Journal of Thrombosis and Circulation Open Access

Dobson and Tsai, J Thrombo Cir 2018, 4:3
DOI: 10.4172/2572-9462.1000127

Research Article Open Access

HIV Infection Increases the Risk of Thrombotic Thrombocytopenic Purpura

Dobson CE[1*] **and Tsai HM**[2]

[1]*Department of Nursing, Lehman College, USA*

[2]*Department of Public Health Sciences, Pennsylvania State University, Penn State, USA*

[*]**Corresponding author:** Cassandra Elaine Dobson, Director of Undergraduate/Associate Professor, Department of Nursing, Lehman College, 250 Bedford Park Blvd West, T3 Bldg, Room 204, Bronx, NY 10468, NYS 10607, United States Tel: +914 919-3613; E-mail: cassandra.dobson@lehman.cuny.edu

Received date: June 30, 2018; **Accepted date:** September 6, 2018; **Published date:** September 10, 2018

Abstract

An association between HIV infection and Thrombotic Thrombocytopenic Purpura (TTP) remains controversial. We conducted a cross-sectional analysis of 39 consecutive, non-referral cases of TTP encountered over 9 years at a single institution. Thirteen cases had HIV infection. The patients were treated with daily plasma exchange until remission. The mean (standard deviation) duration of follow-up was 48 (37) months. Seven patients died. TTP caused 3 of the 4 deaths in the HIV- group but none of the 3 deaths in the HIV+ groups. The age and sex adjusted incidence rate of TTP was 14.5 cases per 10^6 person-years. The relative risk of TTP was 38.5 (95% confidence interval, 19.7-75.0) for HIV infection, 2.7 (1.3-5.7) for female gender and was not increased for the black race. Neither HIV infection nor gender affect the overall and relapse free survivals. While relapse continued to occur throughout the follow-up period in the HIV- group, it did not occur in the HIV+ group after the first year. We conclude that HIV infection is a major risk factor of TTP. The risk of late TTP relapse is low in HIV infected patients treated with anti-retroviral therapies.

Keywords: Human immunodeficiency virus; Thrombotic thrombocytopenic purpura; Incidence rate; Relative risk; ADAMTS13

Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is a type of Thrombotic Microangiopathy (TM) in which Von Willebrand Factor (VWF) rich platelet thrombi are found in the arterioles and capillaries of the brain, heart and other organs. It typically, albeit not invariably, presents with thrombocytopenia, microangiopathic hemolysis and fleeting mental change or focal neurological deficits [1,2].

TTP has been described in patients with HIV infection. At a major urban medical center, HIV infection was present in >50% of the cases [3]. Nevertheless, the magnitude of association between TTP and HIV infection remains controversial. In a recent review of 21 case series in the literature, the prevalence of HIV infection was found to vary from 0% to 83% of the patients carrying the diagnosis of TTP, TTP/HUS, or thrombotic microangiopathy. Most of the cases in these series were not defined at the molecular level. Vagueness in the definition of TTP hampers the interpretation of the prevalence data in the literature.

Traditionally, thrombotic microangiopathy comprises two main entities: TTP and HUS, with distinction between these two disorders being based on the presence or absence of neurological deficits and the severity of renal function impairment. It is well recognized that this distinction does not provide a satisfactory frame of disease classification. Some investigators group the patients under the diagnosis of TTP/HUS, or simply TTP. This approach eliminates the clinical dilemmas in disease classification but obscure important distinctions that may exist among the different patient groups.

Autoimmune deficiency of ADAMTS13 is found in many patients presenting with thrombotic microangiopathy accompanied by mental change or neurological deficits but no or minimal renal dysfunction. These contrast with patients without severe ADAMTS13 deficiency, who tend to have a more profound renal dysfunction and are often grouped under the diagnosis of the Hemolytic Uremic Syndrome (HUS). HUS is a syndrome comprising heterogeneous disease entities. The typical HUS follows exposure to shiga toxin producing microorganisms. Secondary HUS may also develop in patients with systemic autoimmune disorders (e.g. systemic lupus erythematous), exposure to chemicals (e.g. chemotherapeutic agents, calcineurin inhibitors, cocaine or quinine), stem cell or organ transplantations, or certain types of systemic infections. Among patients with the idiopathic (atypical) HUS, mutations or autoantibodies of the complement components are increasingly detected. Nevertheless, the detection of the molecular abnormalities in the complement system requires extensive genetic studies that are not clinically available. While severe ADAMTS13 deficiency identifies a group of patients that share a common pathogenetic defect, current evidence indicates that the group of patients without ADAMTS13 deficiency is likely to harbinger heterogeneous molecular defects, many of which remain unknown. Without knowledge of their molecular defects, it is difficult to compare different TTP or TTP/HUS case series.

