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Cancer Awareness in Atypical Thrombotic Microangiopathies

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Outline the clinical and biological features that would prompt a clinician to investigate an underlying malignancy in a patient suffering from thrombotic microangiopathy.
2. Conduct additional investigation to diagnose or rule out malignancy.
3. Formulate in timely fashion an adapted treatment plan for a patient with a cancer-associated thrombotic microangiopathy.

ABSTRACT

Objective. **To specify the clinical and biological characteristics of thrombotic microangiopathies (TMAs) associated with a recent diagnosis of cancer.**

Patients and Methods. **Multicenter study involving 14**

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national centers. Cross-sectional analysis of 20 patients with cancer-associated TMAs included in our national registry from October 2000 to July 2007. Patients were also compared with 134 adult patients with an acquired idiopathic TMA by univariate analysis.

Results. **Patients with a cancer-associated TMA typically displayed severe weight loss, dyspnea, bone pain, as well as disseminated intravascular coagulopathy and massive erythromyelemia (75%, 55%, 50%, 41%, and 85% of cases, respectively). By contrast, these features were observed with a much lower incidence in patients with an idiopathic TMA (8.9%, 19.7%, 0.8%, 7.1%, and 17.5%, respectively). Moreover, median platelet count was higher (48×10^9/l; range, 21–73×10^9/l versus 19×10^9/l; range, 10–38×10^9/l, respectively) and median serum creatinine level was lower (74 μM [range, 68–102] versus 113 μM [range, 80–225], respectively). The activity of the specific von Willebrand factor-cleaving proteinase ADAMTS13 was detectable in 14/17 studied patients. Platelet count improvement was observed in only seven patients and paralleled the response to chemotherapy. Prognosis of patients with cancer-associated TMAs was very poor, with a 30-day and 2-year mortality rate of 50% and 95%, respectively.**

Conclusion. **Cancer-associated TMAs display specific features at onset that should prompt investigation of an underlying disseminated malignancy. In this context, chemotherapy rather than plasma is mandatory since TMA prognosis parallels that of cancer.** ***The Oncologist*** 2009;14:769–779

Introduction

Thrombotic microangiopathies (TMAs) represent a heterogeneous group of diseases characterized by a microangiopathic hemolytic anemia, a peripheral thrombocytopenia, and organ failure of variable severity. TMAs encompass thrombotic thrombocytopenic purpura (TTP), typically characterized by fever and central nervous system manifestations, and hemolytic uremic syndrome (HUS), in which renal failure is the prominent abnormality. TTP is usually associated with a severe deficiency in ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), an enzyme specifically involved in the cleavage of high-molecular-weight von Willebrand factor (vWF) multimers. ADAMTS13 deficiency leads to excessive accumulation of unfolded vWF in microcirculation, causing intravascular vWF–platelet and platelet–platelet aggregation with organ failure. By contrast, patients with HUS or other TMA syndromes usually display a normal or at least detectable ADAMTS13 activity [1–3]. A TMA syndrome may occasionally develop in patients with HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, with catastrophic antiphospholipid syndrome, with infections, who have undergone transplantation, and who have cancer in association or not with chemotherapy [4,5].

In patients with cancer, TMAs may be related to various antineoplastic drugs or to the malignant disease itself [6]. The reported series of patients with a TMA directly related to cancer are usually heterogeneous, retrospective, and encompass patients with hematologic malignancies, with solid tumor, or receiving chemotherapy [6–9], each of which may have distinct presentations and pathophysiological mechanisms. Moreover, ADAMTS13 activity in this context was rarely explored.

In this study, we investigated prospectively 20 cases of solid-organ cancer-associated TMAs, with a special focus on clinical and biological features of TMA that reveal the malignant processes. Our results provide evidence that cancer-associated TMAs display typical features at presentation, which should alert clinicians of the possibility of an underlying malignancy in a patient with a newly diagnosed TMA.

Subjects, Materials, and Methods

Patients

The TMA Registry of the French Reference Center for the management of thrombotic microangiopathies (http://www.cnr-mat.fr, in preparation) was set up in October 2000, with the aim to collect prospectively and systematically exhaustive clinical and biological data on patients with various forms of TMA, and to build up a biobank including plasma and mononuclear cells on diagnosis and during follow-up (http://www.orpha.net/consor/cgi-bin/index.php?lng=FR, keyword: PTT). To manage patients with TMA consensually throughout our country and to have an exhaustive registry, we officially defined at least one leading academic center in each French region (members listed in Appendix). All defined centers, as well as their respective affiliated regional centers, are involved in the management of patients with TMA in concert with the reference center, according to consensual recommendations or clinical trials [10].

As of July 2007, 400 patients were included. In the current study, we considered all consecutive TMA patients of

our registry with a recently diagnosed solid cancer or with recurrence of a cancer presumed in remission, in order to specify the clinical and biological characteristics of this particular subset of TMAs. To analyze data from a homogeneous group of patients and avoid confounding factors, patients with hematological malignancies (nine cases) or receiving chemotherapy in the previous 4 months (14 cases) and/or who underwent autologous hematopoietic stem cell transplantation (five cases) were not included in this study. Two additional patients were not included because of incomplete data. Twenty patients were finally suitable for analysis. Patients were recruited nonselectively from intensive care and emergency units, and oncology, hematology, hepatology, and internal medicine departments of 14 national centers. To specify accurately the features of cancer-associated TMAs, we compared patients with this diagnosis with patients with an idiopathic TMA. These latter were included consecutively in our registry within the same period of time. The study protocol was reviewed and approved by the institutional review board (no. P020501) and ethical committee.

