Cancer-Related Microangiopathic Hemolytic Anemia
Clinical and Laboratory Features in 168 Reported Cases

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Abstract: Cancer-related microangiopathic hemolytic anemia (CR-MAHA) is a paraneoplastic syndrome characterized by Coombs-negative hemolytic anemia with schistocytes and thrombocytopenia. We reviewed and analyzed all cases of CR-MAHA reported since 1979 (the time of the last published review on this topic) according to predefined criteria. We found 154 cases associated with solid cancer and 14 with lymphoma. Among the solid cancers, gastric, breast, prostate, lung, and cancer of unknown primary (CUP) were most common; 91.8% of cancers were metastatic, and in 19.4% of solid cancers CR-MAHA did not occur until recurrence of cancer. Lymphoma cases included Hodgkin disease, angiotropic lymphoma, diffuse large cell lymphoma, and myeloma. Evaluation of the clinical and laboratory findings revealed that only a minority of cases presented with the features of thrombotic thrombocytopenic purpura (TTP) or atypical hemolytic uremic syndrome (aHUS), with the exception of prostate cancer, where aHUS was a common presentation. Compared to hereditary or immune TTP or aHUS, disseminated intravascular coagulation and pulmonary symptoms were more common in CR-MAHA. Plasma exchange or fresh frozen plasma was rarely effective except in prostate cancer patients with aHUS. CR-MAHA responded to antitumor therapy in many patients with gastric, breast, lung, and CUP cancers. These patients had a superior survival compared to patients without chemotherapy. Compared to the prognosis of patients with metastatic cancer without CR-MAHA, the prognosis of CR-MAHA patients was greatly inferior. There is evidence that some cases of CR-MAHA in lymphoma are immune mediated.

(*Medicine* 2012;91: 00–00)

Abbreviations: ADAMTS = a disintegrin-like and metalloprotease with thrombospondin type 1 repeats, aHUS = atypical hemolytic uremic syndrome, CR-MAHA = cancer-related microangiopathic hemolytic anemia, CUP = cancer of unknown primary, DIC = disseminated intravascular coagulation, MAHA = microangiopathic hemolytic anemia, NHL = non-Hodgkin lymphoma, TTP = thrombotic thrombocytopenic purpura.

INTRODUCTION

Microangiopathic hemolytic anemia (MAHA) is a typical feature of hereditary and immune-mediated thrombotic thrombocytopenic purpura (TTP)[49,93] and of atypical hemolytic uremic syndrome (aHUS).[105] Secondary causes of TTP/aHUS are drugs, collagen vascular disorders, surgery, infections, stem cell transplantation, and malignancies. We conducted the cur-

rent review of cancer-related MAHA (CR-MAHA). CR-MAHA is usually associated with thrombocytopenia and clinical and/or pathologic evidence of microvascular thrombosis in various organs. Since it shares many features with hereditary or acquired immune TTP and/or aHUS, a popular name for this disease is "CR-MAHA with thrombocytopenia (TTP/HUS)." Others, in particular pathologists, prefer the name "thrombotic microangiopathy," a name that emphasizes the tissue changes associated with this clinical syndrome.

To our knowledge, CR-MAHA was first described by Brain et al.[16] Antman et al[8] described the essential causes and clinical and laboratory features of CR-MAHA in an extensive review published in this journal in 1979. Since that review, a number of new clinical and laboratory data, pathologic findings, and treatment advances have been reported in larger[43,106] and smaller case series[25,38,41,48,141] or case reports. CR-MAHA has been reviewed several times,[55,123] but without a data analysis of the reported cases.

We conducted the current study to analyze published data since 1979 on CR-MAHA according to predefined criteria, to get a broader view of this syndrome.

PATIENTS AND METHODS

We retrieved all reported cases of presumed CR-MAHA (TTP/HUS) since 1979 (the date of the review of Antman et al [8]) from the literature using MEDLINE via PubMed (National Library of Medicine, Bethesda, MD). The search terms were "microangiopathic hemolytic anemia and cancer or specific cancer site," "thrombotic thrombocytopenic purpura or HUS and cancer or specific cancer sites," and "microangiopathic hemolytic anemia and lymphoma." We also searched the reference lists of published case reports for additional cases.

