Case Report

The role of chemotherapy in gastric cancer-related microangiopathic haemolytic anaemia

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Abstract: We report a case of a previously well 46-year-old man who presented with microangiopathic haemolytic anaemia (MAHA) of unknown origin. After extensive investigations, he was diagnosed with cancer-related microangiopathic haemolytic anaemia (CR-MAHA) secondary to gastric adenocarcinoma. Initial treatment with plasmapheresis was ineffective, but the patient's haematological abnormalities improved markedly with chemotherapy directed against his gastric cancer. Our case amplifies previous experience of gastric cancer-associated MAHA which responded to treatment with chemotherapy. We review current understanding of the proposed pathophysiology of CR-MAHA and conclude that this condition is ideally treated with chemotherapy.

Keywords: Thrombotic microangiopathies; anemia; hemolytic; thrombocytopenia; stomach neoplasms; drug therapy

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Introduction

Microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia are the key clinical features of thrombotic microangiopathy (TMA) syndromes, which include primary and secondary TMA syndromes.(1) Common underlying disorders associated with secondary TMA include malignancy, systemic infection, severe hypertension and severe pre-eclampsia, eclampsia or HELLP syndrome (1). Cancer-related MAHA (CR-MAHA) refers to non-immune haemolytic anaemia caused by intravascular red blood cell fragmentation in the setting of malignancy and was first described by Brain *et al.* (2). Investigations typically reveal a negative Coombs' test and fragmented red blood cells, or schistocytes, on peripheral blood smear. Gastric cancer is the most commonly reported malignancy associated with MAHA, followed by breast, prostate, lung and cancer of unknown origin (3). We report a case of a patient presenting with CR-MAHA secondary to a gastric adenocarcinoma treated with plasmapheresis and chemotherapy. We also review previous cases of gastric cancer-associated MAHA and current understanding of their pathophysiology and optimal treatment.

Case presentation

A previously well 46-year-old man presented with several weeks of increasing lethargy and 2 days of palpitations and shortness of breath on exertion. The patient denied any episodes of melaena, rectal bleeding or haematemesis. He did not have any significant medical or family history, did not take regular medications and had no known drug allergies.

On examination, the patient appeared pale and was neurologically intact. His blood pressure was stable, but he was febrile to 38.1 ℃ and mildly tachycardic with a heart rate of 104 beats per minute. His abdomen was soft and non-tender, with a palpable liver edge and tippable spleen.

A full blood count revealed normocytic, normochromic anaemia with a haemoglobin of 53 g/L. He was thrombocytopenic with platelets of 82×10^9/L and his white cells were mildly elevated at 11.36×10^9/L. Haematinic

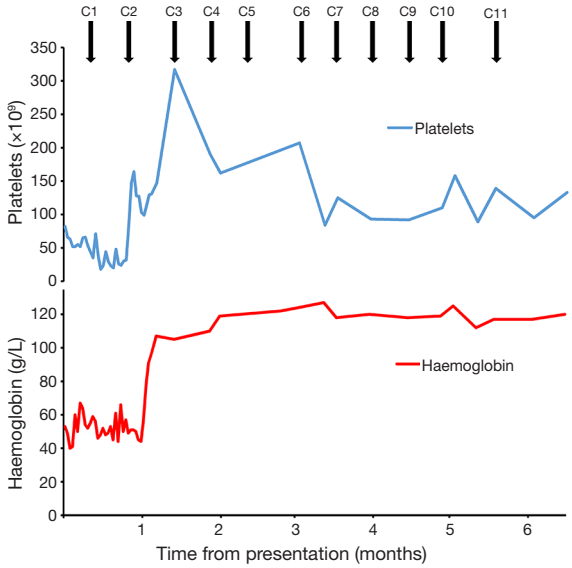

Figure 1 Changes in patient's haemoglobin and platelet in response to chemotherapy (cycles of chemotherapy marked with black arrows).

studies showed normal ferritin, iron saturation and red cell folate levels. A positive haemolysis screen revealed elevated LDH (553 unit/L), elevated reticulocytes (223.6×10^9/L) and low haptoglobin (<0.1 g/L). A direct antiglobulin test (Direct Coombs test) was negative. His blood film showed marked polychromasia, spherocytes, schistocytes and nucleated red blood cells consistent with MAHA. Coagulation studies showed mildly elevated PT 18.7 and INR 1.6, with normal APTT 29.6. His ADAMTS13 levels were normal at 30%, as was his creatinine at 89 µmol/L.