The diagnostic criteria for TMA were the presence of a Coombs-negative microangiopathic hemolytic anemia and/or a peripheral thrombocytopenia ($<150 \times 10^9$/l) as reported previously [11, 12], with the exception of severe disseminated intravascular coagulopathy that was not considered here as an exclusion criterion, but rather as a possible manifestation of the underlying malignancy. The diagnosis of cancer was established by clinical, laboratory, and radiological data, and confirmed by pathologic examination of lesion biopsy, bone marrow biopsy, or aspiration, or after necropsy, showing tumor cells. For each patient, a detailed clinical examination was systematically performed on admission, with particular attention paid to cerebral, respiratory, and digestive manifestations and general status. Treatment and outcome were also recorded. All data were reported in a pre-established questionnaire.

Laboratory Tests

Biological investigations included blood numeration with hemoglobin level, hematocrit and platelet count, reticulocyte count, serum lactate dehydrogenase (LDH), and haptoglobin levels. All analyses were performed before any treatment. The presence of erythromyelemia and schistocytes was confirmed by blood smear examination. Renal function was estimated by the serum creatinine level and the estimated glomerular filtration rate (GFR), according to the Cockcroft-Gault method. Disseminated intravascular coagulopathy was defined by the presence of D-dimers by enzyme-linked immunosorbent assay (ELISA) and decreased prothrombin time and fibrinogen level. Some patients with cancer had bone marrow examination by aspiration and/or biopsy.

Evaluation of ADAMTS13 Activity and Inhibitory Anti-ADAMTS13 Antibodies

ADAMTS13 activity was measured in most patients. Blood collection, plasma preparation, and measurement of ADAMTS13 activity were performed before treatment, as previously described [4]. ADAMTS13 deficiency was considered severe in patients with an undetectable enzymatic activity (<5% of normal activity). In patients with severe ADAMTS13 deficiency, inhibitory anti-ADAMTS13 antibodies were systematically sought [4].

Treatment and Outcome

Plasma therapy and chemotherapy were considered in all patients. Plasma administration was performed according to written recommendations based on a previous study [11]. Briefly, patients were treated with daily therapeutic plasma exchange (TPE) immediately after TMA diagnosis. Replacement fluid consisted of plasma 60 ml/kg for the first TPE, and 40 ml/kg for each subsequent TPE session, combined with 15 ml/kg 4% albumin until complete response was achieved. TPE sessions were then progressively tapered and stopped. Some patients were treated with high-dose (20 to 30 ml/kg per day) plasma infusion (HD-PI). Response to plasmatherapy was evaluated after 3 to 5 days. This treatment was then stopped if considered inefficient. Steroids and antiplatelet agents were not systematically administered. Antineoplastic drug administration was performed according to the clinicians' experience. TMA remission was defined as a complete disappearance of clinical manifestations related to TMA and platelet count recovery. In this study, LDH could not be used as a tool reflecting treatment responsiveness of TMA because their increase was also related to cancer. For patients treated with chemotherapy, TMA remission was evaluated after hematological recovery.

Statistical Analysis

Continuous variables were not normally distributed and summarized by median (interquartile range). Wilcoxon two-sample test was used to compare continuous variables, and chi-square test or Fisher's exact test was used to compare binary data. Statistical significance was tested at the 5% level. Data were analyzed using SAS 9.1 (SAS Institute, Cary, NC).

Results

Clinical Characteristics

Thirteen patients were women. Median age was 62 years (range, 53–70) (Table 1).

Table 1. Clinical findings

Patient no.	Sex	Age (years)	Type of cancer	Metastasis	Symptom duration before TMA diagnosis	Weakness associated with weight loss and anorexia	Fever	Bone pain	Dyspnea	Abdominal pain	Thoracic pain	CNS involvement[a]
1	F	74	Lung	Bone	30 days	Y	N	Y	Y	N	Y	N
2	F	54	Colon	Bone; bone marrow; lymph nodes	30 days	Y	N	Y	Y	N	N	Y
3	F	70	Breast	Bone; bone marrow	3 days	N	Y	N	N	N	N	Y
4	F	55	Breast	Liver; pleural; bone	6 days	Y	Y	N	N	Y	N	Y
5	F	65	Breast	Liver; bone marrow	30 days	Y	N	N	N	N	N	Y
6	F	51	Breast	Bone marrow	10 days	N	N	N	N	N	N	N
7	F	38	Stomach	Bone marrow; lymph nodes	30 days	Y	N	N	N	Y	N	N
8	F	75	Breast	Lung	30 days	Y	N	Y	Y	N	N	Y
9	M	52	Stomach	Bone; bone marrow; liver	15 days	Y	Y	Y	Y	N	Y	N
10	M	51	Stomach	Bone; lung	15 days	Y	N	Y	Y	Y	Y	N
11	F	59	Stomach	Pleura; bone	5 days	Y	N	Y	Y	N	N	N
12	M	79	ACUP	Bone; bone marrow; lymph nodes	30 days	Y	N	Y	Y	N	N	N
13	F	60	Liver	Lymph nodes; bone marrow	190 days	Y	N	N	Y	N	N	N
14	M	69	Prostate	Bone	1 day	N	N	Y	N	Y	N	N
15	F	53	Lung	Liver	7 days	Y	N	Y	Y	N	N	N
16	M	74	Liver	Bone; bone marrow; lymph nodes	180 days	N	N	Y	N	N	N	Y
17	M	65	Prostate	Bone; lung; meninges	NA	Y	Y	N	N	N	N	Y
18	F	64	Breast	Bone; liver	60	Y	Y	N	N	N	N	N
19	F	38	Breast	Bone; bone marrow	85	N	N	N	Y	N	N	Y
20	M	66	Lung	Brain	19	Y	N	N	Y	N	N	Y

