

Microangiopathic Hemolytic Anemia in a Patient with Recurrent Anal Cancer And Liver Metastasis

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Microangiopathic hemolytic anemia (MAHA) is a late but fatal complication in advanced cancers (cancer-associated). It may also appear in complete remission after chemotherapy (chemotherapy-related). Mucin-producing adenocarcinoma has been extensively studied in relation to this phenomenon. Squamous cell carcinoma with MAHA, on the other hand, has not often been reported in the English literature. Because of the difficulty of case collection, understanding of the association of MAHA and anal squamous cell carcinoma remains vague. We present a 60-year-old woman with anal cancer and liver metastasis. This patient received chemotherapy (mitomycin C, 5-fluoruracil, and cisplatin) and reached a good partial response. MAHA developed 2 months later, and tumor recurrence with rapid deterioration appeared 5 months later. The patient died 5 months after MAHA was diagnosed. We consider that the MAHA in this patient is chemotherapy-related. However, the possibility of cancer-associated MAHA could not be excluded. (*Chang Gung Med J* 2002;25:706-10)

Key words: MAHA, anal cancer, mitomycin C.

Microangiopathic hemolytic anemia (MAHA) is an uncommon but clinically serious complication of advanced cancers. The clinical presentation of MAHA is an abrupt and often severe hemolytic anemia that is characterized by fragmented erythrocytes and thrombocytopenia in the peripheral blood. MAHA predominantly occurs in mucinous adenocarcinoma. The most frequent cancers are stomach, lung, and breast cancers.^(1,2) Mucin-secreting cancer with MAHA is associated with disseminated diseases (cancer-associated) or clinical remission after chemotherapy (chemotherapy-related). Chemotherapy-related MAHA usually leads to thrombotic lesions, a syndrome resembling thrombotic thrombocytopenia purpura and hemolytic uremic syndrome. Unless it is identified and treated early, MAHA is

life-threatening and has a poor prognosis.

The association between MAHA and squamous cell carcinoma has only been sporadically identified.⁽³⁻⁷⁾ The cervix, bronchus, and nasopharynx are the most commonly primary sites. As in adenocarcinoma, these squamous cancers exist in an advanced status or occur after a good response to chemotherapy followed by development of MAHA.

In a review of the English literature from 1967 to 2000, we found only 2 cases with squamous cell carcinoma of the anal canal which were associated with MAHA.^(3,4) MAHA in anal cancer has never been reported in Taiwan. Herein we describe a case of MAHA in recurrent anal squamous cancer with liver metastasis.

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CASE REPORT

A 60-year-old Taiwanese woman was hospitalized with a ten-day history of epigastric fullness and bloody stool. In December 1997, physical examination showed hepatomegaly and a soft 2 × 2 cm mass in the rectum. Sigmoidoscopy revealed an annular tumor 3 cm from the anal verge. A biopsy specimen from this annular tumor showed squamous cell carcinoma and a computed tomography (CT) scan of the abdomen indicated multiple hypodense nodules of various sizes in both lobes of the liver. Alpha-fetoprotein was 6 ng/mL (normal range < 20 ng/mL), and carcinoembryonic antigen (CEA) was 270 µg/L (normal range < 5 µg/L). Hence a diagnosis of anal squamous cell carcinoma with multiple liver metastases was made. She received chemotherapy consisting of cisplatin (50 mg/m², on day 1), 5-fluorouracil (750mg/m² daily for 3 days), and mitomycin C (6 mg/m² on day 1), every 3-4 weeks, for a total of six cycles over a 6-month period. The total cumulative dose of mitomycin C was 48 mg (30 mg/m²). In June 1998, a follow-up CT scan of the abdomen showed that there was no definite tumor in the lower abdomen and pelvis, and the metastatic liver nodules had regressed to an almost undetectable size. The CEA level had been reduced to 1.71 µg/L.

In August 1998, she was admitted because of oral bleeding, pallor and dyspnea on exertion. The complete blood count showed a hemoglobin concentration of 4.7 g%, a white blood cell count of 5.2 × 10⁹/L with 83% neutrophil, 7.5% monocyte, 7% lymphocyte and 2.5% basophil, and a platelet count of 31 × 10⁹/L. Laboratory data on coagulation revealed an activated partial thromboplastin time of 22.9 sec (control 26.0 sec), a prothrombin time of 12.4 sec (control 12.6 sec), and fibrinogen of 469 mg% (control 190-380 mg%). The laboratory findings were a total bilirubin of 2.4 mg% with a conjugated fraction of 0.7 mg%, a serum lactate dehydrogenase of 381 U/L (normal range 47-140 U/L), blood creatinine of 1.3 mg% (normal range 0.4-1.4 mg%), and a negative direct Coombs' test, but a positive indirect Coombs' test. The peripheral blood smear showed fragmented red blood cells and spherocytes (Fig. 1). Bone marrow studies revealed hypocellularity with mildly decreased megakaryocytes, normal erythroid series, and absence of tumor cells. MAHA with thrombocytopenia was thus diagnosed. The symp-

toms including dyspnea and oral bleeding improved after multiple transfusions with packed red blood cells, fresh frozen plasma, and platelet concentrate.

