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Microangiopathic Hemolytic Anemia: A Rare Clue to Diagnose Bone Marrow Metastatic Gastric Adenocarcinoma

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Abstract:

Microangiopathic Hemolytic Anemia (MAHA) is a hematological condition which is very rare for the primary presentation of a gastric adenocarcinoma with bone marrow metastases. When it emerges as initial findings in a previously undetected case of malignancy, the diagnosis is often missed and results in inappropriate management. Carcinoma stomach associated with MAHA is generally having fulminant course. This is a case report of a 30-year-old male who presented with widespread bone marrow infiltration along with Coomb's negative haemolytic anemia, thrombocytopenia and schistocytes in peripheral blood typical of MAHA. The combination of MAHA and bone marrow infiltration in gastric adenocarcinoma is a very rare entity. When the cause of progressive MAHA is unknown, the possibility of cancer-associated MAHA must be excluded by performing additional tumor workup, including the detection of tumor markers, Endoscopy of upper GIT, colonoscopy, bone marrow examinations, and PET-CT or bone scans.

Keywords: *Microangiopathic hemolytic anemia (MAHA); gastric adenocarcinoma; bone marrow metastasis.*

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Introduction:

Microangiopathic hemolytic anemia (MAHA) is a rare paraneoplastic syndrome in different solid tumors specially in advanced adenocarcinoma.[1] It is defined as a severe hemolytic anemia with a negative Coombs test and schistocytes in the peripheral blood smear.[2] When a malignancy first presents as MAHA, it is often misdiagnosed and treated as thrombotic thrombocytopenic purpura (TTP). Progressive MAHA of unknown origin, therefore, warrants a search for occult malignancy. Among malignant conditions, association with carcinoma stomach, lung, breast, unknown primary and lymphoma are common.[2] Bone marrow study in such cases may help locate the primary by unmasking tumor deposits, but extensive bone marrow necrosis (BMN) is another unusual finding in disseminated malignancy. However, both MAHA and BMN indicate grave prognosis in this setting.

Case summary:

A 30-year-old, sailor, previously normotensive, nondiabetic male presented with low grade intermittent fever without chill and rigor for 8 months with a maximum recorded temperature of 100°F, which mostly came at evening, subsided spontaneously or by taking medication with sweating. Seven days prior to admission in hospital patient has been suffering from high grade, continued fever with a maximum recorded temperature of 104ºF without chills and rigor and not subsided completely with medication. Just before the day of admission patient became semiconscious, couldn't recognize his own people and talked irrelevantly. There was no history of diarrhea, vomiting, urinary

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complaints, cough, Haemoptysis, contact with TB patients, hematemesis, melaena, skin rash, oral ulcer, joint pain, history of travel to malaria endemic zones, IV drug abuse, any other bleeding manifestation. Physical examination showed a GCS score of 4/15, severely anaemic, mildly icteric and dehydrated without any cyanosis, clubbing, koilonychia, Leuconychia, lymphadenopathy, thyromegaly. Pulse - 118/min, Blood pressure- 110/70 mm of Hg, temperature- 103º F, respiratory rate – 21/min. Systemic examination revealed altered level of consciousness with left sided hemiplegia as evidenced by unable to localize the painful stimuli by left upper limb and no movement of left lower limb, bilateral extensor plantar response with no signs of meningeal irritation and no apparent cranial nerve palsy. Other systemic examinations were normal. On routine blood examination, his haemoglobin level was only 3.3 g/dL with an elevated WBC count of 20,240/mm^3 and a low platelet count of 14,000/mm^3, ESR- 40 mm in 1st hour. Initial Peripheral blood film revealed leucoerythroblastic blood picture with thrombocytopenia. Repeated CBC results showed same picture but subsequent PBF revealed schistocytes, anisocytosis, polychromatic RBC, few nucleated red blood cells with thrombocytopenia suggestive of MAHA. Then Work-up to identify the cause of haemolysis was initiated on an emergency basis. Liver function tests showed serum bilirubin- 1.9mg/dl, SGPT- 34, lactate dehydrogenase (LDH)—1184 U/L. Serum creatinine was 1.5 mg/dl, reticulocyte count- 8.06%, FDP - 74.16mg/dl, D-dimer - 1.5ug/ml. Direct and indirect Coomb's tests were negative ruling out immune mediated hemolysis. Routine urine analysis revealed albumin+, pus cell- 10-12/HPF, RBC- 15-20/HPF. ANA, ICT for malaria, blood culture (Fan method), HBsAg were negative. CT scan of brain was normal. USG of Whole Abdomen revealed few prominent upper para aortic and mesenteric lymph nodes (3.4x1.6cm & smaller), slightly coarse hepatic parenchymal echotexture with prominent spleen. The patient received supportive transfusions without significant improvement in blood counts. With TTP as diagnostic consideration and for the evaluation of total presentation a bone marrow study was done which showed small clumps of medium sized cells seems to be of non-haemopoitic origin, some cluster exhibit glandular pattern; Comment: suggestive of secondary metastasis of bone marrow. Then upper GIT endoscopy was done and it revealed large area of diffuse nodular irregular growth seen at the body and part of the antrum (Figure 1). Biopsy result from the gastric antrum revealed poorly differentiated adenocarcinoma. (Figure 2).

