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ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA WITH A POOR RESPONSE TO TREATMENT CAN BE AN INITIAL MANIFESTATION OF OCCULT SIGNET RING CELL CARCINOMA AND OTHER MALIGNANCIES

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ABSTRACT

Introduction: Acquired thrombotic thrombocytopenic purpura (aTTP) is a severe microangiopathic hemolytic anemia (MAHA) characterized by profound ADAMTS13 deficiency. MAHA can also manifest as a paraneoplastic syndrome, particularly in advanced malignancies, with cancer-associated MAHA (CA-MAHA) linked to signet ring cell carcinoma being exceptionally rare.

Case description: We present the case of a 42-year-old Arab male who initially presented with classic features of aTTP, including severe MAHA, profound thrombocytopenia, and renal and neurological dysfunction, confirmed by an ADAMTS13 activity level of 6%. Despite standard TTP therapy including plasma exchange, his atypical response and rapid deterioration prompted further investigation, leading to the diagnosis of aggressive, metastatic signet ring cell carcinoma. Tragically, he passed away less than a week after first presentation.

Conclusion: This case underscores the critical importance of maintaining a high index of suspicion for occult malignancies in patients with atypical thrombotic microangiopathy presentations, especially those with an incomplete response to conventional TTP therapies. It emphasizes the need for comprehensive diagnostic workup and a multidisciplinary approach to manage these complex and often fatal conditions, as early identification of underlying cancer is crucial for guiding appropriate, often tumour-directed, therapy and improving patient outcomes.

KEYWORDS

Microangiopathic hemolytic anemia, thrombotic thrombocytopenic purpura, thrombotic microangiopathy, ADAMTS13

LEARNING POINTS

- An atypical response to standard thrombotic thrombocytopenic purpura therapy warrants immediate investigation for alternate diagnoses.
- Underlying malignancy should be actively considered in patients presenting with thrombotic microangiopathy, particularly in cases with atypical features, poor response to standard therapy, or rapid clinical deterioration.

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INTRODUCTION

Microangiopathic haemolytic anaemia (MAHA) is a condition defined by the fragmentation of red blood cells due to their passage through constricted or obstructed small blood vessels. This phenomenon occurs secondary to intravascular platelet-fibrin thromboses within the microvasculature, which shear circulating erythrocytes and produce characteristic schistocytes on blood smear[1].

The term "thrombotic microangiopathy (TMA)" encompasses syndromes characterized by MAHA, thrombocytopenia, and thrombotic lesions within small blood vessels. The most prominent diagnoses falling under TMA are thrombotic thrombocytopenic purpura (TTP) and haemolytic uremic syndrome (HUS). However, numerous conditions, including preeclampsia, infections, certain drug reactions, hematopoietic stem cell transplantation, autoimmune diseases, and malignancies, can precipitate TMA, leading to what is termed secondary TMA[2].

MAHA can manifest as a paraneoplastic syndrome in the context of various malignancies, representing a grave and often fatal complication of metastatic cancer. While several tumour types have been linked to MAHA, including gastric, breast, and lung cancers, as well as malignancies of unknown primary origin, MAHA specifically associated with signet ring cell carcinoma is considered exceptionally rare[3].

Acquired thrombotic thrombocytopenic purpura (aTTP) is a severe haematological disorder characterized by the abrupt onset of severe MAHA and profound thrombocytopenia, often occurring in individuals with no prior medical history[4]. TTP arises from either a congenital or acquired deficiency or absence of ADAMTS13, a crucial von Willebrand factor-cleaving protease[4].

CASE DESCRIPTION

A 42-year-old Arab male, with no significant past medical or family history, presented to the emergency department exhibiting symptoms of fatigue, headache, and altered mental status. Patient also mention a more than 10 kg weight-loss during past 2 months with intermittent abdominal pain. Physical examination revealed widespread petechiae and ecchymoses on both skin and mucosal surfaces. Further assessment identified mild jaundice and neurological signs including confusion, and altered sensorium, notably without focal neurological deficits or seizures. No hepatomegaly, splenomegaly or lymphadenopathy were observed. Initial laboratory investigations yielded the following results *(Table 1)*.

