Frequency and Significance of HIV Infection among Patients Diagnosed with Thrombotic Thrombocytopenic Purpura

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Background. Case series of patients with a diagnosis of thrombotic thrombocytopenic purpura (TTP) have reported different frequencies of human immunodeficiency virus (HIV) infection; some series suggest that HIV infection may cause TTP.

Methods. We systematically reviewed all reports of HIV infection in case series of patients with TTP. We analyzed data from the Oklahoma TTP-HUS (hemolytic uremic syndrome) Registry, an inception cohort of 362 consecutive patients, for 1989–2007.

Results. Nineteen case series reported the occurrence of HIV infection at the time of diagnosis of TTP in 0%–83% of patients; individual patient data were rarely described. The Oklahoma TTP-HUS Registry determined the HIV status at the time of diagnosis of TTP in 351 (97%) of 362 patients. HIV infection was documented in 6 (1.84%; 95% CI, 0.68%–4.01%) of 326 adult patients (age, 26–51 years); follow-up data were complete for all 6 patients. The period prevalence of HIV infection among all adults in the Oklahoma TTP-HUS Registry region for 1989–2007 was 0.30%. One patient had typical features of TTP with 5 relapses. Five patients had single episodes; in 4, the clinical features that had initially suggested the diagnosis of TTP were subsequently attributed to malignant hypertension (in 3 patients) and disseminated Kaposi sarcoma (in 1 patient).

Conclusions. HIV infection, similar to other inflammatory conditions, may trigger acute episodes of TTP in susceptible patients. More commonly, acquired immunodeficiency syndrome–related disorders may mimic the clinical features of TTP. If the diagnosis of TTP is suggested in a patient with HIV infection, there should be careful evaluation for alternative diagnoses and cautious consideration of plasma exchange, the required treatment for TTP.

Soon after the first reports of AIDS, there were reports of thrombotic thrombocytopenic purpura (TTP) in patients with HIV infection, suggesting that TTP was a "new manifestation of infection with HIV" [1, p. 195]. Recent case series of TTP that reported a high frequency of patients who also had HIV infection have suggested that HIV-associated TTP is a specific entity [2–5], that HIV infection can cause TTP [6–8], and that TTP may be an AIDS-defining disorder [9]. However, a different interpretation, based on analysis of 350 consecutive hospitalized patients with HIV infection, was that the characteristic clinical features of TTP, microangiopathic hemolytic anemia, thrombocytopenia, and abnormal renal function, were manifestations of advanced HIV infection [10]. These different perspectives reflect the fact that the diagnosis of TTP is often uncertain, especially in patients with other complex medical problems, because of the absence of specific diagnostic criteria for TTP [11].

In patients with TTP, the only consistent abnormalities are microangiopathic hemolytic anemia, which is defined by schistocytes (fragmented RBCs on the peripheral blood smear) and a negative direct antiglobulin

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Table 1. Case series of patients with thrombotic thrombocytopenic purpura (TTP) that report the occurrence of HIV infection.

Case series	Location	Patient accrual period	No. of patients with TTP	No. (%) of patients with TTP and HIV infection	No. (%) of patients with TTP who were tested for HIV infection	Authors' comments and interpretation
Leaf et al. [1][a]	New York, NY	1980–1987	14	4	NR	Report "established TTP as a new manifestation of infection with HIV" (p. 195)
Thompson et al. [16][a]	San Francisco, CA	1980–1991	44	7	NR	Reports "suggested a possible relationship between TMA and HIV" (p. 1894)
Ucar et al. [17][a]	Miami, FL	1979–1991	50	11 (22)	50 (100)	"HIV infection appears to be associated with TMA" (p. 304)
Hayward et al. [18]	Toronto, Ontario, Canada	1977–1988	52	0	NR	1 Patient had transfusion-acquired HIV infection, which probably occurred after TTP
Dawson et al. [19]	Baltimore, MD	NR	50	0	NR	1 Patient became HIV infected after receiving PEX for TTP
Tsai et al. [20]	New York, NY	NR	37	2	NR	No comments about HIV infection
Lara et al. [21]	Sacramento, CA	1978–1998	126	6	NR	HIV infection reported as a "comorbid condition" (p. 575)
Dervenoulas et al. [22]	Athens, Greece	1985–1998	48	0 (0)	48 (100)	No comments about HIV infection
Haas et al. [23]	Vienna, Austria	1992–2000	30	1	NR	HIV infection reported as a "TTP/HUS associated condition" (p. 416)
Chang et al. [24]	Dayton, OH	1981–2000	74	2	NR	HIV infection reported as "significant underlying pathology" (p. 203)
Tostivint et al. [2] and Maslo et al. [27]	Paris, France	1990–1998	55	18	NR	AIDS-associated HUS reported as a specific entity; 8 (44%) of 18 patients with HIV infection had CMV infection
Coppo et al. [25]	Paris, France	NR	30	9	NR	8 (89%) Of 9 patients with HIV infection had an acute bacterial infection; selected from intensive care unit patients
Kremer Hovinga et al. [26]	Berne, Switzerland	1997–2003	396	1	NR	Report from a reference laboratory testing ADAMTS13 activity with limited clinical data
Pene et al. [6]	Paris, France	1998–2001	63	13	NR	HIV infection reported as an "etiology or favoring condition" (p. 74)
Miller et al. [3][a]	London, England	1998–2004	64	8	NR	"HIV-associated TTP" is "a rare cause of thrombocytopenia in patients with HIV" (p. 542)
Novitzky et al. [4][a]	Cape Town, South Africa	1996–2003	44	21 (48)	44 (100)	Comparative study of patients with "classic TTP" and patients with "HIV infection–related TTP" (p. 374)
Outschoorn et al. [7]	Philadelphia, PA	1984–2004	61	8	NR	HIV infection reported as an "etiology" of TTP (p. 897)

