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Case Report

Cancer-Related Microangiopathic Hemolytic Anemia Mimicking Thrombotic Thrombocytopenic Purpura in Metastatic Gastric Signet Ring Cell Carcinoma: A Fatal Diagnostic Pitfall

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Abstract

Cancer-related microangiopathic hemolytic anemia is a rare but severe paraneoplastic syndrome most commonly associated with advanced solid tumors, particularly gastric signet ring cell carcinoma. Its presentation often mimics thrombotic thrombocytopenic purpura, leading to diagnostic challenges that delay appropriate management.

This is a case of a 44-year-old male patient with a history of stage IV gastric diffuse large B-cell lymphoma in remission presented with one-week history of jaundice, generalized bone pain, and one episode of loose stool.

Laboratory findings revealed anemia, thrombocytopenia, elevated lactate dehydrogenase, and hyperbilirubinemia, consistent with microangiopathic hemolytic anemia. Schistocytes on peripheral blood film and negative Coombs test supported the diagnosis of thrombocytopenic purpura, however, there was no clinical improvement after plasma exchange, and ADAMTS-13 activity result was later found to be normal. Computed tomography showed new lymphadenopathy, splenomegaly, and bone lesions. Bone marrow biopsy revealed 60% infiltration by metastatic signet ring cell adenocarcinoma of gastric origin. Despite aggressive supportive care, the patient rapidly deteriorated and died on day 6 of hospitalization.

This case highlights the importance of considering cancer-related microangiopathic hemolytic anemia in patients with Coombs-negative hemolytic anemia and thrombocytopenia non-responding to plasma exchange. Early evaluation with bone marrow biopsy and imaging is essential to guide timely appropriate therapy of the underlying oncologic disease.

Keywords: Microangiopathic hemolytic anemia; Stomach neoplasms; Paraneoplastic syndrome; Thrombotic thrombocytopenic purpura

Abbreviations

SRCC: Signet Ring Cell Carcinoma; MAHA: Microangiopathic Hemolytic Anemia; CR-MAHA: Cancer-Related Microangiopathic Hemolytic Anemia; TTP: Thrombotic Thrombocytopenic Purpura; DLBCL: Diffuse Large B-Cell Lymphoma; LDH: Lactate Dehydrogenase; CT: Computed Tomography; HUS: Hemolytic Uremic Syndrome; DIC: Disseminated Intravascular Coagulation; PE: Plasma Exchange; TPE: Therapeutic Plasma Exchange; INR: International Normalized Ratio; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; CHOP: Cyclophosphamide, Doxorubicin (Hydroxydaunorubicin), Vincristine (Oncovin), and Prednisone; R-CHOP: Rituximab-CHOP; CNS: Central Nervous System; H&E: Hematoxylin and Eosin; Pan-CK: Pan Cytokeratin; FOLFOX: Folinic Acid, Fluorouracil, and Oxaliplatin; ELF: Etoposide, Leucovorin, and Fluorouracil

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Introduction

Gastric cancer is the fifth most common malignancy worldwide and ranks the fourth leading cause of cancer-related death [1]. Signet Ring Cell Carcinoma (SRCC) is a rare subtype accounting for 10% of gastric adenocarcinomas, it is characterized histologically by the presence of tumor cells with mucinous cytoplasm and crescent-shaped nuclei, and is commonly aggressive with presentation at an advanced stage [2].

Gastric SRCC often initially presents with Microangiopathic Hemolytic Anemia (MAHA), a rare paraneoplastic syndrome observed in patients with solid tumors including metastatic gastric SRCC, and it typically indicates poor prognosis [3]. The pathophysiology of Cancer-Related Microangiopathic Hemolytic Anemia (CR-MAHA) is not fully understood; however, tumor cell emboli, circulating immune complexes, and tumor-derived factors are thought to contribute to the Coombs-negative hemolytic process that occurs [4].

CR-MAHA presentation can mimic Thrombotic Thrombocytopenic Purpura (TTP), Disseminated Intravascular Coagulation (DIC), and Hemolytic Uremic Syndrome (HUS), causing

diagnostic challenges that may delay appropriate cancer treatment [3]. This report describes a 44-year-old male presented with MAHA secondary to metastatic gastric SRCC, highlighting the importance of considering underlying malignancy in patients presenting with unexplained hemolytic anemia, and to avoid potentially ineffective treatments.