The patient was admitted for further inpatient investigation of his thrombocytopenia and anaemia. Early in his admission, he was transfusion-dependent and required up to 2 units of packed red blood cells each day. He also received multiple platelet transfusions when his platelets fell to <20×10^9/L. Various investigations performed to look for an underlying cause of his abnormal blood count were normal, including HIV antigen/antibody testing, serum electrophoresis and autoimmune screen (ANA, ANCA, dsDNA, C3 and C4 levels, ENA).

A Vascath was inserted to facilitate treatment with 7 days of plasmapheresis in conjunction with prednisone 100 mg daily, with no resultant improvement in the patient's anaemia. A bone marrow aspirate and trephine showed a hypercellular bone marrow with infiltration by non-haemotopoietic cells. On immunohistochemistry, these infiltrating cells were consistent with adenocarcinoma, likely arising from the upper gastro-intestinal tract.

Gastroscopy revealed an actively bleeding, ulcerated, malignant gastric tumour on the anterior wall and greater curvature of the stomach. Computed tomography (CT) of his abdomen and chest showed widespread non-specific prominent upper abdominal para-aortic lymph nodes measuring up to 10 mm with no evidence of any visceral lesions. A FDG-PET scan showed tracer uptake in his primary gastric tumour, as well as in loco-regional abdominal lymph nodes, axial skeleton and medullary cavities of long bones consistent with bone metastases and bone marrow infiltration.

The patient was commenced on modified FOLFOX-6 chemotherapy (5-fluorouracil 2,400 mg/m^2 continuous intravenous infusion over 46 h D1, leucovorin 350 mg D1, oxaliplatin 85 mg/m^2 D1 q2weekly) for metastatic gastric cancer. After 2 cycles of chemotherapy, his haemoglobin stabilised at 91 g/L. He did not require further red blood cell transfusions and his haemoglobin continued to rise to 125 g/L with further cycles of chemotherapy (*Figure 1*). The patient's CA19.9 was elevated at 332 kU/L when measured shortly after commencing chemotherapy and fell with further cycles of treatment. Progress CT scan showed a decrease in the size of his intra-abdominal lymphadenopathy, and gastric thickening and sclerotic bone metastases which have remained stable over a 7-month period.

The patient was initially treated with 11 cycles of modified FOLFOX-6 chemotherapy. His oxaliplatin was subsequently ceased due to tetany and early neuropathic symptoms. He continues on treatment with single agent 5FU (5-fluorouracil 2,400 mg/m^2 continuous intravenous infusion over 46 h D1, leucovorin 350 mg D1, q2weekly) and remains transfusion-free more than 7 months after his initial presentation.

Discussion

We identified 24 case reports of patients with gastric cancer-associated MAHA who underwent treatment with chemotherapy (*Table 1*) (4-24). The median age of reported cases was 51 years (range, 19–71 years) and cases were reported more frequently in men than women. This is younger than the median age at diagnosis (69 years) for the general gastric cancer population, while the gender distribution is concordant (25). Eight patients had been previously diagnosed with and treated for gastric cancer, so their haematological derangements heralded disease recurrence. Only two patients were reported to have

Table 1 Published cases of gastric cancer-associated MAHA treated with chemotherapy