The basic inclusion criterion for cases was a definite diagnosis of cancer associated with Coombs-negative hemolytic anemia with schistocytes and thrombocytopenia. We included all accessible papers published in English, German, French, Italian, and Spanish. Papers in other languages were included only if there was an extensive English abstract, and detailed laboratory data were presented in tables or figures in English. We excluded all cases in languages not mentioned above, cases published in papers that could not be retrieved, and cases with uncertain diagnosis of MAHA or insufficient data. We also excluded all cases with potentially drug-induced MAHA (patients in whom MAHA [TTP/HUS] occurred <1 year after the end of chemotherapy), except patients after autologous stem cell transplantation.

Data Collection and Definitions

Using predefined criteria, we collected and analyzed the following data: 1) Site, histology, and stage of cancer. Metastatic cancers were cancers with distant metastases. 2) Time of diagnosis of MAHA from or to cancer (prior, concurrent, postoperative, or at recurrence). 3) Relevant clinical signs such as central nervous symptoms, pulmonary symptoms, and diffuse bleeding. We counted only severe central nervous system symptoms,

according to the criteria of Vesely et al.[152] Pulmonary symptoms or findings included severe noncardiac dyspnea, pulmonary reticulonodular infiltrates (on X-ray), and pulmonary carcinomatous lymphangitis, tumor emboli, and pulmonary TTP (at autopsy). 4) Laboratory features such as renal abnormalities (creatinine levels), leukoerythroblastic blood presentation (defined according to Delsol et al[35]), hypofibrinogenemia (fibrinogen <200 mg/dL), elevated dimer or fibrin degradation products, and, in a few cases, ADAMTS 13 (a disintegrin-like and metalloprotease with thrombospondin type 1 repeats, 13) activity. Disseminated intravascular coagulation (DIC) could not be classified according to the ISTH criteria,[144] because thrombocytopenia and fibrin-related markers[11] are often elevated in cancers without DIC and/or MAHA. We assumed overt DIC—similar to Sallahet al[128]—if the fibrinogen level was below 200 mg/dL and the fibrin degradation products and/or dimer was elevated. Acute renal failure was defined as an increase of creatinine by >0.5 mg/dL per day or to >4 mg/dL.[152] Patients with MAHA and severe neurologic symptoms[152] were classified as "MAHA (TTP like)," and those with acute renal failure, as "MAHA (HUS like)." All others were classified as "MAHA (not specified)." 5) Histologic findings (biopsy or autopsy) with particular reference to marrow infiltration, tumor emboli, and fibrin thrombi in various organs. 6) Efficacy of treatment with plasma exchange, fresh frozen plasma, hormonal treatment, cancer surgery, and/or chemotherapy. In patients undergoing hormonal treatment and/or chemotherapy, the response of MAHA to treatment was recorded.

The data extraction and analysis were made independently by the 2 authors and the final result was resolved by consensus.

Statistical Methods

For the Kaplan-Meier analysis, overall survival was taken as endpoint. If no data on survival were provided, disease-free survival was used as a substitute for overall survival. Patients undergoing chemotherapy received many different treatments. They were included in the analysis even when chemotherapy was not according to the current state of the art. Patients were included in the chemotherapy group even when they had prior plasma exchange or fresh frozen plasma. In prostate and breast cancer, hormonal treatment was also counted as chemotherapy. In the category "patients without chemotherapy," all patients were included who had no chemotherapy, independent of whether they had no therapy at all or plasma exchange, fresh frozen plasma, or hemodialysis. The survival times of individual patients were rounded to nearest half-month intervals. Because response criteria were rarely provided, we used only the term "response," but probably most patients had at least a partial remission.

RESULTS

Malignancies Associated With MAHA

We identified 168 cases of CR-MAHA reported since the review of Antman et al,[8] 154 in solid cancers and 14 in lymphoma. We did not count cancer patients with postoperative MAHA. The cancers associated with MAHA are listed in Table 1; the most common cancers were gastric, breast, prostate, lung, and cancer of unknown primary (CUP), in this order. Abdominal, genitourinary, and endocrine cancers were much less common. Abdominal cancers included 3 cases of colon cancer,[79,84,106] 3 of pancreatic,[43,141,156] 3 of liver,[106,134] and 1 case of appendix cancer.[99] Genitourinary cancers included 1 case of renal cell[43] and 2 cases of ovarian cancer.[63,119] MAHA occurred in a relatively small number of patients with Hodgkin disease, aggressive non-Hodgkin lymphoma (NHL), and myeloma.