[a]Headache: two cases; confusion: two cases; seizure with blurred vision and focal dysesthesia: one case; drowsiness: one case; encephalopathy: one case; coma: one case.
Abbreviations: ACUP, adenocarcinoma with unknown primitive tumor; CNS, central nervous system; F, female; M, male; N, no; NA, not available; Y, yes.

The primitive cancer was breast (seven cases), stomach (four cases), lung (three cases), prostate and liver (two cases each), and colon (one case). One patient had an adenocarcinoma with unknown primitive tumor (one case). Sixteen patients had an adenocarcinoma, two patients with lung cancer had an undifferentiated tumor, and two patients had a hepatocellular carcinoma. TMA was usually diagnosed rapidly after admission: within the first hospitalization day (15 cases) or 3 to 4 days after admission (3 cases). In two other patients, TMA was diagnosed later. In the first case, TMA was diagnosed after 12 days of hospitalization, within a context of recent onset polyarthritis, which initially suggested a flare-up of a previously diagnosed rheumatoid arthritis. In the second case, TMA occurred within a context of unexplained liver failure that lasted for 2 months, and that finally led to the diagnosis of hepatocellular carcinoma. Nine patients had a past history of cancer, which was considered in remission until TMA diagnosis. The median time between the initial diagnosis of cancer and relapse was 25 months (range, 8–215). In 8 of 9 patients, TMA revealed cancer recurrence. In the remaining patient, cancer recurrence was diagnosed at necropsy. In the other 11 patients with no past history of cancer, TMA revealed the malignancy. All patients had a disseminated disease. The main metastatic localization was bone and/or bone marrow (17 cases), and then liver (5 cases), lung or pleura (5 cases), and brain and meninges (1 case each).

The most frequent presenting symptom was weakness, associated (15 cases) or not (4 cases) with anorexia and weight loss. Twelve patients presented with pain, which involved bones (10 cases), stomach or liver (4 cases), and chest (3 cases). Dyspnea and cerebral manifestations (head-

ache, focal dysesthesia, confusion, and/or seizure) were noted in 11 and 9 cases, respectively. Median duration of symptoms prior to TMA diagnosis was 30 days (range, 7–30).

Laboratory Features (Table 2)

Thrombocytopenia was present in all patients but one, who had, however, a typical microangiopathic hemolytic anemia. Median platelet count was 48×10^9/l (range, 21–73). All patients had a microangiopathic hemolytic anemia. Median hemoglobin level and reticulocyte count were 8.3 g/dl (range, 6.9–9.3) and 193×10^9/L (range, 143–259), respectively. Median LDH level was 4.5 times upper the normal values (range, 3.2–8.9). Erythromyelemia was present in 17 patients, suggesting bone marrow involvement by tumor cells. D-dimers were measured in 12 patients, and were found severely increased in all cases. Fibrinogen was decreased (<2 g/l) in 7/18 patients. Fifteen patients had a bone marrow aspiration and/or biopsy. Medullar metastases were found in 12 patients and myelofibrosis in 4 (Table 3).

Median serum creatinine level and GFR were 74 μM (range, 68–102) and 70 ml/minute (range, 48–82), respectively. Renal failure was severe in two cases (estimated creatinine GFR <30 ml/minute) or moderate in six others (estimated creatinine GFR <60 ml/minute). No patient required dialysis.

ADAMTS13 activity was studied in 17 patients. The median value was 39% (range, 0–70) (Fig. 1). ADAMTS13 activity was normal (eight patients) or mildly decreased (six patients). In the three remaining patients, ADAMTS13 activity was undetectable, and associated (two patients) or not (one patient) with inhibitory anti-ADAMTS13 antibodies. There was no apparent difference on clinical presentation between patients with a severe ADAMTS13 deficiency and those with a detectable ADAMTS13 activity (Tables 1–3).

