

REVIEW

HIV associated thrombotic microangiopathy

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Thrombotic microangiopathy (TMA) is a known complication of HIV infection. Endothelial cell injury appears to be the primary event causing platelet activation and deposition in the microvasculature. Direct cytopathic roles of HIV as well as other factors such as malignancy, drugs, and infectious agents have been implicated in the pathogenesis of HIV-TMA. Although the majority of patients present in a more advanced stage of HIV disease, TMA can be the initial presenting symptom of HIV infection. Clinical features are those of idiopathic TMA, and the diagnosis should be suspected in any patient with new onset thrombocytopenia and microangiopathic haemolytic anaemia. Therapy with plasma exchange or infusion appears to be efficacious. A rapid diagnosis and institution of plasmapheresis is crucial for a favourable outcome. The long term prognosis of HIV-TMA is unfavourable and may depend on the stage of HIV infection. The recent data after the use of highly active retroviral treatment, however, are unavailable and current prognosis is therefore uncertain.

another. Epidemic HUS in young children initiated by infections with shiga toxin-producing strains of shigella or *Escherichia coli* (typically *E coli* 0157:H7) appears to be distinct from all other forms of HUS in terms of prognosis and response to treatment.^{6–8}

The pathophysiology of TMA is incompletely understood but injury to the endothelial cell is considered to be the central and likely inciting factor. The triggers of TMA include infections, drugs, collagen vascular disease, cancer, and pregnancy among others; however, often no triggering condition is apparent (box 1). TMA is a rare but a well known complication of HIV infection. The association of TMA with HIV infection was first described in 1984.⁹ Subsequently TMA has been increasingly reported in HIV infected patients over the past decade.^{10–19} In the present review, we discuss the pathophysiology, clinical features, diagnosis, treatment, and prognosis of TMA in HIV infected patients.

EPIDEMIOLOGY

TMA occurs with an annual incidence of 3.7 cases per 100 000 persons in the general population.²⁰ It is slightly more common in females (female: male ratio 3:2) and has a peak incidence in the third decade.^{21 22} The incidence of TMA is found to be raised in patients with HIV infection compared with the general population, and a higher incidence is found in advanced HIV infection.^{10–19 23 24} HIV infection was found in 14%–20% of patients presenting with TMA in a retrospective series, and the association has been confirmed in a case-control study.^{14 16} Among patients with HIV-TMA, males are predominantly affected, and homosexual behaviour and intravenous drug abuse are identified as two major risk factors for their HIV infection.¹⁸

AETIOLOGY AND PATHOGENESIS

Idiopathic TMA

Endothelial cell injury appears to be the primary event in the pathogenesis of TMA causing platelet activation and deposition in arterioles and capillaries. Potential factors that have been implicated in causing endothelial injury and activation are bacterial shiga toxin/endotoxin, viral infection, antibodies, and immune complexes and drugs among others.^{25–28} Evidence also indicates that the capacity of endothelial cells to inhibit platelet activation and mediate vasodilation through the elaboration of prostacyclin may be impaired.²⁹

Thrombotic microangiopathy (TMA) is clinical syndrome characterised by microangiopathic haemolytic anaemia, thrombocytopenia, microvascular thrombosis, and multisystem organ dysfunction.^{1–3} Pathologically TMA is defined as a lesion of vascular wall thickening, intraluminal platelet thrombosis (hyaline thrombi), and vascular occlusion.¹ The thrombotic lesions typically involve terminal arterioles and capillaries. Two pathologically indistinguishable but clinically distinct entities have been described, haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

TTP is a diffuse thrombotic microangiopathy which classically manifests with microangiopathic haemolytic anaemia, thrombocytopenia, renal dysfunction, neurological symptoms, and fever. A central nervous system microangiopathy that leads to the emergence of neurological symptoms constitutes an important component of the disorder. Without appropriate treatment, TTP is a fatal entity; but a marked improvement in the survival rate has been demonstrated when therapy with plasma exchange or plasma infusion is instituted promptly.^{4 5} HUS on the other hand, is a more localised form of thrombotic microangiopathy that is characterised by severe renal dysfunction with a paucity of neurological abnormalities.^{1–3} In practice, however, the differences between TTP and HUS are seldom clear cut, and symptoms may shift from one syndrome to

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Box 1: A classification of thrombotic microangiopathy

- Idiopathic thrombotic microangiopathy (TMA): with thrombotic thrombocytopenic purpura (TMA-TTP); with sporadic haemolytic uraemic syndrome (TMA-HUS).
- Familial TMA.
- Toxin associated TMA: childhood epidemic HUS; sporadic HUS.
- Drug associated TMA: quinine, ticlopidine, mitomycin C, cyclosporin.
- Transplant associated TMA.
- Malignancy associated TMA.
- Pregnancy associated TMA.
- Collagen vascular disease associated TMA.
- HIV associated TMA.