TABLE 1. Malignancies Associated With MAHA

Cancer Site	No.	Reference
Gastric	44	[4,5,9,14,15,21,24,27,32,38,52,54,58, 65,67,68,71,77,78,89,91,92,103,106, 108–111,115,124,131,141,142,151]
Breast	36	[10,12,22,24,29,38,40,41,43,47,48,60, 88,98,104,106,126,139,153,155,160]
Prostate	23	[18,39,48,70,83,90,96,97,106,129,133, 137,147,150]
Lung	16	[17,24,33,38,43,101,106,115,120,135]
CUP	12	[1,9,52,67,82,87,100,106,117,141,148]
Abdominal	10	[43,79,84,99,106,134,141,156]
Genitourinary	3	[43,63,119]
Endocrine tumor	6	[38,51,74,75,127,132]
Other tumor	4	[13,43,94,102]
Lymphoma	14	[7,20,31,37,43,48,61,69,72,95,136]

In the large majority of patients (91.8%) the solid cancer was metastatic at the time of MAHA (Table 2). However, there were some cases of gastric, lung, and prostate cancer that were apparently not metastatic at the time of MAHA. All evaluable gastric, breast, prostate, and CUP cancers; 5 of 10 abdominal cancers; and 2 of 3 evaluable genitourinary cancers were adenocarcinomas. Among the lung cancers 5 were adenocarcinomas, 4 were small cell cancers, and 2 were squamous cell cancers. In most cases MAHA was diagnosed concurrently with the first diagnosis of the cancer, but in 30 (19.4%) cases it was not diagnosed until the time of cancer recurrence. MAHA at the time of recurrence was most common in gastric and breast cancers (23/80), but much rarer in other cancers. The median time to MAHA-associated recurrence was 7 years (range, 7 mo to 13 yr) in gastric, 4 years (range, 6 mo to 10.5 yr) in breast, and 3 years (range, 14 mo to 12 yr) in prostate cancer. In a few cases of CR-MAHA at cancer diagnosis, a relapse of cancer was again associated with MAHA,[33,106] but in some other cases MAHA did not recur when the cancer relapsed.[70,106]

The median age of gastric patients with CR-MAHA was 52 years (5 yr younger than patients without MAHA), and the female to male ratio was 1:1 (in contrast to 2–3:1 in patients without MAHA[2]). The median age of women with CR-MAHA and breast cancer was 54 years (range, 19–82 yr).

TTP-Like, aHUS-Like, and Not Specified MAHA in Solid Tumors

In most cases of gastric, breast, lung, CUP, and abdominal cancers, the patients did not show clinical or laboratory features of TTP or aHUS, but essentially had MAHA with no or only mild signs of cerebral dysfunction and/or renal abnormalities (see Table 2). However, in each cancer category there were a few cases of typical TTP or aHUS. In prostate cancer a high proportion of patients (17/23) had an aHUS-like presentation. In some of these cases aHUS was recurrent.[150]

Bone Marrow Findings

In the vast majority (90/111; 81.1%) of evaluable cases, bone marrow infiltration with cancer cells was documented (see Table 2), by bone marrow biopsy or in some cases only at autopsy. Unfortunately, in a relatively large number (43/154; 28%) of cases, bone marrow biopsies were not done or were not evaluable. The extent of marrow infiltration was not described in all cases, but from a number of well-documented cases[38] it is

TABLE 2. Clinical and Hematologic Data of Patients With CR-MAHA

Characteristic	All Solid Cancers	Gastric	Breast	Prostate	Lung	CUP	Other*
No. of patients	154	44	36	23	16	12	23
CR-MAHA at recurrence	30/154 (19.4%)	10	13	7	0	0	0
Metastatic, no. (%)†	134/146 (91.8%)	39	33	21	13	12	16
Nonmetastatic, no. (%)†	12/146 (8.2%)	3	0	2	3	0	4
Patients with TTP-like clinical picture	11	1	3	2	1	0	4
Patients with HUS-like clinical picture	26	3	1	17	0	1	4
BM infiltration‡	90/111 (81.1%)	33	24	4	7	10	12
No BM infiltration‡	21/111 (18.9%)	5	1	7	3	0	5
Leukoerythroblastic blood presentation	36	11	11	3	6	4	1
Hypofibrinogenemia (<200 mg/dL)	39/108 (36.1%)	13/28	8/17	5/21	2/13	4/9	7/20
Pulmonary complications	49	16	13	4	8	3	5

Abbreviation: BM = bone marrow.