One approach to address the variable association between TTP and HIV is to restrict the diagnosis of TTP to those patients with severe ADAMTS13 deficiency. In the Oklahoma registry, only two of the 39 cases with severe ADAMTS13 deficiency were HIV infected, raising questions on whether HIV infection is a risk factor of TTP. On the other hand, in a French multicenter series, 17 (24%) of the 62 cases with severe ADAMTS13 deficiency were HIV infected. Thus, the role of HIV infection remains uncertain in patients with severe autoimmune ADAMTS13 deficiency.

To further delineate the contribution of HIV infection to the development of TTP, we have analyzed the cases of TTP encountered at a single institution in a community with a high HIV prevalence rate.

Methods

Patients

The study cases were identified by reviewing the entire records of the Hematology and Transfusion/Apheresis Services and the Advanced Coagulation Laboratory at Montefiore Medical Center in the Bronx. The criteria for the diagnosis of acquired TTP included the presence of thrombocytopenia and microangiopathic hemolysis, severe (<0.1 U/mL) deficiency of plasma ADAMTS13 activity, and evidence of inhibitory plasma activity against ADAMTS13. For cases without detectable ADAMTS13 inhibitors in plasma mixing studies, we inferred the presence of inhibitors if the ADAMTS13 activity remained below <0.3 U/mL immediately after one or more sessions of plasma exchange.

Clinical and laboratory data were extracted from the medical records. All patients with suspected TTP were tested for HIV antibodies, HIV viral load and CD4 T-cell count if they had parents with HIV infection, history of intravenous drug use, blood product transfusion, or multiple sexual partners or sexual contacts with someone with HIV risk factors.

For the management of TTP, the patients were treated with 1-1.5 volume plasma exchange therapy, which was continued daily until the platelet count was normal on two consecutive days. The patients were pre-medicated with methyl prednisone and diphenhydramine prior to plasma exchange if they had developed allergic transfusion reactions. The treatment was tapered to every other day for 3-6 sessions. The patient was considered to have achieved remission and the plasma exchange therapy was discontinued if the platelet count remained in the normal range. Subsequently, the complete blood count was checked every 1-3 days for 1-2 weeks, then weekly for up to 1 month. Thereafter, the patients were followed at the discretion of their attending physicians.

The patients were interviewed during their remission on one or more occasions to assess their overall medical status and to identify interim relapses of TTP, new disease diagnosis or therapies. Blood samples were also obtained for complete blood count, LDH, urea nitrogen, creatinine, ANA as well as ADAMTS13 activity assay.

For each patient, day 1 referred to the first day ever of plasma exchange therapy during the study period. The day of TTP relapse referred to the day when plasma exchange therapy was instituted for recurrent thrombocytopenia. The diagnosis of TTP relapse was validated by evidence of severe ADAMTS13 deficiency. For each patient presenting with multiple episodes of TTP during the study period, only the first episode was enumerated.

ADAMTS13 assays

Analysis of plasma ADAMTS13 activity was performed using previously described methods [4,5]. The assay was based on cleavage of von Willebrand Factor multimers pre-treated with 1.5 mol/L guanidine HCl. The proteolytic fragments were visualized with SDS polyacrylamide gel electrophoresis and immunoblotting. Inhibitors titers were analyzed by measuring the ADAMTS13 activity level of normal human plasma mixed with heated patient plasma at various volume ratios.