Case Presentation

A 44-year-old male patient with a history of stage IV germinal center-type Gastric Diffuse Large B-Cell Lymphoma (DLBCL), diagnosed in July 2019, had an International Prognostic Index (IPI) score of 3 and a CNS-IPI score of 4, indicating advanced stage with renal involvement, multiple extra-nodal sites, and elevated Lactate Dehydrogenase (LDH). He received one cycle of DHAP (Dexamethasone, High-dose cytarabine (Ara-C), and Platinol (Cisplatin)), with rituximab withheld due to positive hepatitis B PCR and elevated bilirubin at presentation. After that, he received one cycle of CHOP (Cyclophosphamide, Doxorubicin (Hydroxydaunorubicin), Vincristine (Oncovin), and Prednisone), six cycles of R-CHOP (Rituximab-CHOP), and two cycles of HD-MTX (high-dose methotrexate) for Central Nervous System (CNS) prophylaxis. He achieved remission by December 2019.

In December 2024, the patient was admitted to the King Hussein Cancer Center after presenting to the emergency department with a one-week history of jaundice and generalized bone pain. He also reported a single episode of loose stool, without nausea, vomiting, or any sign of gastrointestinal bleeding. On admission, he was hemodynamically stable, and physical examination was notable only for conjunctival icterus, with no neurologic abnormalities.

Laboratory evaluation (Table 1) revealed a significant hemoglobin drop from his baseline of 15 g/dL to 10.1 g/dL, in addition to thrombocytopenia, hyperbilirubinemia, elevated LDH, low haptoglobin, and elevated liver enzymes, consistent with active hemolysis. Coagulation studies showed mildly prolonged Prothrombin Time (PT) and International Normalized Ratio (INR). Serum creatinine was also mildly elevated, and a direct Coombs test was negative. Peripheral blood smear showed normochromic red blood cells with schistocytes, consistent with MAHA. Given the minimal renal impairment, a diagnosis of TTP was favored over HUS.

ADAMTS-13 activity was sent prior to initiating plasma exchange, and daily plasma exchange therapy was started. Three days later, the patient's blood count had not improved (Table 1), and corticosteroid therapy was started with prednisolone (1 mg/kg), later switched to intravenous methylprednisolone (1000 mg) on day 5. Rituximab was not administered due to positive Hepatitis B PCR.

Table 1: Labs at admission.

Parameter (Reference Range)	Admission Value	S/P plasmapheresis (Day 3)
Hb (13-18 g/dL)	10.1	6.5
MCV (80-94 fL)	79.1	79.8
Platelets (150-400 x 10^3/µL)	42	12
Total Bilirubin (0.28-1 mg/dL)	4.32	3.99
Direct Bilirubin (0.01-0.3 mg/dL)	1.34	2.01
LDH (122-222 U/L)	2007	2298
Alkaline Phosphatase (37-130 U/L)	1224	1068
AST (8-48 U/L)	173	273
ALT (7-47 U/L)	42.5	35.9
Haptoglobin (30-200 mg/dL)	<10	<10
Creatinine (0.5-1.15 mg/dL)	1.2	0.8
PT (11.7-15.2 s)	18.6	16
INR (0.87-1.21)	1.43	1.22
PTT (28.1-38.1 s)	34.6	43.4
Fibrinogen (187-394 mg/dL)	116	
Reticulocytes count	0.051	

During admission, oncologic re-evaluation with Computed Tomography (CT) of the neck, chest, abdomen and pelvis showed new supra- and infra-diaphragmatic lymphadenopathy, splenomegaly, and sclerotic bone lesions suggestive of marrow involvement, hence a biopsy was performed.