*Other tumors include abdominal, genitourinary, endocrine, and various cancers.

†No data for 8 patients.

‡No data for 43 patients.

clear that the extent of infiltration was not uniform, and MAHA occurred in many cases with only limited (focal) infiltration. Most cases with bone marrow infiltration also had bone metastases. Bone marrow infiltration was sometimes associated with bone marrow necrosis[25,78,109,124,135,141] or fibrosis.[38,106] Tumor emboli in the marrow have been found in some cases at autopsy.[141]

Pulmonary Abnormalities in CR-MAHA

Clinical, radiologic, or histologic evidence of pulmonary involvement was documented in 49 cases. Clinical findings included noncardiac dyspnea and respiratory distress syndrome. Radiologic findings were reticulonodular infiltration of the lung.[43,67,89,126,135,156] Histologic findings of pulmonary involvement (most at autopsy) were pulmonary carcinomatous lymphangitis,[14,92,115,151] pulmonary microvascular tumor emboli,[12,28,43,151] and pulmonary thrombotic microangiopathy.[47,108,115,116,131]

Thromboembolic Complications and Skin Necrosis

Venous thromboembolism (deep venous thrombosis, pulmonary embolism, cerebral sinus vein thrombosis) was observed in 5 cases,[38,68,96,120,139] and skin necrosis in 2 cases.[78,100]

Association of CR-MAHA With Hypofibrinogenemia

Thirty-nine of 108 patients had fibrinogen levels <200 mg/dL, usually with elevated levels of fibrin degradation products or dimer (see Table 2). These patients most likely had overt DIC, although formally they did not fulfill the ISTH criteria for DIC. In most cases the fibrinogen level was not excessively reduced, and clinically none of these patients had definite signs of severe fibrinogen depletion (that is, bleeding from puncture sites). Nevertheless the bleeding rate in CR-MAHA patients was high, and many patients died from cerebral bleedings.

ADAMTS 13 Deficiency and CR-MAHA

ADAMTS 13 activity was determined in a limited number of cases. In most cases ADAMTS 13 was either normal or moderately reduced, as expected in metastatic malignancy.[42,86] However, in a small number of cases,[15,68,75,106] ADAMTS 13 activity was very low or absent at presentation and normalized

after successful treatment of MAHA and cancer. In MAHA associated with lymphoma, ADAMTS 13 antibodies were detected in a few cases and disappeared after successful lymphoma treatment (see below).

MAHA in Endocrine Tumors

MAHA occurred in 3 cases of pheochromocytoma,[51,127,132] 2 cases of pituitary tumor,[74,75] and 1 case of neuroendocrine tumor.[38] Two of these tumors were malignant,[38,127] and both had bone marrow infiltration. Clinically, 2 cases were TTP like and 2 were HUS like. In the 2 cases of pheochromocytoma, 1 patient in whom the tumor was removed had complete remission,[132] the other had complete remission of MAHA but persistent renal failure.[51] Both patients with pituitary tumors had no bone marrow infiltration. Prolactin was elevated (prolactin is often secreted with growth hormone in this tumor). Plasma exchange was not effective; both patients died within a few days.

MAHA in Lymphoma: An Immune-Mediated Disease?