The patient, however, began to complain of progressive abdominal fullness in November 1998. An abdominal CT scan showed increased number of metastatic liver nodules, recurrence of the rectal mass, and massive ascites, which indicated tumor recurrence with rapid disease progression. Although treatment with one course of cisplatin, bleomycin, and 5-FU was initiated in November 1998, her general condition deteriorated rapidly and multiple organ failure developed. The patient died in January, 1999.

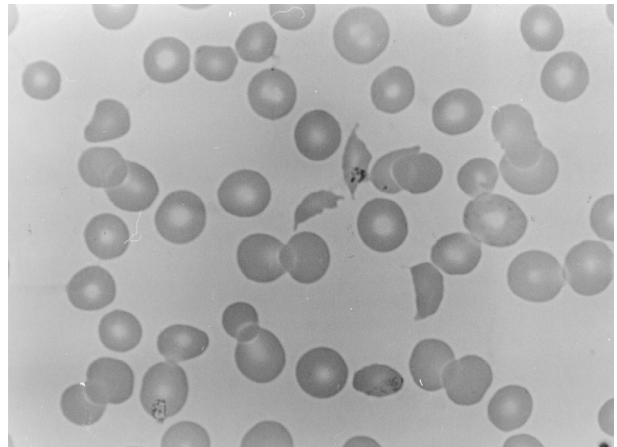


Fig. 1 Peripheral blood smear of showing many fragmented red blood cells and spherocytes (Wright stain, 1000 ×).

DISCUSSION

We report a patient of squamous cell carcinoma of the anus with liver metastasis developed MAHA during her course. In the literature, only 3 cases including the present case, have been reported on anal cancer associated with MAHA.^(3,4) All three patients were women, at their ages 49, 51 and 60, respectively. The tumors in the first 2 cases were localized and removed by surgical resection. The patients were then treated with adjuvant chemotherapy (mitomycin C and 5-fluorouracil) and radiotherapy. They were free of detectable carcinoma after treatment. One year later, both progressively developed

consciousness disturbance, hemolytic anemia, thrombocytopenia, and renal insufficiency, suggestive of hemolytic uremic syndrome. Plasmapheresis and hemodialysis followed. Both patients had no evidence of recurrent carcinoma when the reports were published. On the other hand, our patient had metastatic and inoperable cancer. Although she received palliative chemotherapy and achieved a good partial response, MAHA occurred and followed 3 months later with rapid progression of tumor. The patient died of disease eventually.

In cancer patients with MAHA, the bone marrow would show normal erythroid and megakaryocytic hyperplasia.⁽⁸⁾ However, the result of this patient's bone marrow smear revealed hypocellularity with mildly decreased megakaryocytes. This discrepancy was probably a cumulative effect of previous chemotherapy.

Both direct and indirect Coombs' tests are generally negative in cancer-associated MAHA.^(1,3,4) The present case showed negative direct Coombs' but positive indirect Coombs' tests. This finding implied that the patient's serum contained antibodies of an uncertain nature that could have led to hemolytic anemia. Whether the presence of antibodies was related to chemotherapy, infection or both in this patient was not clear.

When MAHA occurred in the 2 previously reported patients neurological deficits and renal insufficiency were present but without tumor recurrence. On the other hand, our patient did not have these deficiencies, but instead, the tumor grew rapidly after a short time of 3 months. This observation raised an important issue: was MAHA in this patient cancer-associated, chemotherapy-related, or both? Tapp and Ralston had reported that cancer-associated MAHA usually occurred in patients with disseminated squamous cell cancer.⁽⁹⁾ Chemotherapy-related MAHA often occurred in patients with limited disease or in clinical remission after several courses of chemotherapy following mitomycin C use.⁽¹⁾ Hemolytic uremic syndrome in patients with chemotherapy-related MAHA usually occurs within 4 to 8 weeks of the last dose of chemotherapy, or 6 to 20 months after the initiation of chemotherapy, but not all patients with mitomycin C-induced MAHA develop renal failure.^(1,10) Based on our observation, chemotherapy-related MAHA was considered a more likely diagnosis.

On the contrary, Collins et al. reported that a case of MAHA association with breast adenocarcinoma. Nordstrom and Strang pointed out that unlike chemotherapy-related MAHA, renal function deterioration in cancer-associated MAHA is uncommon.⁽¹⁾ These 2 reports suggested that cancer-associated MAHA could occur in the absence of tumor dissemination and renal dysfunction. Sack et al. demonstrated that chronic disseminated intravascular coagulation (DIC) may contribute to MAHA in metastatic carcinomas.⁽¹²⁾ In this patient after completing 6 cycles of chemotherapy and achieving a good partial response, some undetectable residual tumor may well be present in the liver, and these tumor might imbalance overall hemostasis, and led to chronic DIC and subsequent MAHA. Nonetheless, underlying cancer status was not evaluated when MAHA developed. Whether cancer-associated MAHA was present in this patient remains open to question.