Statistics summary such as mean and standard deviation, range, or proportion are provided for patient characteristics as appropriate for the data type. Student's t-test or ANOVA was used to analyze the difference among groups of normally distributed continuous data. Fisher's exact or chi-square test was used for categorical data analysis. The relative risks of TTP are estimated by Poisson regressions. Kaplan-Meier estimates and Cox proportional hazards models are used for analyzing overall and relapse free survival. All the analyses are conducted in GraphPad Prism 5.0 and SAS 9.1 statistics software. We used the U.S. census data of year 2000 to estimate the gender and age adjusted incidence rate (US census bureau, 2002), and assumed that our TTP cases accounted for 24% of the cases in the Bronx borough of New York City. This estimate was based on the Bronx emergency room utilization data that the New York City controller complied for year 2006 (NYC controller, 2006). The HIV prevalence rates were based on officially published data (Centers for Disease Control and Prevention, 2009; HIV Epidemiology Program of the New York City, 2004). This study was approved by the institutional review boards.

Results

Over a period of 9 years (1999-2006), we identified 39 consecutive, non-referral cases of TTP, which accounted for 53% of all the patients referred to the Transfusion/Apheresis Service for suspected TTP or thrombotic microangiopathy. The patients without a severe ADAMTS13 deficiency comprised primarily of two groups: patients with myelodysplasia with thrombocytopenia and poikilocytosis of the red blood cells; and patients with hypertension and advanced renal failure. These patients were not investigated extensively for complement abnormalities and are not further analyzed in this study.

All the patients received plasma exchange therapy. Other modalities of treatment included prednisone (64%), which was tapered off once the patients achieved remission; intravenous vincristine 1-2 doses (27%); splenectomy (5%) and acetylsalicylic acid (5%). None of the patients received rituximab, intravenous immunoglobulin, cytotoxic agents or calcineurin inhibitors during their initial TTP episodes. Two patients were treated with rituximab during their subsequent TTP relapses.

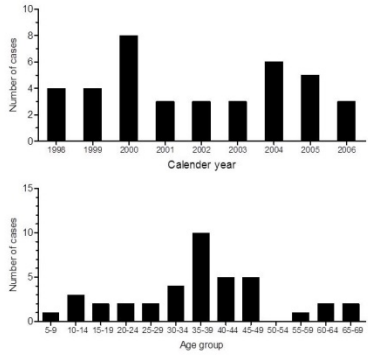

Figure 1: Number of TTP cases by calendar year and age group.

The case numbers by calendar years and by age groups are depicted in Figure 1.

Parameters	HIV- group	HIV+ group
Number of cases	26	13
Age, yrs, median (range)	39.0 (14.2-62.2)	37.5 (9.4-65.3)
Sex, F, no. (%)*	22 (84.6)	6 (46.2)
Black, no. (%)	22 (84.6)	12 (92.3)
Prior TTP, no. (%)	2 (7.7)	2 (15.4)
WBC, per µL, median (range)	8.0 (3.6-34.5)	8.0 (3.6-16.3)
Hb, gm/L, median (range)	84 (36- 121)	70 (51-84)
Platelet count, per µL, median (range)	11.0 (4-60)	12.5 (4-28)
LDH, U/L, median (range)	1231 (170- 2920)	1075 (602-3271)
ADAMTS13 inhibitor, U/mL, mean (SD)	1.20 (0.86)	1.21 (1.14)
Serum creatinine, mg/dL, mean (SD)	1.0 (0.4)	1.1 (0.3)
Serum creatininemax, mg/dL, mean (SD)	1.2 (0.4)	1.3 (0.3)
CD4 cells, per mL, median (range)	-	187 (16-634)*
Viral copies, per mL, median (range)	-	91,534 (<50->750,000)*
No. of plasma exchange, median (range)	13 (3-42)	16 (7-39)
Follow-up duration, mean (SD), months	53 (37)	39 (37)
Number of death (%)	--	--
During initial episode (TTP + not TTP)	2 (7.7%) (2+0)	2 (15.4%) (0+2)
After remission (TTP + not TTP)	2 (8.3%) (1+1)	1 (9.1%) (0+2)

Table 1: Demographics and laboratory data of the patients with a diagnosis of TTP. *The data of one case was not available for review.

There was no evidence of increasing trend in the case numbers during the study period. Fifty-six percents of the TTP cases, compared to 29% of the Bronx population, was in the age group of 30-49 years (P<0.001).

