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Case Report

A Case of Microangiopathic Hemolytic Anemia Associated with Breast Cancer: Improvement with Chemoendocrine Therapy

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Microangiopathic hemolytic anemia (MAHA) is a term which describes the association of hemolytic anemia with red cell fragmentation caused by microangiopathy mechanically. This paper reports a 45-year-old woman with bone metastases from breast cancer. She developed MAHA and disseminated intravascular coagulation (DIC). Although the prognosis of MAHA associated with malignant tumor has been very poor, she achieved remission of the syndrome after chemoendocrine therapy.

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Key words: Microangiopathic hemolytic anemia (MAHA), Disseminated intravascular coagulation (DIC), Medroxyprogesterone acetate (MPA), Breast cancer

Microangiopathic hemolytic anemia (MAHA) is a term which describes the association of hemolytic anemia with red cell fragmentation on the peripheral blood smears caused mechanically by microangiopathy. Abnormally shaped red cells such as schistocytes, burr cells and helmet cells may be produced by being forced through abnormally small blood vessels, but the mechanism is not fully understood. MAHA is observed in various diseases such as thrombotic thrombocytopenic purpura (TTP), congenital vascular abnormalities, hemolytic uremic syndrome, consumption coagulopathy and neoplastic diseases[1-3]. In particular, the prognosis of cancer-related MAHA is quite poor and its clinical course is generally catastrophic[3].

In this paper, we report a case of MAHA associated with bone metastases from mucinous carcinoma of the breast in which remission of the MAHA was achieved after chemoendocrine therapy.

Case Report

A 45-year-old woman was admitted because of chest pain and acute thrombocytopenia 4 years after adenectomy with axillary dissection for breast carcinoma which was mucinous carcinoma, t2, n1α, m0, stage II[4]. Both estrogen and progesterone receptors were positive. She had been given tamoxifen and tegafur・uracil for 3 years after operation without obvious sign of recurrence. Except for breast cancer, she had no history of systemic disease including hypertension, cardiopulmonary diseases, diabetes, hematological disorders or collagen disease. On this occasion, she had ecchymoses particularly over the extremities and no splenomegaly on admission. Her temperature was 36.4℃. The cardiovascular sound was normal. There were no neurologic or psychological abnormalities.

On admission, the urine was normal. The hemoglobin concentration was 9.9 g/dl, hematocrit was 28.8% with a normal corpuscular value, leukocytes were 3900 / mm^3 and platelets were 19 000/mm^3, indicating mild anemia and severe

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Abbreviations:
MAHA, Microangiopathic hemolytic anemia, TTP, Thrombotic thrombocytopenic purpura; DIC, Disseminated intravascular coagulation, FDP, Fibrinogen degradation products, CEA, Carcinoembryonic antigen, MPA, Medroxyprogesterone acetate

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thrombocytopenia. Anemia progressed markedly after admission and red cell fragmentation was reported on the blood film. The reticulocyte level was elevated to 30%. The LDH was 1113 U/ml, total bilirubin was 1.5 mg/dl, indirect bilirubin was 1.1 mg/dl, and GOT was 100 U/l which was compatible with hemolytic anemia. The fibrinogen was 116 mg/dl, serum fibrinogen degradation products (FDP) was 23.7 μg/ml, D-dimer was 3412 ng/ml and thrombin-antithrombin III (TAT) was 41.0 ng/ml. The prothrombin and partial thromboplastin were normal. The urea nitrogen and creatinine were 19.7 mg/dl and 0.9 mg/dl, respectively and they remained within the normal range during her hospitalized period. The CEA and CA15-3 were 89.4 ng/ml and 3500 U/l, respectively. Bone marrow centesis of the sternum and ilium performed due to acute thrombocytopenia on the first day of admission resulted in a dry tap and revealed metastatic breast cancer cells. The bone scintigram also indicated multiple bone metastases 5 days after admission (Fig 1, left).

We strongly suspected MAHA with disseminated intravascular coagulation (DIC) associated with bone metastasis of breast carcinoma. Medroxyprogesterone acetate (MPA) (1200 mg/day) was given orally from 3 days before admission. Goserelin was administered subcutaneously 8 and 36 days after admission. She underwent one course of chemotherapy with cyclophosphamide, epirubicin hydrochloride and 5-fluorouracil 12 days after admission. She was also treated with packed red blood cells and packed platelets. The tumor marker levels decreased markedly, and the platelet count and chest pain gradually improved (Fig 2). She was discharged 40 days after admission. Bone scintigram performed 4 months after treatment revealed decreased uptake in the lumbar spine (Fig 1, right).

