Microangiopathic haemolytic anaemia in metastatic malignancy

A Craig Lockhart

CASE REPORT

In May 1998, a middle-aged woman with a history of breast cancer, diagnosed and treated with a right-sided mastectomy 9 years previously, presented to the Duke University Medical Center with intermittent headaches, slurred speech, left arm numbness and a right facial droop.

Physical examination was notable for mild dysarthria and decreased biceps and triceps strength on the left. Her vital signs were normal, she had no evidence of bruising or bleeding, and there was no hepatosplenomegaly.

Radiological evaluation, including head computed tomography (CT), head magnetic resonance imaging and angiography of the head and neck, showed no evidence of carcinomatosis, parenchymal disease or vascular abnormalities.

Cerebrospinal fluid (CSF) evaluation showed an elevated total protein and cytology returned showing the presence of malignant cells.

Laboratory values included haemoglobin = 9.1 g/dl, haematocrit = 29%, white blood cell count = 18.0×10^9, platelets = 301×10^9, haptoglobin = <5.8 mg/dl, lactate dehydrogenase = 2790 U/litre, bilirubin = 1.5 mg/dl, protime = 15.2 seconds, partial thromboplastin time = 31.6 seconds, reticulocyte count = 169×10^9, fibrinogen = 248 mg/dl, CA15-3 = 136 U/litre.

Her peripheral blood film was consistent with microangiopathic haemolytic anaemia with the presence of frequently seen schistocytes. Bone marrow aspirate and biopsy revealed the presence of Signet cells, consistent with carcinoma invading the bone marrow (*Figures 1* and *2*). Hormone receptor testing on the bone marrow biopsy was notable for the presence of oestrogen receptors and the absence of progesterone receptors.

The rest of the patient's evaluation showed no masses on CT scans of the chest, abdomen and pelvis and no gastrointestinal malignancy after endoscopy.

Owing to the previous history of breast cancer, the elevated CA15-3 and the presence of oestrogen receptors on the cancer cells in the bone marrow, she was treated with chemotherapy for metastatic breast cancer.

She received six cycles of combination chemotherapy consisting of docetaxel, doxorubicin and cyclophosphamide. She was then treated with intrathecal methotrexate for her central nervous system disease.

On evaluation in April 1999, almost 1 year later, she was clinically well with no measurable disease and no laboratory evidence of haemolysis. She is currently receiving treatment with an antioestrogen.

INTRODUCTION

Anaemia is frequently associated with malignancy. Microangiopathic haemolytic anaemia (MAHA), although only occasionally associated with metastatic cancer, is nevertheless well described in this disorder (Brain et al, 1962). This paper reports a patient who presented with MAHA and was also found to have carcinoma cells on bone marrow aspirate and biopsy. Some of the proposed mechanisms of MAHA in patients with disseminated malignant disease are then reviewed.

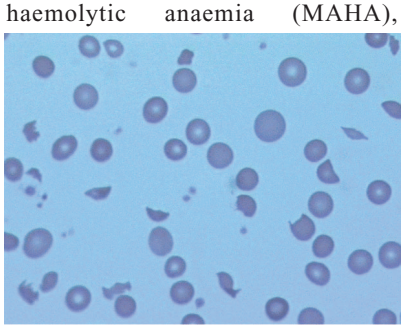

Figure 1. Peripheral blood film showing schistocytes (x100).

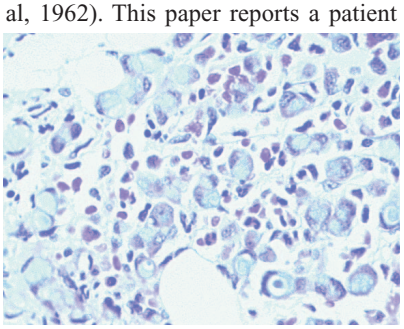

Figure 2. Bone marrow core biopsy showing tumour cell infiltration (x400).

DISCUSSION

Incidence

Since Brain's first description of malignancy-related MAHA there have been at least 145 cases of this disorder described in the literature. Almost all of the cases reported have been associated with widely disseminated cancer (Lohrmann et al, 1973). The presence of MAHA in localized malignancy that is not a tumour of vascular origin is extremely rare (Brain et al, 1962).

The median age of these patients is approximately 50 years and there is a slight male to female predominance (1:1.2) (Antman et al, 1979). The frequency with which MAHA occurs in patients with malignancy is unclear, but two studies have evaluated this. Davis et al (1985) examined blood films of 167 patients who were diagnosed with small cell undifferentiated lung cancer. They found that three of their patients (1.8%) had MAHA. Lohrmann et al (1973) evaluated this question when they examined 3200 blood films, of which 140 (4.4%) of the patients had metastatic cancer. Eight (5.7%) of the patients with metastatic carcinoma had MAHA.

Adenocarcinomas, particularly mucin-producing tumours, are most often associated with MAHA (Brain et al, 1962). Malignancy of the stomach is the tumour most commonly associated with MAHA. Stomach, breast and lung cancer account for over 70% of the cases of patients with cancer-related MAHA.

