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Disseminated Malignancy Misdiagnosed as Thrombotic Thrombocytopenic Purpura: A Report of 10 Patients and a Systematic Review of Published Cases

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Key Words. Cancer • Thrombotic thrombocytopenic purpura • Hemolytic-uremic syndrome Microangiopathic hemolytic anemia

LEARNING OBJECTIVES

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

1. List the diagnostic criteria for thrombotic thrombocytopenic purpura.
2. Describe how occult disseminated malignancy can mimic the clinical features of thrombotic thrombocytopenic purpura.
3. Identify the clinical clues that indicate additional diagnostic evaluation for possible malignancy in a patient with suspected thrombotic thrombocytopenic purpura.

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ABSTRACT

***Background*. Patients with disseminated malignancy who present with microangiopathic hemolytic anemia and thrombocytopenia may be misdiagnosed as thrombotic thrombocytopenic purpura (TTP), resulting in inappropriate plasma exchange treatment, a procedure with major risk, and delay of appropriate chemotherapy.**

***Purpose*. To assess clinical features that may distinguish occult disseminated malignancy from TTP.**

***Patients and methods*. We report the 17-year experience of The Oklahoma TTP-Hemolytic-Uremic Syndrome (HUS) Registry (1989–2005) and a systematic review of previously published case reports.**

***Results*. Ten of 351 patients in the Oklahoma Registry who were initially diagnosed with TTP and treated with plasma exchange were subsequently discovered to have disseminated malignancy. Only one patient had a history of cancer. In these 10 patients, neurologic abnormalities, hematocrit, platelet count, and serum creatinine were not different from the 133 concurrent patients with idiopathic TTP. Patients with disseminated malignancy had a longer duration of symptoms, more frequent presence of respiratory symptoms, higher lactate dehydrogenase levels, and more often failed to respond to plasma exchange treatment. Diagnosis of malignancy was made by bone marrow biopsy in six patients but not until autopsy in two patients. A systematic literature review identified 19 additional pa-**

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tients, reported from 1965 to 2005, in whom TTP or HUS was initially suspected and systemic malignancy was subsequently discovered. Fourteen different malignant disorders were diagnosed in these 29 patients.

Conclusions*. Occult disseminated malignancy may mimic TTP. A search for systemic malignancy, including a bone marrow biopsy, is appropriate when patients with TTP have atypical clinical features or fail to respond to plasma exchange.** ***The Oncologist 2007;12:11–19

Introduction

The initial diagnosis of thrombotic thrombocytopenic purpura (TTP) may be uncertain because other disorders that can cause microangiopathic hemolytic anemia and thrombocytopenia, the principal diagnostic criteria, may not be initially apparent [1]. Disseminated malignancy is an important consideration in the differential diagnosis of TTP [2] since cancer has been well described for many years as a cause of microangiopathic hemolytic anemia and thrombocytopenia [3–7]. Although in most patients the disseminated malignancy that causes microangiopathic hemolytic anemia and thrombocytopenia is easily recognized, in some patients, the malignancy is not clinically apparent, and therefore TTP is diagnosed and plasma exchange treatment is begun. Failure to diagnose disseminated malignancy exposes the patient to the major risks of plasma exchange [8] and causes delay of appropriate chemotherapy. However, failure to urgently initiate plasma exchange treatment in a patient with TTP may result in death.

To address this diagnostic dilemma, we reviewed the clinical features of patients in The Oklahoma TTP-Hemolytic-Uremic Syndrome (HUS) Registry who were initially diagnosed as TTP and treated with plasma exchange before a disseminated malignancy was discovered. We also performed a systematic literature review to identify all previously published reports of patients with disseminated malignancy who presented with microangiopathic hemolytic anemia and thrombocytopenia and in whom the diagnosis of TTP or HUS was considered. Our goal was to define the clinical features of these patients that may suggest a search for disseminated malignancy.

Patients and Methods

The Oklahoma TTP-HUS Registry

The Registry, begun on January 1, 1989, includes all consecutive patients for whom the Oklahoma Blood Institute (OBI) is requested to provide plasma exchange treatment for clinically diagnosed TTP or HUS [2, 9] based on the presence of microangiopathic hemolytic anemia and thrombocytopenia without an apparent etiology [1]. Since the OBI is the sole provider of plasma exchange services for all hospitals in central, western, and southeastern Oklahoma, the Registry is an inception cohort of all consecutive patients in a defined geographic region. The standard practice in our region is to treat all adult patients who have clinically diagnosed TTP or HUS, as well as children with TTP or atypical HUS, with plasma exchange. Therefore, the only patients systematically excluded from the Registry are children with typical (diarrhea-associated) HUS who are not treated with plasma exchange. Because the Registry enrolls patients at the time of the initial clinical diagnosis of TTP when plasma exchange treatment is begun, these patients describe the complete community experience and spectrum of disorders that can mimic TTP.