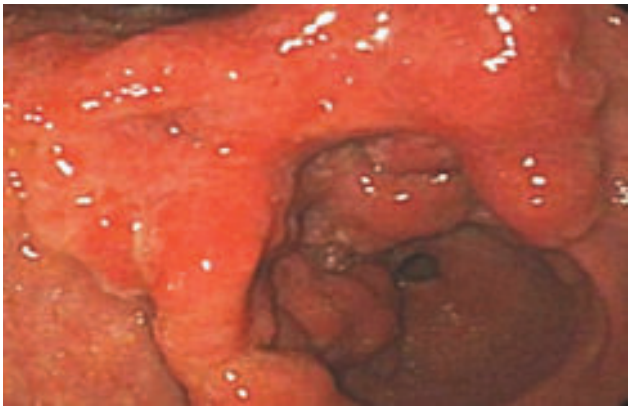

Figure 1: *Nodular irregular growth at antrum of stomach*

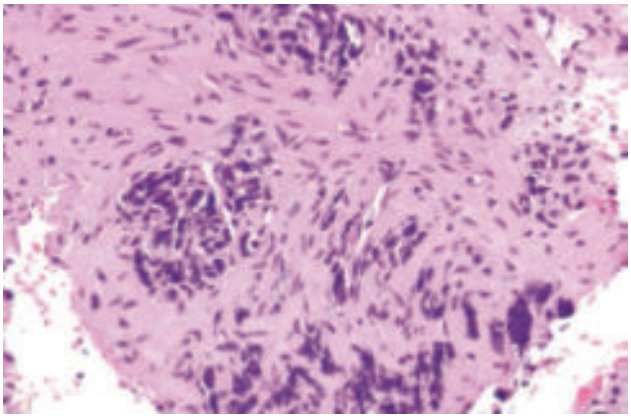

Figure 2: *Poorly differentiated adenocarcinoma of stomach*

Discussion:

Since its first description in 1962 MAHA was only published in few case reports. It can occur as a paraneoplastic syndrome in cancer patients, and may present as the first manifestation characterized by Coombs-negative hemolytic anemia with schistocytes and thrombocytopenia. The most common tumors associated with MAHA are gastric, breast, and lung cancers.[3-5] A Korean study reported that 14 (25.5%) out of 55 MAHA patients had gastric cancer.[5] In a review of 168 reported cases of Cancer related-MAHA (CR- MAHA) by Lechner and Obermeier in 2012, the more frequently associated malignancies were adenocarcinomas of stomach, breast, prostate and lung. Another study included 60 patients with MAHA of different cancer origin revealed that approximately 50% of MAHA was associated to gastric carcinoma, followed by breast and lung cancer, 15% and 10% respectively.[1] CR-MAHA is a rare and fatal complication of malignant tumors Most CR-MAHA patients die within a few weeks after the diagnosis, and the most common cause of death is infection.[6] Our patient died within 4 weeks. 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.[7] Most cases of MAHA have an abrupt onset. In our patient hemolytic anemia and thrombocytopenia and focal neurological deficit were the leading symptoms. These findings are in accordance with other cases and are typical for MAHA associated with TTP (thrombotic thrombocytopenic purpura).[8-10] Where systemic malignancy is not initially apparent, the combination of microangiopathic hemolytic anemia and thrombocytopenia in CR-MAHA is often misdiagnosed as TTP, a medical emergency. The classical pentad of TTP includes fever, microangiopathic hemolytic anemia, and thrombocytopenia, renal and neurological abnormalities. However, the urgency for its diagnosis in view of the effective early treatment options has decreased the stringency of these criteria.[11] This exposes patients to the risks of plasma exchange therapy which is effective for TTP, but inappropriate in CR-MAHA. In fact, disseminated malignancy is an alternative disorder that only mimics TTP and is not TTP associated.[12] Fatigue and dizziness mostly appear in advanced stages of anemia. Gastrointestinal bleedings can occur. A common and severe complication in advanced stages of disease are intracranial bleedings.[13,14] One third of the patients present with jaundice due to hemolytic anemia, liver metastasis or extrahepatic bile duct obstruction. 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 schistocytes which was also seen in our patients. Most patients present with platelet counts less than 50.000 /mm^3. Typical constellations which also appeared in our cases are a negative Coombs test, elevated lactic dehydrogenase levels. In patients with cancer associated MAHA renal failure is a rare condition but can appear in advanced stages.[1, 15, 16]

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.[14, 17, 18]

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).[19] 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. Examination of the histology has shown that more than 80% of bone metastasis from gastric cancer was poorly differentiated adenocarcinoma. Thoracic and lumbar vertebrae are the most frequent sites of bone metastasis.[20] although there are reported cases of deposits in pelvis.[21] Patients with bone metastases have mean survival times of less than 5 months with the longest survival period reported being 3 years.[22] 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). Elevated alkaline phosphatase-, lactic dehydrogenase and c-reactive protein-levels may therefore help to identify patients with bone metastasis and MAHA.

Conclusion:

Till now no definitive treatment schedule exists 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. An additional application of glucocorticoids is discussed controversial.[14, 23] The main focus of treatment is to reduce the tumor mass. A chemotherapy should be started as soon as possible after diagnosis.[16] In our 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.

Conflict of interest: None

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