The demographics and laboratory values at the time of the first presentation are summarized in Table 1. Thirteen cases had HIV infection and 26 did not. The group with HIV infection consists of a lower percentage of females than the group without HIV infection (P<0.05). ADAMTS13 inhibitors were undetectable by plasma mixing analysis in 3 of the HIV+ group but none of the HIV- group (P<0.05). However, the mean inhibitor level was not different between the two groups.

For both groups, the mean (SD) serum creatinine level increased slightly from 1.0 (0.4) mg/dL at admission to a maximum of 1.2 (0.3) mg/dL (P <0.001 by paired t-test) after admission. However, none of the patients had overt renal failure that caused hypertension, fluid overload or electrolyte imbalance, or required dialysis.

None of the HIV infected patients were receiving anti-retroviral therapy at the time of the TTP events. The CD4 T-cell count was <200/µL in 54% of the cases. Overall, the median number of plasma exchange therapy was 15 (range 3-42) and was not different between the HIV+ and HIV- groups. All the HIV infected patients were started on anti-retroviral therapy during or immediately after the hospitalization.

The average number of TTP cases was 4.33 cases per annum, corresponding to an apparent incidence rate of 18.5 per 10^6 person-years. The age and sex adjusted incidence rate was 14.5 case per 10^6 person-years.

To explore the factors that may affect the TTP incidence rate, we classified the TTP cases according to their HIV status, gender (female *vs.* male), race (black *vs.* non-black) and age (middle age group of 30-49 years *vs.* the younger and older groups). The computed incidence rates are provided in Table 2.

HIV	Gender	Race	Age (years) 30-49	Number of cases	Exposure (person-years)	Incidence rate (per 10^6 person years)
+	F	B	Yes	4	46,121	86.73
+	F	B	No	2	25,943	77.09
+	F	NB	Yes	0	2,943	0
+	F	NB	No	0	1,655	0
+	M	B	Yes	4	50,902	78.58
+	M	B	No	2	28,632	69.85
+	M	NB	Yes	1	4,426	225.9
+	M	NB	No	0	2,489	0
-	F	B	Yes	9	12,88,598	6.984
-	F	B	No	12	28,95,162	4.145
-	F	NB	Yes	1	6,60,869	1.513

-	F	NB	No	1	14,84,811	0.673
-	M	B	Yes	1	10,47,269	0.955
-	M	B	No	0	25,89,083	0
-	M	NB	Yes	1	5,37,102	1.862
-	M	NB	No	1	13,27,835	0.753

Table 2: Incidence rates of TTP by HIV status, gender, race and age. *Abbreviations: F: female; M: male; B: black; NB: non-black.

We assessed the risk factors of the TTP by using Poisson regression analysis. Univariate regression with one risk factor at a time showed that all 4 parameters were risk factors (Table 3). Multivariate Poisson analysis showed that after adjusted for HIV infection and gender, race and age were not significant risk factors. The relative risk for HIV and female gender remained quite similar to those in the univariate analysis; it was 38.5 (95% confidence interval [CI], 19.7-75.0) for HIV infection and 2.7 (95% CI, 1.3-5.7) for female gender. When analyzed separately, the incidence rate was 2.20 cases and 79.7 cases per 10^6 person years respectively for the HIV- and HIV+ groups.

Risk factor	HIV+ *vs.* HIV-	Female *vs.* male	Black *vs.* non-black	Age 30-49 *vs.* others
Univariate analysis*	36.2 (18.6, 70.5)	2.5 (1.23, 5.2)	3.4 (1.3, 8.8)	2.6 (1.4, 5.1)
Multivariate analysis*	38.5 (19.7 75.0)	2.7 (1.3, 5.7)	--	--

Table 3: The relative risk (95% confidence interval) of TTP according to HIV status, gender, race and age (*Poisson regression).

The mean (SD) duration of follow-up was 48 (37) months and was not different between the HIV+ and HIV- groups. Four patients, two each in the HIV- and HIV+ groups, died during the initial episodes. Thus, the case fatality rate was 7.7% and 15.4% respectively (P>0.05). The causes of death were active TTP on days 3 and 19 respectively in the two HIV- cases, and central venous line related staphylococcal sepsis on days 11 and 73 respectively in the two HIV+ cases. Three additional patients died after their discharge from the hospital. The post-hospitalization causes of death were relapsing TTP and staphylococcal osteomyelitis respectively in two HIV- cases, and hepatitis C with liver failure and bacterial sepsis in one HIV+ case.