Table 1. ***(Continued.)***

Case series	Location	Patient accrual period	No. of patients with TTP	No. (%) of patients with TTP and HIV infection	No. (%) of patients with TTP who were tested for HIV infection	Authors' comments and interpretation
Tuncer et al. [5]	Birmingham, AL	1996–2004	90	6	NR	HIV infection reported as an "associated condition" of TTP (p. 109)
Gunther et al. [8][a]	Johannesburg, South Africa	2003–2005	24	20 (83)	24 (100)	HIV infection "is now by far the commonest cause of TTP" (p. 1711)
Current report	Oklahoma	1989–2007	362 (all patients); 336 (adults)	6 (1.7) of 351; 6 (1.8) of 326	351 (97); 326 (97)	In 4 patients with HIV infection, the presenting features were subsequently attributed to another diagnosis

NOTE. CMV, cytomegalovirus; HUS, hemolytic uremic syndrome; NR, not reported; PEX, plasma exchange treatment; TMA, thrombotic microangiopathy.

[a] These citations were identified by the keyword search; these articles describe ⩾10 patients and specifically addressed the association of HIV infection and TTP.

test result, and thrombocytopenia—features that can occur in other conditions. Severely deficient activity of ADAMTS13, a plasma von Willebrand–cleaving protease, caused by autoantibody inhibition is characteristic of TTP and was initially thought to be diagnostic of TTP [12]. However, measurements of ADAMTS13 activity are not sufficiently sensitive or specific to consistently distinguish TTP from other severe systemic disorders [11].

To investigate the association of HIV infection and TTP, we had 4 objectives. First, to provide a comprehensive background, we systematically reviewed case series of patients with TTP to document the reported frequency of HIV infection. Second, to describe our experience of HIV infection among patients who have received a diagnosis of TTP, we analyzed data from the Oklahoma TTP-HUS (hemolytic uremic syndrome) Registry, an inception cohort of all 362 consecutive patients with an initial episode of clinically diagnosed TTP within a defined geographic region in 1989–2007 [13, 14]. Third, to interpret our experience, we compared the frequency of HIV infection among registry patients with the prevalence of HIV infection among all adults in the registry region. Fourth, to determine possible reasons for an association of HIV infection and TTP, we analyzed the clinical course and continuous follow-up of each patient in the registry who had HIV infection at the time of his or her diagnosis of TTP.

METHODS

Systematic literature review. OVID software was used to search the Medline database on 30 May 2008. Articles containing both a keyword or medical subject heading in the title or available text for TTP ("thrombotic thrombocytopenic purpura," "TTP," "hemolytic-uremic syndrome," "HUS," "thrombotic thrombocytopenic purpura–hemolytic uremic syndrome," "TTP-HUS," "thrombotic microangiopathy," "TMA," "microangiopathy," "intravascular hemolysis," and "plasma exchange") and also for HIV ("human immunodeficiency virus," "HIV," "acquired immunodeficiency syndrome," and "AIDS") were identified. Case series involving ⩾10 patients with TTP that reported data on the presence or absence of HIV infection were selected for review. The bibliographies of the selected articles were searched to identify additional articles.

To search for additional articles that may have reported HIV infection, we identified all case series involving ⩾25 patients with TTP published since 1981 by reviewing the titles and relevant abstracts of English-language articles that were retrieved by the search terms "thrombotic thrombocytopenic purpura" and "TTP."

Oklahoma TTP-HUS Registry patients. The Oklahoma TTP-HUS Registry includes data on all consecutive patients for whom the Oklahoma Blood Institute was requested to provide plasma exchange treatment for patients with a diagnosis of TTP or HUS since 1 January 1989 [13, 14]. The Oklahoma Blood Institute is the sole provider of plasma exchange services for all hospitals in 58 of the 77 Oklahoma counties. Because the standard practice in this region is to treat all adult patients who have received a diagnosis of either TTP or HUS with plasma exchange, the registry is an inception cohort of consecutive patients for whom a diagnosis of TTP or HUS was made and for whom plasma exchange treatment was requested. Because these syndromes in adults are commonly known as TTP [11], we describe patients in this report as having TTP. Serum samples were obtained for HIV testing and ADAMTS13 assays immediately before the first plasma exchange; ADAMTS13 activity and its inhibition were measured by previously described methods [12, 15]. Deficiency of ADAMTS13 was defined as activity of <10% [14]. The Oklahoma TTP-HUS Registry is

approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Prevalence of HIV infection in the Oklahoma TTP-HUS Registry region. Data regarding the cumulative frequency of people with HIV infection who are currently or were living in each county of Oklahoma during 1989–2007 were available from the Oklahoma State Department of Health. We limited our analysis to adults (age, ⩾20 years), because the patients in the Oklahoma TTP-HUS Registry with HIV infection were all adults and because the prevalence of HIV infection was much lower among children. To calculate period prevalence for 1989–2007, we used 2000 US Census data for population estimates for each of the 58 counties of the registry region.