Clinical Course (Table 4)

Two patients died before treatment could be initiated. Eight patients were treated with TPE, either with or without HD-PI (four cases each). Eight others received only HD-PI. One patient first received HD-PI for 4 days with a slight improvement in platelet count, and then four infusions of rituximab for a severe acquired ADAMTS13 deficiency-associated TMA. The last patient received only chemotherapy. The median duration of HD-PI treatment was 3 days (range, 2–5.5), whereas the median number of TPE sessions was 4.5 (range, 3.25–8). Steroids were administered in 14 patients; 1 patient received vincristine for TMA. Chemotherapy was administered to 13 patients. Seven patients received platelet transfusions, without apparent worsening of TMA.

Eight patients initially responded to treatment. All but one received chemotherapy, along with HD-PI and/or TPE. Seven patients had normalized platelet count 6–60 days after treatment initiation. In one patient, platelet count recovered for 6 weeks after rituximab administration. Chemotherapy was subsequently performed when TMA recurred, but the patient died after two courses of treatment. One patient, who received chemotherapy without plasma, increased platelet count up to 135×10^9/l 16 days after treatment initiation, with a resolution of hemolytic anemia. The response to treatment was transient in 7/8 patients, and death occurred after a median time of 6 months (range, 3.5–7 months) in a context of progressive malignancy (six cases) or liver failure (one case). In three patients, TMA relapse and cancer progression occurred simultaneously. Only one patient is alive after 9 months of follow-up, with no evidence of cancer progression or TMA recurrence.

Twelve other patients died after a median time of 14 days (range, 5.75–17.25) following TMA diagnosis, in a context of both refractory TMA and malignancy.

Of the three patients with a severe ADAMTS13 deficiency, one died within a context of refractory TMA after 2 days of HD-PI, one had normalized platelet count 31 days following HD-PI and chemotherapy, and one had transiently normalized platelet count and hemoglobin level after four courses of rituximab. In the latter two, ADAMTS13 activity rose up to 24% 5 months after the first infusion of rituximab. However, both patients also died after 1 month within a context of both progressive malignancy and TMA.

Comparison Between Cancer-Associated TMA and Idiopathic TMA

To specify further the clinical and biological characteristics of cancer-associated TMA, we compared those patients with 134 patients with an idiopathic TMA (either with [102 cases] or without [32 cases] a severe ADAMTS13 deficiency) who were included in our registry during the same period (Table 5). We found that patients with a cancer-associated TMA were older ($p < .0001$) and had more frequently a past history of cancer ($p < .0001$). The median duration of symptoms preceding TMA diagnosis was longer ($p < .0001$). We also observed more frequently severe weight loss, asthenia, bone pain ($p < .0001$ for all), and dyspnea ($p < .01$). Diarrhea before hospitalization or at initial diagnosis as well as neurologic symptoms were less frequent ($p < .05$ for both). Disseminated intravascular coagulopathy was observed only in cancer-associated TMA, with lower median fibrinogen level and prothrombin ratio ($p = .01$ and $p = .0001$, respectively), and consistently high D-

Table 2. Biological findings

Patient no.	ADAMTS13 activity (%)	ADAMTS13 inhibitor[a]	Hemoglobin level (g/dl)	Reticulocyte count (10^3/mm^3)	Schistocytes	LDH (×N)	Platelet count ($10^3/\mu$l)	Prothrombin rate (%)	Fibrinogen level (g/l)	D-dimers (μg/ml)	Creatinine level (μM)	Estimated GFR (ml/minute)
1	49	—	7	164	+	3.8	60	72	3	>4	50	70
2	118	—	8.7	142	+++	3.2	20	63	NA	NA	59	82
3	NA	NA	6.4	295	+	4.5	116	80	1	>4	110	30
4	41	—	5.5	331	+++	21.5	17	58	1.7	>4	80	54
5	NA	NA	13	258	++	7.8	21	57	2.1	NA	71	50
6	64	—	9.1	213	+++	2.5	45	85	2.8	>4	72	83
7	28	—	7.5	144.5	+++	5.3	39	64	1.4	>4	62	103
8	58	—	9.3	196	+	8.9	190	84	NA	NA	94	44
9	21	—	6.8	146	++	6.9	18	72	2.7	>4	76	103
10	126	—	7.4	212	+++	3.3	74	75	0.9	>4	74	79
11	NA	NA	6.6	138	+++	18.1	39	57	3.4	NA	74	70
12	0	1	8.7	89	+	2.9	109	76	1.71	>4	129	39
13	0	1	9.2	NA	++	6.2	103	47	1.1	>4	51	110
14	20	0	10.4	50	++	NA	14	67	2.1	NA	636	10
15	129	—	6.9	343	++	3.7	50	77	3.4	NA	72	75
16	37	—	9.3	76	+	8.9	60	62	7	NA	343	16
17	0	0	9.2	337	++	3	35	74	2.7	>4	92	73
18	93	—	6.8	NA	+	3.6	58	69	8.3	>4	73	64
19	75	—	7.9	190	++	3.2	72	59	1.9	>4	65	101
20	57	—	11.7	220	++	14.3	21	68	4.3	NA	120	50

[a]0: Absent; 1: present; —, not investigated.
Abbreviations: +, rare schistocytes; ++, several schistocytes; +++, many schistocytes; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; GFR, glomerular filtration rate; LDH, lactate dehydrogenase; N, normal; NA, not available.

