

Thrombotic Microangiopathy Syndrome as an AIDS-Defining Illness: The Experience of J. Stroger Hospital of Cook County

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Abstract: Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are severe life-threatening disseminated thrombotic microangiopathies (TMA). Although many cases are idiopathic, TMA can occur in association with pregnancy, malignancy, autoimmune diseases, and HIV infection. We retrospectively analyzed the cases of 17 patients with TMA coexistent with HIV infection admitted to our institution. Median T-cell count at presentation was 28 cells/mm³. Patients presented with severe thrombocytopenia (median platelet count $19 \times 10^9/L$) and high lactate dehydrogenase levels (median 1,057 U/L). The majority of patients (82%) presented with renal dysfunction. Forty-one percent of patients had fever and 29% had neurological signs at presentation, which were associated with inferior outcome. Despite plasma exchange, inpatient mortality for the first TMA episode was 47%. Some patients relapsed following an initial TMA episode. However, there were responders with remissions lasting 5 years. We conclude that TMA, coexistent with an HIV-associated low CD4 count, is a treatable condition. Considering TMA as an AIDS-defining illness may help clinicians recognize this syndrome earlier, leading to prompt treatment and improved survival rates.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are severe thrombotic microangiopathies, characterized by systemic platelet aggregation causing organ ischemia, profound thrombocytopenia, and fragmentation of erythrocytes. TTP was first described by Moschcowitz in 1924.¹ In a 1966 review, Amorosi and Ultmann established the pentad of clinical symptoms: thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal failure, and fever.² Because of wide variation in the clinical presentation of TTP/HUS, in current practice thrombocytopenia and microangiopathic hemolytic anemia are sufficient for diagnosis of TTP.³ The introduction of

Keywords

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plasma exchange therapy has dramatically improved the survival rates of patients with acute TTP from 10% to 80–90%.^{4,6}

In recent years understanding of the pathophysiology of TTP has increased considerably. In 1982, unusually large von Willebrand factor (vWF) multimers in the plasma of 4 patients with chronic relapsing TTP were described.⁷ Later, vWF-cleaving protease activity was found to be severely deficient in patients with TTP.⁸ Today, two forms of TTP are recognized: congenital and acquired. The congenital type is due to severe ADAMTS13 deficiency caused by mutations in the *ADAMTS13* gene.^{9,10} Acquired TTP is caused by circulating autoantibodies inhibiting ADAMTS13 activity.¹¹ Recent findings may also help to explain the effectiveness of plasma infusion (supply of ADAMTS13) or plasma exchange (additional removal of autoantibodies and ultra-large vWF multimers). Acquired TTP can be further divided into idiopathic or secondary (eg, autoimmune disease, malignancy, HIV, stem cell transplantation, pregnancy, drugs).

HUS is a thrombotic microvascular disorder, predominantly affecting glomeruli, and it occurs mainly in children. Sometimes presenting symptoms of HUS and TTP can overlap and the two disorders are difficult to distinguish. For this reason the term thrombotic microangiopathy (TMA) has been widely used.

An association between HUS and HIV was first recognized in 1984.¹² Complete deficiency of the vWF cleaving protease and inhibitor has been reported in HIV-associated TTP.¹³ The prognosis for HIV patients with TMA is usually very poor,¹⁴ but literature for HIV-associated TMA is scarce.

Patients, Materials, and Methods

All consecutive cases of HIV patients with a clinical diagnosis of TTP/HUS admitted to J. Stroger Hospital of Cook County from September 1992 to December 2004 were reviewed. Two diagnostic criteria for TTP/HUS were used: microangiopathic hemolytic anemia (schistocytes >3 per high-power field) and thrombocytopenia. There were no requirements for renal impairment, fever, or neurological signs. All patients had documented positive HIV test results.

Results

Between September 1992 and December 2004, 17 HIV patients were admitted with TMA. One patient was diagnosed with HUS, 2 patients with TTP/HUS, and the remaining 14 with TTP. The clinical and laboratory data at presentation from our patients are summarized in Tables 1

and 2. The median age at presentation was 40 years (range 29–56 yr). The female to male ratio was 1:16.

Patients presenting with TMA were at an advanced stage of HIV infection (median CD4 count was 28 cells/mm³). Two patients had a CD4 count of more than 500 cells/mm³, 1 patient had a CD4 count between 200–499 cells/mm³, and the other 14 had CD4 counts of less than 200 cells/mm³ (Figure 1).