RESULTS

Systematic literature review. The keyword search retrieved 78 articles; 7 retrospective case series involving ⩾10 patients with a diagnosis of TTP were identified that specifically described the presence of HIV infection [1–4, 8, 16, 17]. The search terms "thrombotic thrombocytopenic purpura" and "TTP" retrieved 3317 articles; 65 additional retrospective case series published after 1981 that described ⩾25 patients were identified: 43 (66%) did not mention HIV infection, 10 (15%) specifically excluded patients with HIV infection, and 12 (19%) [5–7, 18–26] described the presence (9 articles) or absence (3 articles) of patients with HIV infection at the time of diagnosis of TTP. These 19 case series are presented in table 1. In 4 articles, all patients were tested for HIV, and the reported frequencies of HIV infection were 0% [22], 22% [17], 48% [4], and 83% [8]. In the other 15 articles, the number of patients tested for HIV infection was not reported. Most articles described HIV infection as an associated condition or cause of TTP. Only 2 studies presented individual patient data [2, 17, 27]. In 1 article [17], 3 of 4 patients with HIV infection had potential causes other than TTP for their clinical features: malignant hypertension [28], sepsis [14], and cocaine intoxication [29]. Eight (44%) of 18 patients in the other study had cytomegalovirus infection [2, 27].

Oklahoma TTP-HUS Registry patients. The Oklahoma TTP-HUS Registry enrolled 362 patients with an initial episode of clinically diagnosed TTP during 1989–2007. Tests for HIV infection were performed for 351 patients (97%); HIV infection was documented in 6 patients (age, 26–51 years) at the time of their initial diagnoses of TTP. All 6 patients have been continuously followed up to the present time or until death. Because all patients with HIV infection were adults, all subsequent analyses were limited to adult patients. The period prevalence of HIV infection during 1989–2007 among the 326 adult patients (age, ⩾20 years) who were tested for HIV was 1.84% (95% CI, 0.68%–4.01%) [30]. The period prevalence of HIV infection during 1989–2007 among all adults aged ⩾20 years in the 58 counties of the registry region was 0.30%.

Table 2. Clinical categories of 326 adult patients with a clinical diagnosis of thrombotic thrombocytopenic purpura in the Oklahoma TTP-HUS (hemolytic uremic syndrome) Registry, 1989–2007.

Clinical category	No. of patients	
	HIV negative (n = 320)	HIV positive (n = 6)
HSCT	21	0
Pregnancy	23	0
Drug associated	42	0
Bloody-diarrhea prodrome	22	0
Additional or alternative diagnoses		
Sepsis	26	0
Disseminated malignancy	11	1
Autoimmune disorder	34	0
Malignant hypertension	3	3
Multiorgan failure	10	0
Idiopathic	128	2

NOTE. These categories, as previously defined [13], represent associated conditions and potential etiologies. Patients are assigned to one of these categories in sequential, hierarchical order (from top to bottom in this table) on the basis of their initial episode of thrombotic thrombocytopenic purpura [13]. HSCT, hematopoietic stem cell transplantation.

Table 2 describes the 326 adult patients in the Oklahoma TTP-HUS Registry according to clinical categories based on their associated conditions and additional or alternative diagnoses [13]. One hundred thirty patients are described as idiopathic because they had none of the conditions that define the other categories. Two of the patients in the idiopathic category were HIV positive. In 6 patients, the clinical features that had initially suggested the diagnosis of TTP were subsequently attributed to malignant hypertension; 3 were HIV positive. Disseminated malignancy was diagnosed in 12 patients after plasma exchange treatment for TTP was begun; 1 was HIV positive.

Among the 236 adult patients who were enrolled in the registry since 13 November 1995, when routine testing for ADAMTS13 activity was begun, and who were also tested for HIV infection, ADAMTS13 activity was measured in 226 (96%). Among the 220 HIV-negative patients, ADAMTS13 deficiency was present in 38 (46%) of 82 idiopathic patients and 12 (9%) of 138 patients in other clinical categories. ADAMTS13 activity was measured in all 6 HIV-positive patients. In 2 patients, ADAMTS13 activity was deficient (<10%): 1 with typical relapsing TTP (patient 1, table 3) and 1 whose final diagnosis was disseminated Kaposi sarcoma (patient 4). ADAMTS13 activity was 12% in the other patient (patient 3) in the idiopathic category and 45%-65% in the 3 patients whose presenting clinical features were subsequently attributed to malignant hypertension.

Table 3. Presenting features and clinical course of 6 patients who had HIV infection at the time of their initial diagnosis of thrombotic thrombocytopenic purpura (TTP).