Table 3. Bone marrow aspiration and/or biopsy findings

Patient no.	Results of bone marrow exploration
1	Erythroblastic hyperplasia
2	Metastatic cells; fibrosis
3	Metastatic cells
4	Metastatic cells
5	Metastatic cells
6	Metastatic cells
7	Metastatic cells
8	Erythroblastic hyperplasia
9	Metastatic cells; fibrosis
10	Metastatic cells
11	Erythroblastic hyperplasia
12	Metastatic cells; fibrosis
13	Metastatic cells; fibrosis
14	NA
15	NA
16	Metastatic cells
17	NA
18	NA
19	Metastatic cells
20	NA

Abbreviation: NA, not available.

dimers >4 μg/ml ($p < .0001$) in all tested patients. Myelemia and erythromyelemia were also more frequent in cancer-associated TMA ($p < .0001$ for both), with a higher median percentage of circulating erythroblasts ($p < .01$). Median platelet count was higher than in idiopathic TMA ($p < .001$), whereas renal involvement was less severe ($p < .01$). As expected, prognosis of cancer-associated TMA was very poor, with a much higher 30-day and long-term mortality ($p < .0001$ for both).

Discussion

We attempted here to specify the clinical and biological features of TMA that reveal the solid tumors. We excluded from the analysis hematological malignancies, as well as patients treated with chemotherapy and/or autologous hematopoietic stem cell transplantation, since these latter conditions may be associated with distinct TMA presentations. Indeed, cancer was either recently diagnosed or occurred as a relapse in a patient with a previous history of cancer considered long in remission. In accordance with previous reports, the main cancer histological types were stomach and breast adenocarcinomas [6]. We found that patients with cancer-associated TMAs had a typical presentation on diagnosis that was clearly distinct from that of idiopathic TMA. In particular, patients usually displayed a longer duration of symptoms; they had a recent history of weight loss, dyspnea, waste, and bone pain, as well as massive erythroblastosis in peripheral blood and disseminated intravascular coagulopathy. Our results, accurately assessed from a homogeneous series of patients and further ascer-

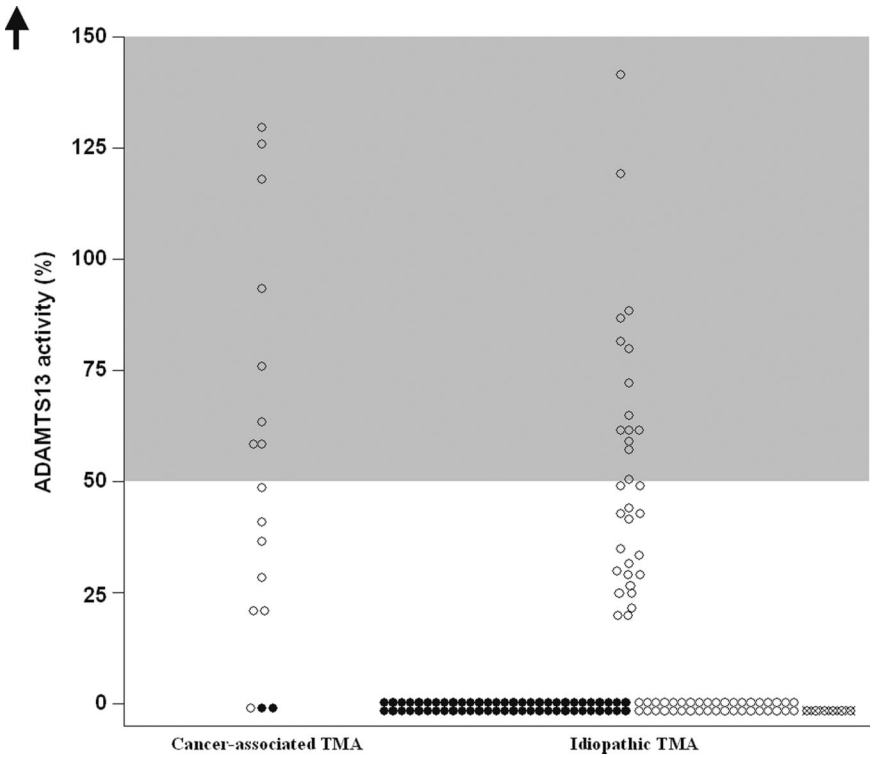

Figure 1. ADAMTS13 activity on admission. Left column corresponds to patients with cancer-associated TMA and right column, to patients with idiopathic TMA. We identified patients with severe ADAMTS13 deficiency (<5% of normal activity) and patients with detectable enzyme activity (≥5% of normal activity). Black symbols correspond to patients with an ADAMTS13 inhibitor. Cross symbols correspond to patients with undetectable ADAMTS13 activity in whom inhibitor was not investigated. Grey area indicates ADAMTS13 values of individuals without TMA.

