Plasmapheresis and HIV-Associated Thrombotic Microangiopathy: An Institutional Review

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a systemic disorder that classically results from a deficiency in the von Willebrand factor-cleaving enzyme, ADAMTS13. The human immunodeficiency virus (HIV) is a secondary cause of TTP. It has been recognized that some patients with HIV-associated TTP do not have a deficiency in ADAMTS13 activity. The role of plasmapheresis (PLEX) in these patients is unclear. This study reviewed 8 cases of HIV-associated TTP at Thomas Jefferson University Hospital. All patients responded to treatment; however, we were unable to make any conclusions regarding the use of PLEX in patients with normal ADAMTS13 activity. HAART initiation is recommended to treat the underlying HIV infection.

INTRODUCTION

Thrombotic microangiopathy (TMA) describes a group of systemic diseases characterized by platelet aggregation and formation of microthrombi. Thrombotic thrombocytopenic purpura (TTP) is a TMA defined by unexplained thrombocytopenia and microangiopathic hemolytic anemia (MAHA). Classical TTP results from a deficiency of ADAMTS13, the von Willebrand factor-cleaving metalloprotease, due to an autoantibody that inhibits function of the enzyme. In the absence of functional ADAMTS13, ultra large von Willebrand factor (ULvWF) multimers initiate the widespread formation of microthrombi. Classical TTP is treated with plasmapheresis (PLEX), which both removes the inhibitor and infuses the patient with functional ADAMTS13 from donor plasma.

The human immunodeficiency virus (HIV) has been identified as a cause of TTP. TTP is more commonly observed in patients with advanced HIV, and fewer cases have been reported since the advent of highly active antiretroviral therapy (HAART). There are a subset of patients who develop HIV-associated TTP without severely decreased ADAMTS13 levels or a detectable inhibitor. It has been suggested that this subset of patients may develop TTP due to an alternative mechanism whereby the HIV directly infects endothelial cells, leading to endothelial cell dysfunction, release of vWF, and direct ADAMTS13 consumption.

Like classical TTP, HIV-associated TTP is treated with PLEX; however, studies have indicated that initiation of HAART is essential for recovery and prevention of future relapse. It is unclear if PLEX is as essential in those patients without an ADAMTS13 inhibitor.

METHODS

We retrospectively identified all patients treated with PLEX for HIV-associated TTP at Thomas Jefferson University Hospital between 2002 and 2013. Data collected included the number of PLEX procedures and the total volume of plasma processed. Also noted were the hemoglobin, platelet count, haptoglobin, and lactate dehydrogenase (LDH) at the initiation and completion of the course of PLEX. Daily platelet counts during the course of treatment were also recorded. ADAMTS13 activity level and the presence or absence of an inhibitor were also documented, if available. The approximate date of HIV diagnosis was noted, as were HIV viral load, CD4 count at presentation, and current or prior treatment with HAART. HAART initiation during admission was determined.

Paired t-tests, linear and logistic regression and Fisher's exact testing were used to analyze our data. Statistical analysis was performed using STATA version 12.0 (StataCorp, 2011).

This study received approval by the Thomas Jefferson University Institutional Review Board.

TABLE 1. Laboratory Data and Treatment Outcomes of HIV-Infected Patients with TTP

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (years)	51	49	30	27	51	34	31	36
Gender	F	F	M	M	M	F	M	M
ADAMTS13 Level (%)	200	1	1	5	Unk	Unk	Unk	Unk
Inhibitor Detected	N	Y	Y	Y	Unk	Unk	Unk	Unk
Number of Procedures	10	9	7	8	7	39	10	11
Total Plasma Volume Processed (L)	30.035	34.471	32.213	30.437	21.624	Unk	Unk	Unk
Viral Load at time of Presentation (copies/mL)	2911	209134	53200	1130000	156280	745674	21074	150369
CD4 (cells/μL)	2	47	166	191	45	230	54	4
Initial Hemoglobin (g/dL) (ref. range: 12.0-17.5 g/dL)	6.7	7.6	8.4	7.9	8.2	8.4	5.3	9.5
Initial Platelet Count (X 10^9/L) (ref. range: 150-400 X 10^9/L)	67	7	5	6	10	7	7	68
Initial Haptoglobin (mg/dL) (ref. range: 41-165 mg/dL)	<10	Unk	<10	<10	<10	<10	<10	<10
Initial LDH (U/L) (ref. range: 45-90 U/L)	720	1903	904	490	606	1339	1709	779
Final Hemoglobin (g/dL) (ref. range: 12.0-17.5 g/dL)	7.7	10.0	7.7	9.4	9.2	11.5	9.8	9.7
Final Platelet Count (X 10^9/L) (ref. range: 150-400 X 10^9/L)	178	219	330	206	119	135	186	287
Final Haptoglobin (mg/dL) (ref. range: 41-165 mg/dL)	42	86	112	111	69	160	132	101
Final LDH (U/L) (ref. range: 45-90 U/L)	226	230	204	334	138	209	227	232
HAART Initiated	Y	Y	Y	Y	N	N	Y	Y
Relapse	N	N	N	N	N	Y	Y	N
Death	N	Y	N	N	N	N	N	N

F = Female; M = Male; Y = Yes; N = No; Unk = Unknown

RESULTS

Eight patients met the study criteria. Patients' lab data at initiation and completion of treatment are presented in Table 1.

At the time of presentation, none of the patients were on HAART and 7 of 8 patients had a CD4 count of less than 200 cells/μL (range: 2 - 230 cells/μL). Of the 4 patients whose ADAMTS13 activity level and inhibitor status were available, three patients had a severe deficiency of ADAMTS13 activity (<5%) and a detectable inhibitor. One patient did not have a deficiency of ADAMTS13 activity. All patients were treated with PLEX, and HAART was initiated in 6 of 8 patients.

There was a significant increase in the mean hemoglobin (p=0.0277), platelet count (p=0.0002) and haptoglobin (p=0.0007) from initiation to completion of PLEX. Likewise, a significant decrease in mean LDH was observed (p=0.0033). None of our continuous or dichotomous outcomes of interest (death, relapse, volume processed, number of procedures, rate of platelet rise) were significantly related to our independent variables of interest after adjusting for temporal variation in our procedure and after performing Fisher's exact testing. Additionally, none of our independent covariates were predictive of inhibitor status.

CONCLUSION

Consistent with the literature, patients with HIV-associated TMA may or may not have an inhibitor and low ADAMTS13 level. All identified patients responded to inpatient treatment; however, the number of identified patients precludes conclusions about response to PLEX in HIV-associated TMAs with or without an inhibitor and low ADAMTS13 level. Initiation of HAART to treat the underlying HIV infection is recommended.

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