

Microangiopathic Hemolytic Anemia (MAHA) As Paraneoplastic Syndrome In Metastasized Signet Ring Cell Carcinomas: Case Reports And Review Of The Literature

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Citation

H Arkenau, O Müssig, T Buhr, H Jend, R Porschen. *Microangiopathic Hemolytic Anemia (MAHA) As Paraneoplastic Syndrome In Metastasized Signet Ring Cell Carcinomas: Case Reports And Review Of The Literature*. The Internet Journal of Gastroenterology. 2004 Volume 3 Number 2.

Abstract

We report two cases with microangiopathic hemolytic anemia (MAHA) due to metastasized signet ring carcinoma one of gastric and one of unknown origin. The patients presented with an acute onset of Coombs negative hemolytic anemia and fragmentocytes in the peripheral blood smear which is typical for MAHA.

After the patients received chemotherapy (ELF and PLF-regimen, respectively) we were able to control MAHA and cancer progression. These case reports present MAHA as a rare paraneoplastic syndrome in patients with metastasized signet ring carcinoma.

BACKGROUND

Microangiopathic hemolytic anemia (MAHA) is an uncommon hematological disorder which can appear in different diseases like thrombotic thrombocytopenic purpura (TTP, Morbus Moschcowitz), hemolytic uremic syndrome (HUS, Morbus Gasser), malignant hypertension and vasculitis.

MAHA occurs also as a paraneoplastic syndrome in different solid tumors (1). It is defined as a severe hemolytic anemia with a negative Coombs test and fragmentocytes in the peripheral blood smear (2). The clinical findings overlap from hemolytic uremic syndrome to thrombotic thrombocytopenic purpura. We report on two different cases of microangiopathic hemolytic anemia due to metastasized signet ring carcinoma.

CASE REPORT 1

A 62-year old man was referred to our hospital because of a suspected choledocholithiasis as cause of his jaundice for an endoscopic retrograde cholangio-pancreatography (ERCP). The patient presented with pain in the right upper abdominal quadrant, back pain and jaundice which appeared two days before hospital admission. An external ultrasound of the abdomen showed cholecystolithiasis; the ductus hepatocholedochus was slightly dilated. The patient had a

R0-gastrectomy four years before admission due to gastric carcinoma (pT1pN0pM0; signet ring cell carcinoma). After gastrectomy the patient was without any medical complaints. Regular medical check-ups for two years showed no signs of local recurrence or metastatic disease.

On admission the medical examination showed no pathological findings; there were no weight loss, night sweats or fever reported. Due to the gastrectomy (procedure: Longmire-Guetgemann with jejunal pouch) a ERCP was not possible. The patient presented with the following laboratory results (references): hemoglobin 10.7g/dl (14-18 g/dl); platelet count 86 /nl (150-440 /nl); WBC 7.8 /nl (4.3-10 /nl); haptoglobin <0.08 g/l (0.34-2.0 g/l); total bilirubin 2.8 mg/dl (<1.3 mg/dl); lactic dehydrogenase 1222 U/l (<240 U/l); alkaline phosphatase 3140 U/l (<180 U/l); GOT 30 U/l (<18 U/l); GPT 30 U/l (<22 U/l); c-reactive protein 131 mg/l (<4 mg/l); fibrinogen 428 mg/dl (200-400 mg/dl); carcinogenic antigen (CEA) 202 µg/l (< 3,4µl). Creatinine, urea levels, INR (International Normalized Ratio), prothrombin time and AT III were normal. Direct and indirect Coombs' tests were negative. Peripheral blood smear test showed fragmentocytes ++ (+ - +++), anisocytosis ++ (+ - +++), poikilocytosis + (+ - ++++) and polychromatosis + (+ - +++). Radionuclide bone scan revealed diffuse bone metastases (figure 1). Bone marrow biopsy showed hemangiosis

carcinomatosa of a signet ring cell carcinoma (figure 2). Immunohistological findings demonstrated that the bone marrow infiltration was related to the origin gastric carcinoma. Endoscopy of the upper gastrointestinal tract, plus endoscopic ultrasound (EUS), colonoscopy, ultrasound of the abdomen/thyroid gland and a CT-scan of the abdomen revealed no signs of local recurrence, metastatic disease or of choledocholithiasis. A CT-scan of the chest showed multiple fractures of thoracic spines 6-11.