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; TMA, thrombotic microangiopathy.

tained by a comparison with patients with idiopathic TMA, confirm previous reports from single cases or a heterogeneous series of patients [6–9, 13–17]. Those clinical features are particularly reminiscent of those found by the Oklahoma group [9]. However, we found that patients with cancer-associated TMA had less severe thrombocytopenia than patients with idiopathic TMA, whereas renal dysfunction was absent or mild. Those differences between both studies may be explained at least in part by our stringent criteria that led us to exclude from the analysis patients with hematological malignancies, in whom the underlying disease may worsen thrombocytopenia and renal failure by marrow infiltration and massive tumoral lysis, respectively. Overall, our results provide clear evidence that TMA-revealing cancers harbor typical features, which should help clinicians to investigate promptly an underlying disseminated malignancy, especially within a context of past history of cancer [14]. In this regard, marrow explorations through aspiration and/or biopsy should be systematically performed in this context as they may rapidly confirm the diagnosis of cancer [8, 9, 15–18] (and current study).

In most of our cases, time between TMA diagnosis and cancer did not exceed 1 day, and antitumoral treatment was initiated rapidly after admission. Despite rapid adapted management, the overall prognosis remained dramatically poor, with only six patients who survived more than 3 months [7, 9]. Of note, all but one patient whose TMA improved received a specific treatment for cancer. By contrast, patients treated with only TPE and/or HD-PI responded poorly and died rapidly. Interestingly, one patient had an increased platelet count with/during chemotherapy. These findings thus emphasize that chemotherapy is probably the most efficient treatment in these patients, with a TMA prognosis that parallels that of cancer [8, 17, 19–22]. Indeed, a prolonged intensive plasmatherapy should be questioned in those patients when initial treatment with plasma is inefficient. Another particular observation in those patients is that platelet transfusions did not apparently worsen TMA. This finding may be explained by the distinct and specific pathophysiology of cancer-associated TMA, and suggests that platelet transfusions are not a contraindication in this context, as they are for idiopathic TMA in the absence of severe bleeding [23].

As did others, we found that ADAMTS13 activity was

Table 4. Treatment and clinical course

Patient no.	Time from TMA diagnosis to death	Outcome	Cause of death	Time to platelet count recovery	TMA treatment	Days of HD-PI infusion	No. of TPEs	Steroids	Chemotherapy	TMA relapse
1	15 days	Death	Cancer	No recovery	TPE; HD-PI	5	14	Y	Carboplatin, gemcitabine	N
2	2 days	Death	Coma	No recovery	HD-PI	2	0	Y	Folinic acid, 5-FU, oxaliplatin	N
3	7 months	Death	Cancer, TMA	11 days	TPE; HD-PI	2	4	Y	Docetaxel, adriamycin	Y
4	10 days	Death	Coma	No recovery	TPE; HD-PI	2	1	Y	Paclitaxel	N
5	16 days	Death	Cancer	No recovery	HD-PI	3	0	N		N
6	5 days	Death	Coma	No recovery	TPE	0	4	N		N
7	6 days	Death	Digestive hemorrhage	No recovery	TPE; HD-PI	1	1	Y	5-FU, cisplatin, hydroxyurea	N
8	17 days	Death	Unknown	No recovery	0	0	0	Y		N
9	3 months	Death	Cancer, TMA	No recovery	0	0	0	N	5-FU, cisplatin, hydroxyurea	Y
10	4 months	Death	Cancer	43 days	HD-PI	3	0	Y	Gemcitabine, oxaliplatin, folinic acid, 5-FU, irinotecan, docetaxel	N
11	44 days	Death	Respiratory distress	No recovery	TPE	0	6	N		N
12	2 months	Death	Cancer	31 days	HD-PI	11	0	Y	Folinic acid, 5-FU, oxaliplatin	N
13	6 months	Death	Cancer, TMA	60 days	HD-PI; RTX	4	0	N	Docetaxel	Y
14	-	Alive at 9 months	-	8 days	TPE	0	5	N	Leuproreline, bicalutamide	N
15	18 days	Death	Unknown	No recovery	HD-PI	6	0	Y		Y
16	45 days	Death	Cancer, TMA	No recovery	HD-PI	10	0	Y	Salvage chemotherapy (NA)	N
17	13 days	Death	Cancer	No recovery	HD-PI	2	0	Y		N
18	7 months	Death	Liver failure	5 days	HD-PI	NA	0	Y	FEC	N
19	29 months	Death	Cancer	Platelets normalized (time to recovery NA)	TPE	0	14	Y	FEC, tamoxifen, anastrozole, paclitaxel/ trastuzumab, vinorelbine/ trastuzumab	N
20	1 day	Death	Cancer, TMA	No recovery	0	0	0	Y		N

Abbreviations: 5-FU, 5-fluorouracil; FEC, 5-FU, epirubicin, and cyclophosphamide; HD-PI, high-dose plasma infusion; N, no; NA, not available; RTX, rituximab; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; Y, yes.