MAHA has been described in 4 cases of Hodgkin lymphoma,[20,31,37] 3 cases of intravascular lymphomatosis/angiotropic lymphoma,[69,72,136] 3 cases of NHL (2 with diffuse large B-cell lymphoma),[20,43] 3 cases of myeloma,[7,61] and 1 case of hairy cell leukemia.[95] In most instances, lymphoma-associated MAHA seems to be different from MAHA in solid tumors. An instructive case of MAHA (TTP like) was described in a patient with angiotropic lymphoma.[72] This patient had a TTP-like clinical picture, very low ADAMTS 13 activity, and antibody to ADAMTS 13. The patient responded to fresh frozen plasma. Complete remission of lymphoma and MAHA and recovery of ADAMTS 13 was achieved after chemotherapy. The patient had a long remission (>20 mo) of lymphoma and TTP. In 2 other cases of MAHA in angiotropic lymphoma,[69,136] no data on ADAMTS 13 activity were available.

Two other cases of presumably immune-mediated MAHA were described with myeloma.[61] One patient with IgA kappa myeloma had a history of MAHA associated with IgA monoclonal gammopathy of undetermined significance (MGUS), which was controlled by treatment with fresh frozen plasma. Thirteen years later he developed IgA myeloma with MAHA (ADAMTS 13 activity of 0.7% and ADAMTS 13 antibody of

TABLE 3. Treatment of Patients With CR-MAHA

Treatment and Response	All Solid Cancers	Gastric	Breast	Prostate	Lung	CUP	Other*
Any cancer therapy (CT, CS, or hormonal)	78/128 (60.9%)	25	17	11	8	6	11
No cancer treatment	50/128 (39.1%)	11	12	10	6	4	7
No data	26	8	7	2	2	2	5
Response to CT, CS, or hormonal treatment (of evaluable cases)	42/56	13/21	12/14	†	5/7	5/6	7/8

Abbreviations: CS = cancer surgery, CT = chemotherapy.

*Other tumors include abdominal, genitourinary, endocrine, and various cancers.

†In prostate cancer plasma exchange and hormonal treatment were given concurrently in most cases. Therefore, the efficacy of these treatments could not be evaluated separately.

1 BU/mL). MAHA did not respond to plasma exchange, but complete remission of MAHA was obtained with chemotherapy (dexamethasone/bortezomib), which lasted for 5 months. However, ADAMTS 13 activity remained low. A complete remission of ADAMTS 13 activity was achieved after autologous stem cell transplantation. Five months later ADAMTS 13 activity dropped again, but without recurrence of myeloma. Another myeloma patient with IgA kappa myeloma developed MAHA (TTP like, ADAMTS 13 activity zero with an antibody titer of 1.4 BU/mL) in very good partial remission after treatment with thalidomide, dexamethasone, and lenalidomide. Drug-induced TTP cannot be excluded because the patient was treated with lenalidomide at the onset of MAHA. The patient achieved complete resolution of MAHA and complete recovery of ADAMTS 13 after plasma exchange and cyclosporine. A further progression of myeloma was not associated with ADAMTS 13 deficiency and MAHA.

MAHA occurred in 3 advanced Hodgkin cases[31] In 1 case MAHA occurred in a splenectomized (for staging) patient with active disease (stage IV with skin involvement). MAHA improved after antiplatelet therapy. In another Hodgkin case,[20] MAHA developed in a patient in complete hematologic remission late after chemotherapy and improved after steroid therapy. The patient remained in complete remission for 9 years after this event. Two similar cases with MAHA in complete remission of NHL were reported.[20] Both died from MAHA.

MAHA After Cancer Surgery: Not Really a Paraneoplastic Syndrome

In 5 cases MAHA occurred a few days (2–5 d) after cancer surgery in patients with glioblastoma multiforme,[23] small bowel,[56] endometrial,[57] cecal,[125] or bladder carcinoma.[143] None of these cancers was metastatic, and none had bone marrow infiltration. All patients achieved complete remission of MAHA either spontaneously[125] or after plasma exchange.[23,57,143]

## Efficacy of CR-MAHA Treatment in Solid Tumors

Most patients had a variety of treatments, usually starting with fresh frozen plasma and/or plasma exchange followed by chemotherapy when the diagnosis CR-MAHA was established. An at least transient response of MAHA to antitumor therapy occurred in 42 of 56 evaluable patients with solid cancers (prostate cancer excluded) (Table 3). The overall survival in patients who received chemotherapy was superior to those without chemotherapy in cases of gastric, breast, CUP, and lung cancer combined (Figure 1). The median survival times with or without chemotherapy in gastric, breast, lung, CUP, and prostate cancers are shown in Table 4. In contrast to patients with other cancers associated with MAHA, patients with prostate cancer with MAHA had a good response to plasma exchange and fresh frozen plasma (14/16). Some of these patients received addi-

tional hormonal treatment, but from the description of the cases it is very likely that plasma exchange was the primary effective treatment.