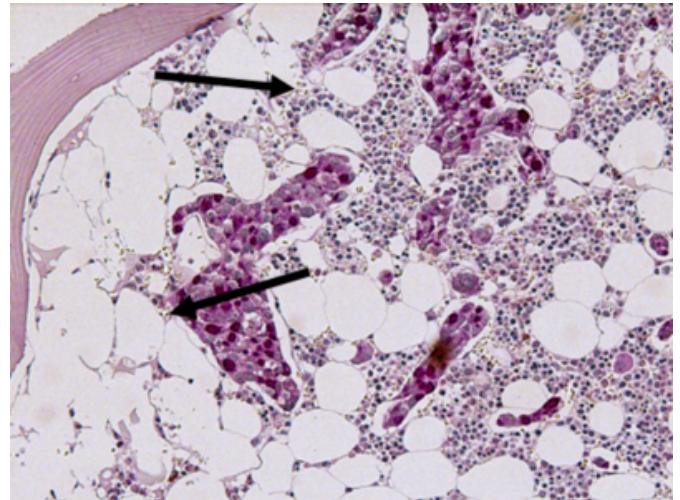
Figure 1

Figure 1: Radionuclide bone scan revealed diffuse bone metastasis (see black spots).



Figure 2

Figure 2: Bone marrow biopsy with hemangiosis carcinomatosa of a signet ring cell carcinoma (see arrows (40x, Giemsa)).



THERAPY

We started chemotherapy with an ELF-schedule on an outpatient basis (etoposid 120 mg/m², leucovorin 300mg/m², 5-fluorouracil 500mg/m² d1-3, qd21). As supportive care we administered a six-weekly biphosphonate-infusion and put the patient on a cortison medication (50mg/day). After the first cycle the hemoglobin level stabilized (11.1 g/dl), the platelet count increased (110 /nl), alkaline phosphatase and lactic dehydrogenase levels decreased (2350 and 736, respectively). After receiving 12 cycles of ELF the patient again was admitted to hospital with severe epistaxis due to a low platelet count (15 /nl). After administration of platelet and blood transfusions the platelet count and hemoglobin stabilized. Lactic dehydrogenase and alkaline phosphatase levels started to increase again; the creatinine [2.5 mg/dl (<1.3 mg/dl)] and urea [110 mg/dl (<50 mg/dl)] levels were elevated for the first time. At this time we changed the chemotherapy regimen to 5-fluorouracil/leucovorin plus oxaliplatin which was administered bi-weekly (5-fluorouracil 2000 mg/m², leucovorin 500mg/m², oxaliplatin 130mg/m² d1, qd14). After 4 cycles the patient presented with progression of disease so we stopped chemotherapy application. Four weeks later the patient died.

CASE 2

A 58-year old male was admitted to the hospital with acute onset of severe abdominal pain and jaundice. On admission the patient presented also with fever (38.9 Celsius) and sweats. The examination showed a slightly enlarged liver and a hematoma of the abdominal wall. To this time the

patient had only mild hypertension in medical history. An annual medical check up with blood tests three weeks before admission showed no noticeable medical results and blood tests. The patient presented with following laboratory results (references): hemoglobin 7.8g/dl (14-18 g/dl); platelet count 80/nl (150-440/nl); WBC 7.2/nl (4.3-10/nl); haptoglobin <0.08 g/l (0.34-2.0 g/l); total bilirubin 1.53 mg/dl (<1.3 mg/dl); lactic dehydrogenase 833 U/l (<240 U/l); alkaline phosphatase 924 U/l (<180 U/l); GOT 70 U/l (<18 U/l); GPT 117 U/l (<22 U/l); c-reactive protein 18 mg/l (<4 mg/l); fibrinogen 412 mg/dl (200-400 mg/dl); ATIII 132%; CEA 42 µg/l (< 3,4µg/l); CA 19-9 3970 U/ml (<27 U/ml). Creatinine, urea levels, INR (International Normalized Ratio), prothrombin time were normal. Direct and indirect Coombs' tests were negative. Peripheral blood smear test showed fragmentocytes + (+ - +++), anisocytosis +++ (+ - +++), poikilocytosis ++ (+ - +++), and polychromatosis ++ (+ - +++). Bone marrow biopsy showed hemangioendotheliomatosis of a signet ring cell carcinoma. Radionuclide bone scan revealed diffuse bone metastasis. A magnetic resonance tomography showed multiple metastasis of the bone marrow.

Endoscopy of the upper gastrointestinal-tract plus endoscopic ultrasound (EUS), colonoscopy, ultrasound of the abdomen/thyroid gland and a CT-scan of the abdomen/chest revealed no signs of primary tumor or metastatic disease. After two months we repeated endoscopy of the upper gastrointestinal-tract plus endoscopic ultrasound, ultrasound of the abdomen/thyroid/prostate gland and a CT-scan of the abdomen/chest with no sign of primary tumor or metastatic disease.