All patients had thrombocytopenia, hemolytic anemia, and schistocytosis in peripheral blood smear. Median hemoglobin was 8.3 g/dL, while median platelet count was $19 \times 10^9/L$. Sixteen of seventeen patients had elevated lactate dehydrogenase (LDH) levels (the median LDH level was 1,057 U/L).

Forty-one percent of patients presented with fever and 29% of patients presented with neurological symptoms (headache, seizures, altered mental status). Neurological symptoms at presentation were associated with poor prognosis (4 of 5 patients who presented with these symptoms died). The majority of patients (14 of 17) presented with renal disease (median creatinine level 2.6 mg/dL, range 0.8–7.9 mg/dL).

All 17 patients were treated with plasma exchange and 88% received steroids (Table 3). Six patients received highly active antiretroviral therapy. Inpatient mortality during first TMA episode was 47% (7 of 17). Five deaths were due to TMA. Four patients (#1, 7, 11, 13) showed no response to the treatment and their deaths were attributed to TMA. One patient (#4) had a relapsing course of TMA during prolonged hospitalization and died due to relapsed TMA. Two patients (#6, a responder, and #15, a nonresponder) died due to sepsis. Renal function improved in all responders, and in 6 patients renal function completely normalized.

Four patients experienced a relapsing course of TTP (Table 4). Three patients had a single relapse and 1 patient relapsed twice. Although all relapsed patients responded to treatment during the first episode of TTP, 2 patients failed to respond to the treatment during relapse. Patient #3 relapsed twice (3 and 11 months after diagnosis) and continued to respond to the same treatment. There are long-term survivors (#5, 12, 14) surviving 5 years.

Discussion

Patients with TMA and HIV were found to have more advanced disease, as indicated by lower CD4 counts and higher HIV-1 RNA levels, than patients with HIV and without TMA in a prospective study.¹⁵ At our institution HIV patients who presented with TMA had median CD4 counts of 28 cells/mm³. The frequency of TMA has been

Table 1. Demographic and Laboratory Data at Presentation

Patient No.	Age	Sex	CD4 Count	Plt	Hb	LDH	Cr
1	37	F	1	29	9.5	3911	6.6
2	56	M	4	68	12	486	2.7
3	38	M	338	19	10.8	1328	1.1
4	36	M	28	8	6.3	6106	6.8
5	46	M	144	6	8.6	185	1.4
6	43	M	594	43	8.6	612	6.7
7	30	M	4	25	8	782	1.9
8	40	M	9	22	6.6	1178	3
9	38	M	540	4	5.7	N/A	1.5
10	51	M	127	9	5.4	966	1.7
11	38	M	3	55	8.3	744	1.7
12	49	M	6	15	11.4	1206	1.8
13	49	M	8	33	6	887	5.4
14	50	M	162	14	8.6	2147	0.8
15	29	M	64	13	7.6	1004	2.6
16	41	M	145	15	10.3	2881	4.4
17	40	M	3	90	6.8	1110	7.9

Cr = creatinine (mg/dL), creatinine normal range: 0.6–1.4 mg/dL; Hb = hemoglobin (g/dL); LDH = lactate dehydrogenase (U/L), LDH normal range: 85–210 U/L; N/A = data not available; Plt = platelet count ($10^9/L$).

Table 2. Clinical and Laboratory Characteristics of Patients at Presentation

Characteristics	
Sex, F:M	1:16
Median age, yr (range)	40 (29–56)
Median CD4 count, cells/mm ³ (range)	28 (1–594)
Median platelet count, $10^9/L$ (range)	19 (4–90)
Median hemoglobin, g/dL (range)	8.3 (5.4–12)
Median LDH level, U/L (range)	1,057 (185–6,106)
No. of patients with renal dysfunction	14
Median creatinine level, mg/dL (range)*	2.6 (0.8–7.9)
No. of patients with fever†	7
No. of patients with CNS signs	5

* Creatinine normal range: 0.6–1.4 mg/dL.

† Fever was defined as temperature of at least 37.5° C.

CNS = central nervous system; LDH = lactate dehydrogenase, LDH normal range: 85–210 U/L.