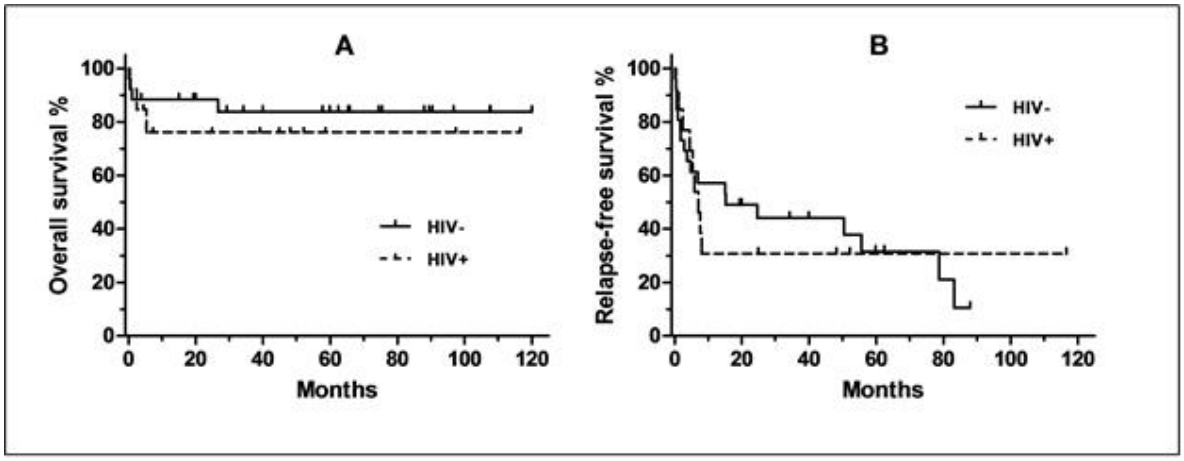

Figure 2: Analysis of overall and relapse free survivals of TTP in patients with or without HIV infection. A shows the overall survival in the HIV- and HIV+ groups. B shows the relapse free survival of each group. The median relapse free survival was 15.2 months for the HIV-group and 7.0 months for the HIV+ group (ratio=2.17, 95% confidence interval, 1.72-2.62). No relapse occurred in the HIV+ group after the first year. The difference between the two curves in either panel did not reach a level of significance (0.05) by multivariate Cox proportional hazards model.

We then used overall survival and relapse-free survival as the two main clinical endpoints for Kaplan-Meier estimates of overall and relapse-free survival rates (Figure 2). Nevertheless, the median relapse free survival was 15.2 months for the HIV- group and was 7.0 months for the HIV+ group (ratio=2.17, 95% CI 1.72-2.62). Log-rank test found that HIV infection caused no difference (P>0.5) for either overall or relapse free survival. Further analysis using multivariate Cox proportional hazards model revealed that none of HIV status, gender,

race or age group affected either overall or relapse free survival in a systematic manner (P>0.05).

Table 4 lists other medical disorders that were diagnosed before or after the patients achieved remission of TTP. Immunological diseases were detected in 13 cases (50%) of the HIV- group, including 7 with systemic lupus erythematosis or related disorders, and in one case (7.7%, P<0.05) of the HIV+ group. One patient with systemic lupus erythematosis developed renal failure requiring dialysis and eventually a renal allograft. Her TTP remained inactive during these events. *Staphylococcal* sepsis due to infected central lines occurred in 2 cases of the HIV- group and 3 cases of the HIV+ group, with 2 in the latter group succumbing to the infection. Two patients in the HIV-group (breast and dermatofibrosarcoma) and one in the HIV+ group (prostate) developed cancers 3-6 years after the diagnosis of TTP. Intriguingly, two patients developed TTP immediately after cholecystectomy or gastric bypass operation.