measurable in most cases [24, 25], suggesting that ADAMTS13 dysfunction is not the prominent abnormality involved in cancer-associated TMA pathophysiology. A mild to moderate decrease in ADAMTS13 activity was observed in four cases. However, whether this feature has a role in the occurrence of TMA is questionable since malignancy, either localized or disseminated, was reported to be a condition associated with a low but detectable ADAMTS13 activity even in the absence of TMA [26]. Rather, postmortem studies support the view that microscopic tumor cell embolisms may induce both local activation of coagulation and fibrocellular intimal proliferation, with severe microvessel lumen reduction [27]. In pulmonary tumor TMA, a rare entity causing severe pulmonary hypertension in patients with disseminated malignancies [28, 29], it was suggested that tissue factor and vascular endothelial growth factor, by inducing fibrin deposits and vascular hyperplasia, respectively, may be involved in the occlusion or stenosis of the pulmonary vasculature [30, 31]. Additionally, malignant cells may produce substances favoring TMA, such as mucins [8]. By favoring vasoconstriction and endothelial cell apoptosis, tumor necrosis factor-α may have a role in the occurrence of TMA in patients with cancer [32]. Other more hypothetical mechanisms, involving soluble antigen-antibody complexes [33], were also reported. These findings strongly suggest a direct role of malignant cells in the occurrence of TMA, and account for the frequent, although transient, improvement of TMA with chemotherapy, whereas plasmatherapy in this context is usually inefficient [25]. Three patients had a severe ADAMTS13 deficiency, which involved an acquired immune-mediated mechanism in at least two cases. Clinical features and outcome in these patients were apparently comparable with those observed in patients with a detectable ADAMTS13 deficiency, and

Table 5. Comparison of patients with cancer-associated thrombotic microangiopathy with patients with an idiopathic TMA

	Idiopathic TMA ($n = 134$)	Cancer-associated TMA ($n = 20$)	p-value
Clinical and biological features			
Sex (% female)	74.6	65.0	ns
Age (years)	41 (29–55)	62 (53–70)	<.0001
Past history of cancer (%)	3.0	45.0	<.0001
Symptoms duration (days)	7 (2–14)	30 (7–30)	<.0001
Clinical symptoms (%)			
Fever	34.6	25.0	ns
Weight loss, weakness, anorexia	8.9	75.0	<.0001
Asthenia	39.5	95.0	<.0001
Bone pain	0.8	50.0	<.0001
Abdominal pain	17.4	20.0	ns
Thoracic pain	3.3	15.0	ns
Dyspnea	19.7	55.0	<.01
Current or past history of diarrhea	33.1	10.0	<.05
Cerebral manifestations	69.3	45.0	<.05
Biological results			
Hemoglobin level (g/dl)	7.8 (6.4–9.4)	8.3 (6.9–9.3)	ns
Reticulocyte ($\times 10^9$/l)	122 (77–288)	193 (143–259)	ns
Platelet count ($\times 10^9$/l)	19 (10–38)	48 (21–73)	<.001
Creatinine (μM)	113 (80–225)	74 (68–102)	<.01
LDH ($\times$ N upper value)	5.0 (3.0–7.7)	4.5 (3.2–8.9)	ns
ADAMTS13 (% activity)	0 (0–13)	39 (0–70)	<.0001
D-dimers >4 (%)	32.1	100.0	<.0001
Fibrinogen level (g/l)	3.5 (2.6–4.4)	2.4 (1.7–3.4)	<.01
Prothrombin rate	84 (74–92)	69 (61–76)	<.0001
Myelemia (%)	33.8	90.0	<.0001
Erythromyelemia			
Positive (%)	17.5	85.0	<.0001
Median (% WBC)	2 (1–5)	6 (3–21)	<.01
Evolution			
Death (within 2 years) (%)	10.5	95.0	<.0001
Death (within 30 days) (%)	8.2	50	<.0001

Groups and data recording are detailed in Subjects, Materials, and Methods. Values are expressed in percentage of subjects or in median numbers (interquartile range). Statistical comparisons were made using Wilcoxon two-sample test continuous variables, and chi-square test or Fisher's exact test was used to compare binary data.
Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; LDH, lactate dehydrogenase; ns, nonsignificant; TMA, thrombotic microangiopathy; WBC, white blood cells.

whether a severe ADAMTS13 deficiency in cancer-associated TMA defines a distinct group of patients with a specific presentation remains to be assessed with accuracy. TMAs associated with disseminated malignancies and a severe acquired ADAMTS13 deficiency were reported in rare cases [4], which recovered during chemotherapy in conjunction with TMA improvement [34]. These observations provide evidence that paraneoplastic TMA with antibody-mediated ADAMTS13 deficiency may be part of the autoimmune manifestations encountered in patients with malignancies. In these rare cases, the efficiency of a plasmatherapy, by supplying ADAMTS13 deficiency, also remains to be investigated.

In conclusion, our study emphasizes that in patients with a newly diagnosed TMA, atypical features at presentation such as bone pain and wasting, erythroblastosis, and

disseminated intravascular coagulation should promptly lead to complementary investigations to show evidence of an underlying, often disseminated, malignancy, particularly in patients with a past history of cancer. In these patients, the rapid initiation of cancer-specific treatment is mandatory since TMA prognosis appears to closely parallel that of cancer. On the contrary, plasmatherapy has a very limited role in these patients.