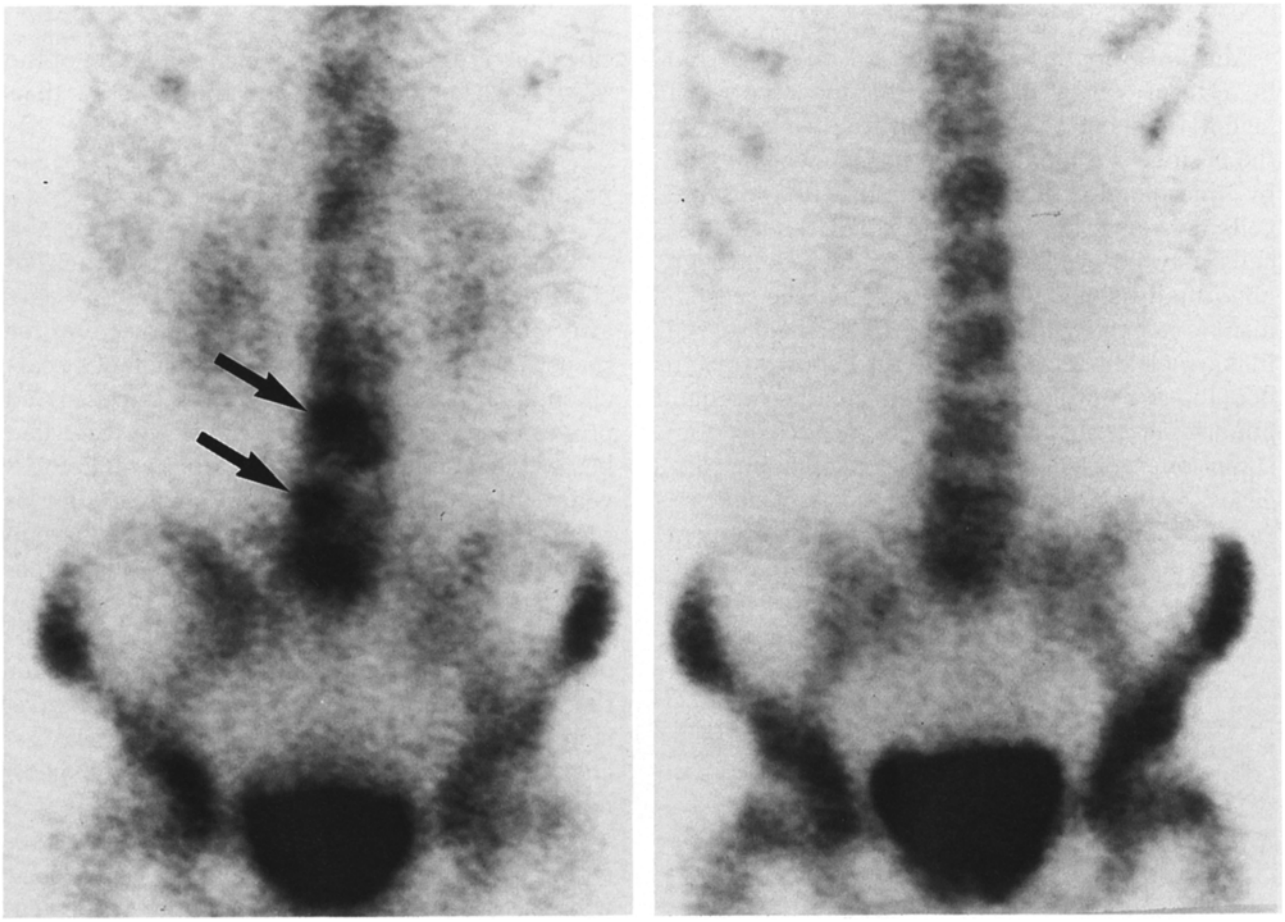

Fig 1. Bone scintigram 5 days after admission revealed multiple bone metastases (left), and 4 months later, bone scintigram showed decreased uptake in the lumbar spine (arrow) (right).