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Clinical and laboratory features

Most of the presenting signs and symptoms of patients diagnosed with cancer-related MAHA are related to anaemia. These include fatigue, dyspnoea, tachycardia and pallor. The majority of patients also have thrombocytopenia, so features related to this finding are also common, including bruising, bleeding and neurological findings as a result of intracranial haemorrhage. Other clinical signs and symptoms can be related to the patient's underlying malignancy and its areas of dissemination.

Laboratory findings consistent with a haemolytic anaemia are usually present, with the majority of patients having a moderate to severe decrease in serum haemoglobin. Thrombocytopenia has been the most common finding noted in the cases in the literature, other common laboratory findings from case reports are listed in *Table 1*. Schistocytes, which need to be present in order to make the diagnosis of MAHA, are present to varying degrees with usual levels between 1 and 20% (Lohrmann et al, 1973). Laboratory findings related to disseminated intravascular coagulopathy (DIC) were not always reported in prior case reports.

Pathophysiology

MAHA can be seen in metastatic malignancy as a result of traumatic destruction of red cells. The disorder was originally described by Brain et al in 1962, when they described five patients with metastatic cancer who also had haemolytic anaemia characterized by schistocytes in the peripheral blood. They suggested that the erythrocyte destruction was as a result of passage of the red cells through abnormal blood vessels which contained fibrin thrombi or tumour cells. In a follow-up paper 8 years later, Brain and colleagues (1970) theorized that fibrin formation from intravascular coagulation probably played a greater role in red cell destruction rather than passage through abnormal blood vessels.

In 1979 Antman and colleagues re-addressed the mechanism of malignancy-induced MAHA after reviewing four cases. The problems that they had with the Brain hypothesis were that the patients that most frequently presented with malignancy-related DIC and those that presented with malignancy-related MAHA are two different patient populations. Specifically, DIC is more common than MAHA and is seen most often in patients with pancreatic, lung and prostate cancer (Antman et al, 1979), while MAHA is more often seen in gastric or breast cancer. In addition to this, some patients who have malignancy-induced MAHA do not have DIC (Lohrmann et al, 1973). In the patients that do have MAHA and DIC, the two conditions are not necessarily parallel, in that in some cases the DIC responds to heparin therapy, but the haemolysis persists. Their final argument was that, despite evidence of DIC, fibrin thrombi were rarely found on post-mortem examination of these patients.

Alternatively, Antman et al (1979) postulated that erythrocyte shearing may be the result of direct intraluminal contact with embolic tumour cells. In the cases presented in their paper, marked pulmonary vascular abnormalities were noted associated with emboli of adenocarcinoma cells to the pulmonary vessels. Fibrin and platelet deposition was seen around tumour cells in the pulmonary vasculature on histological evaluation. Their cases suggested that frequent tumour emboli to the pulmonary arterioles resulted in intimal proliferation. The mechanical stresses of intimal proliferation and contact with embolized tumour cells could result in shearing of erythrocytes.

In addition to mechanical factors, it has also been shown that mucin extracted from the tumours has procoagulant activity (Pineo et al, 1973). This is important because, as noted earlier, the majority of malignancies which produce MAHA are mucin producing. Antman and colleagues then concluded that the MAHA was probably the result of a combination of the tumour cells' procoagulant activity and the mechanical damage induced by the vascular changes.

Other proposed mechanisms have included prostacyclin deficiency (Byrnes and Moake, 1986) and circulating antigen–antibody complexes (Morat et al, 1965) which both lead to platelet aggregation.

The mechanisms responsible for malignancy-associated MAHA are multifactorial. The predominating mechanism is likely related to the tumour type and to the condition of the host. Further study is needed to investigate the possible role of antigen–antibody complexes and prostacyclin deficiency as well as their relationship to the other more well-described proposals of DIC and mechanical destruction.

TABLE 1.
Commonly reported laboratory values in patients presenting with microangiopathic haemolytic anaemia

Laboratory finding	Percentage of patients
Anaemia (haemoglobin < 8 g/dl)	57% *
Thrombocytopenia (platelets < 100K)	86% *
Disseminated intravascular coagulopathy	48% *
Reticulocytosis	56% *,†,‡
Leukocytosis	42% §
Elevated lactate dehydrogenase	62% †,‡
Hyperbilirubinaemia	92% *
Malignant cells on bone marrow biopsy	60% §

*From Antman et al (1979), †from Brain et al (1962), ‡ from Lohrmann et al (1973), § from Murgo (1987)

Treatment and prognosis

Treatment of malignancy-related MAHA is largely ineffective; however, some cases have responded to treatment of the underlying cancer with chemotherapy or hormonal therapy resulting in haematological improvement (Rodenberg et al, 1985). Therefore if an underlying malignancy can be identified and effective therapy exists, an attempt to treat is worthwhile.

Treatment of the DIC with heparin has also been mixed, with most patients having an improvement in DIC parameters, but no change in haemolysis (Lohrmann et al, 1973). Heparin can be considered in patients with laboratory evidence of DIC.

Owing to the disseminated nature of cancer at the time of diagnosis in most patients with MAHA, the outlook for these patients is very grave, with Antman et al (1979) reporting a median survival of 21 days. Therefore a patient's clinical status should be strongly considered before undertaking treatment with chemotherapy.