Urinalysis revealed dark yellow urine with +3 haemoglobinuria. Taking into account low haemoglobin 7.2 g/dl, elevated LDH 2200 U/l and low haptoglobin <10 mg/dl, we considered the diagnosis of MAHA. A peripheral blood smear further supported this diagnosis demonstrating the presence of schistocytes, microspherocytes, and thrombocytopenia *(Fig. 1)*. Crucially, the ADAMTS13 activity level was found to be severely deficient at 6%, which, alongside the observed renal and neurological dysfunction, definitively confirmed the diagnosis of TTP.

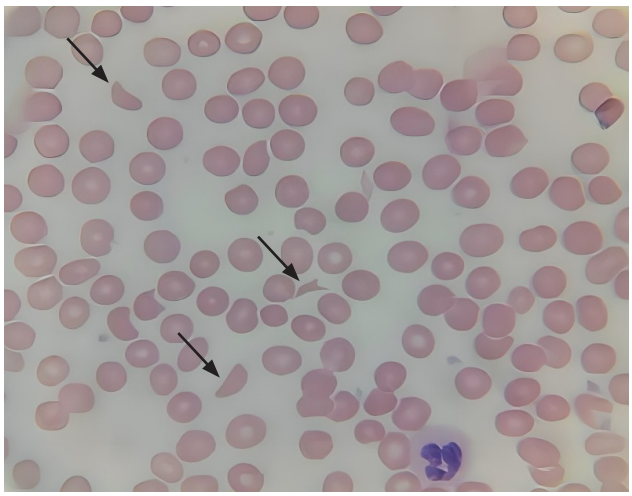


Figure 1. *A peripheral blood smear demonstrating the presence of schistocytes.*

The patient was initiated on daily plasma exchange at 1–1.5 plasma volumes per day, in conjunction with intravenous methylprednisolone 1,000 mg/day for three days. Despite this aggressive management, the haemolytic criteria showed only a partial response with haemoglobin rising to 9 g/dl, reticulocytes decreasing to 3.5%, total bilirubin decreasing to 2.2 mg/dl, lactate dehydrogenase (LDH) rising to 2900, aspartate aminotransferase as 82 U/l, alkaline phosphatase 1328 U/l and platelets showing a significant decrease with a count of 13,000/µl. which indicated a refractory response, raising suspicion for an underlying aetiology.

Subsequent imaging studies were performed to investigate the patient's condition further. A computed tomography scan revealed suspicious lesions involving the L1 and L3 lumbar vertebrae. Additionally, a 2 cm nodular lesion was noted at the tracheal bifurcation, suggestive of mediastinal lymphadenopathy. Bone scintigraphy demonstrated focal, heterogeneous areas of increased radiotracer uptake throughout the axial skeleton, consistent with possible bone metastases *(Fig. 2)*. However, a bone marrow biopsy revealed only hypocellularity (40%) with fibrosis, without evidence of malignancy. Upper gastrointestinal endoscopy identified a 2.5 cm ulcer with elevated margins, located 3 cm distal to the cardia, raising concern for malignant gastric ulceration. Lower gastrointestinal endoscopy (colonoscopy) revealed multiple colonic polyps, the largest measuring 4 mm in diameter. All detected polyps were endoscopically resected for histopathological evaluation which indicated hyperplastic polyps. Based on the histopathological evaluation of the malignant gastric ulcer, the patient was ultimately diagnosed with signet ring cell carcinoma *(Fig. 3)*. The patient's condition rapidly deteriorated, leading to a sudden death.

DISCUSSION

TMAs are characterized by MAHA, thrombocytopenia, and organ damage due to microvascular thrombosis[2].