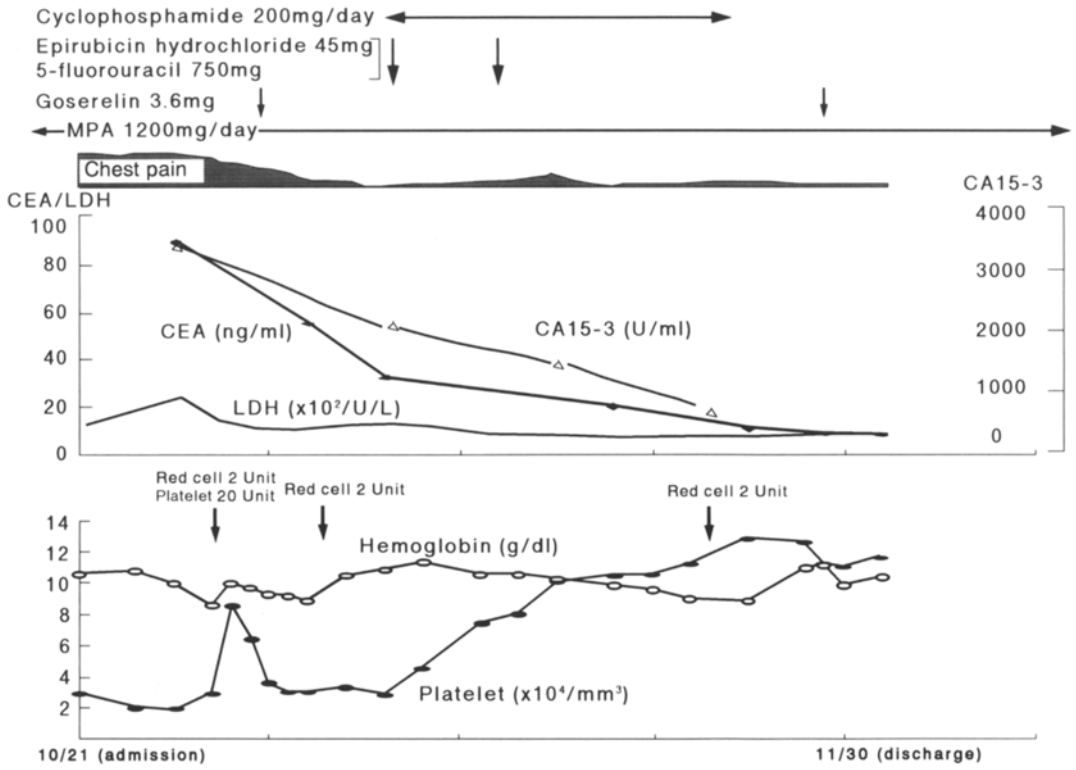

Fig 2. Clinical course of the present case.

Discussion

MAHA was first defined as a hemolytic anemia associated with fragmented red cells produced by shearing of red cells forced through abnormally small blood vessels[1]. The incidence of cancer-related MAHA is quite rare. Antman *et al* reviewed 55 patients with cancer-associated MAHA among which breast cancer was found in 13% (7/55). The course of this case is compatible with that of severe microangiopathic hemolytic anemia associated with metastatic adenocarcinoma of the breast, without fever and diverse neurologic signs, which are characteristic for TTP. She also lacked renal failure, which is compatible with hemolytic-uremic syndrome, and systemic disorders which could induce MAHA.

The pathogenesis of cancer-related MAHA is unclear. Brain *et al*[6] suggested that MAHA develops secondarily to DIC caused by thromboplastins derived from mucin-forming tumor cells. However, this mechanism does not completely explain the pathogenesis of cancer-related MAHA because MAHA without DIC has been reported[3,5]. An alternative explanation for cancer-related MAHA is red cell shearing secondary to direct contact with intraluminal embolic tumor cells[6]. However, intraluminal injury produced by tumor emboli causes fibrin mesh formation and red cell fragmentation is thought to be made when red cells go through the mesh[7,8]. Even MAHA without DIC, therefore, also is related to coagulopathy.

The prognosis of cancer patients who develop MAHA has been extremely poor, with an average survival of 21 days despite aggressive supportive therapy, while the prognosis of non-cancer patients with MAHA is not bad[3]. There is no standard therapy for cancer-related MAHA but the aim of treatment should be the eradication of the underlying tumor[9]. Therefore, the outcome would be highly dependent on the underlying cancer and the response to therapy for the cancer[10]. Some cases of breast cancer-related MAHA that achieved remission after chemotherapy have been reported[11-13], possibly indicating better response of breast cancer to therapy than other adenocarcinomas. The present patient showed progressive anemia and DIC, but chemoendocrine therapy achieved marked effects against bone metastases of breast cancer, with recovery from MAHA as a result. In particular,

MPA, which was given first, was considered to be a very effective drug because tumor markers and chest pain began decreasing and platelet count begin increasing before chemotherapy was started

