A Case of Bone Marrow Necrosis with Thrombotic Thrombocytopenic Purpura as a Manifestation of Occult Colon Cancer

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Thrombotic thrombocytopenic purpura (TTP) is a disseminated form of thrombotic microangiopathy. Although most cases are held to be idiopathic, its association with malignancy is well recognized and it usually occurs at the terminal stage of cancer. Bone marrow necrosis (BMN) is another rare disorder defined pathologically as the necrosis of myeloid tissue and medullary stroma with preservation of bone. While hematologic malignancy is the most common underlying disease associated with BMN, it can also be caused by solid tumors. Neither TTP nor BMN associated with colon cancer has been reported. We describe here a patient with the rare association of TTP and BMN displayed as the first manifestation of an advanced colon cancer. The anemia and thrombocytopenia responded not to plasma exchange but to the combination chemotherapy. This case indicates that metastatic cancer should be included in the differential diagnosis of TTP and BMN, and that the chemotherapy may improve the detrimental clinical course.

Key words: thrombotic thrombocytopenic purpura – bone marrow necrosis – colon cancer – microangiopathic hemolytic anemia

INTRODUCTION

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). Although most cases are held to be idiopathic, its association with malignancy, which is actually infrequent, is well recognized (2). About 50% of malignancy-associated TTP pertain to gastric carcinoma (3). In addition, it usually occurs at the terminal stage of cancer and is extremely rare as an initial presentation in patients with cancer. Bone marrow necrosis (BMN), first reported by Wade and Stevenson in 1941 (4), is another rare disorder defined pathologically as the necrosis of myeloid tissue and medullary stroma in large areas of the hematopoietic bone marrow with preservation of bone (5). Common symptoms and signs include fever, pancytopenia, leukoerythroblastic features and back pain. While hematologic malignancy is the most common underlying disease associated with BMN, it can also be caused by solid tumors. As for non-hematologic malignancies, excluding metastatic carcinoma of unknown primary site, those of the stomach are most often reported (5). BMN has never been reported to be associated with colon cancer.

We report here a patient with the rare association of TTP and BMN displayed as the first manifestation of an advanced colon cancer. As far as we know, this is the first case of TTP and BMN associated with clinically occult metastatic colon cancer.

CASE REPORT

A 67-year-old Korean man with no previous significant medical problems nor contact with drugs presented with a 1-month-long history of low back pain, intermittent mild abdominal pain, night fever, weight loss and intermittent confusional mentality. Physical examination showed global pallor, icteric sclera, increased bowel sound and mild abdominal tenderness. Remarkable laboratory findings were hemoglobin...
level 9.7 g/dl (NL, 13–15) with MCV 89 fl, reticulocyte count 5.2%, platelet count 23 × 10^9/l and WBC 7.7 × 10^9/l. Serum haptoglobin was 0.9 mg/dl (NL, 50–200), creatinine 0.8 mg/dl, total bilirubin 9.4 mg/dl (direct, 3.5 mg/dl), lactate dehydrogenase (LDH) 1239 IU/l (NL, 150–550) and alkaline phosphatase (ALP) 1541 IU/l (NL, 30–90). Routine coagulation tests were normal but fibrinogen degradation products were slightly increased. Direct and indirect Coombs' tests were negative. A peripheral blood smear study demonstrated 5% schistocytes and 3% nucleated RBC (Fig. 1). Chest X-ray and abdominal CT scan revealed no abnormality. Under the impression of TTP, we started daily plasmapheresis and exchange plasma transfusion, but the response was disappointing by the end of 2 weeks, and the LDH and nucleated RBC count were rising during that period. The pattern of von Willebrand factor (vWF) multimer in a platelet-poor plasma sample before the initiation of plasma exchange was normal. Bilateral bone marrow aspiration revealed BMN without viable hematopoietic component (Fig. 2A). In the biopsy specimen, the marrow spaces were totally replaced by coagulative necrotic cells with only preservation of basic outlines of the cells (Fig. 2B). Reticulin stain showed grade 1 fibrosis (Fig. 2C) (6). There were no viable cells thought to be of extramedullary origin. The serum CEA level was 105 ng/ml (0–10 ng/ml), but testing showed no occult blood in the stool. Gastrofiberscopy revealed a chronic gastritis. Colonofiberscopy found a colon cancer at the hepatic flexure (Fig. 3A), poorly differentiated adenocarcinoma with signet ring cell component in histopathology (Fig. 3B). Whole-body bone scan revealed increased uptake in multiple ribs, pelvic bone and spine. Whole-spine MRI revealed an increase in water content due to watery changes of the bone marrow and replacement of the fat by serous materials (Fig. 4).

