

# A Metastatic Signet Ring Cell Carcinoma Presented as Acquired Thrombotic Thrombocytopenic Purpura: A Case Report

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## Abstract

Microangiopathic hemolytic anemia (MAHA) may occur as a paraneoplastic syndrome in some solid tumors, but MAHA accompanied by signet ring cell carcinoma (SRCC) of an unknown origin is very rare. We report a patient who presented with an acute onset of Coombs negative hemolytic anemia and frequent schistocytes in the peripheral blood smear which are typical for MAHA as initial presentation of metastatic SRCC. Our patients fulfilled the criteria of thrombotic thrombocytopenic purpura (TTP) and received the specific treatment for TTP without improvement.

**Keywords:** Microangiopathic hemolytic anemia; Signet ring cell carcinoma; Thrombotic thrombocytopenic purpura

## Introduction

Microangiopathic hemolytic anemia (MAHA) refers to any hemolytic anemia related to RBC fragmentation, occurring in association with small vessel disease. In disseminated intravascular coagulopathy (DIC), RBC fragmentation is thought to result from the deposition of fibrin or platelets within the microvasculature. The term “thrombotic microangiopathy (TMA)” is also used to describe syndromes characterized by MAHA, thrombocytopenia, and thrombotic lesions in small blood vessels. The most prominent diagnoses associated with TMA are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Many different disorders, including preeclampsia, infections, some drug reactions, hematopoietic stem cell transplantation, autoimmune diseases,

and malignancies, can cause TMA (i.e., secondary TMA) [1].

Secondary MAHA as a paraneoplastic syndrome in different solid tumors is a serious, often a serious complication of malignancy. Tumor-derived factors, procoagulants, immune complexes, some chemotherapeutic agents, fibrinoid necrosis of bone marrow, and tumor cell emboli of arteries, arterioles, and capillaries are responsible for occurrence of cancer-associated MAHA (CA-MAHA). Chemotherapy is the only effective therapy [2].

MAHA occurs occasionally as a paraneoplastic syndrome in some solid tumors, but MAHA accompanied by signet ring cell carcinoma (SRCC) of an unknown origin is very rare [3]. Herein, we describe a case of SRCC in which MAHA was the initial presentation.

## Case Report

A 31-year-old male presented with bone aches for more than 2 months followed by easy fatigability in October, 2017 associated with recurrent fever. Upon examination, the patient had severe pallor, jaundice, palpable splenomegaly, but no lymphadenopathy. The patient was admitted to the Hematology Unit, Oncology Center, Mansoura University with laboratory tests showing anemia (Hb 6.6 g/dL; MCV: 92 fL; MCH: 28 pg), normal WBC (5,500/ $\mu$ L), and thrombocytopenia with platelet count  $17.6 \times 10^9$ /L and total bilirubin 3.1 mg/dL (direct 1.4 mg/dL). High lactate dehydrogenase (LDH, 2,137 U/L), with negative viral screen for HCV, HBV and HIV was shown. High serum ferritin (5,052 ng/mL) with negative direct and indirect Coombs test and the pelvi-abdominal ultrasound showed mild hepatosplenomegaly. The blood smear showed frequent schistocytes and polychromatic, nucleated red blood cells and reticulocytosis. Blood coagulation tests were normal to rule out DIC.

According to these clinical and laboratory findings, we planned to start treatment as TTP and continue the essential workup to rule out secondary TTP. We asked for CT of chest, abdomen and pelvis, bone marrow aspiration and biopsy, tumor markers and some immunological markers.

The patient received packed RBCs, pulse steroid for 5 days in parallel with plasma exchange, however, no improvement with deterioration in the performance status and intolerable bone aches which decreased by opioids. Follow-up with

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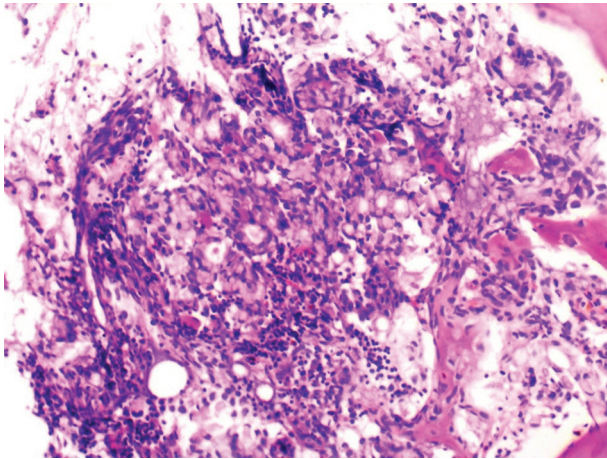
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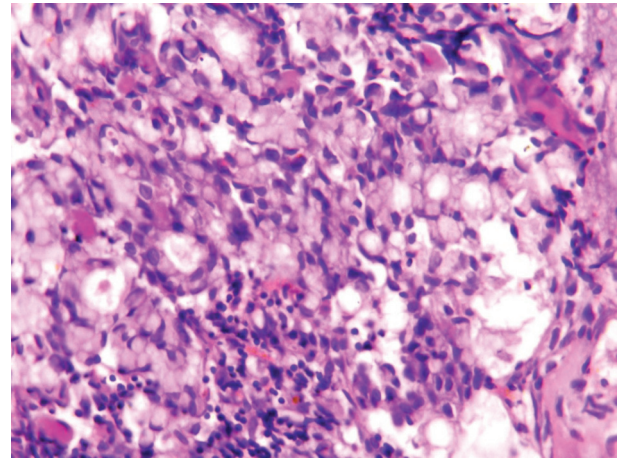
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**Figure 1.** Metastatic carcinoma in the form of signet ring cells seen admixed within a background of bone marrow hemopoietic elements.