On day 6 of admission, ADAMTS-13 activity returned within normal range (0.79 IU/ml; reference 0.4-1.3 IU/ml). Concurrently, bone marrow biopsy showed an extensive infiltration of approximately 60% by a non-hematopoietic malignancy, composed of sheets of signet ring cells with foamy cytoplasm (Figure 1a and 1b), involving marrow sinusoids and associated with areas of necrosis. Immunohistochemistry was positive for Pan Cytokeratin (Pan-CK) and MUC5AC (Figure 1c and 1d), supporting the diagnosis of metastatic signet ring cell adenocarcinoma of gastric origin.

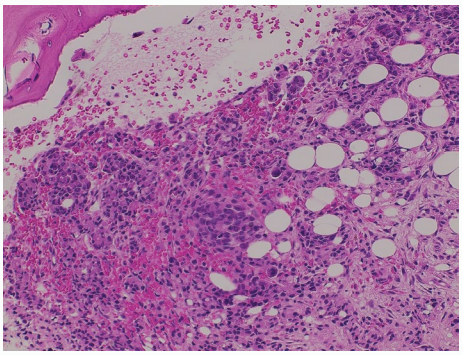

Figure 1A: Hematoxylin and Eosin (H&E)-stained sections of bone marrow biopsy showing diffuse bone marrow infiltration by malignant non-hematopoietic tumor cells in groups and singly some with signet ring morphology.

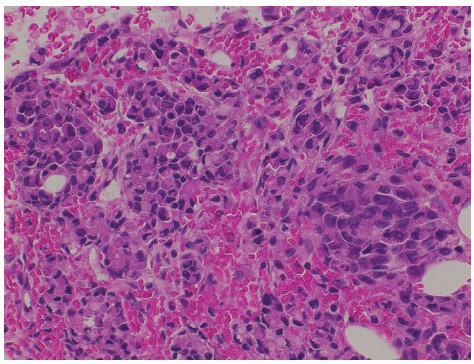

Figure 1B: Few residual normal bone marrow elements are noted in the background.

Despite aggressive supportive care, the patient developed persistent fever on day 6 of admission and his condition continued to rapidly deteriorate despite broad-spectrum antibiotics. He required intubation and died the following day after a cardiac arrest.

Discussion

This case highlights the importance of maintaining a broad differential diagnosis when dealing with MAHA, especially in patients with a history of malignancy.

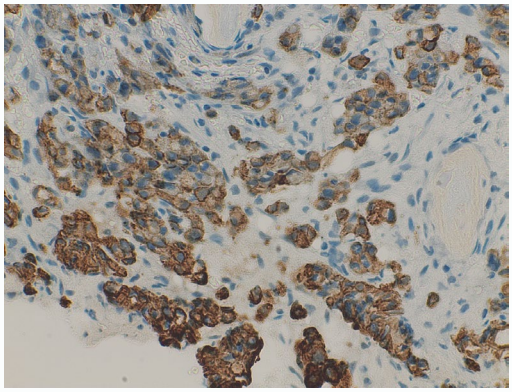

Figure 1C: The tumor cells are immune reactive for (Pan-CK) immune stain.

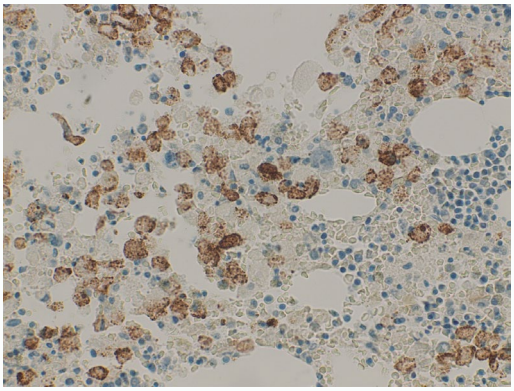

Figure 1D: The tumor cells are immune reactive to MUC5AC.

MAHA is a mechanical red-cell injury syndrome characterized by schistocytes, elevated LDH, indirect hyperbilirubinemia and decreased haptoglobin [3]. Although these findings overlap with TTP, lack of response to plasma exchange and normal ADAMTS-13 activity should raise suspicion for CR-MAHA [5].