Appendix

The members of the Reference Center for the Management of Thrombotic Microangiopathies are as follows: Elie Azoulay (Service de Réanimation Médicale, Hôpital Saint-Louis, Paris), Dominique Bordessoule (Service d'Hématologie, Hôpital Dupuytren, Limoges, France), François Brivet (Service de Réanimation Médicale, Hôpital Antoine Béclère, Clamart, France), Marc Buffet (Service d'Hématologie clinique et de Thérapie Cellulaire, Hôpital Saint-Antoine, Paris), Annette Bussel (Unité de Clinique Transfusionnelle, Hôpital Cochin, Paris), Paul Coppo (Service d'Hématologie clinique et de Thérapie Cellulaire, Hôpital Saint-Antoine, Paris), Christophe Charasse (Service de Néphrologie, Centre Hospitalier de Saint-Brieux, France), Gabriel Choukroun (Service de Néphrologie, Hôpital Sud, Amiens, France), Karine Clabault (Service de Réanimation, CHU Charles Nicolle, Rouen, France), Cédric Daubin (Service de Réanimation Médicale, Hôpital de Caen, France), Georges Deschenes (Service de Néphrologie Pédiatrique, Hôpital Robert Debré, Paris), Alain Devidas (Service d'Hématologie, Hôpital Sud-Francilien, Corbeil-Essonnes, France), Olivier Fain (Service de Médecine Interne, Hôpital Jean Verdier, Bondy, France), Véronique Frémeaux-Bacchi (Laboratoire d'Immunologie, Hôpital Européen Georges Pompidou, Paris), Lionel Galicier (Service d'Immunopathologie, Hôpital Saint-Louis, Paris), Bertrand Guidet (Service de Réanimation Médicale, Hôpital Saint-Antoine, Paris), Didier Gruson (Service de Réanimation Médicale, Hôpital Pellegrin, Bordeaux, France), Mohamed Hamidou (Service de Médecine Interne, Hôtel-Dieu, Nantes, France), Raoul Herbrecht (Service d'Oncologie et d'Hématologie, Hôpital de Hautepierre, Strasbourg, France), Norbert Ifrah (Service d'Hématologie, CHU Larrey, Angers, France), Jean-Michel Korach (Service de Réanimation Médicale, Hôpital Châlon-en-Champagne, France), Sandrine Malot (Service d'Hématologie clinique et de Thérapie Cellulaire, Hôpital Saint-Antoine, Paris), Chantal Loirat (Service de Néphrologie Pédiatrique, Hôpital Robert Debré, Paris), Jean-Paul Mira (Service de Réanimation Médicale, Hôpital Cochin, France), Matthieu Monge (Service de Néphrologie, Hôpital Nord, Amiens, France), Bruno Moulin (Service de Néphrologie, Hôpital Civil, Strasbourg, France), Christiane Mousson (Service de Néphrologie, CHU de Dijon, France), Hubert Nivet (Service de Néphrologie Pédiatrique, Hôpital Bretonneau, Tours, France), Mario Ojeda Uribe (Service d'Hématologie, Hôpital Emile Muller, Mulhouse, France), Abdelkader Ouchenir (Service de Réanimation, Hôpital Louis Pasteur, Le Coudray, France), Jean-Bernand Palcoux (Service de Néphrologie Pédiatrique B, Hôpital Hôtel-Dieu, Clermont-Ferrand, France), Pascale Poullin (Service d'hémaphérèse et d'autotransfusion, Hôpital la Conception, Marseille, France), Jacques Pourrat (Service de Néphrologie et Immunologie Clinique, CHU Rangueil, Toulouse, France), Claire Pouteil-Noble (Service de Néphrologie, CHU Lyon-Sud, Lyon, France), François Provôt (Service de Néphrologie, Hôpital Albert Calmette, Lille, France), Michel Ramakers (Service de Réanimation Médicale, Hôpital de Caen, France), Bernard Regnier (Service de Réanimation Médicale, Hôpital Bichat, Paris), Jean-Antoine Ribeil (Service de Thérapie Cellulaire, Hôpital Necker-Enfants Malades, Paris), Eric Rondeau (Service de Néphrologie, Hôpital Tenon, Paris), Benoît Schlemmer (Service de Réanimation Médicale, Hôpital Saint-Louis, Paris), Thierry Leblanc (Service de Pédiatrie à orientation Hématologique, Hôpital Saint-Louis, Paris), Jean-Paul Vernant (Service d'Hématologie, Hôpital la Pitié-Salpétrière, Paris), Agnès Veyradier (Service d'Hématologie Biologique, Hôpital Antoine Béclère, Clamart, France), Cécile Vigneau (Service de Néphrologie, Hôpital Pontchaillou, Rennes, France), François Vincent (Service de Réanimation Médicale, Hôpital Avicenne, Bobigny, France), François Vrtovsnick (Service de Néphrologie, Hôpital Bichat, Paris), Alain Wynckel (Service de Néphrologie, Hôpital Maison Blanche, Reims, France), Martine Wolf (Service d'Hématologie Biologique, Hôpital Antoine Béclère, Clamart, France), Patricia Zunic (Service d'Hématologie, Groupe Hospitalier Sud-Réunion, la Réunion, France).

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