Reference	Age	Sex	Histopathology	Recurrence	Hb (g/L)	Platelets ($\times 10^9$)	BM infiltration	Plasma-pheresis	Chemotherapy 1st line	Chemotherapy subsequent	Survival after chemotherapy or presentation
Alexopoulou 2002 (4)	70	M	Gastric adenocarcinoma	Yes	72	80	No	Yes	Carboplatin, paclitaxel		14 days
Antman 1979 (5)	63	M	Gastric signet ring adenocarcinoma	No	HCT 0.2	85	Yes	No	5FU, adriamycin, mitomycin C	Cyclophosphamide	3 months
Arkenau 2005 (6)	62	M	Signet ring carcinoma	No	107	86	NR	No	Etoposide 120 mg/m^2, leucovorin 300 mg/m^2, 5FU 500 mg/m^2 D1–3 q3weekly	5FU 2,000 mg/m^2, leucovorin 500 mg/m^2, oxaliplatin 130 mg/m^2 D1 q2weekly	12 months
Bisetti 1985 (7)	19	M	Mucin-producing adenocarcinoma	No	100	98	Yes	No	5FU, adriamycin, mitomycin C	–	6 days
Blot 2002 (8)	61	F	Oesophageal adenocarcinoma	Yes	NR	NR	Yes	No	Infusional 5FU 250 mg/day	–	35 days
Carr 1986 (9)	60	M	Gastric adenocarcinoma	Yes	NR	43	Yes	Yes	5FU, adriamycin, mitomycin C	–	6 months
Chang 2003 (10)	65	F	Gastric adenocarcinoma	No	80	86	Yes	No	Paclitaxel	–	11 months
Elliott 2010 (11)	50	M	Gastric adenocarcinoma	Yes	73	50	Yes	Yes	Docetaxel, 5FU, platinum	–	12 days
Hansen 1980 (12)	25	F	Gastric adenocarcinoma	No	74	100	Yes	No	5FU 600 mg/m^2 D1 D8 D15, adriamycin 40 mg/m^2 D1, q3weekly	Mitomycin-C 10 mg/m^2 q4weekly	7 months
Kadikoylu 2010 (13)	28	F	Signet ring adenocarcinoma	No	52	111	Yes	Yes	Cisplatin, infusional 5FU, leucovorin		NR
Kaidar-Person 2011 (14)	32	F	Gastric signet ring cell carcinoma	No	NR	NR	Yes	Yes	Cisplatin 20 mg/m^2 D1-5, etoposide 60 mg/m^2 D1–5 q3weekly	5FU 425 mg/m^2/day D1-5, leucovorin 20 mg/m^2 D1–5, weekly cetuximab 500 mg	9 weeks (approx)
Kaidar-Person 2011 (14)	45	M	Gastric signet ring adenocarcinoma	No	59	50	Yes	No	Cisplatin 60 mg/m^2 D1, 5FU 600 mg/m^2/day D1–4 q3weekly		7 weeks (approx)
Kanou 1986 (15)	71	F	Gastric carcinoma	No	56	15.6	Yes	No	Mitomycin C 10 mg, neothramycin, FOY		3 months
Martin 2010 (16)	47	F	Signet ring adenocarcinoma	Yes	49	9	Yes	No	Cisplatin 80 mg/m^2 D1, 5FU 1,000 mg/m^2/day D1–5, zoledronic acid	2nd line: FOLFIRI 3rd line: docetaxel 75mg/m^2 D1, cisplatin 75mg/m^2 D1, 5FU 750mg/m^2/day D1–5	19 months

Table 1 (*continued*)

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Reference	Age	Sex	Histopathology	Recurrence	Hb (g/L)	Platelets ($\times 10^9$)	BM infiltration	Plasma-pheresis	Chemotherapy 1st line	Chemotherapy subsequent	Survival after chemotherapy or presentation
Mauron 2010 (17)	69	F	Mucin-producing adenocarcinoma	No	69	104	Yes	No	Adriamycin	–	4 weeks
Noda 1996 (18)	57	M	Signet ring carcinoma	Yes	58	39	Yes	No	Methotrexate 100 mg/m^2 D1, 5FU 600 mg/m^2 D1, leucovorin 10 mg/m^2 D2–3 weekly	–	10 months
Oberic 2009 (19)	38	F	Gastric adenocarcinoma		75	39	Yes	Yes	5FU, cisplatin, hydroxyurea	–	6 days
Oberic 2009 (19)	51	M	Gastric adenocarcinoma		74	74	Yes	No	Gemcitabine, oxaliplatin, leucovorin, 5FU, irinotecan, docetaxel	–	4 months
Oberic 2009 (19)	52	M	Gastric adenocarcinoma		68	18	Yes	No	5FU, cisplatin, hydroxyurea	–	3 months
Otrock 2007 (20)	51	F	Gastric signet ring carcinoma	No	67	40	Yes	Yes	Vincristine 2 mg	Cisplatin 50 mg/m^2 D1, 5FU 150 mg/m^2 D1, D8, leucovorin 500 mg D1, D8 q2weekly	3 months
Ozguroglu 1999 (21)	66	M	Gastric adenocarcinoma	No	70	250	No	No	5FU 425 mg/m^2, leucovorin 20 mg/m^2	–	26 months
Rauh 2011 (22)	NR	NR	Gastric adenocarcinoma with few signet ring cells	Yes	43	45	Yes	No	Cisplatin, 5FU	–	2 days
Sanatani 2013 (23)	49	M	Gastric adenocarcinoma	No	52	76	NR	Yes	Cisplatin 50 mg/m^2 D1, 5FU 1,000 mg/m^2/day D1-4 q3weekly	Docetaxel 25 mg/m^2 D1, 8, 15, cisplatin 60 mg/m^2 D1, 5FU 200 mg/m^2 D1-21, q3weekly	16 months
Takeuchi 1983 (24)	43	M	Gastric adenocarcinoma	Yes	78	62	NR	No	Mitomycin C, 5FU, Ara-C, heparin	–	6 months
Current case	46	M	Gastric adenocarcinoma	No	53	82	Yes	Yes	5-FU 1,200 mg/m^2/day D1–2, leucovorin 350 mg D1 (plus oxaliplatin 85 mg/m^2 D1 for 11 cycles) q2weekly	–	7+ months