Disorders	**Number of cases**						**Total**
Parameters	HIV- group (26 cases)			HIV+ group (13 cases)			
--	Before[4]	After[4]	Total	Before[4]	After[4]	Total	
Autoimmune disorders	7	6	13	0	1	1	14
Lupus and related disorders	5	2	7	0	0	0	7
APS	0	3	3	0	0	0	3
Cold Agglutinin disease	1	0	1	0	1	1	2
Sarcoidosis	1	0	1	0	0	0	1
Hypothyroidism	0	1	1	0	0	0	1
HIV related	0	0	0	0	3	3	7
Castleman's disease	0	0	0	0	1	1	2
CMV retinitis	0	0	0	0	1	1	2
Nephropathy	0	0	0	0	1	1	2
Red cell aplasia	0	0	0	0	0	1	1
Venous line-related sepsis	0	2	2	2	1	3	5
Neoplastic diseases[1]	1	2	3	0	1	1	4
Other disorders[2]	14	6	20	2	5	7	27
Surgery[3]	3	1	4	1	1	2	6

1 Breast cancer, 2 cases; dermatofibrosarcoma, 1 case; prostate cancer, 1 case.
Congestive heart failure, 1 case; cerebrovascular event unrelated to TTP/antiphospholipid antibody syndrome (APS), 2 cases; cholelithiasis, 2 cases; deep vein thrombosis, 2 cases; diabetes mellitus, 8 cases; G6PD deficiency, 1 case; hemochromatosis, 1 case; histoplasmoma, 1 case; hypertension, 7 case; viral hepatitis B or C, 3 cases.
3Bariatric gastric surgery, 2; cholecystectomy, 1; splenectomy, 2 (one each for TTP and Castleman's disease)
4 Before and after: before or after achieving TTP remission.

Table 4: Other medical conditions in the patients with TTP.

Discussion

We estimate the incidence rate of TTP to be 14.5 cases per 1×10^6 person-years. Furthermore, we find that HIV is a highly potent risk factor of TTP. None of the HIV+ patients with TTP were receiving anti-retroviral therapy at the time of initial presentation. The size of this TTP series is smaller than that of the French multicenter series (62 cases), but similar to that of the Oklahoma registry (41 cases).

The incidence rate of TTP was estimated to be 1.45-3.8 per 10^6 person-years in 4 previous studies [6-9]. In only one study were the TTP cases defined with ADAMTS13 analysis. In contrast, in the Collaborations in HIV Outcome Research/US cohort [10], the incidence rate of TTP (90 cases per 10^6 person-years) is closer to our incidence rate for the HIV+ group. Taken together, the data of this and previous studies suggest that the risk of TTP is markedly increased for HIV+ individuals. Since our incidence rate of TTP for the HIV- group (2.2 cases per 10^6 person-years) is not substantially different from the Oklahoma Registry data (1.74 cases per 10^6 person-years), the higher HIV prevalence rate in our community, 1.36% *vs.* 0.3% in the Oklahoma [11], probably accounts for most of the observed difference in the overall TTP incidence rate.

How HIV infection may increase the risk of TTP remains speculative. In our series, none of the cases were being treated with anti-retroviral therapies at the time of their TTP diagnosis.

Nevertheless, the CD4 T-cell count was not invariably decreased, nor was the viral copy number invariably increased. Thus, we speculate that the development of TTP in HIV+ cases may result from B-cell hyper reactivity in association with HIV infection, rather than a direct consequence of active HIV replication or defective CD4 T-cell functions.

It has been reported that female gender and black race are risk factors of TTP [6]. Our data also shows that female gender is a significant albeit relatively modest risk factor of TTP, but does not substantiate an independent effect of black race on the risk of TTP. The discrepant results with the black race cannot be accounted for by difference in the size of the study series, since our case number is greater than that of the Oklahoma Registry.

Classification of black race is quite imprecise. On the average, African Americans have approximately 17% white genetic ancestry, and this figure varies considerably geographically [12]. Therefore, we speculate that a more plausible explanation for the discrepant race impact on the risk of TTP is that the black population in our community is genetically more diverse. Many of the patients had ancestor from the Caribbean islands. The genetic heterogeneity among the black population may have diminished the race effect on the risk of TTP. Alternatively, it is also possible that difference in certain environmental factors may contribute to the discrepant impact of race on the risk of TTP.