DISCUSSION

Hereditary or immune-mediated TTP and aHUS are well defined disorders[25,45,49,93,105,114] with established effective treatments.[50] CR-MAHA is a rare cause of secondary MAHA. It is a serious, often fatal complication of malignancy. For an experienced hematologist the diagnosis of MAHA may not be difficult, but in practice the delay from the beginning of symptoms to diagnosis of TTP or aHUS is often long.[43] However, making the diagnosis of CR-MAHA is important, because the usual treatment of TTP and aHUS (fresh frozen plasma, plasmapheresis) is rarely effective, but with early chemotherapy the survival of some of these patients may be considerably prolonged, with good quality of life.

In 2 studies the prevalence of CR-MAHA among patients with TTP/aHUS was 3.5%[152] and 7.8%.[80] Since the incidence of TTP is estimated at 4.5 persons/million per year,[152] the incidence of CR-MAHA may be about 0.25 to 0.45 persons/million. There are no data on the incidence of CR-MAHA in cancers overall or in special cancer types. The incidence of CR-MAHA must be extremely low: in a recent study of breast cancer patients with bone metastasis, there was no case of CR-MAHA among
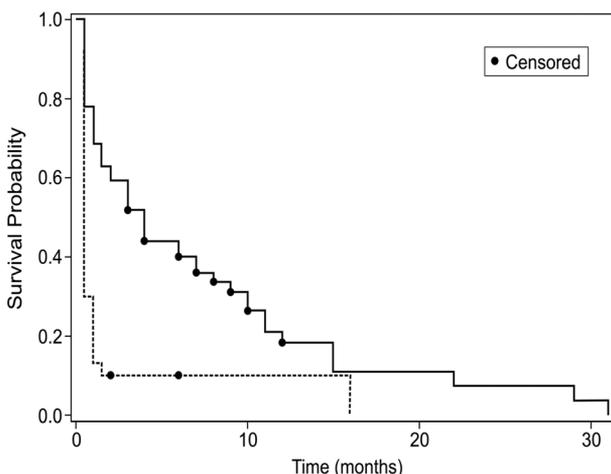
FIGURE 1. Overall survival (gastric, lung, breast, CUP). X axis: months from diagnosis. Solid line: patients treated with chemotherapy or hormonal drugs. Dashed line: patients treated with plasma exchange, fresh frozen plasma, or no treatment.

TABLE 4. Survival of CR-MAHA Patients With Various Cancers According to Treatment*

	Survival, Median (Range)					
Treatment	All Cancers (n = 99)* (mo)	Gastric (n = 34) (mo)	Breast (n = 26) (mo)	Lung (n = 13) (mo)	CUP (n = 11) (mo)	Prostate (n = 15) (mo)
CT/CS	4 (0.5–31)	3 (0.5–2)	4 (0.5–31)	5 (0.5–15)	3.5 (2–9)	10.5 (2–26)
NCT/CS	0.5 (0.5–84)	0.5 (0.5–1.5)	0.5 (0.5–16)	0.5 (0.5–1)	0.5 (0.5–2.0)	4 (0.5–84)

Abbreviations: CT/CS = chemotherapy or cancer surgery, NCT/CS = no chemotherapy or cancer surgery.

*Only patients with survival data available.

2046 patients with a median observation time of 17 months[140] (AT Stopeck, personal communication).