NR, not reported.

neurological symptoms (including confusion, disorientation and seizure) while none of the cases reported associated renal dysfunction (9,13). This contrasts with neurological and renal involvement typically associated with primary TMA syndromes such as ADAMTS13 deficiency-mediated TMA and Shiga toxin-mediated TMA [previously known as thrombocytopenic purpura (TTP) and haemolytic-uraemic syndrome (HUS), respectively] (1).

Twenty-one patients in our literature review underwent bone marrow biopsy, of whom 19 were found to have bone marrow infiltration by malignant cells. This suggests that bone marrow failure due to malignant replacement may contribute to the anaemia and thrombocytopenia seen in these patients. This is unlikely to be the only explanation for these abnormalities, however, as not all patients with malignant bone marrow infiltration develop peripheral blood features of MAHA (3). The pathogenesis of CR-MAHA is poorly understood, as it appears to differ from primary TMA syndromes such as hereditary and immune-mediated TTP and HUS (3,23). Current theories implicate red cell fragmentation and platelet destruction in small vessels of malignant tissue, potentially mediated by tumour-induced cytokine production and/or endothelial injury (3). We hypothesise that chemotherapy leads to improvement of haematological parameters by two mechanisms: it reverses the processes leading to microangiopathic destruction of red blood cells and platelets; and it also clears malignant cells from the bone marrow, allowing recovery of normal haematopoietic cells and blood counts.

In the literature, seven patients with gastric cancer-related MAHA underwent plasmapheresis, of whom only one patient experienced an improvement in clinical symptoms and haematological indices. Primary ADAMTS13 deficiency-mediated TMA is an autoimmune disorder caused by inhibition of ADAMTS13 activity by ADAMTS13-directed antibodies, which are removed during treatment with plasmapheresis (1). A case series of 4 patients with gastric cancer-associated MAHA reported that none had sufficiently low ADAMTS13 levels warranting measurement of ADAMTS13 antibodies (19). In a report of 10 patients referred for plasmapheresis for various malignancy-related MAHA, which included one case of gastric cancer, no patient had severe ADAMTS13 deficiency or responded to plasmapheresis (11). The normal ADAMTS13 levels measured in our patient is consistent with these other reports of CR-MAHA, as is his lack of improvement with plasmapheresis, providing evidence that antibodies are not implicated in the pathogenesis of CR-MAHA. Hence plasmapheresis in CR-MAHA appears to be of little use and treatment of the underlying cancer should be the focus of management.

The patients in our review were treated with a variety of chemotherapy regimens, resulting in a wide spread of survival times ranging from 6 days up to 26 months (median 3 months). Most patients (20 of 24) were treated with a fluoropyrimidine and/or platinum agent, reflecting the chemotherapy drugs in common usage in gastric carcinoma. There was no obvious association between any particular drug and prolonged survival.

In conclusion, malignancy-associated MAHA and thrombocytopenia are secondary TMA syndromes that have been reported most commonly in gastric cancers. They may represent the first presentation of metastatic gastric cancer or disease recurrence. Plasmapheresis appears to have a limited role in their treatment. This is most likely due to the absence of ADAMTS13-directed antibodies, which feature prominently in primary autoimmune TMA syndromes. Chemotherapy should be the mainstay of treatment for CR-MAHA as it improves haematological parameters, although overall prognosis is still poor with a median survival of 3 months with chemotherapy.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this article and any accompanying images.

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