			Presenting clinical features								
Patient, no. TTP episode	Age, years/ race/sex	Year	Hematocrit, %	Platelet count, platelets $\times 10^3/\mu L$	Creatinine level, mg/dL	LDH level, U/L	Neurological features	ADAMTS13, %	HIV infection data	Clinical course	Final diagnosis
1											
1	41/NA/B/M	1998	19	5	1.2	1946	Transient focal abnormalities	53 (inhibitor was not tested)	Diagnosed at time of TTP; CD4 cell count, 260 cells/μL; HIV RNA level, 110,000 copies/mL	Response to 6 PEXs; never treated for HIV infection	TTP
2	…	2000	18	5	1.9	1200	None	Not available	CD4 cell count, 216 cells/μL; HIV RNA level, 72,064 copies/mL	Response to 23 PEXs	TTP
3	…	2000	19	11	1.3	1688	Syncope	15 (no inhibitor)	CD4 cell count, 154 cells/μL	Response to 13 PEXs	TTP
4	…	2001	24	12	1.0	1056	None	<5 (trace inhibitor)	…	Response to 12 PEXs	TTP
5	…	2003	23	32	1.8	2293	Confusion	<5 (inhibitor: 1 BU)	CD4 cell count, 79 cells/μL; HIV RNA level, >750,000 copies/mL	Response to 14 PEXs	TTP
6	…	2006	20	24	1.2	603	None	<5 (inhibitor was 1.4 BU)	CD4 cell count, 168 cells/μL	Response to 9 PEXs	TTP
2	39/B/M	1999	17	51	13.9	1545	Seizure	60 (inhibitor was not tested)	Diagnosed at time of TTP; CD4 cell count, 84 cells/μL	No response to 13 PEXs; renal biopsy: HIVAN, no thrombotic microangiopathy; died in 2000	Malignant hypertension, HIVAN
3	26/B/M	2001	18	11	11.1	2953	Seizure, coma	12 (inhibitor: 1.7 BU	Diagnosed 3 weeks before TTP; CD4 cell count, 4 cells/μL; HIV RNA level, 632,353 copies/mL	No response to 7 PEXs; subsequent recovery; remains well with HAART treatment; 2007: CD4 cell count, 917 cells/μL; HIV RNA level, 97 copies/mL	TTP
4	45/W/M	2003	20	2	4.6	1021	None	6 (inhibitor was 0.9 BU)	Diagnosed 2 weeks before TTP; CD4 cell count, 189 cells/μL; HIV RNA level, 343,840 copies/mL	No response to 5 PEXs; died in 10 days; autopsy: systemic Kaposi sarcoma, no thrombotic microangiopathy	Kaposi sarcoma
5	29/B/M	2005	17	47	29.2	319	None	65 (inhibitor was not tested)	Diagnosed at time of TTP; CD4 cell count, 395 cells/μL; HIV RNA level, 10,100 copies /mL	Response to 5 PEXs and control of hypertension; maintained with HD, no treatment for HIV; 2006: CD4 cell count, 386 cells/μL; HIV RNA level, 29,000 copies/mL	Malignant hypertension
6	51/W/F	2007	22	71	5.3	2419	None	45 (inhibitor was not tested)	Diagnosed 12 years before TTP; CD4 cell count, 18 cells/μL; HIV RNA level, 343,000 copies/mL	No response to 5 PEXs; maintained with HD; no treatment for HIV since 2002	Malignant hypertension

NOTE. The presenting laboratory data are the most abnormal values within 7 days before and after the day of diagnosis, designated as the day of the first plasma exchange treatment (PEX). Lactic dehydrogenase (LDH) values were adjusted to an upper limit of normal of 200 U/L. Neurologic abnormalities occurred within 7 days before diagnosis or during the course of PEX. CD4 cell counts and HIV RNA levels are from samples obtained at the time of diagnosis of TTP, except for patients 3 and 4; their data are from the time of diagnosis of HIV infection. BU, Bethesda units; HD, hemodialysis; HIVAN, HIV-associated nephropathy; NA, Native American.

Table 4. Clinical features in patients presenting with thrombocytopenia and anemia that are uncommon in thrombotic thrombocytopenic purpura (TTP) and suggest an alternative diagnosis.

Clinical features that are uncommon in patients with TTP	Possible alternative diagnoses
Systemic symptoms	
Fever (temperature, >38.8°C [102°F]), shaking chills, and myalgias	Sepsis
Severe hypertension (blood pressure, >200/120 mm Hg) with retinopathy (flame hemorrhages, papilledema)	Malignant hypertension with renal thrombotic microangiopathy
Hematopoietic system	
Disseminated intravascular coagulation (low plasma fibrinogen level, prolonged prothrombin time, and activated partial thromboplastin time)	Sepsis, disseminated malignancy
Systemic, confluent purpuric or ecchymotic rash, and ischemic digits	Sepsis
Neutropenia	Sepsis, drug toxicity
Peripheral blood smear findings	
Nucleated RBCs and immature granulocytes	Marrow infiltration with tumor or granulomatous disease
Oval macrocytes and neutropenia	Megaloblastic anemia (vitamin B_{12} or folate deficiency)
Vascular system: arterial or venous thrombosis	Heparin-induced thrombocytopenia and thrombosis
Pulmonary system	
Pulmonary infiltrate	Infection or malignancy
Cough with hemoptysis	Malignancy
Liver and biliary system: jaundice with high conjugated bilirubin	Toxic or infectious hepatic failure, malignancy
Neurologic system: stiff neck	Meningitis