Registry patients are assigned in a hierarchical order to one of six clinical categories based on their initial presentation: (a) patients who have had a hematopoietic stem cell transplantation; (b) patients who are pregnant or postpartum; (c) patients with drug-associated TTP or HUS; (d) patients who have a prodrome of bloody diarrhea; (e) patients who have a concurrent additional disorder known to be associated with TTP or HUS or who have the diagnosis of an alternative etiology made after plasma exchange is begun; and (f) patients whose presentation is idiopathic [2, 9]. Data are recorded in Microsoft Access for all patients. Lactate dehydrogenase (LDH) levels are normalized to an upper limit of normal of 200 U/l to compare results among different hospitals. All hospital and follow-up data are complete to the present time for 349 of 351 patients enrolled through December 2005. Since November 13, 1995, serum samples have been obtained immediately before beginning the first plasma exchange treatment [2, 9]. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was measured by Drs. Bernhard Lämmle and Johanna Kremer Hovinga (University Hospital Inselspital, Berne, Switzerland) using their previously published immunoblotting method [10, 11]. The Registry is approved by the institutional review board of each participating hospital.

Systematic Review of Published Reports

Ovid software was used to search the Medline database through January 2006. The keywords and medical subject heading (MeSH) terms searched for TTP were "thrombotic thrombocytopenic purpura," "hemolytic uremic syn-

drome," "microangiopathic hemolytic anemia," and "thrombotic microangiopathy." The key words and MeSH terms searched for malignancy were "cancer," "carcinoma," "sarcoma," "neoplasm," and "malignancy." The search was limited to the English language. All articles identified by both one of the TTP terms and one of the malignancy terms were reviewed, and their bibliographies were searched for additional relevant articles. Articles were excluded after review if they had no primary patient data or focused on complications of chemotherapy for malignancy. Patients reported in the selected articles were included in our analysis if they fulfilled the following criteria: (a) TTP or HUS was initially suspected; (b) malignancy was not considered as an initial diagnosis and the patient had not received chemotherapy or had evidence for malignancy within the past year; and (c) there was no evidence for disseminated intravascular coagulation (DIC). Patient selection was performed independently by three of the authors (N.K., K.K.F., and J.N.G.).

RESULTS

Oklahoma Registry Patients

Patient Characteristics

The Oklahoma TTP-HUS Registry has enrolled and prospectively followed 351 consecutive patients who were treated with plasma exchange for a diagnosis of TTP or HUS for 17 years, from January 1, 1989 to December 31, 2005. Ten (3%) patients were initially diagnosed with TTP and began treatment with plasma exchange, and systemic malignancy was subsequently discovered. Their presenting features and clinical courses are described in Table 1. Each of these patients fulfilled the diagnostic criteria for TTP: microangiopathic hemolytic anemia and thrombocytopenia without an apparent alternative etiology [1]. These 10 patients presented in seven different years from 1995 to 2005 and in nine different hospitals; the diagnosis of TTP was made by 10 different hematologists. Initially, 9 of the 10 patients were considered to have idiopathic TTP; one had human immunodeficiency virus (HIV) infection and therefore was in the clinical category described as having a concurrent additional disorder [9].

The median age of the 10 patients was 56 years; seven patients were men. Patient 6 was the only patient with a history of previous cancer. She was diagnosed with breast cancer 3 years earlier; 4 of 17 axillary lymph nodes had been involved with metastatic carcinoma, and she received adjuvant chemotherapy. She was thought to be cancer-free at the time of her presentation; her physical examination, chest x-ray, and computed tomography (CT) scans of her chest and abdomen were normal. Her case has been previously reported [12].

Presenting Clinical and Laboratory Features

Weakness, dyspnea and cough, fever, and abdominal pain were the most common presenting symptoms. Among the seven patients with symptoms of dyspnea and cough, the chest x-ray was normal in patient 6; patient 3 had only a right pleural effusion; the other five patients had bilateral pulmonary infiltrates or congestion. Patients 2, 4, and 9 also had normal bronchoscopies. The median duration of symptoms prior to the diagnosis of TTP in all 10 patients was 21 days (range, 1–85 days); however, in some patients, the illness seemed to become acute on the day of hospitalization. Two patients had severe neurologic abnormalities; six others had confusion. Six patients had increased creatinine levels; patients 4, 9, and 10 had acute renal failure that required dialysis. All patients had increased LDH levels; four had values exceeding 5,000 U/l. Prothrombin time, activated partial thromboplastin time, and fibrinogen levels were normal in seven patients; in patient 4, abnormal coagulation tests were attributed to acute liver failure; in patient 5, DIC was suspected; no coagulation tests were done in patient 1. ADAMTS13 activity was measured in eight patients; the median value was 50% (range, 13%–100%). Patient 9, who had HIV infection, had the lowest value.

Clinical Course

The median number of plasma exchange treatments was five (range, 1–9). Patient 2 fulfilled criteria for response to plasma exchange treatment with an increased platelet count to $>150{,}000/\mu l$; in retrospect, it was assumed that effective treatment for pneumonia and hypotension was responsible for the platelet count recovery.