CONCLUSION

Malignancy-related MAHA is an uncommon disorder, occurring in less than 5% of patients with cancer. The disorder is usually seen in patients with widely disseminated cancer. The actual mechanism of the red cell destruction is unclear, but several factors including destruction by fibrin strands formed during DIC, mechanical destruction in vessels occluded by tumour cells, direct contact between tumour cells and erythrocytes, or antibody-mediated processes may play a role. Treatment results are mixed, but heparin or chemotherapy should be considered in appropriate patients. Underlying malignancy should be considered in patients with MAHA when another source cannot be determined. HM

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Brain MC, Dacie JV, Hourhaine DO (1962) Microangiopathic hemolytic anemia: the possible role of vascular lesions in pathogenesis. *Br J Haematol* **8:** 358–74

Brain MC, Azzopardi JG, Baker LR, Pineo GF, Roberts PD, Dacie JV (1970) Microangiopathic haemolytic anaemia and mucin forming adenocarcinoma. *Br J Haematol* **18:** 183–93

Byrnes JJ, Moake JL (1986) Thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome: evolving concepts of pathogenesis and therapy. *Clin Hematol* **15:** 413–42

Davis S, Rambotti P, Grignani F (1985) Microangiopathic hemolytic anemia and pulmonary small cell carcinoma. *Ann Int Med* **103:** 638

Lohrmann HP, Adam W, Heymer B, Kubanek B (1973) Microangiopathic hemolytic anexia in metastatic carcinoma: report of eight cases. *Ann Int Med* **79:** 368–75

Morat HZ, Mustard F, Taichman NS, Uriuhara T (1965) Platelet aggregation and release of ADP, serotonin and histamine associated with phagocytosis of antigen-antibody complexes. *Proc Sci Exp Biol Med* **120**: 232–7

Murgo AJ (1987) Thrombotic microangiopathy in the cancer patient including those induced by chemotherapeutic agents. *Semin Hematol* **24(3):** 161–77

Pineo GF, Regoeczi E, Hatton MW, Brain MC (1973) Activation of coagulation by extracts of mucus: a possible pathway of intravascular coagulation accompanying adenocarcinoma. *J Lab Clin Med* **82:** 255–66

Rodenberg CJ, Noodly MA, Briet E (1985) Microangiopathic haemolytic anemia with advanced breast carcinoma: improvement with chemotherapy. *Neth J Med* **28:** 169–71

IN THE PUBLIC'S VIEW...

Real improvements or more propaganda?

In the red corner: *NHS Plan News*, the new quarterly publication for NHS staff. Read all about how the plan is driving a culture change, how there is new breed of specialist GPs, how nurses' expanded role is bringing patient benefits, how a consultant-led service (that's consultants resident on call in oldspeak) will mean better patient care, and how long trolley waits could be consigned to history.

To understand better exactly how trolley waits will be consigned to history, come to the blue corner: *Panorama* Condition Red, BBC1, 25 March. You just make sure that there are beds in A&E. Magic: no trolley waits. There may be 26 patients in A&E, and no beds anywhere in the hospital, but redefinition works wonders. A&E looks pretty much like any other ward now; there is even a morning cornflakes round.

The BBC spent 2 months at St Peter's Hospital, Surrey. They showed the constant juggling of patients between beds when A&E has a 212% bed occupancy and all neighbouring hospitals are condition red. We saw patients due to have major surgery, these days increasingly elderly because of the successes of modern medicine, have their operations cancelled because of the lack of intensive care beds. We saw the disparagingly named bed blockers, who no longer have acute illnesses but have nowhere to go; nursing homes are closing because the money from social services does not cover costs. One night, the sister in A&E has no permanent staff with her at all; they are all agency. A number of staff nurses leave the orthopaedic ward because of the demoralising conditions. One goes to the day surgery unit; another prefers the USA: 'It's private care. When they are better, they go home. And that's it.' When the nurse vacancies approach 30%, the only solution is to close a surgical ward.

Considering the whole picture, a consultant urologist observes that if animals were treated the way some people are treated in the NHS there would be trouble from the animal rights lobby. He and the chief executive are both happy that the government's NHS Plan is a move in the right direction, but ask if it will be enough.

St Peter's is not alone. Today four patients could not be found beds for my morning list. I anaesthetised just one patient this afternoon; I don't know how many were cancelled. There are wards closed because of Norwalk virus, and medical outliers all over the hospital.

Panorama was completely non-judgmental. It posed no questions and gave no answers. The mess is not the government's fault. It is the fault of all of us. Years of Thatcherism, which has leaked perniciously and soiled this government's good intentions, have weakened the social fabric, although perhaps it was already crumbling. Taxes are referred to as a burden. Families are no longer so protective.

What is the government's fault is that they ignored underfunding for so long and, Tony Blair's recent conversion notwithstanding, their attacking NHS staff for refusing to 'modernise'. They now make things appear better than they are, and staff fear more criticism is on the way. We don't need the government propaganda of *NHS Plan News* in our workplaces; if things begin to improve we will see it all around us. HM

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