The clinical courses of the 6 HIV-positive patients are presented in table 3. Patients 1 and 3 were assigned to the idiopathic category in table 2. Patient 1 had characteristic clinical features of TTP and responded promptly to plasma exchange treatment. HIV infection was discovered incidentally at the time of TTP diagnosis and progressed to AIDS (defined on the basis of a CD4 cell count of 154 cells/μL). He was not compliant with prescribed HAART. During 9 years, he had 6 episodes of TTP with no apparent preceding infectious or other illnesses. ADAMTS13 deficiency was present in his last 3 episodes. After recovery from his last episode of TTP, he died at home; an autopsy revealed systemic infection with gram-positive cocci and no evidence of recurrent TTP.

Patient 3 had been ill for 6 months with fever and weight loss. AIDS was diagnosed 3 weeks before his diagnosis of TTP, when he developed esophageal candidiasis. Treatment was begun with zidovudine, lamivudine, efavirenz, and fluconazole. He was hospitalized for repeated seizures, became comatose, and required intubation. CT demonstrated cerebral atrophy consistent with HIV encephalopathy. Coagulation studies suggested disseminated intravascular coagulation. When there was no evidence of sepsis, plasma exchange treatment for TTP was begun but was stopped when there was no clinical or hematologic response. Three days after stopping plasma exchange, the patient regained consciousness and subsequently recovered. Although coagulation abnormalities, lack of response to plasma exchange treatment, and recovery after plasma exchange treatment was stopped were not typical of TTP, no alternative diagnosis was discovered. Currently, he is doing well with HAART.

In the other 4 patients, the clinical features that had initially suggested the diagnosis of TTP (thrombocytopenia, anemia with schistocytes, and acute renal failure) were subsequently attributed to other conditions. Patient 4 had been diagnosed as having AIDS 2 weeks previously and began treatment with lamivudine, tenofovir, and efavirenz. Chest radiography demonstrated pulmonary infiltrates; plasma exchange for TTP was begun when evaluation for *Pneumocystis* species yielded negative results. He subsequently developed violaceous papules on both legs. Plasma exchange was stopped because of no response, and he died 5 days later. Autopsy demonstrated disseminated Kaposi sarcoma; thrombotic microangiopathy characteristic of TTP was not present. In the other 3 patients, the clinical features were subsequently attributed to malignant hypertension; none responded to plasma exchange treatment. Patient 2 had progressive weakness for 4 months. HIV infection was diagnosed during routine testing at the time of TTP diagnosis. A renal biopsy specimen demonstrated diffuse sclerosing glomerulopathy consistent with HIV-associated nephropathy with no thrombotic microangiopathy. The patient developed progressive multifocal leukoencephalopathy and died 10 months after the diagnosis of HIV/AIDS. Patient 5 had progressive weakness for 2 months. He had severe hypertension and bilateral small kidneys. HIV infection was diagnosed during routine testing at

the time of TTP diagnosis. He continues to require hemodialysis. He has never taken treatment for HIV infection. Patient 6 had progressive weakness and weight loss for 3 months before her TTP diagnosis. She had received a diagnosis of AIDS 11 years previously and had received HAART for the initial 6 years, but then received no antiretroviral treatment for the next 5 years. She had bilateral pulmonary infiltrates attributed to congestive heart failure. A renal biopsy specimen demonstrated end-stage renal disease with thrombotic microangiopathy attributed to malignant hypertension. She continues to undergo hemodialysis without treatment for her HIV infection.

DISCUSSION

Although most case series of patients with TTP do not mention HIV infection, some have reported a high frequency of HIV infection among patients diagnosed as having TTP and have suggested that it may cause TTP [6–8]. However, the disparity of reported frequencies of HIV infection among patients who have received a diagnosis of TTP is great (0%–83%) [4, 8, 17, 22]. The reports describing the highest frequency of HIV infection among patients diagnosed as having TTP (48% [4] and 83% [8]) may reflect the high regional prevalence of HIV infection among the population of South Africa [31]. Other reports describing HIV infection among patients in whom TTP has been diagnosed are from hospitals that may also serve populations with a high prevalence of HIV infection (table 1). The lack of individual patient data and follow-up in these reports limits the ability to interpret the relationship between HIV infection and the clinical features suggesting TTP. The reports that describe individual patient data suggest the possibility that other disorders may have caused these clinical features [2, 17, 27]. Because diagnostic criteria for TTP, requiring only the presence of microangiopathic hemolytic anemia and thrombocytopenia with no alternative cause [11], are not specific, and because AIDS-related disorders may cause these abnormalities [10], the diagnosis of TTP is often uncertain in patients with HIV infection.