Disseminated malignancy was diagnosed 2–14 days (median, 6 days) after the initial diagnosis of TTP. In six patients, disseminated malignancy was diagnosed by bone marrow biopsy. In patient 3, the serum alkaline phosphatase was 1,003 IU/l, suggesting obstructive liver disease. Although CT scans were normal, a subsequent bone scan indicated metastatic cancer that was then documented by bone marrow biopsy. Pancreatic carcinoma was suggested by a serum cancer antigen 19-9 level of 14,541. In patient 10, the extremely elevated LDH level of 10,126 U/l and a serum uric acid level of >24 mg/dl suggested tumor lysis; therefore, bone marrow biopsy was done on the day after initiation of plasma exchange that diagnosed diffuse large B-cell lymphoma. In four other patients, the diagnosis was also made by bone marrow biopsy. A bone marrow biopsy was done in patient 4 because of neutropenia (absolute neutrophil count, $684/\mu l$) in addition to the anemia and throm-

Table 1. Presenting features and clinical course of 10 patients with systemic malignancy from the Oklahoma Registry who were initially diagnosed as TTP

Pt	Age, race, sex	Year	Previous diagnosis of cancer, interval (years)	Duration of symptoms (days)	Presenting symptoms	Neurologic abnormality	Hct (%)	Plt ($10^{-3}/\mu l$)	Cr (mg/dl)	LDH (U/l)	Coagulation assays	Days from diagnosis of TTP to diagnosis of malignancy	Final diagnosis	Method of diagnosis	Days from diagnosis of malignancy to death
1	91 WM	1995	No	16	Weakness, melena	None	21	18	1.0	680	NA	7	Refractory anemia with excess blasts	Bone marrow biopsy	17
2	49 HM	1997	No	37	Cough, fever	Coma	23	71	3.0	9,000	PT 11.1; PTT 34; Fgn 380	10	Non-small cell lung cancer	Open lung biopsy	12
3	73 HM	1998	No	27	Weakness, abdominal pain, dyspnea, fever	Confusion	19	17	1.0	2,538	PT 15.6; PTT 25.6; Fgn 206	3	Pancreatic carcinoma	Bone marrow biopsy	2
4	20 AIM	1999	No	85	Weakness, abdominal pain, cough, fever, arthralgia	Confusion	28	31	16.0	3,249	PT 13; PTT 33; Fgn 62	3	Acute lymphocytic leukemia	Bone marrow biopsy	0
5	66 WM	1999	No	30	Weakness, dyspnea, weight loss	Confusion	19	24	1.4	5,865	PT 16; Fgn 117	9	Non-small cell lung cancer	Bone marrow biopsy	4
6	52 WF	2000	Breast, 3	19	Weakness, abdominal pain, dyspnea	Confusion	25	12	1.0	1,431	INR 1.2; PTT 25; Fgn 424	3	Breast carcinoma	Autopsy	0
7	86 WF	2001	No	8	Weakness	Left-sided weakness, slurred speech	19	24	1.7	401	PT 11; PTT 28; Fgn 375	4	Breast carcinoma	Bone marrow biopsy	14
8	59 WF	2003	No	1	Chest pain	None	25	23	3.0	6,757	PT 19.9; INR 2.5; PTT 32.7; Fgn 326	14	Renal cell carcinoma	CT scan	61
9	45 WM	2003	No	23	Fever, abdominal pain, dyspnea, edema	None	20	2	4.0	1,021	PT 12.3; INR 1.2; PTT 34; Fgn 258	10	Kaposi's sarcoma	Autopsy	0
10	50 BM	2005	No	14	Cough, fever, myalgias	Confusion	20	16	6.8	10,126	INR 1.4; PTT 36; Fgn 301	1	Non-Hodgkin lymphoma	Bone marrow biopsy	9

Clinical features of the 10 patients from The Oklahoma TTP-Hemolytic-Uremic Syndrome Registry who were initially diagnosed with TTP and subsequently discovered to have systematic malignancy. Duration of symptoms describes the interval from the onset of symptoms until the initial diagnosis of TTP and first plasma exchange treatment.
Abbreviations: AIM, American Indian male; BM, black male; Cr, serum creatinine; CT, computerized tomography; Fgn, fibrinogen; Hct, hematocrit; HM, Hispanic male; INR, international normalized ratio; LDH, serum lactate dehydrogenase (normalized to an upper limit of normal of 200 U/l); NA, not available; Plt, platelet count; Pt, patient; PT, prothrombin time; PTT, activated partial thromboplastin time; TTP, thrombotic thrombocytopenic purpura; WF, white female; WM, white male.

bocytopenia. Bone marrow biopsy was done after the discovery of a breast mass in patient 7 and because of no response to plasma exchange in patients 1 and 5. An additional indication for the bone marrow biopsy in patients 5 and 7 was the presence of many nucleated red cells on the peripheral blood smear.