Our data shows that overall the ADAMTS13 inhibitor levels were not different between the HIV+ and HIV- groups at presentation. Although the inhibitors were undetectable by plasma mixing tests in 3 of the HIV+ group, this does not mean that these three cases did not have ADAMTS13 inhibitors. We have previously observed that plasma mixing study may fail to detect ADAMTS13 inhibitors in some cases of TTP whose IgG molecules nevertheless exhibit inhibitory activity against ADAMTS13 [13]. Other studies have also observed that not infrequently the inhibitors of ADAMTS13 are not detectable by plasma mixing studies in patients with HIV infection and TTP. Although not tested in this study, ELISA for ADAMTS13 binding IgG yields positive results in most cases. We infer the presence of ADAMTS13 inhibitors in the three cases with negative plasma mixing studies based on the observations that their plasma ADAMTS13 activity levels remained <0.3 U/mL after one or more plasma exchanges, as the ELISA for ADAMTS13 antibodies was not then available. The patients with severe ADAMTS13 deficiency but negative plasma mixing studies for ADAMTS13 inhibitors are considered to have TTP and are distinct from those without severe ADAMTS13 deficiency.

In accordance with the observation of a previously report [14], our survival analysis shows that the HIV infection status did not affect the overall survival. Furthermore, while TTP caused 3 of the 4 deaths in the HIV- group, it caused none of the 3 deaths in the HIV+ group. In contrast, staphylococcal or other bacterial sepsis caused all 3 deaths in the HIV+ group but only one death in the HIV- group. Thus, HIV+ cases may be more likely to succumb to therapy related infection.

Our study shows that other autoimmune disorders were quite common in the HIV- group, although none of these autoimmune disorders were active at the time of TTP presentation. This data is consistent with another report demonstrating high prevalence of autoimmune disorders among patients with TTP [15]. In contrast, autoimmune disorders were less common in our HIV+ group. This may appear to be unexpected, since HIV infection has been associated with various autoimmune antibodies [16,17]. However, in HIV infected individuals, autoimmune disorders tend to be mild or only are detectable with laboratory tests. Except for ANA, other autoantibodies were not systemically tested in our cases during remission. Therefore, we cannot exclude the possibility that asymptomatic or mild autoimmune disorders were not detected in our series.

It is widely recognized that TTP has a propensity to relapse. We observed that the risk of relapse is substantially higher than 19%-60% in previous reports. However, in the previous studies, ADAMTS13 analysis was not used in the case definition. Inclusion of patients without ADAMTS13 deficiency is likely to decrease the relapse rate. Another compounding factor in comparing the relapse rate data is the difference in the definition of relapse. We define relapse as any exacerbation requiring re-institution of plasma exchange therapy. Other studies count an exacerbation as a relapse only when it occurs after a certain number of days or weeks of clinical stability. Irrespective of how relapse is defined, the relapse free survival curve depicted in Figure 2 suggests that TTP will eventually relapse in many if not all of the HIV- cases. Interestingly, late relapses were not observed beyond the first year in the HIV+ group. This observation needs to be validated in larger series. Nevertheless, we speculate that anti-retroviral therapy may have diminished the risk of late TTP relapses in this group. Relapse of TTP has been observed in HIV+ patients when anti-retroviral therapy is discontinued [18].

The cases in this series were collected over a period of 9 years. We used the U.S. census data of year 2000 and the year 2004 HIV infection data of the Bronx for the incidence rate calculation. Thus, the incidence rates may be associated with a certain level of inaccuracy. On the other hand, there is no reason to suspect that the demographics of either the US or the Bronx changed substantially during the study period. Therefore, we believe that our incidence rate estimates are not significantly compromised. Another potential weakness of this study is the extrapolation of our annual case rate at a single institution to the incidence rate for the Bronx borough. Since the population served by the study institution cannot be clearly defined, it is impossible to accurately determine the denominator population. We use the emergency room utilization data of the Bronx to estimate the total TTP cases in the borough. This approach is premised on the observations that the vast majority of TTP cases were admitted to the hospital via the emergency services, and the non-specific nature of TTP presenting symptoms are unlikely to have triggered diversion of the TTP cases to or away from our institution. Thus, the emergency room utilization data should provide a reasonable approximation of the total number of TTP in the Bronx borough.