Although TTP is characterized by systemic microvascular thrombosis that may cause abnormalities of multiple organ systems, some clinical features are uncommon and suggest alternative diagnoses (table 4). The critical initial clinical decision is whether to initiate plasma exchange—the specific treatment for TTP but also a procedure with a high risk of serious complications. A prospective analysis of 206 consecutive patients treated with plasma exchange for TTP documented that 57 patients (28%) had 75 major complications; 5 patients (2.4%) died of these complications: 3 died of complications of central venous catheter insertion, and 2 died of sepsis attributed to the indwelling central venous catheter [32].

ADAMTS13 deficiency is a characteristic abnormality of TTP [14]. However, the interpretation of ADAMTS13 activity levels among our 6 patients with HIV infection was uncertain. Patient 1, who had typical relapsing TTP, had normal ADAMTS13 activity in his first episode before becoming deficient as a result of an inhibitor in later episodes. Patient 4, with disseminated Kaposi sarcoma but no evidence of TTP at autopsy, also had ADAMTS13 deficiency with an inhibitor. ADAMTS13 activity was 12% with a demonstrable inhibitor in patient 3, who was considered to have idiopathic TTP despite atypical clinical features. The 3 patients whose presenting features were subsequently attributed to malignant hypertension had normal ADAMTS13 activity. These data suggest that, among HIV-infected patients, ADAMTS13 activity measurements cannot distinguish patients with typical TTP from patients whose clinical features were subsequently attributed to another diagnosis. Although the frequency of alternative diagnoses among HIV-positive patients is greater than among HIV-negative patients, similar alternative diagnoses occurred [28, 33].

Table 5. Possible reasons why patients with HIV infection may be diagnosed as having thrombotic thrombocytopenic purpura (TTP).

Inflammatory disorders may trigger an acute episode of TTP in a susceptible patient, such as a patient with ADAMTS13 deficiency
Infection (HIV infection itself or an opportunistic infection)
Immune reconstitution with response to HAART
AIDS-related disorders may mimic TTP
Opportunistic, angioinvasive infections (e.g., CMV or HHV-8 infection)
Disseminated malignancy
HIV-associated nephropathy with malignant hypertension
HIV-induced endothelial injury may cause thrombotic microangiopathy
The occurrence of TTP in a patient with HIV infection may be coincidental

NOTE. CMV, cytomegalovirus; HHV-8, human herpesvirus 8.

The period prevalence of HIV infection among patients in the Oklahoma TTP-HUS Registry (1.84%; 95% CI, 0.68%–4.01%) was low compared with many published case series but was greater than the period prevalence of HIV infection among adults in the registry region (0.30%). The higher prevalence of HIV infection among patients with a diagnosis of TTP may be related to the fact that the presenting clinical features in 4 of the 6 patients were subsequently attributed to AIDS-related disorders. Also, HIV testing was not performed for all individuals in the registry region population, resulting in the estimate that 25% of patients living with HIV infection in the United States have undiagnosed conditions [34]. In contrast, HIV testing was performed for 97% of patients in the registry.

There may be multiple reasons why patients with HIV infection are diagnosed as having TTP (table 5). First, HIV infection, AIDS-related disorders, or treatment-induced immune reconstitution [35] may trigger episodes of TTP in susceptible

patients. This sequence is similar to observations that infections [36], inflammatory conditions [37], and pregnancy [38] can trigger episodes of TTP in patients without HIV infection. This could have been the basis for the association of HIV infection with TTP in patient 1. Second, AIDS-related disorders can mimic the clinical features of TTP; this was the conclusion for patients 2, 4, 5, and 6.

Third, there may be a specific entity of HIV-associated thrombotic microangiopathy [39], suggested by observations of endothelial dysfunction with deposition of thrombi in the vessel wall [40]. Human herpesvirus 8 infection, which is common among HIV-infected patients, involves vascular endothelial cells and may contribute to development of thrombotic microangiopathy [41]. Analogous to HIV-associated thrombotic microangiopathy, transplantation-associated thrombotic microangiopathy, a syndrome that occurs after allogeneic hematopoietic stem cell transplantation and may result from conditioning regimen toxicity, graft-versus-host disease, and infections [42], was also previously considered to be TTP and therefore was treated with plasma exchange. Transplantation-associated thrombotic microangiopathy is now considered to be a specific entity, distinct from TTP, for which plasma exchange treatment is not appropriate [43]. Describing HIV-associated thrombotic microangiopathy as a specific entity could help to avoid plasma exchange treatment in HIV-infected patients whose clinical features are not typical of TTP [39].

HIV-associated thrombotic microangiopathy and AIDS-related disorders that may mimic TTP occur in patients with more advanced HIV infection [10, 44]. This finding is consistent with observations of decreased frequency of the diagnosis of TTP among patients with HIV infection during the HAART era [39, 45, 46]. The ability of HAART to down-regulate inflammation may also contribute to the decreased development of thrombotic microangiopathy [47]. Four of our 6 HIV-infected patients (patients 2, 3, 4, and 6) had AIDS-defining criteria documented before or at the time of their diagnosis of TTP; none had received HAART except for patient 6, and she had not been treated for 5 years.

Strengths of this study are the inception cohort of all 362 consecutive patients with an initial episode of clinically diagnosed TTP in a defined geographic region across 19 years, the documentation of the presence or absence of HIV infection in 97% of these patients, and analysis of the clinical course with complete follow-up of the 6 patients with HIV infection. Limitations are the small number of patients with HIV infection, their complex illnesses, and the nonspecific diagnostic criteria for TTP.