In patients 2, 8, and 9, bone marrow biopsies were normal. Patient 2 was the only patient who did not have evidence for multiorgan dissemination. In this patient, diffuse, extensive squamous cell carcinoma was diagnosed by an open-lung biopsy after bronchoscopy had been normal. It was then assumed that cancer was the etiology of his bilateral pulmonary infiltrates and that he did not have concomitant TTP. Patient 8 presented with an ST-elevation myocardial infarction; sepsis was initially suspected to be the etiology of her anemia and thrombocytopenia; TTP was diagnosed and plasma exchange begun on her second hospital day. When there was no response to plasma exchange, CT scans were done that demonstrated metastatic renal cancer. Patient 9 was initially assumed to have a systemic infection because of his HIV infection and interstitial pulmonary infiltrates. TTP was diagnosed and plasma exchange begun on his sixth hospital day when no infection or malignancy was found by CT scans or bronchoscopy. Disseminated Kaposi's sarcoma was discovered at autopsy. Patient 6 did not have a bone marrow biopsy; she died sud-

denly on her third hospital day, and systemic microvascular metastatic breast cancer was identified at autopsy, but only by microscopic examination. Marrow involvement at autopsy suggested that a bone marrow biopsy would have demonstrated the metastatic cancer [12].

All 10 patients died soon after the initial diagnosis of TTP (median, 12 days; range, 3–75 days). Of the eight patients who were diagnosed before death, only patient 10 received chemotherapy, but he died 6 days after beginning cyclophosphamide/ doxorubicin/vincristine/prednisone/ rituximab treatment. Patients 2 through 5 died before chemotherapy could be administered; patients 1, 7, and 8 were considered to be too ill to receive chemotherapy.

The final diagnoses included eight different malignancies: breast carcinoma (two patients), non-small cell lung cancer (two patients), pancreatic carcinoma, renal carcinoma, myelodysplasia (refractory anemia with excess blasts), acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and Kaposi's sarcoma (one patient each).

Comparison of Patients with Disseminated Malignancy to Patients with Idiopathic TTP

Table 2 compares the 10 patients in whom disseminated malignancy was diagnosed to the 133 patients enrolled during the same period of time (1989–2005) whose final clinical category assignment was idiopathic TTP. Patients with idiopathic TTP were selected for this comparison because this was the initially assigned clinical category for 9 of our 10 patients and would have been their definitive clinical category assignment if malignancy had not been diagnosed. Patients with malignancies were more often men, had a longer duration of symptoms before the diagnosis of TTP, more frequently presented with respiratory symptoms of dyspnea and cough, and had greater elevations of serum LDH. Only 3 (2%) of the 133 patients with idiopathic TTP had LDH values over 5,000 U/l (5,955–12,587 U/l). However, there was no significant difference in age, race, frequency of neurologic abnormalities, severity of anemia and thrombocytopenia, serum creatinine, or ADAMTS13 activity. Although no patients with disseminated malignancy had severely deficient ADAMTS13 activity (<5%), this was not different from patients with idiopathic TTP, 70% of whom also did not have severely deficient ADAMTS13 activity. Patients with disseminated malignancy responded less often to plasma exchange and had a higher mortality rate.

Previously Reported Patients

The literature search identified 445 articles; 318 were excluded because of the criteria described in Patients and Methods; 18 of the 127 reviewed articles reported 19 patients in whom cancer was not initially apparent and TTP or HUS was suspected as the etiology for microangiopathic hemolytic anemia and thrombocytopenia (Table 3) [13–30]. The presenting clinical features of these 19 patients were similar to our 10 patients (Table 1): 11 were male; the median age was 58 years. Fourteen patients had no previous diagnosis of cancer. The median duration of symptoms, reported for 11 patients, was 21 days; in five patients, the duration of symptoms was only 2–5 days. Six patients had presenting symptoms of pain other than abdominal pain (four back pain, one bone pain, and one jaw pain), symptoms that were not reported by our 10 patients with disseminated malignancy. Among our 133 patients with idiopathic TTP, a presenting symptom of back pain was rare; presenting symptoms of bone or jaw pain were not reported. Respiratory symptoms were reported in only 3 of the 19 patients. Four patients had severe neurologic abnormalities. The severity of anemia was similar to our 10 patients, with a median hematocrit of 26%; the thrombocytopenia was less severe, with a median platelet count of 59,000/μl. The median time from the initial presentation to the diagnosis of malignancy was 14 days. In six patients, the malignancy was diagnosed by bone marrow biopsy. Bone marrow biopsies were done in eight other patients; they were normal in six; one had marrow necrosis and one had an inaspirable marrow with no biopsy. In six patients, malignancy was not diagnosed until autopsy; in patients 2 and 9, the malignancy was apparent only when microscopic examination of the autopsy tissues was performed.

Sixteen of these 19 patients had malignancies that were different from those of our 10 patients: gastric carcinoma (five patients), prostate carcinoma (four patients), carcinoma of unknown primary (three patients), anal squamous cell carcinoma (two patients), and colon carcinoma and multiple endocrine neoplasia type I (one patient each). Outcomes were reported for 18 patients. As opposed to our 10 patients, five were in remission at the time of the report.