There is no linear correlation between the frequencies of a paraneoplastic syndrome and the incidence or prevalence of a cancer. In immune-mediated paraneoplastic syndrome, the highest association is lung cancer with immune thrombocytopenia,[76] renal cell cancer with autoimmune hemolytic anemia,[122] prostate cancer with factor VIII antibodies,[59] and small cell lung cancer with anti-HU antibodies (a type I antineural nuclear antibody).[62] In general, adenocarcinoma was the most common histologic type of cancer in CR-MAHA. Gastric carcinoma was the most common cancer in the current survey, followed by breast, prostate, and lung cancer. In another study MAHA was highly associated with prostate cancer.[48] The reasons for these discrepancies are unknown; they may be due to ethnic differences.[145] A special feature of CR-MAHA is that, unlike in other paraneoplastic syndromes, a relatively high proportion of CR-MAHA cases occurred at the time of cancer recurrence, in particular in gastric, breast, and prostate cancers. One may speculate that this is due to clonal selection after chemotherapy. It is well known that a tumor may change its properties when it recurs.[34,81,121,146,154]

In most case reports and reviews, the term "CR-MAHA (TTP/aHUS)" has been used, because it is not always easy to clinically distinguish TTP and aHUS. ADAMTS 13 measurement is a powerful diagnostic test in hereditary or immune TTP, but it is not a useful diagnostic tool in CR-MAHA. Nevertheless we have tried to assign the diagnosis of TTP or aHUS (according to criteria of an experienced center) to the published cases. We found that the classical clinical and laboratory pattern of TTP or aHUS was present in only a minority of cases and in most cases the MAHA was associated with rather unspecific symptoms. Highly noteworthy and to our knowledge not yet recognized was the finding that aHUS was highly prevalent in prostate carcinoma, in contrast to other cancers.

Bone marrow was the most common site of metastasis in CR-MAHA, but a substantial number of cases had cancer-free bone marrow, and in some cases of bone marrow involvement the infiltration was only focal. In a study of 25 patients with bone marrow cancer infiltration, only half had the typical peripheral blood findings of MAHA.[157] Thus, cancer infiltration of the bone marrow cannot be the only explanation for the blood abnormalities. Bone marrow necrosis or fibrosis was described in a number of CR-MAHA cases, but these abnormalities cannot be regarded as specific for CR-MAHA because they occur in many other conditions.[113] CR-MAHA was highly associated with bone metastases, but the prevalence of MAHA in patients with bone metastases is very low[140] (AT Stopeck, personal communication).

Signs of pulmonary thrombotic microangiopathy seem to be more common in CR-MAHA patients compared to patients with nonmalignant TTP/aHUS or patients with metastatic cancer without MAHA.[106,158] This may be due to the site of tumors (lymphatic metastases). In contrast, myocardial infarction seems to be less common compared to noncancer-related TTP.[46,64,112] DIC was highly associated with CR-MAHA, in contrast to hereditary or immune-mediated TTP.

To our knowledge, MAHA in endocrine tumors was not mentioned in earlier reviews. The 3 patients with pheochromocytomas had severe hypertension. It is known that MAHA may occur in patients with malignant hypertension.[149] In a 2011 study,[3] 7 of 16 patients with malignant hypertension had aHUS-like MAHA. All hematologic abnormalities resolved after normalization of the blood pressure. Thus, it may be that the pheochromocytoma patients did not have CR-MAHA, but had hypertension-associated MAHA. The 2 patients with pituitary tumors had high prolactin levels. High prolactin levels may be a risk factor for MAHA.[85]

Postoperative MAHA after cancer surgery cannot be regarded as true cancer-related MAHA because it occurs after removal of a nonmetastatic cancer and disappears spontaneously, and may occur also after noncancer surgery.[130] Thus, this type of MAHA is considered a surgery-associated MAHA.

There is no doubt that there is a close association of MAHA with DIC. About one-third of patients with MAHA had laboratory signs indicative of DIC, but it was not possible to define DIC according to the ISTH criteria. It may be that in some cases, among the probably-many circulating cytokines, clotting activators play an important role. The degree of hypofibrinogenemia is modest in most cases, which may be due to a low fibrinolytic activity. The generation of small vessel platelet thrombi in patients with MAHA may be increased by simultaneous DIC. It is interesting to compare the tumors that are associated with MAHA and DIC without MAHA. Prostate cancer is highly prevalent in both conditions, but gastric and breast cancers are much less prevalent in DIC.[6,138] The low prevalence of thrombosis in CR-MAHA with or without DIC may be surprising, but may be due to the short observation time, severe anemia and thrombocytopenia, and nondetection of silent thrombi.