Although HIV infection and AIDS-related disorders may trigger acute episodes of TTP, similar to other infections and inflammatory disorders, our experience does not support the existence of HIV-associated TTP as a specific entity or the hypothesis that HIV infection can cause TTP. If the diagnosis of TTP is suggested in a patient with HIV infection, there should be careful evaluation for alternative origins in addition to appropriate treatment of the HIV infection. Treatment with plasma exchange must be considered cautiously.

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References

1. Leaf AN, Laubenstein LJ, Raphael B, Hochster H, Baez L, Karpatkin S. Thrombotic thrombocytopenic purpura associated with human immunodeficiency virus type 1 (HIV-1) infection. Ann Intern Med **1988**; 109: 194–7.
2. Tostivint I, Mougenot B, Flahault A, et al. Adult haemolytic and uraemic syndrome: causes and prognostic factors in the last decade. Nephrol Dial Transplant **2002**; 17:1228–34.
3. Miller RF, Scully MF, Cohen H, et al. Thrombotic thrombocytopaenic purpura in HIV-infected patients. Int J STD AIDS **2005**; 16:538–42.
4. Novitzky N, Thomson J, Abrahams L, du Toit C, McDonald A. Thrombotic thrombocytopenic purpura in patients with retroviral infection is highly responsive to plasma infusion. Br J Haematol **2005**; 128:373–9.
5. Tuncer HH, Oster RA, Huang ST, Marques MB. Predictors of response and relapse in a cohort of adults with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: a single institution experience. Transfusion **2007**; 47:107–14.
6. Pene F, Vigneau C, Auburtin M, Zahar J-R, Coste J, Heshmati F, Mira JP. Outcome of severe acute thrombotic microangiopathies in the intensive care unit. Intensive Care Med **2005**; 31:71–8.
7. Outschoorn UM, Ferber A. Outcomes in the treatment of thrombotic thrombocytopenic purpura with splenectomy: a retrospective cohort study. Am J Hematol **2006**; 81:895–900.
8. Gunther K, Garizio D, Nesara P. ADAMTS13 activity and the presence of acquired inhibitors in human immunodeficiency virus-related thrombotic thrombocytopenic purpura. Transfusion **2007**; 47:1710–6.
9. Tamkus D, Jajeh A, Osafo D, Hadad L, Bhanot B, Yogore MG. Thrombotic microangiopathy syndrome as an AIDS-defining illness: the experience of J. Stroger Hospital of Cook County. Clin Adv Hematol Oncol **2006**; 4:145–9.
10. Moore RD. Schistocytosis and a thrombotic microangiopathy-like syndrome in hospitalized HIV-infected patients. Am J Hematol **1999**; 60: 116–20.
11. George JN. Thrombotic thrombocytopenic purpura. N Engl J Med **2006**; 354:1927–35.
12. Furlan M, Robles R, Galbusera M, et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med **1998**; 339:1578–84.
13. 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**; 102:60–8.
14. George JN, Kremer Hovinga JA, Terrell DR, Vesely SK, Lämmle B. The Oklahoma Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome Registry: the Swiss Connection. Eur J Haematol **2008**; 80: 277–86.
15. Kremer Hovinga JA, Mottini M, Lämmle B. Measurement of ADAMTS-13 activity in plasma by the FRETS-VWF72 assay: comparison with other assay methods. J Thromb Haemost **2006**; 4:1146–8.