Discussion

Microangiopathic hemolytic anemia and thrombocytopenia caused by systemic malignancies have been well described [3–7], but it is uncommon for microangiopathic hemolytic anemia and thrombocytopenia to be the predominant presenting clinical features in patients whose systemic malignancy is not initially apparent. Although occult malignancy causing microangiopathic hemolytic anemia and thrombocytopenia may be uncommon, it is an important consideration in the evaluation of patients for TTP. In the Oklahoma TTP-HUS Registry, 10 (3%) of 351 patients who were initially diagnosed as having TTP and treated with plasma exchange were subsequently and unexpectedly diagnosed

Table 2. Comparison of Oklahoma Registry patients with a final diagnosis of systemic malignancy to patients with idiopathic TTP

Clinical features	Disseminated malignancy ($n = 10$)	Idiopathic TTP ($n = 133$)	p
Age, years	56	47	.106
Race, % black	10	28	.290
Sex, % female	30	73	.008
Duration of symptoms, days	21	8	.005
Presenting symptoms, %			
Weakness	70	53	.347
Cough, dyspnea	70	26	.007
Fever	50	31	.292
Abdominal pain	40	35	.745
Chest pain	30	10	.085
Nausea/vomiting	20	53	.052
Diarrhea	10	23	.456
Bleeding/purpura	10	32	.282
Neurologic abnormalities, %			
Severe	20	47	.128
Minor	60	29	
None	20	24	
Laboratory data			
Hematocrit, %	21	22	.868
Platelet count, $10^3/\mu l$	21,000	13,000	.328
Creatinine, mg/dl	2.4	2.0	.761
LDH, U/l	2894	1260	.045
ADAMTS13			
Median activity, %	50 (8)	23 (81)	.167
<5% activity, % of patients	0	30%	.102
Response to PE, %	10	82 (125)	<0.001
Death (within 30 days), %	90	20	<0.001

Clinical features of the 10 patients from The Oklahoma TTP-Hemolytic-Uremic Syndrome Registry who were initially diagnosed with TTP and subsequently discovered to have systematic malignancy are compared to the 133 patients enrolled during the same period of time (1989–2005) whose final clinical category assignment was idiopathic TTP. Medians are shown for continuous variables. Statistical comparisons between groups were made using the Wilcoxon rank-sum test for continuous data and the chi-square or Fisher's exact test for categorical data. Duration of symptoms describes the interval from the patient's description of their onset of symptoms until the initial diagnosis of TTP and first plasma exchange treatment. The severe neurologic abnormalities that were present at diagnosis of TTP or occurred during the hospital course were coma, stroke, seizure, or focal neurologic signs. Common minor abnormalities were confusion, transient visual symptoms, and severe headache. Laboratory data are median values. Values for LDH are normalized to an upper unit of normal of 200 U/l. ADAMTS13 activity was measured on 8 of 10 and 81 of 133 patients; values <5% are considered to be characteristic of TTP [38]. Response is defined as achievement of a normal platelet count within 7 days of completing plasma exchange [2]; eight patients are not included in the analysis of patients with idiopathic ITP: five died before plasma exchange could be begun and three resolved without plasma exchange. Death is recorded if it occurred within 30 days of plasma exchange treatment [9].
Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; LDH, lactate dehydrogenase; PE, plasma exchange; TTP, thrombotic thrombocytopenic purpura.

with disseminated malignancy. Only systemic infections have been a more common cause of an incorrect initial diagnosis of TTP in the Oklahoma Registry [2]. Many different malignancies may mimic TTP; there were 14 different malignant disorders (Tables 1, 3) in the 29 patients described in this report.

The importance of prompt diagnosis of the systemic malignancy is to provide an opportunity for treatment with ap-

Table 3. Presenting features and clinical course of 19 previously reported patients with systemic malignancy who were initially diagnosed as TTP