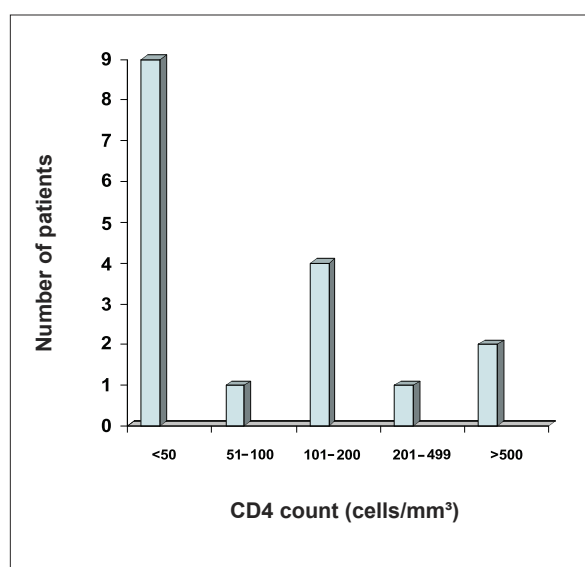
**Figure 1.** CD4 count distribution at presentation.

Table 3. Treatment, Response, and Outcome at the First TMA Episode

Patient	Diagnosis	Plasma Exchange	Steroids	HAART	Response, Outcome
1	TTP	Yes	No	No	NR, died
2	TTP	Yes	Yes	No	RS
3	TTP	Yes	Yes	Yes	RS
4	TTP	Yes	Yes	Yes	RS, relapsed, died
5	TTP	Yes	Yes	Yes	RS
6	TTP	Yes	Yes	No	RS, died
7	TTP/HUS	Yes	Yes	No	NR, died
8	TTP	Yes	Yes	Yes	RS
9	TTP	Yes	No	No	RS
10	TTP	Yes	Yes	No	RS
11	TTP	Yes	N/A	N/A	NR, died
12	TTP	Yes	Yes	Yes	RS
13	HUS	Yes	Yes	No	NR, died
14	TTP	Yes	Yes	No	RS
15	TTP	Yes	Yes	No	NR, died
16	TTP	Yes	Yes	No	RS
17	TTP/HUS	Yes	Yes	Yes	RS

HAART = highly active antiretroviral therapy; HUS = hemolytic uremic syndrome; N/A = no data available; NR = no response; RS = response seen; TTP = thrombotic thrombocytopenic purpura.

reported to be higher in HIV-positive patients than in the normal population and even greater in those with advanced disease. In a prospective evaluation of 350 HIV-infected patients admitted consecutively to the Johns Hopkins Hospital, TMA was reported in 25 patients, with an incidence of 7%.¹⁶ Patients had median CD4 cell counts of 36 cells/mm³ and median HIV-1 RNA levels of 94,000 copies/mL; 72% of patients presented with AIDS-defining illness. The prognosis for HIV-infected patients with TMA has been reported to be extremely poor. Our study showed inpatient mortality reaching almost 50%.

An accurate diagnosis of TMA in patients with HIV can be complicated because the clinical presentation is highly variable and symptoms may be similar to those of other HIV-associated diseases. HIV-related thrombocytopenia may have many causes (eg, HIV-associated immune thrombocytopenic purpura, lymphoma, infections, drugs, HIV-related dysmyelopoiesis, or hemophagocytosis). HIV-infected patients are also susceptible to developing thrombocytopenia for reasons unrelated to their HIV infection, such as alcohol use, hepatitis C, splenomegaly, and liver disease. It is very important to suspect TMA in HIV patients who present with thrombocytopenia and anemia and to look for signs

of hemolysis (eg, increased LDH, reticulocyte count, or unconjugated bilirubin) and schistocytes in peripheral blood smear.

There are more reasons to have a high index of TMA suspicion in HIV patients. Several AIDS-related infections and neoplasms have been shown to be associated with TMA; thus it is sometimes difficult to distinguish the cause of TMA in HIV patients. However, it would seem appropriate to start plasma exchange as soon as possible in patients with renal impairment and neurological signs because these patients had significantly inferior outcomes in our and other studies. Plasma exchange, if instituted early, may produce clinical remission in half of HIV patients with TMA. ADAMTS13 inhibitor titers may be useful to identify patients with a high likelihood of relapse, and this subgroup of patients may benefit from antiretroviral therapy in addition to plasma exchange.