16. Thompson CE, Damon LE, Ries CA, Linker CA. Thrombotic microangiopathies in the 1980s: clinical features, response to treatment, and the impact of the human immunodeficiency virus epidemic. Blood **1992**; 80: 1890–5.
17. Ucar A, Fernandez HF, Byrnes JJ, Lian ECY, Harrington WJ Jr. Thrombotic microangiopathy and retroviral infections: a 13-year experience. Am J Hematol **1994**; 45:304–9.
18. Hayward CPM, Sutton DMC, Carter WH Jr, et al. Treatment outcomes in patients with adult thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Arch Intern Med **1994**; 154:982–7.
19. Dawson RB, Brown JA, Mahalati K, et al. Durable remissions following prolonged plasma exchange in thrombotic thrombocytopenic purpura. J Clin Apheresis **1994**; 9:112–5.
20. Tsai HM, Lian ECY. Antibodies to von-Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med **1998**; 339:1585–94.
21. Lara PN Jr, Coe TL, Zhou H, Fernando L, Holland PV, Wun T. Improved survival with plasma exchange in patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Am J Med **1999**; 107: 573–9.
22. Dervenoulas J, Tsirigotis P, Bollas G, et al. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS): treatment outcome, relapses, prognostic factors: a single-center experience of 48 cases. Ann Hematol **2000**; 79:66–72.
23. Haas M, Leko-Mohr Z, Lang T, et al. The LDH ratio as a marker for response to plasma exchange in HUS/TTP of the adult. Clin Nephrol **2002**; 57:414–20.
24. Chang JC, Kathula SK. Various clinical manifestations in patients with thrombotic microangiopathy. J Investig Med **2002**; 50:201–6.
25. Coppo P, Adrie C, Azoulay E, et al. Infectious diseases as a trigger in thrombotic microangiopathies in intensive care unit (ICU) patients? Intensive Care Med **2003**; 29:564–9.
26. Kremer Hovinga JA, Studt J-D, Alberio L, Lämmle B. Von Willebrand factor-cleaving protease (ADAMTS-13) activity determination in the diagnosis of thrombotic microangiopathies: the Swiss experience. Semin Hematol **2004**; 41:75–82.
27. Maslo C, Peraldi MN, Desenclos JC, et al. Thrombotic microangiopathy and cytomegalovirus disease in patients infected with human immunodeficiency virus. Clin Infect Dis **1997**; 24:350–5.
28. Egan JA, Bandarenko N, Hay SN, Paradowski L, Goldberg R, Nickeleit V, Brecher ME. Differentiating thrombotic microangiopathies induced by severe hypertension from anemia and thrombocytopenia seen in thrombotic thrombocytopenic purpura. J Clin Apheresis **2004**; 19:125–9.
29. Volcy J, Nzerue CM, Oderinde A, Hewen-Iowe K. Cocaine-induced acute renal failure, hemolysis, and thrombocytopenia mimicking thrombotic thrombocytopenic purpura. Am J Kidney Dis **2000**; 35:1–5.
30. Brill I, Maculuso M, Meinzen-Derr J, Allen S. A SAS program for the computation of seroconversion rates in a prospective study of HIV discordant couples in Lusaka, Zambia [paper 241-26]. In: Proceedings of the 26th Annual SAS Users Group International Conference. Cary, NC: SAS Institute, **2001**.
31. UNAIDS. South Africa. **2008**. Available at: http://www.unaids.org/en/CountryResponses/Countries/south_africa.asp. Accessed 12 August **2008**.
32. Howard MA, Williams LA, Terrell DR, Duvall D, Vesely SK, George JN. 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**; 46:154–6.
33. Francis KK, Kalyanam N, Terrell DR, Vesely SK, George JN. Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: a report of 10 cases and a systematic review of the literature. Oncologist **2007**; 12:11–9.
34. Bartlett JG, Branson BM, Fenton K, Hauschild BC, Miller V, Mayer KH. Opt-out testing for human immunodeficiency virus in the United States. JAMA **2008**; 300:945–51.
35. Mounzer K, DiNardo A, Goldstein K. Thrombotic thrombocytopenic purpura during immune reconstitution. AIDS **2007**; 21:2559–60.
36. Cserti CM, Landaw SA, Uhl L. Do infections provoke exacerbations and relapses of thrombotic thrombocytopenic purpura? J Clin Apheresis **2007**; 22:21–5.
37. Swisher KK, Doan JT, Vesely SK, et al. Pancreatitis preceding acute episodes of thrombotic thrombocytopenic purpura: report of five patients with a systematic review of the literature. Haematologica **2007**; 92:936–43.
38. George JN. The association of pregnancy with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Curr Opin Hematol **2003**; 10:339–44.
39. Brecher ME, Hay SN, Park YA. Is it HIV TTP or HIV-associated thrombotic microangiopathy? J Clin Apher **2008**; 23:186–90.
40. Alpers CE. Light at the end of the TUNEL: HIV-associated thrombotic microangiopathy. Kidney Int **2003**; 63:385–96.
41. Sullivan RJ, Pantanowitz L, Casper C, Stebbing J, Dezube BJ. HIV/AIDS: epidemiology, pathophysiology, and treatment of kaposi sarcoma-associated herpesvirus disease: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. Clin Infect Dis **2008**; 47:1209–15.
42. Siami K, Kojouri K, Swisher KK, Selby GB, George JN, Laszik ZG. Thrombotic microangiopathy after allogeneic hematopoietic stem cell transplantation: an autopsy study. Transplantation **2008**; 85:22–8.
43. George JN. Hematopoietic stem cell transplantation-associated thrombotic microangiopathy: defining a disorder. Bone Marrow Transplant **2008**; 41:917–8.
44. Bell WR, Chulay JD, Feinberg JE. Manifestations resembling thrombotic microangiopathy in patients with advanced human immunodeficiency virus (HIV) disease in a cytomegalovirus prophylaxis trial (ACTG 204). Medicine **1997**; 76:369–80.
45. Gervasoni C, Ridolfo AL, Vaccarezza M, et al. Thrombotic microangiopathy in patients with acquired immunodeficiency syndrome before and during the era of introduction of highly active antiretroviral therapy. Clin Infect Dis **2002**; 35:1534–40.
46. Becker S, Fusco G, Fusco J, et al. HIV-associated thrombotic microangiopathy in the era of highly active antiretroviral therapy: an observations study. Clin Infect Dis **2004**; 39:S267–75.
47. Torriani F, Komarow L, Cotter B, et al. Control of HIV viral replication is associated with rapid improvement in endothelial function sustained over twenty-four weeks: A5152s, a substudy of A5142. In: Proceedings of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (Sydney, Australia). 22–25 July **2007**. Available at: http://www.ias2007.org/abstract.aspx?elementId = 200703301. Accessed 22 November 2008.