Pt	Reference	Age, race, sex	Previous diagnosis of cancer, interval (years)	Duration of symptoms (days)	Presenting symptoms	Neurologic abnormality	Hct (%)	Plt ($10^3/\mu l$)	Cr (mg/dl)	LDH (U/l)	Coagulation assays	Days from presentation to diagnosis of malignancy	Final diagnosis	Method of diagnosis	Days from diagnosis of malignancy to death
1	[13]	37 HM	No	5	Epistaxis	Vertigo, blurred vision	22	32	—	—	Nl	35	Gastric carcinoma	Lymph node biopsy	26
2	[14]	56 F	Anus, 5	3	Weakness	Right-side weakness, dysphasia	11	65	—	—	—	4	Anal squamous carcinoma	Autopsy	0
3	[15]	55 M	No	4	Epistaxis, intestinal bleeding	None	11	20	—	—	PT 14; Fgn 500	4	Gastric carcinoma	Autopsy	0
4	[16]	25 BF	No	21	Weakness, bone pain	None	24	100	Nl	2,500	Nl	1	Gastric carcinoma	Bone marrow biopsy	210
5	[17]	35 M	No	40	Fever, weight loss, jaw pain	Disorientation, left hemiparesis	26	70	Nl	950	PT 56; Fgn 270	6	Non-small cell lung cancer	Autopsy	0
6	[18]	81 M	Colon, 5	—	—	—	37	20	10.8	—	Fgn 265	120	Prostate carcinoma	Bone biopsy	—
7	[19]	72 WM	No	3	Oliguria, hematuria	Transient right-side weakness	35	21	10.9	—	PT Nl; PTT 30; Fgn 250	154	Prostate carcinoma	Prostate biopsy	Remission
8	[20]	55 F	Breast, 2	21	Dyspnea	None	37	34	Nl	3,525	PT 13.2; PTT 32.1	14	Breast carcinoma	Autopsy	0
9	[21]	69 WF	No	—	Fever	Disorientation	24	64	1.5	1,743	PT 13.5; Fgn 978	—	Non-Hodgkin lymphoma	Autopsy	0
10	[22]	36 F	No	56	Back pain, dyspnea	None	25	59	0.5	1,119	PT 13.5; PTT 29.6; Fgn 342	3	Carcinoma, unknown origin	Bone marrow biopsy	156
11	[23]	44 WF	No	—	Abdominal pain, fever, petechiae	Confusion	40	8	1.8	3,585	PT 12; PTT 30; Fgn 500	11	Multiple endocrine neoplasia, type I	Autopsy	0
12	[24]	67 M	No	—	Back pain	None	36	4	11.8	1,968	Nl	14	Prostate carcinoma	PSA, ultra-sound, bone scan	Remission
13	[25]	33 M	No	30	Abdominal and back pain	None	19	66	0.8	7,455	Nl	1	Gastric carcinoma	Bone marrow biopsy	30
14	[26]	60 AF	Anus, ⅔	—	Dyspnea, oral bleeding	None	14	31	1.3	381	PT 12; PTT 23; Fgn 469	90	Anal squamous carcinoma	CT scan	60
15	[27]	87 M	No	—	Vomiting	No	28	61	8.3	↑	Nl	—	Prostate carcinoma	Prostate biopsy	Remission
16	[28]	67 AM	No	30	Back and abdominal pain, fever, weight loss	Confusion	29	23	0.8	1239	Nl	14	Colon carcinoma	Colono-scopy	Remission
17	[29]	62 M	Stomach, 4	2	Abdominal and back pain, jaundice	None	32	86	Nl	1,222	Nl	1	Gastric carcinoma	Bone scan, bone marrow biopsy	336
18	[29]	58 M	No	—	Abdominal pain, jaundice	No	23	80	Nl	833	Nl	1	Carcinoma, unknown origin	Bone marrow biopsy, bone scan	Remission
19	[30]	69 F	No	—	—	None	23	124	—	1,733	Nl	14	Carcinoma, unknown origin	Bone marrow biopsy, bone scan	3

Clinical features of the previously reported 19 patients who were initially suspected of having TTP and subsequently discovered to have systematic malignancy. Duration of symptoms describes the interval from the onset of symptoms until the initial diagnosis of TTP and first plasma exchange treatment; —, data not reported.
Abbreviations: AM, Asian male; BF, black female; Cr, serum creatinine; CT, computerized tomography; F, female; Fgn, fibrinogen; Hct, hematocrit; HM, Hispanic male; LDH, serum lactate dehydrogenase (normalized to an upper limit of normal of 200 U/l); M, male; Nl, described in the case report as normal; Plt, platelet count; PSA, prostate-specific antigen; Pt, patient; PT, prothrombin time; PTT, activated partial thromboplastin time; WF, white female.

propriate chemotherapy. Early recognition of cancer may not benefit many patients who present with microangiopathic hemolytic anemia and thrombocytopenia since these patients often have widely disseminated cancer. This is evident from our experience, in which only 1 of 10 patients received chemotherapy, and even that one patient died soon after beginning treatment. Nine of 19 previously reported patients received chemotherapy and five achieved remission, but selection bias for reporting favorable outcomes may have influenced these data. Even though treatment success may be limited, prompt diagnosis is important for appropriate management.

Prompt diagnosis of systemic malignancy is also important in avoiding unnecessary risks of plasma exchange treatment for TTP. In a recent 9-year cohort study of 206 consecutive patients treated with plasma exchange for TTP, five patients died due to complications of the central venous catheter insertion or catheter-related sepsis; an additional 53 (26%) patients had nonfatal major complications, such as sepsis, venous thrombosis, and pericardial tamponade [8].

The difficulty of diagnosing a systemic malignancy presenting with microangiopathic hemolytic anemia and thrombocytopenia is apparent from the presentations of our 10 patients. The onset of symptoms may be abrupt. The severity of anemia, thrombocytopenia, and neurologic and renal abnormalities were not different from patients with idiopathic TTP. In 8 of the 29 patients, malignancy was not discovered until an autopsy was done; in three of these eight patients, malignancy was apparent only when microscopic sections from the autopsy were examined. Therefore, other patients with presumed idiopathic TTP who do not have an autopsy may have also had occult disseminated malignancy.