In summary, the incidence rate of TTP is much higher than what other studies have suggested and HIV infection is a strong risk factor of TTP. Thus, the prevalence rate of HIV infection and the compliance of anti-retroviral therapy should be taken into consideration when the TTP incidence rate is assessed. The presence of HIV infection is not associated with a higher risk of death from TTP. Other autoimmune disorders are common in HIV- patients but may be less common in the HIV+ group. TTP may continue to relapse for many years in HIV- patients but rarely relapses after the first year in HIV+ patients treated with anti-retroviral therapy. Further studies are needed to determine the mechanisms of how HIV infection increases the risk of TTP with severe ADAMTS13 deficiency.

References

1. Bukowski RM (1982) Thrombotic thrombocytopenic purpura: A review. Prog Hemost Thromb 6: 287-337.

2. Tsai HM (2006) Current concepts in thrombotic thrombocytopenic purpura. Annu Rev Med 57: 419-436.
3. Hymes KB, Karpatkin S (1997) Human immunodeficiency virus infection and thrombotic microangiopathy. Semin Hematol 34: 117-125.
4. Tsai HM, Chandler WL, Sarode R, Hoffman R, Jelacic S, et al. (2001) von Willebrand factor and von Willebrand factor-cleaving metalloprotease activity in Escherichia coli O157: H7-associated hemolytic uremic syndrome. Pediatr Res 49: 653-659.
5. Tsai HM, Li A, Rock G (2001) Inhibitors of von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura. Clin Lab 47: 387-392.
6. Terrell DR, Williams LA, Vesely SK, Lammle B, Hovinga JA, et al. (2005) The incidence of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: all patients, idiopathic patients, and patients with severe ADAMTS-13 deficiency. J Thromb Haemost 3: 1432-1436.
7. Torok TJ, Holman RC, Chorba TL (1995) Increasing mortality from thrombotic thrombocytopenic purpura in the United States-Analysis of national mortality data, 1968-1991. Am J Hematol 50: 84-90.
8. Miller DP, Kaye JA, Shea K, Ziyadeh N, Cali C, et al. (2004) Incidence of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. Epidemiology 15: 208-215.
9. Schech SD, Brinker A, Shatin D, Burgess M (2006) New-onset and idiopathic thrombotic thrombocytopenic purpura: incidence, diagnostic validity, and potential risk factors. Am J Hematol 81: 657-663.
10. Becker S, Fusco G, Fusco J, Balu R, Gangjee S, et al. (2004) HIV-associated thrombotic microangiopathy in the era of highly active antiretroviral therapy: An observational study. Clin Infect Dis 5: S267-S275.
11. Benjamin M, Terrell DR, Vesely SK, Voskuhl GW, Dezube BJ, et al. (2009) Frequency and significance of HIV infection among patients diagnosed with thrombotic thrombocytopenic purpura. Clin Infect Dis 48: 1129-1137.
12. Parra EJ, Kittles RA, Shriver MD (2004) Implications of correlations between skin color and genetic ancestry for biomedical research. Nat Genet 36: S54-S60.
13. Tsai HM, Lian EC (1998) Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 339: 1585-1594.
14. Malak S, Wolf M, Millot GA, Mariotte E, Veyradier A, et al. (2008) Human immunodeficiency virus-associated thrombotic microangiopathies: Clinical characteristics and outcome according to ADAMTS13 activity. Scand J Immunol 68: 337-344.
15. Coppo P, Bengoufa D, Veyradier A, Wolf M, Bussel A, et al. (2004) Severe ADAMTS13 deficiency in adult idiopathic thrombotic microangiopathies defines a subset of patients characterized by various autoimmune manifestations, lower platelet count, and mild renal involvement. Medicine (Baltimore) 83: 233-244.
16. Cadogan M, Dalgleish AG (2008) Pathogenesis of HIV: Non-specific immune hyperactivity and its implications for vaccines. Clin Med 8: 267-271.
17. Zandman-Goddard G, Shoenfeld Y (2002) HIV and autoimmunity. Autoimmun Rev 1: 329-337.
18. Miller RF, Scully M, Cohen H, Roedling S, Starke R, et al. (2005) Thrombotic thrombocytopaenic purpura in HIV-infected patients. Int J STD AIDS 16: 538-542.