The US Centers for Disease Control and Prevention first listed conditions and infections associated with AIDS in 1982. The AIDS surveillance case definition was substantially expanded in late 1987 and again 1993. The surveillance case definition of AIDS now includes all individuals presenting with the 23 clinical conditions from previous case definitions or with three new conditions

Table 4. Relapsed TTP: Treatment, Response, and Outcome

Patient	Diagnosis	Time to Relapse	Plasma Exchange	Steroids	HAART	Response, Outcome
3	TTP	3 and 11 months	Yes	Yes	Yes	RS, RS
4	TTP	Same admission	Yes	Yes	Yes	NR, died
8	TTP	11 months	Yes	No	Yes	NR, died
14	TTP	2 months	Yes	Yes	No	RS

HAART = highly active antiretroviral therapy; NR = no response seen; RS, = response seen; TTP = thrombotic thrombocytopenic purpura.

(invasive cervical cancer, pulmonary tuberculosis, recurrent pneumonia), or with CD4 T-lymphocyte counts of less than 200 cells/mm³.¹⁷ This new definition of AIDS reflects increased knowledge of the natural history of HIV and provides a consistent method to monitor trends of serious HIV-associated mortality and morbidity.

The purpose of this article is to consider TMA syndrome as an AIDS-defining illness by consideration of a review of TMA cases in HIV-positive patients at J. Stroger Hospital of Cook County, as well as the studies published in the literature. The data demonstrate TMA association with an advanced HIV disease. Considering TMA as an AIDS-defining illness may help to recognize the syndrome and start effective treatment earlier in order to improve survival rates in this severe but treatable condition.

References

- Moschowitz E. Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. *Proc NY Patbol Soc.* 1924;24:21-24.
- Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine.* 1966;45:139-159.
- Moake JL. Thrombotic microangiopathies. *N Engl J Med.* 2002;347:589-600.
- Henon P. Treatment of thrombotic thrombocytopenic purpura: results of a multicenter randomized clinical study. *Presse Med.* 1991;20:1761-1767.
- Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: clinical experience in 108 patients. *N Engl J Med.* 1991;325:398-403.
- Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma transfusion in the treatment of thrombotic thrombocytopenic purpura. *N Engl J Med.* 1991;325:393-397.
- Moake JL, Rudy CK, Troll JH, et al. Unusually large plasma factor VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. *N Engl J Med.* 1982;307:1432-1435.
- 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;339:1578-1584.
- Schneppenheim R, Buddle U, Oyen F, et al. von Willebrand factor cleaving protease and ADAMTS 13 mutations in childhood TTP. *Blood.* 2003;101:1845-1850.
- Antoine G, Zimmermann K, Plaimauer B, et al. ADAMTS 13 gene defects in two brothers with constitutional thrombotic thrombocytopenic purpura and normalization of von Willebrand factor-cleaving protease activity by recombinant human ADAMTS 13. *Br J Haematol.* 2003;120:821-824.
- Tsai HM, Lian ECY. Antibodies to von-Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med.* 1998;339:1585-1594.
- Boccia R, Gelmann E, Baker C, Marti G, Longo DL. A hemolytic-uremic syndrome with the acquired immunodeficiency syndrome. *Ann Intern Med.* 1984;101:716-717.
- Sahud MA, Claster S, Liu L, et al. von Willebrand factor-cleaving protease inhibitor in a patient with human immunodeficiency syndrome-associated thrombotic thrombocytopenic purpura. *Br J Haematol.* 2002;116:909-911.
- Gadallah MF, el-Shahawy MA, Campese VM, Toff JR, King JW. Disparate prognosis of thrombotic microangiopathy in HIV-infected patients with and without AIDS. *Am J Nephrol.* 1996;16:446-450.
- Becker S, Fusco G, Fusco J, Balu R, et al. HIV-associated thrombotic microangiopathy in the era of highly active antiretroviral therapy: an observational study. *Clin Infect Dis.* 2004;39(suppl):S267-S275.
- Moore RD. Schistocytosis and a thrombotic microangiopathy-like syndrome in hospitalized HIV-infected patients. *Am J Hematol.* 1999;60:116-120.
- From the Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *JAMA.* 1993;269:729-730.