The diagnosis of disseminated malignancy excludes the diagnosis of TTP or HUS; these patients should not be considered to have "cancer-associated TTP" [31–33]. Although multiple etiologies may contribute to the syndromes recognized as TTP and HUS, disseminated malignancy is a pathologically and clinically distinct disorder. Disseminated malignancy can cause microangiopathic hemolytic anemia and thrombocytopenia, in the absence of DIC, by microvascular tumor emboli [7]. This has been most frequently observed with diffuse microscopic pulmonary involvement [20, 34]. ADAMTS13 activity is not severely deficient [35] but may be lower than normal in some patients with disseminated malignancy due to high plasma levels of von Willebrand factor [35, 36]. Plasma exchange has no role in management when a malignant disorder is recognized.

Clues that may suggest the presence of an occult systemic malignancy include presenting symptoms of dyspnea, cough, and pain other than abdominal pain. These symptoms were not common in our patients with idiopathic TTP but were common among the patients with malignancies. Although increased serum LDH is characteristic of patients with TTP, extreme elevations are not typical and may suggest tumor lysis. The presence of many nucleated red cells plus immature granulocytes may also create a suspicion of metastatic malignancy in the marrow [37]. Although many patients with systemic malignancy causing microangiopathic hemolytic anemia and thrombocytopenia may have DIC, the absence of evidence for DIC does not exclude the possibility of malignancy [7]. DIC was considered in only 1 of the 10 patients from Oklahoma and, by our selection criteria, in none of the previously reported patients. History of previous malignancy would be an obvious clue for the possibility of disseminated malignancy. However, 23 of 29 patients had no previous cancer history, suggesting that this presentation reflects a biologic property that accelerates systemic invasiveness. Perhaps the most convincing clue that a patient with presumed TTP may have a disseminated malignancy is failure to respond to plasma exchange.

If systematic malignancy is suspected, bone marrow biopsy is appropriate. Twenty-three of the 29 patients had a bone marrow biopsy, and it provided the diagnosis in 12 patients. Perhaps immunohistochemistry could have increased the diagnostic sensitivity of bone marrow biopsies. CT or bone scans provided the diagnosis in four additional patients. In eight patients, the diagnosis of malignancy was not made until autopsy.

Summary

The evaluation and management of patients who present with an acute onset of microangiopathic hemolytic anemia and thrombocytopenia remain critical challenges for clinicians. Although the diagnosis of TTP and urgent treatment with plasma exchange must be considered in patients with microangiopathic hemolytic anemia and thrombocytopenia, the possibility that all of the clinical features of TTP may be caused by an occult disseminated malignancy must be appreciated. With increased awareness of the possible diagnosis of disseminated malignancy, the diagnosis can be made sooner, avoiding unnecessary plasma exchange treatment and allowing appropriate chemotherapy treatment.

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Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

References

1 George JN. Thrombotic thrombocytopenic purpura. New Eng J Med 2006; 354:1927–1935.

2 George JN, Vesely SK, Terrell DR. The Oklahoma Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome (TTP-HUS) Registry: A community perspective of patients with clinically diagnosed TTP-HUS. Semin Hematol 2004;41:60–67.

3 Waugh TR. Hemolytic anemia in carcinomatosis of the bone marrow. Am J Med Sci 1936;191:160–169.

4 Brain MC, Dacie JV, Hourihane OB. Microangiopathic hemolytic anemia: The possible role of vascular lesions in pathogenesis. Br J Haematol 1962; 8:358–374.

5 Forshaw J, Harwood L. Poikilocytosis associated with carcinoma. Arch Intern Med 1966;117:203–205.

6 Lohrmann HP, Adam W, Heymer B et al. Microangiopathic hemolytic anemia in metastatic carcinoma. Ann Int Med 1973;79:368–375.

7 Antman KH, Skarin AT, Mayer RJ et al. Microangiopathic hemolytic anemia and cancer: A review. Medicine 1979;58:377–384.

8 Howard MA, Williams LA, Terrell DR et al. Complications of plasma exchange in patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. III. An additional study of 57 consecutive patients, 2002–2005. Transfusion 2006;46: 154–156.

9 Vesely SK, George JN, Lämmle B et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: Relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood 2003;101:60–68.

10 Furlan M, Robles R, Galbusera M et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. New Engl J Med 1998;339:1578–1584.

11 Furlan M, Robles R, Lämmle B. Partial purification and characterization of a protease from human plasma cleaving von Willebrand factor to fragments produced by in vivo proteolysis. Blood 1996;87:4223–4234.

12 Francis KK, Kojouri K, George JN. Occult systemic carcinoma masquerading as thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Community Oncology 2005;2:339–343.