After that we stopped plasma exchange and the patient received combination chemotherapy with oxaliplatin and 5-FU/LV (FOLFOX4) (7). After two cycles of chemotherapy, follow-up bone marrow examination was carried...
out and revealed normocellular marrow with focal BMN (Fig. 5A) and scar-like fibrosis (Fig. 5B). Reticulin fibrosis was markedly increased up to grade 4 (Fig. 5C), and metastatic cancer cells were not identified. At that time, the patient’s hemoglobin was 10.2 g/dl, WBC 3.6 × 10⁹/l and platelets 98 × 10⁹/l. LDH and ALP decreased to 785 IU/l and 843 IU/l, respectively. Figure 6 depicts hematologic and serum chemistry responses to the treatment during the hospital course. At the time of this report, 4.5 months from the diagnosis, his performance status is generally good and hematologic findings are stable.

DISCUSSION

BMN is a rare disorder defined pathologically as necrosis of myeloid tissue and medullary stroma in large areas of the bone marrow with preservation of bone (4). Clinically, it is characterized by bone pain and fever. Anemia and thrombocytopenia accompanied by a leukoerythroblastic feature in peripheral blood smear are the most frequent hematologic abnormalities. An elevated level of LDH and ALP can be found in half of the cases. An underlying malignancy is found in the majority of the cases of BMN and...
hematologic malignancies are most frequently associated with BMN. Most of the reported cases of BMN related to non-hematologic malignancies had gastric cancer, followed by metastatic carcinoma of unknown primary site and ovary (5). We found no previous report that emphasized BMN as an initial presentation of metastatic colon cancer.

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).

The pathogenesis of BMN and TTP associated with cancer is not clear. Both diseases seem to be caused by endothelial injury and resultant failure of the microcirculation, which is widespread in TTP but is limited to medullary tissue in BMN. Aggregates of cancer cells, which may cause mechanical obstruction, could be found in BMN in metastatic carcinoma, and tumor necrosis factor without bone marrow metastasis could be responsible for the prothrombotic effect involved in BMN (5). Recent studies have reported a deficiency of the vWF cleaving protease, ADAMTS13, due to autoimmune inhibitors or genetic mutations, and the detection of unusually large (uL) vWF multimer in some patients with TTP (8–10). It is known that the protease cleaves uL vWF multimers to smaller ones, and the uL vWF multimers, if not cleaved, promote 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 (11). Plasma exchange transfusion induces hematologic remission by replenishing the missing ADAMTS13 (10). However the contribution of ADAMTS13 deficiency in TTP associated with cancer is controversial. Literature review indicates that only three of eight cases of TTP related to disseminated cancer have a suboptimal level of ADAMTS13 (12), which may explain the poor response to the plasma exchange in our patient, who had a normal vWF multimer pattern, which might mean a biologically optimal level of ADAMTS13.

The prognosis of BMN and TTP generally depends on the underlying disease. Most patients with BMN related to a solid tumor had widespread metastasis with or without bone marrow involvement, which has a grave prognosis. The median survival has been reported to be 5 weeks. The relatively longer survival of >4 months in our patient was probably attributable to the hematologic response to the chemotherapy.

In conclusion, when the physician is confronted by a patient with clinical findings of TTP, especially when associated with the presence of a leukoerythroblastosis which often occurs in bone marrow metastasis or the rare BMN, the physician must remain vigilant for an additional diagnosis such as occult malignancy, including colon cancer. Although the exact pathogenesis of cancer-associated TTP and BMN and its

Figure 5. After two cycles of chemotherapy. (A) Bone marrow aspiration smear reveals normocellular marrow with normal differentiation of all three hematopoietic lineages (×100). (B) Bone marrow trephine biopsy demonstrated the hematopoietic repair following bone marrow necrosis showing normocellular marrow and focal area of fibrous scarring (right lower rectangle) (H&E stain, ×100). (C) Reticulin stain shows diffuse coarse fiber network (Gomori’s reticulin stain, ×100).
management are still controversial, treatment of underlying disease might improve the devastating clinical course.

References