**Figure 2.** Scattered aggregates of signet ring carcinoma cells seen within the bone marrow elements ( $\times 40$ ).

laboratory tests showed more rise in LDH, more high serum bilirubin, rising ALT and AST with no improvement of the blood picture and the patient developed two attacks of fits with normal brain CT. Our patient was not responding with more deterioration according to clinical setting and laboratory findings, so we started rituximab 100 mg/m<sup>2</sup> once weekly.

The pre- and post-contrast CT revealed a multiple mixed lytic sclerotic lesion seen in all scanned bones, few tiny nodules seen in right lung parenchyma measuring 6 mm mostly metastatic, mild enlarged liver with multiple non-enhancing focal lesions, largest 4  $\times$  7 mm.

Among the tumor markers that were assessed, both carcinoembryonic antigen level (807.0 ng/mL) and cancer antigen 19-9 (80 U/mL) were elevated. The subsequent bone marrow biopsy revealed bone marrow infiltrated by malignant tumor tissue in the form of malignant acini lined by malignant epithelial cells that show moderate atypia and pleomorphism, and scattered signet ring cells are also seen in Figures 1 and 2. Immunostaining revealed positive staining for CK in neoplastic cells.

After these results, the patient referred to Medical Oncology ward with poor general condition, feverish with high liver function tests (total bilirubin: 13.3 mg/dL, ALT: 610.37 UI/L, AST: 349.56 UI/L), anemia (Hb 6.5 g/dL), and thrombocytopenia with platelet count 12  $\times 10^9$ /L.

The patient planned for CT-guided biopsy and upper GIT endoscopy after improvement to detect the primary site but unfortunately, the patient continued to deteriorate despite repeated blood transfusions, antibiotics and had been expired 2 days later.

## Discussion

Primary TMA syndromes are specific disorders that require specific treatments. They include TTP, HUS, and drug-induced TMA. Although these disorders have been studied separately in the past, in recent decades, they have been combined as common TMA syndrome, which includes definitive clinical

and pathological features, MAHA, thrombocytopenia, and organ injury [4]. CR-MAHA is distinguished from primary TMA in terms of its underlying disorders and treatment options. CR-MAHA has been reported in association with several types of carcinoma since the 1980s. Lechner et al conducted a literature review of 168 reports of CR-MAHA; according to cancer type, gastric cancer was the most frequent, followed by breast, prostate, and lung cancers [5].

A Korean study reported that 14 (25.5%) out of 55 MAHA patients had gastric cancer [6]. In our patient, MAHA was the initial finding of SRCC in the bone marrow; however, we did not reach the primary site due to rapid deterioration in general condition. CR-MAHA is a rare and fatal complication of malignant tumors. Among patients with bone marrow metastases from cancer, MAHA patients have a worse prognosis than patients without MAHA [7]. Our patients had expired 22 days after initial presentation which is parallel with the different literature that proved most of CR-MAHA cases die within few weeks, majority with infection as final insult [8, 9].

Our patient was diagnosed with CA-MAHA on the basis of the findings of bone marrow examination and CT conducted 7 days after the diagnosis of MAHA. Many studies have recommended a thorough tumor workup, including bone marrow examination, in cases of progressive MAHA of unknown origin [6].

There are some clinical symptoms and signs which are more prominent in CA-MAHA than in non-CA-MAHA like bone pains and respiratory symptoms [8, 10]. Actually our patient experienced both significant bone pain and dyspnea.

Although several studies have suggested that fibrinoid necrosis of the bone marrow and tumor cell emboli of the arteries, arterioles, and capillaries are the causes of CA-MAHA, the pathogenesis of CA-MAHA remains unclear [11, 12]. Some studies have reported a decrease in the level of the von Willebrand factor (vWF)-cleaving protease, and ADAMTS13 plays a role in CA-MAHA [8]. We were unable to evaluate the presence of tumor emboli of the arteries, ADAMTS13, or tumor necrosis factor alpha (TNF- $\alpha$ ) in this case because the patient expired rapidly.

SRCC is a subtype of mucin-producing adenocarcinomas. However, mucin-producing adenocarcinomas and SRCC show clinicopathological differences [13, 14]. Our patient is a 31-year-old male with the fact that the gastrointestinal tract SRCC is more common in the young and in males and has a worse prognosis than mucin-producing adenocarcinomas. SRCC is frequently complicated by metastases to the regional lymph nodes, peritoneal surfaces, ovaries, lungs, and bone marrow [15].

There is no definitive treatment of choice for CA-MAHA. The low platelet count and hemoglobin level make red blood cell and platelet transfusion obligatory. Actually in our patient, we started urgent treatment for TTP in the form of plasma exchange and pulse steroids with no response, then second line added in the form of rituximab; however, he showed progression because the treatment of CA-MAHA differed than that of non-CA-MAHA. And the optimal treatment is to give the specific chemotherapy protocols with supportive blood transfusion. An additional heparinization and administration of glucocorticoids are subjects of controversial discussion. The main focus of treatment is to reduce the tumor mass. A chemotherapy should be started as soon as possible after diagnosis [6, 16-19].

## Conclusions

CR-MAHA is an uncommon paraneoplastic syndrome with rapidly serious outcome. Its association with carcinoma specifically signet ring cell variant deliberates a worse prognosis. Consequently, laboratory findings which suggest MAHA make it necessary to search for the primary carcinoma as early as possible as aggressive tumor control is possibly the most effective treatment for CR-MAHA as well.

## Conflict of Interest

The authors have no conflict of interest.

## Disclaimers

The submitted article is our own and not an official position of the institution or funder.

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