Several studies have been performed to clarify the influence of MPA on blood coagulation systems, but the results have been controversial. Furthermore, the relation between DIC and MPA has not been demonstrated and the question of whether MPA could improve DIC directly or not is unclear. Yamamoto[14] *et al* studied the effects of high-dose MPA in the treatment of breast cancer. Their results stated that, concerning the coagulation system, levels of factor VII and fibrinogen decreased, while factor II and factor IX increased, with shortened activated partial thromboplastin time, while in the fibrinolytic system, plasminogen and α_2-plasmin inhibitor-plasmin complex increased and FDP remained low. Furthermore, in the anticoagulation system antithrombin III increased. These results indicate that MPA might simultaneously induce hypercoagulable state and promote anticoagulation. A clinical trial of The Japan Advanced Breast Cancer Study Group II and the Japan Clinical Oncology Group[15] showed an increase in protein C and antithrombin III caused by MPA, indicating promotion of anticoagulation. These data suggest that MPA induces not only a hypercoagulable state but also hyperactivity of the anticoagulation system. The significance of these effects of MPA on anticoagulation is unclear and these data could also be interpreted as reflecting compensatory hyperactivity of the anticoagulation system for hypercoagulable state, or a direct promoting effect on protein synthesis[14,15]. In the present patient, MAHA and DIC dramatically improved without treatment of DIC itself. Although the main factor that improved DIC might be a marked decrease of tumor cells as mentioned above, MPA's effect of promoting anticoagulation might have partially improved DIC.

References

1) Brain MC, Dacie JV, Hourihane DO'B: Microangiopathic haemolytic anaemia; The possible role of vascular lesions in pathogenesis. *Br J Haematol* 8:358-374, 1962.
2) Sathawarawong W: Thrombotic thrombocytopenic purpura (TTP); 4 cases reports and review of the literature. *J Med Assoc Thai* 78:322-331, 1995.
3) Antman KH, Skarin AT, Mayer RJ, *et al*: Microangiopathic hemolytic anemia and cancer; A review. *Medicine* 58:377-384, 1979.
4) Japan Mammary Cancer Society: General Rules for Clinical and Pathological Record of Mammary Cancer, 11th ed, Kanehara, Tokyo, 1992.
5) Lohrmann HP, Adam W, Heymer, *et al*: Microangiopathic hemolytic anemia in metastatic carcinoma. *Ann Intern Med* 79:368-375, 1973.
6) Brain MC, Azzopardi JG, Baker LRI, *et al*: Microangiopathic hemolytic anemia and mucin-forming adenocarcinoma. *Br J Haematol* 18:183-193, 1970.
7) Bull BS, Rubenberg ML, Dacie JV, *et al*: Microangiopathic haemolytic anemia; Mechanisms of red cell fragmentation *in vitro* studies. *Br J Haematol* 14:643-652, 1968.
8) Hilgard P, Gordon-Smith EC: Microangiopathic haemolytic anaemia and experimental tumour-cell emboli. *Br J Haematol* 26:651-659, 1974.
9) Rauch AE, Tartaglia AP, Kaufman B, *et al*: RBC fragmentation and thymoma. *Arch Intern Med* 144: 1280-1282, 1984.
10) Lin Y-C, Chang H-K, Sun C-F, *et al*: Microangiopathic haemolytic anemia as an initial presentation of metastatic cancer of unknown primary origin. *South Med J* 88:683-687, 1995.
11) Rodenburg CJ, Noony MA, Briët E: Microangiopathic haemolytic anemia with advanced breast carcinoma; Improvement with chemotherapy. *Neth J Med* 28:169-171, 1985.
12) Nordström B, Strang P: Microangiopathic haemolytic anemia (MAHA) in cancer; A case report and review. *Anticancer Res* 13:1845-1850, 1993.
13) Collins PW, Jones L, Pocock C, *et al*: Microangiopathic haemolysis associated with occult carcinoma. *Clin Lab Haematol* 13:245-249, 1991.
14) Yamamoto H, Noguchi S, Miyauchi K: Changes in hematologic parameters during treatment with medroxyprogesterone acetate for breast cancer. *Jpn J Cancer Res* 82:420-425, 1991.
15) Japan Advanced Breast Cancer Group and Japan Clinical Oncology Group: Effects of chemoendocrine therapy on the coagulation-fibrinolytic systems in patients with advanced breast cancer. *Jpn J Cancer Res* 84:455-461, 1993.