The classic triad of hemolytic anemia, thrombocytopenia, and schistocytes, as in our patient, commonly prompts clinicians toward a working diagnosis of TTP, but this can be misleading, as occult disseminated malignancy can mimic TTP in up to one-third of cases [6]. However, bone pain, minimal renal involvement, and a rapidly progressive course should raise suspicion for CR-MAHA rather than primary TTP [7,8]. MAHA in gastric cancer, particularly the signet-ring cell subtype, is frequently associated with diffuse bone and bone-marrow metastasis; as bone infiltration is reported in 68% to 89% of cases, and symptomatic anemia is almost universal [5,6]. As in our patient, ADAMTS-13 levels are typically >10 %, emphasizing that severe deficiency is not a prerequisite for diagnosing CR-MAHA [9]. Moreover, the median interval between MAHA onset and identification of the underlying malignancy is only six days, highlighting the need for early oncologic evaluation [10].

The pathogenesis is thought to be mechanical fragmentation of erythrocytes within the microvasculature, occluded by tumor micro-emboli, fibrin deposition, and mucin-driven platelet aggregation [11]. This is supported by the heavy (≈ 60 %) marrow infiltration and sclerotic bone lesions, reflecting advanced systemic disease.

The overall prognosis of CR-MAHA remains poor, as median survival after MAHA onset ranges from 12 days to two months despite best supportive care, and diffuse marrow disease is associated with an even shorter life-expectancy [6]. PE, although life-saving in immune-mediated TTP, has no evidence of improving survival in CR-MAHA and may delay the only potentially effective therapy, i.e., systemic chemotherapy [4,12,13]. Unfortunately, many patients, including ours, deteriorate rapidly before initiating cytotoxic treatment, highlighting the importance of timely recognition of an underlying malignancy, although challenging.

Table 2 summarizes our patient's timeline in comparison to previously published CR-MAHA cases [3,11,14-25].

Conclusion

Microangiopathic hemolytic anemia can serve as the initial and sometimes only manifestation of occult or recurrent gastric signet-ring cell carcinoma. Clinicians should maintain a high index of suspicion for malignancy-associated MAHA in patients with unexplained Coombs-negative hemolysis and thrombocytopenia, especially when ADAMTS-13 activity is normal and there is no early response to plasma exchange. Misdiagnosis may delay potentially life-prolonging oncologic therapy. Prompt bone-marrow biopsy and staging imaging are critical; as they establish the diagnosis and guide timely management in this rapidly progressive and often fatal condition.

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Table 2: Clinical course timeline compared to previous reported cases.

Case	Presenting features	Key interventions	Median survival time after presentation
Case	Jaundice, bone pain, symptomatic anemia, thrombocytopenia	TPE × 5 and corticosteroids	6 days
Case 1 [3]	Presyncope, back pain, nausea, vomiting and diaphoresis	Chemotherapy (FOLFOX) × 2 and corticosteroids	10 weeks
Case 2 [14]	Epistaxis	TPE and chemotherapy	Unspecified
Case 3 [11]	Anemia and thrombocytopenia	TPE and chemotherapy	2 months
Case 4 [15]	Back pain, fever	Palliative	49 days
Case 5 [16]	Jaundice, right upper quadrant pain and back pain.	Chemotherapy (ELF regimen); bisphosphonate; corticosteroids → later switched to chemotherapy (5-FU/leucovorin + oxaliplatin)	4 weeks
Case 6 [17]	Worsening anemia and thrombocytopenia	Palliative chemotherapy (cisplatin, 5FU, epirubicin)	9 months
Case 7 [18]	Back pain, fatigue and weight loss	Transfusion and TPE	3 days
Case 8 [19]	Back pain and easy fatigability	Transfusion; TPE and corticosteroids	2 days
Case 9 [20]	Refractory anemia and thrombocytopenia	TPE	42 days
Case 10 [21]	Mucocutaneous pallor, asthenia, adynamia, and hematemesis	Transfusion	21 days
Case 11 [22]	Back pain, fatigue and weakness.	Transfusion and steroids	1 day
Case 12 [23]	Dyspnea and spontaneous hematemesis.	Blood and platelets transfusion	17 days
Case 13 [24]	Dyspnea, jaundice and back pain	Transfusion	3 weeks
Case 14 [25]	Chest pain and dyspnea	Did not receive treatment	Few hours

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