MAHA is a fatal complication in advanced cancers, and it may also be an early predictor of tumor recurrence. Ozguroglu et al. reported on a gastric cancer patient who had undergone surgical resection developed MAHA and increased CEA as the initial observations of tumor recurrence.⁽¹³⁾ Our patient also had tumor recurrence with rapid progression 3 months after MAHA developed.

Physicians have reached the consensus that appropriate management of underlying malignancies should be initiated as early as possible. For cancer-associated MAHA the result of chemotherapy appears encouraging, but no effective treatment for chemotherapy-induced MAHA has succeeded beyond supportive care.⁽¹⁾

In conclusion, anal cancer associated with MAHA is rare but important clinically. Our patient with anal cancer and liver metastasis developed MAHA after receiving mitomycin C-based chemotherapy. It is difficult to determine if MAHA was cancer-associated or chemotherapy-related. We consider that the MAHA was chemotherapy-related, and it may also be an initial presentation of tumor recurrence.

REFERENCES

1. Nordstrom B, Strang P. Microangiopathic hemolytic anemia (MAHA) in cancer. A case report and review. *Anticancer Res* 1993;13:1845-50.

2. Antman KH, Skarin AT, Mayer RJ, Hargreaves HK, Canellos GP. Microangiopathic hemolytic anemia and cancer: a review. *Medicine* 1979;58:377-84.
3. Gulati SC, Sordillo P, Kempin S, Reich L, Magill GB, Scheiner E, Clarkson B. Microangiopathic anemia observed after treatment of epidermoid carcinoma with mitomycin C and 5-fluorouracil. *Cancer* 1980;45:2252-7.
4. Huvos AG, Schwartzberg L. Hemolytic anemia, thrombocytopenia and renal failure in a patient apparently cured of anal carcinoma. *Cancer Invest* 1985;3:481-9.
5. Jackson AM, Rose BD, Graff LG, Jacobs JB, Schwartz JH, Yang JP, Rudnick MR, Elfenbein IB, Narins RG. Thrombotic microangiopathy and renal failure associated with antineoplastic chemotherapy. *Ann Intern Med* 1984;101:41-4.
6. Agnew RA, Sutton PH. Hemolytic anemia in association with carcinoma of the bronchus. *J Ir Med Assoc* 1967;60:270-3.
7. Angiola G, Bloss JD, DiSaia PJ, Warner AS, Manetta A, Berman ML. Hemolytic-uremic syndrome associated with neoadjuvant chemotherapy in the treatment of advanced cervical cancer. *Gynecol Oncol* 1990;39:214-7.
8. Cantrell JE Jr, Phillips TM, Scheinj PS. Carcinoma-associated hemolytic-uremic syndrome: a complication of mitomycin C chemotherapy. *J Clin Oncol* 1985;3:723-34.
9. Tapp E, Ralston A. Thrombotic microangiopathy associated with squamous carcinoma. *Br Med J* 1969;4:209-10.
10. Murgo AJ. Thrombotic microangiopathy in the cancer patient including those induced by chemotherapy agents. *Semin in Hematol* 1987;24:161-77.
11. Collins PW, Jones L, Pocock C, Newland AC. Microangiopathic hemolysis associated with occult carcinoma. *Clin Lab Haematol* 1991;13:245-9.
12. Sack GH, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms. *Medicine* 1977;56:1-20.
13. Ozguroglu M, Demirelli F, Mandel NM. Microangiopathic hemolytic anemia as an early predictor of recurrence in gastric cancer. *Am J Clin Oncol* 1999;22:214.

微小血管病變及溶血性貧血於肛門癌復發合併肝轉移的病人

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微小血管病變溶血性貧血可以是末期癌症病患致命的併發症（癌症相關），或者發生在病人接受化學治療且腫瘤完全消失後（化學治療誘發）。以往研究指出分泌黏液性的腺癌易有微小血管病變溶血性貧血現象出現；至於鱗狀上皮癌與微小血管病變溶血性貧血之間的關係，鮮有報導。此篇報告提出一位60歲女性病人，罹患肛門鱗狀上皮癌合併肝轉移。病人在接受化學治療（mitomycin C, 5-fluoruracil及cisplatin）後，其腫瘤幾乎完全消失。然而在完成化學治療2個月後，病人發生微小血管病變溶血性貧血。五個月後，腫瘤復發且迅速變大。病人於診斷微小血管病變溶血性貧血後的第5個月死亡。這篇個案報告並非容易去區分癌症相關和化學治療誘發的微小血管病變溶血性貧血。但就臨床證據而言，作者們較支持這位肛門鱗狀上皮癌合併肝轉移病人，可能發生化學治療誘發的微小血管病變溶血性貧血，但是並不排除癌症相關的微小血管病變溶血性貧血。同時，微小血管病變溶血性貧血可能是腫瘤復發的早期徵兆。（長庚醫誌 2002;25:706-10）

關鍵字：微小血管病變溶血性貧血，肛門癌，mitomycin C。