Parameter	Result	Reference range
Haemoglobin (g/dl)	7.2	13.8-17.2
Haptoglobin (mg/dl)	<10	30-200
Haemoglobin A (%)	97.2	95-98
Haemoglobin A2 (%)	2.8	1.5-3.5
Reticulocytes (%)	5.6	0.5-2.5
Platelets (×10^3/µl)	38	150-450
White blood cell count (cells/µl)	11,200	4,500-11,000
Neutrophils (%)	48	40-60
Lymphocytes (%)	49	20-40
Monocytes (%)	3	2-8
Erythrocyte sedimentation rate (mm/hr)	58	<15
Prothrombin time (sec)	16.5	11-13.5
International normalized ratio	1.6	0.8-1.1
Activated partial thromboplastin time (sec)	39	25-35
D-dimer (µg/ml)	10.2	Up to 0.5
Coombs test	Negative	Negative
Vitamin B12 (pg/ml)	512	190-950
Vitamin B9 (ng/ml)	3.3	2.7-17
Iron (mcg/dl)	65	50-150
Total iron-binding capacity (µg/dl)	201	240-450
Ferritin (ng/ml)	>2000	Male: 30-400
C-reactive protein (mg/l)	280	<0.9
Albumin (g/dl)	3.9	3.5-5.5
Uric acid (mg/dl)	5.6	4.0-8.5
Lactate dehydrogenase (U/l)	2200	125-220
Total bilirubin (mg/dl)	3.1	0.1-1.2
Direct bilirubin (mg/dl)	0.4	<0.3
Indirect bilirubin (mg/dl)	2.7	0.2-0.8
Creatinine (mg/dl)	2.2	0.74-1.35
Calcium (mg/dl)	11	8.5-10.2
Alkaline phosphatase (U/l)	310	44-147
Alanine aminotransferase (U/l)	81	7-55
Aspartate aminotransferase (U/l)	52	8-48
Gamma-glutamyl transferase (U/l)	98	5-40

Table 1. Laboratory findings at time of admission.

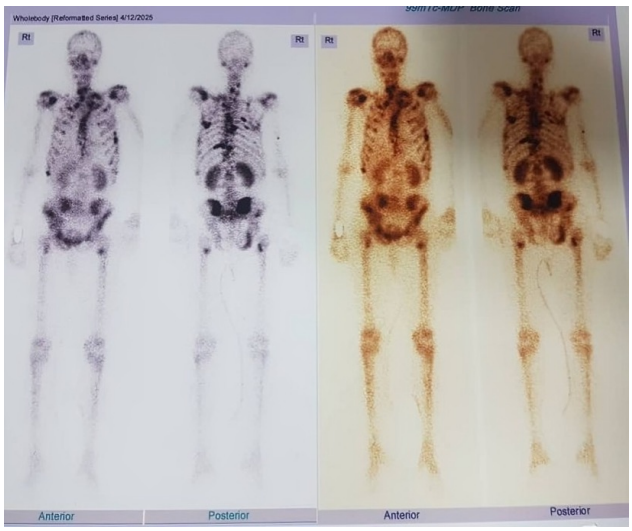


Figure 2. Bone scintigraphy demonstrated focal, heterogeneous areas of increased radiotracer uptake throughout the axial skeleton, consistent with possible bone metastases.

Cancer Associated thrombotic thrombocytopenic purpura (CA-TTP) is a severe secondary TMA caused by profound ADAMTS13 deficiency due to a cancer-driven process[4,5]. Our patient presented with classic features of aTTP, including profound thrombocytopenia (38 ×10^3/µl), severe MAHA (haemoglobin 7.2 g/dl, elevated LDH 2200 U/l, low haptoglobin <10 mg/dl, schistocytes), and significant neurological (disorientation, altered sensorium) and renal (creatinine 2.2 mg/dl) involvement. The diagnosis of TTP was definitively confirmed by a severely deficient ADAMTS13 activity level of 6%, aligning strongly with established criteria with the subsequent malignancy workup revealing an underlying neoplasm, leading to the final diagnosis of CA-TTP.

Secondary MAHA, particularly as a paraneoplastic syndrome in solid tumours, represents a serious complication of malignancy. The pathogenesis of CA-MAHA is multifactorial, involving tumour-derived factors, procoagulants, immune complexes, certain chemotherapeutic agents, fibrinoid necrosis of the bone marrow, and tumour cell emboli within arteries, arterioles, and capillaries[5].

While several tumour types have been linked to MAHA, including gastric, breast, and lung cancers, as well as malignancies of unknown primary origin, MAHA specifically associated with signet ring cell carcinoma is considered exceptionally rare[3]. Our patient's diagnosis of signet ring cell carcinoma, following an initial presentation consistent with TTP, highlights this rare association.