It is well established that in hereditary and acquired TTP, ADAMTS 13 activity is more or less reduced.[30,45,152] Reduced ADAMTS 13 activity has also been found in a number of CR-MAHA patients, but the interpretation of these data is difficult because reduced ADAMTS 13 levels are not uncommon in metastatic cancer patients.[42,44,86,107] In the vast majority of cancer patients, ADAMTS 13 was above 20%.

Severe immune-mediated deficiency of ADAMTS 13 may occur in some patients with lymphoproliferative disorders. aHUS in prostate cancer could be antibody mediated because of the good response to plasmapheresis.[36]

In contrast to hereditary and immune TTP or aHUS, the pathogenesis of CR-MAHA is largely unknown. In CR-MAHA

in solid cancers, the most likely cause may be red cell fragmentation and platelet destruction in small vessels of cancerous tissue—in particular in the bone marrow, the lung, and/or other organs. This does not explain the absence of CR-MAHA in most patients with the same metastatic pattern. Cytokine production by tumor cells may play a role, but we are not aware of a cytokine that experimentally produces the typical symptoms of CR-MAHA. The endothelial cells play a critical role in all types of thrombotic microangiopathy. As long as endothelial cells are functionally intact, even patients with severe congenital defects predisposing to thrombotic microangiopathy may remain asymptomatic, whereas a severe injury of endothelial cells such as in cancer may trigger thrombotic microangiopathy.[53]

CR-MAHA is a serious disease with a very poor prognosis. Almost half (46.5%) of all evaluable patients in the current series died, with or without treatment, within 1 month. Chemotherapy is the only effective therapy (in cancers that respond to chemotherapy). However, it is known from case reports[63,82,106,126] that the hematologic response of CR-MAHA to chemotherapy may be fast, and complete remission may be obtained after 1 chemotherapy cycle. Because almost all the cancers are metastatic, the remission duration and overall survival are short, but some patients responding to chemotherapy may enjoy life with good quality for many months or even years. However, the overall survival of breast cancer patients with MAHA treated with chemotherapy (4 mo) is definitely inferior to that of chemotherapy-treated breast cancer patients without MAHA (11.0–33.5 mo).[19] The median survival of chemotherapy-treated gastric cancer patients with CR-MAHA is about 3 months, which was similar to that of patients with bone marrow involvement without MAHA,[157] but definitely inferior to patients with metastases at other sites.[2] In patients with prostate cancer with aHUS, the prognosis seems to be better. A number of these patients had complete resolution of MAHA after plasmapheresis and enjoyed many years with good quality of life.

The current study has important limitations, as is the case with all retrospective studies. The clinical evaluations and the laboratory examinations were not uniform, and often not all relevant data were provided, but overall the quality of data was sufficient for this analysis. We included only patients in whom the diagnosis of CR-MAHA was well established. Bone marrow biopsies were not done in a substantial number of patients, in particular in patients with prostate cancer. The efficacy of plasmapheresis was difficult to evaluate, because this treatment was often stopped as soon the diagnosis of CR-MAHA was established and chemotherapy and/or hormonal therapy was started. Because of the retrospective nature of the study, no statistical analyses were performed except for the Kaplan-Meier plot. We want to emphasize that the treatment results shown in Figure 1 were not based on results of prospective phase II or III studies.

A strength of our data is that patients came from various ethnic groups and were probably less selected than in prospective studies. We also provide some evidence that CR-MAHA in prostate cancer is different from CR-MAHA in other solid cancers with regards to clinical presentation and response to treatment.

There are 2 challenges for the future treatment of CR-MAHA. The first is to improve treatment of the acute phase of CR-MAHA to prevent early deaths and make patients fit for chemotherapy. There are a few new potential treatment options available, such as treatment with concentrates of recombinant ADAMTS 13[118] or anti-Willebrand factor aptamer (ARC 1779),[66] which may be effective even in patients without ADAMTS 13 deficiency. For patients with aHUS, eculizumab, a monoclonal complement inhibitor licensed for the treatment of paroxysmal nocturnal hemoglobinuria, may be an attractive option; it has already shown efficacy in some cases of aHUS.[26,73,159] The second challenge is to improve the long-term prognosis of patients who survive the acute phase. Finding new effective treatments for the underlying cancer is the only way to prolong the life of patients with CR-MAHA.

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