13 Brook J, Konwaler BE. Thrombotic thrombocytopenic purpura. Association with metastatic gastric carcinoma and a possible auto-immune disorder. Calif Med 1965;102:222–226.

14 Tapp E, Ralson A. Thrombotic microangiopathy associated with squamous carcinoma. Brit Med J 1969;4:209–210.

15 Aksoy M, Erdem S, Tahsinglu M et al. Microangiopathic hemolytic anemia due to adenocarcinoma of the stomach. New Istanbul Contrib Clin Sci 1975;11:103–107.

16 Hansen RM, Hanson GA. Gastric carcinoma in young people. A case report and review of the literature. Am J Gastroenterol 1980;74:497–503.

17 Podzamczer D, Carreras L, Condom E et al. Microangiopathic hemolytic anemia associated with pulmonary adenocarcinoma. JAMA 1985;254: 2554–2555.

18 Eugene M, Deray G, Cacoub P et al. Hemolytic uremic syndrome and prostatic adenocarcinoma. Clin Nephrol 1987;27:46.

19 Van der Merwe WM, Collins JF. The haemolytic uraemic syndrome and prostatic carcinoma. N Z Med J 1987;100:483–485.

20 Systrom DM, Mark EJ. Case records of the Massachusetts Hospital: A 55-year-old woman with acute respiratory failure and radiographically clear lungs. New Eng J Med 1995;332:1700–1708.

21 Sill H, Hofler G, Kaufmann P et al. Angiotropic large cell lymphoma presenting as thrombotic microangiopathy (thrombotic thrombocytopenic purpura). Cancer 1995;75:1167–1169.

22 Lin Y-C, Chang H-K, Sun C-F et al. Microangiopathic hemolytic anemia as an initial presentation of metastatic cancer of unknown primary origin. South Med J 1995;88:683–687.

23 Kouides PA, Phatak PD, Cramer SF. Fatal thrombotic thrombocytopenia purpura (TTP) presenting concurrently with metastatic multiple endocrine neoplasia (MEN) type I. Hematopathol Mol Hematol 1996;10:161–170.

24 Perkovic V, Came NA, Grigg AP et al. Haemolytic uraemic syndrome and prostatic cancer. N Z J Med 1999;29:383–384.

25 Gonzalez N, Rios E, Martin-Noya A et al. Thrombotic thrombocytopenic purpura and bone marrow necrosis as a complication of gastric neoplasm. Haematologia 2002;87:ECR01.

26 Yeh KY, Dunn P, Chang JJ-C et al. Microangiopathic hemolytic anemia in a patient with recurrent anal cancer and liver metastasis. Chang Gung Med J 2002;25:706–709.

27 Mungall S, Mathieson P. Hemolytic uremic syndrome in metastatic adenocarcinoma of the prostate. Am J Kidney Dis 2002;40:1334–1336.

28 Lee JL, Lee JH, Kim MK. A case of bone marrow necrosis with thrombotic thrombocytopenic purpura as a manifestation of occult colon cancer. Jpn J Clin Oncol 2004;34:476–480.

29 Arkenau HT, Mussig O, Buhr T et al. Microangiopathic hemolytic anemia (MAHA) as paraneoplastic syndrome in metastasized signet ring cell carcinomas: Case reports and review of the literature. Z Gastroenterol 2005; 43:719–722.

30 Pirrotta MT, Bucalossi A, Forconi F et al. Thrombotic thrombocytopenic purpura secondary to an occult adenocarcinoma. ***The Oncologist*** 2005;10: 299–300.

31 Gordon LI, Kwaan HC. Thrombotic microangiopathy manifesting as thrombotic thrombocytopenic purpura hemolytic uremic syndrome in the cancer patient. Semin Thromb Hemost 1999;25:217–221.

32 Allford S, Hunt BJ, Rose P et al. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anemias. Br J Haematol 2003;120:556–573.

33 Veyradier A, Meyer D. Thrombotic thrombocytopenic purpura and its diagnosis. J Thromb Haemost 2005;3:2420–2427.

34 Kane RD, Hawkins HK, Miller JA et al. Microscopic pulmonary tumor emboli associated with dyspnea. Cancer 1975;36:1473–1482.

35 Fontana S, Gerritsen HE, Hovinga JK et al. Microangiopathic haemolytic anaemia in metastasizing malignant tumours is not associated with a severe deficiency of the von Willebrand factor-cleaving protease. Br J Haematol 2001;113:100–102.

36 Mannucci PM, Capoferri C, Canciani MT. Plasma levels of von Willebrand factor regulate ADAMTS-13, its major cleaving protease. Br J Haematol 2004;126:213–218.

37 Vaughan JM. Leuco-erythroblastic anaemia. J Path Bacteriol 1936;42: 541–564.

38 Bianchi V, Robles R, Alberio L et al. Von Willebrand factor-cleaving protease (ADAMTS13) in thrombocytopenic disorders: A severely deficient activity is specific for thrombotic thrombocytopenic purpura. Blood 2002; 100:710–713.