Furthermore, CA-MAHA is generally accompanied by multiple bone or bone marrow metastases which represents a poor prognosis, and many studies have recommended a thorough tumour workup, including bone marrow examination, in cases of progressive MAHA of unknown origin[6]. In contrast, despite bone scintigraphy indicating possible bone metastases in our patient, the bone marrow biopsy did not show signs of malignancy,

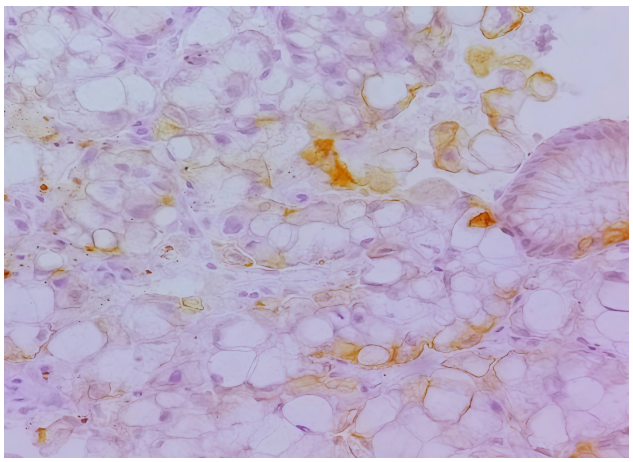


Figure 3. Histologic section of a malignant gastric ulcer infiltrated by signet ring cells. Immunohistochemistry shows cytoplasmic positivity for cytokeratin (CK), confirming epithelial origin. CK7 and epithelial membrane antigen are negative, supporting a diagnosis of signet ring cell carcinoma.

presenting a diagnostic challenge. Distinguishing between primary TTP and secondary TTP, particularly CA-TTP, is crucial due to differing management strategies. However, the patient's partial response to standard TTP therapy (daily plasma exchange and high-dose corticosteroids) was atypical, raising suspicion for an underlying etiology. This refractory response, coupled with the rapid progression of the underlying metastatic signet ring cell carcinoma, suggests that the malignancy likely played a significant role in exacerbating or initiating the TMA, complicating the distinction between autoimmune TTP and a cancer-driven process.

In fact, numerous studies suggest that malignancy should be considered in cases of poor response to treatment for TTP. Additionally, respiratory symptoms and bone pain have been identified as potential clues to an underlying malignancy. In this patient, despite the absence of respiratory or bone-related symptoms, the response to treatment was notably poor, raising the possibility of an associated malignancy[7,8].

Also, it is important to distinguish between typical CA-MAHA and cancer-associated TTP (CA-TTP). In cancer-associated TMA not fulfilling TTP criteria, ADAMTS13 activity is typically normal or only mildly reduced, generally remaining above 20%. This is in contrast to TTP — whether idiopathic, immune-mediated, or malignancy-associated — where ADAMTS13 activity is severely reduced to below 10%. Our patient's ADAMTS13 activity of 6% is consistent with the latter diagnosis of CA-TTP, meeting the established diagnostic threshold for severe ADAMTS13 deficiency[9].

Prognosis for patients with CA-MAHA, especially CA-TTP, is generally poor, particularly with bone marrow metastases with most CA-MAHA cases result in death within a few weeks[10]. Our patient's clinical course was marked by rapid deterioration, leading to death only 7 days after initial presentation.

There is no definitive treatment for CA-MAHA, with optimal management focusing on reducing tumour burden through specific chemotherapy protocols initiated as soon as possible[6]. Despite the urgent need for tumour-directed therapy, our patient's poor prognosis and rapid decline precluded the initiation of specific chemotherapy protocols, before a definitive diagnosis of the primary cancer site could be established.

CONCLUSION

This case report highlights the intricate and often challenging diagnostic landscape encountered when TMA coexists with underlying malignancy. From this case, several key points emerge. Firstly, a high index of suspicion for underlying malignancy is warranted in patients presenting with TMA, especially those with atypical features, an incomplete response to conventional TTP therapies, or rapid clinical decline. Secondly, while ADAMTS13 activity testing is indispensable for TTP diagnosis, it should be interpreted within the broader clinical context, considering the potential for secondary TMAs. Finally, the case underscores the critical need for a multidisciplinary approach in managing these complex patients, involving haematologists, oncologists, and other specialists, to ensure a comprehensive diagnostic workup and timely initiation of appropriate, often tumour-directed, therapy. The unfortunate rapid demise of this patient serves as a stark reminder of the aggressive nature of both CA-MAHA and advanced malignancies, emphasizing the urgency of early recognition and tailored management strategies to improve patient outcomes in these challenging scenarios.

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