THERAPY

We started therapy with platelet and blood transfusions. Due to the acute severe onset of MAHA and the worsening conditions of the patient we began a chemotherapy with a PLF-schedule (5-fluorouracil 2000mg/m², leucovorin 500mg/m² d 1,8,15,22,29,36, qd50 plus cisplatin 50mg/m² d1, 15, 29 qd50). After two cycle hemoglobin stabilized (11.6 g/dl), the platelet count increased (194/nl) and haptoglobin levels increased (0.45 g/l). Alkaline phosphatase and lactic dehydrogenase levels (223 U/l and 221 U/l, respectively) and tumor markers decreased (CEA: 2.9 µg/l and CA19-9: 168 U/ml, respectively).

DISCUSSION

Since its first description in 1962 microangiopathic

hemolytic anemia (MAHA) was only published in few case reports. Only one larger study included 55 patients with MAHA of different cancer origin. This study revealed that approximately 50% of MAHA was associated to gastric carcinoma, followed by breast and lung cancer, 15% and 10% respectively (1). Like case 2 there is only one case report in the literature where MAHA was associated to bone marrow carcinomatosis of a signet ring carcinoma of unknown origin (3).

Most cases of MAHA have an abrupt onset. In our patients abdominal/back pain, hemolytic anemia and thrombocytopenia were the leading symptoms. These findings are in accordance with other cases and are typical for MAHA (4, 5, 6). Fatigue and dizziness mostly appear in advanced stages of anemia. Common pathological findings are bleedings, bruises and purpura which were also seen in our patients. Gastrointestinal bleedings can occur. A common and severe complication in advanced stages of disease are intracranial bleedings (7, 8).

One third of the patients present with jaundice due to hemolytic anemia, liver metastasis or extrahepatic bile duct obstruction. The appearance of jaundice, back/abdominal pain and cholecystolithiasis which was also seen in one of our patients can cause problems finding the right diagnosis.

In this case the laboratory results may help getting the right diagnosis. Almost all patients present with hemolytic anemia, 50% of the patients present with hemoglobin levels <8 g/dl. A characteristic finding in MAHA is the peripheral blood smear test with fragmentocytes which was also seen in our patients. Most patients present with platelet counts less than 50.000 /nl. Typical constellations which also appeared in our cases are a negative Coombs test, decreased haptoglobin and elevated lactic dehydrogenase levels. In patients with cancer associated MAHA renal failure is a rare condition but can appear in advanced stages which was shown in case 1 (1, 9, 10).

Today the pathogenesis of cancer associated MAHA is unclear. Whether tumor derived cell factors like platelet aggregating factors, antiendothelial cell antibodies or procoagulants are involved in MAHA is still under investigation. It is postulated that tumor cell emboli, together with immune complexes could generate endothelial damages which leads to platelet aggregation and endothelial proliferation. The characteristic fragmentation of red blood cells are due to the direct contact between red blood cells

and the pathological arteries, arterioles and capillaries. These microvascular changes were reported in eight cases of cancer associated MAHA (8, 11, 12).

The prognosis of MAHA is extremely poor. Most patients die within a few weeks after diagnosis (1). Patients with bone marrow metastases and MAHA had significant worse median survival times compared to patients without MAHA (2 months versus 11 months, respectively) (13). The bad outcome in patients with bone marrow metastases and MAHA needs special consideration.

Bone marrow metastases occur in 1-11% of patients with gastric cancer. In one study median time leading to the diagnosis of bone marrow metastases was 3.5 years after curative gastrectomy (1 month - 5.8 years). Laboratory findings at diagnosis were elevated levels of alkaline phosphatase, lactic dehydrogenase, c-reactive protein and CEA which were also found in our patients (14). Elevated alkaline phosphatase-, lactic dehydrogenase- and c-reactive protein-levels may therefore help to identify patients with bone metastasis and MAHA.

Today there exists no definitive treatment schedule for patients with MAHA. The acute onset of MAHA with hemolytic anemia and low platelet counts make a fast blood and platelet transfusion in nearly all patients necessary. In our patients we received a stabilization of hemoglobin levels and platelet counts. An additional heparinization and application of glucocorticoids is discussed controversial (8, 15). The main focus of treatment is to reduce the tumor mass. A chemotherapy should be started as soon as possible after diagnosis (10). In our patients we chose ELF- and PLF-schedule, respectively, which are well tolerated and established chemotherapy regimens in gastric cancer. In case 1 we were able to control the disease by nearly one year. Patient 2 received a good clinical and laboratory response after 2 cycles of PLF. To date the patient is still under chemotherapy.

Taken together our reports showed two rare cases of MAHA. In case one MAHA was the first sign of recurrence four years after curative resection of gastric carcinoma. The second case showed MAHA as the first side of metastatic disease, which is seen in approximately one third of all cases with MAHA (1). Therefore, laboratory findings which

suggest MAHA make it necessary to search for the primary carcinoma. Today chemotherapy is the best option to get clinical response.

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