancer.[4]

Since TTP has been seen mostly in adenocarsinoma, this pathology could be another contributing factor, perhaps related to the production of mucin, which may exert a direct detrimental effect on the pathologic endothelial cell to change endothelial function.[4] The pathogenesis of TTP associated with cancer is not clear; however, it seems to be caused by endothelial injury and resultant failure of the microcirculation.[1]

Recent studies have reported a deficiency of vWF cleaving protease, ADAMTS13, due to autoimmune inhibitors or genetic mutations, and the detection of unusually large (uL) vWF multimers in some patients with TTP.[6-8] It is known that the protease cleaves uL vWF multimers to smaller ones, and the uL vWF multimers, if not cleaved, promotes the activation and aggregation of platelets. If the endothelium is injured, uL vWF multimers might be released into the circulation, which, if not cleaved, promote vWF-platelet binding and microvascular thrombosis, resulting ultimately in TTP.[4]

Plasma exchange transfusion induces hamatologic remission by replenishing the missingADAMTS13; However, the contribution of ADAMTS13 deficiency in TTP associated with cancer is controversial.[1]

TTP can be associated with cancer, but only in a very small fraction of cancer patients. Nonetheless, it is important to make an early diagnosis, since hematologic abnormalities in cancer may be the presentation of the combination of bone marrow metastasis and TTP and unnecessary diagnostic procedures, including extensive laboratory and imaging studies to determine the cause of thrombocytopenia and mental changes, may be spared if TTP can be timely recognized.[4]

In conclusion, patients with TTP who do not initially respond to plasma exchange must be investigated suspecting an underlying disorder. Moreover, if alkaline phosphatase is increased, such as in our case, bone marrow biopsy could be performed to rule out bone marrow metastasis. Finally, the assay of ADAMTS13 activity can help to discriminate between idiopathic and secondary TTP[3] and patients should be monitored carefully for hemolytic anemia and renal impairment, and signs of pancytopenia should not be automatically ascribed to myelosuppressive treatment. Plasma samples should be obtained for determination of immune complex concentrations in patients who develop this syndrome, and empiric treatment with plasmapheresis and azathioprine should be started.[2]

REFERENCES

1. Lee JL, Lee JH, Kim MK, Cho HS, Bae YK, Cho KH, et al. A Case of Bone Marrow Necrosis with ThromboticThrombocytopenic Purpura as a Manifestation of Occult Colon Cancer. Jpn J Clin Oncol 2004;34(8)476-480.
2. Zimmerman SE, Smtth FP, Phillips TM, Coffey RJ, Schein PS. Gastric carcinoma and thrombotic thrombocytopenic purpura: Association with plasma immune complexconcentrations. BMJ (Clin Res Ed) 1982;284(6327):1432-4.
3. Pirrotta MT, Bucalossi A, Forconi F, Bocchia M, Mazzotta S, Sammassimo S, et al. Thrombotic thrombocytopenic purpura secondary to an occult adenocarcinoma. Oncologist 2005;10(4):299-300.
4. Chang JC, Naqvi T, Thrombotic Thrombocytopenic Purpura Associated wiith Bone Marrow Metastasis and Secondary Myelofibrosis in Cancer. Oncologist 2003;8(4):375-80.
5. Francis KK, Kalyanam N, Terrell DR, Vesely SK, George JN. Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: A report of 10 patients and a systematic review of published cases. Oncologist 2007;12(1):11-9.
6. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 1998;339(22):1585-94.
7. Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome. N Engl J Med 1998;339(22):1578-84.
8. Moake JL, McPherson PD. Abnormalities of von Willebrand factor multimers in thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome Am J Med 1989;87(3N):9N-15N.