Loss of physiological thromboresistance, leucocyte adhesion to damaged endothelium, complement consumption, abnormal von Willebrand factor release and fragmentation, and increased vascular shear stress may then sustain and amplify the microangiopathic process.¹

Endothelial cell injury may also promote platelet adhesion to the vasculature by disrupting the production or processing of von Willebrand factor. The unusually large multimers of von Willebrand factor are found in TMA patients, presumably after being released into the circulation from damaged endothelial cells.³⁰⁻³¹ These ultralarge von Willebrand factor multimers could directly agglutinate platelets, especially when they are subjected to high shear stress.³² The partial arteriolar obstruction may result in a high shear stress in the vasculature of patients with TMA that could augment platelet reactivity with von Willebrand factor.³³ Endothelial cell injury may promote platelet adhesion to the vasculature by disrupting the production or processing of von Willebrand factor.³² It has been reported that loss or dysfunction of the von Willebrand factor-cleaving protease is related to the development of acute or chronic TTP-HUS.³⁴⁻³⁶ The deficient plasma von Willebrand factor-cleaving metalloprotease activity may either be inherited as in patients with the familial or chronic relapsing form of TTP-HUS or acquired caused by autoantibody inhibition of protease activity.³⁷⁻³⁸ However, low plasma levels of the protease are not specific for TMA and low protease level is found in several other conditions as well.³⁹

HIV-TMA

The mechanism involved in the pathogenesis of HIV related TMA remains speculative. Because the patients with HIV related TMA present at varied stages of HIV infection and with diverse infections and neoplasms, multiple factors can probably produce endothelial damage and/or platelet aggregation resulting in TMA. A direct cytopathic role of HIV by causing endothelial cell injury has been implicated in the pathogenesis of TMA. Other factors that may possibly be involved in HIV associated TMA include: drugs, malignancies, and direct vascular injury by infectious agents.¹⁶⁻¹⁸ A high prevalence of various malignancies has been noted in those patients who developed TMA.¹⁸ Likewise, in approximately one third of the reviewed cases of HIV-TMA, the syndrome was preceded by some infection.¹⁸⁻⁴⁰ An increased susceptibility to herpes, cytomegalovirus, and other infectious agents with endothelial tropism may be an inciting event in some cases of HIV-TMA. For example, cytomegalovirus has been shown to increase the procoagulant activity of endothelial cells,⁴¹⁻⁴² and a high incidence of symptomatic cytomegalovirus infection was found in transplant related TMA.⁴³ Drugs such as valacyclovir, fluconazole, and clofazamine have also been implicated in the pathogenesis of HIV-TMA.¹⁶⁻⁴⁴ However, the association between these drugs and TMA may be circumstantial as no cases of TMA were observed in 700 HIV infected patients treated with valacyclovir.⁴⁵

Endothelial cell injury and activation are commonly observed in HIV infection.⁴⁶ Endothelial activation in HIV infection may be mediated by direct viral invasion of endothelial cells, indirectly by the effect of secreted cytokines or by the action of HIV associated proteins such as Tat and gp120 on endothelial cells.⁴⁷⁻⁴⁹ Both in vivo and in vitro studies demonstrated that endothelial cells are permissive to HIV infection in various tissues such as bone marrow, retina, brain, and glomeruli.⁵⁰⁻⁵³ Moreover, the presence of the HIV-1 p24 antigen in endothelial cells has been described in a patient with HIV related TMA.¹³ HIV infection of endothelial cells can occur both CD4 dependent or CD4 independent mechanisms. Some HIV-2 isolates have been described that use a chemokine receptor CXCR4 for virus entry in a CD-4 independent fashion.⁵⁴ Expression of these chemokine receptors has been demonstrated on endothelial cells.⁵⁵⁻⁵⁶ This raises the possibility that HIV may be able to infect endothelial cells that express CXCR4 or perhaps other chemokine receptors. Various markers of endothelial cell damage such as von Willebrand factor, soluble thrombomodulin, adhesion molecule E-selectin, tissue type plasminogen activator, plasminogen activator inhibitor, fibronectin, angiotensin converting enzyme, and endothelin have been shown to be increased in the course of HIV infection.⁵⁷⁻⁶⁰ Similarly, various inflammatory cytokines such as tumour necrosis factor alpha and interleukin-1 are found to be raised in HIV infected patients.⁶¹ These cytokines increased the expression of adhesion molecules on the endothelial cell surface and may be important in the pathway leading to endothelial damage.⁶²⁻⁶³

A characteristic histological feature of TMA is the paucity of inflammation.¹ Evidence supports enhanced apoptosis or programmed cell death of microvascular endothelial cells in patients with TMA.⁶⁴ Likewise, an increased endothelial cell apoptosis was also demonstrated in HIV infection.⁶⁵ It has been also reported that plasma from patients with both idiopathic and HIV associated TMA can cause apoptosis of microvascular endothelial cells through a pathway involving induction of Fas (CD95).⁶⁶⁻⁶⁷ Various investigators have shown that endothelial cells acquire procoagulant properties upon activation of apoptosis.⁶⁸⁻⁷⁰ Hence, increased endothelial cell apoptosis may play a part in the pathogenesis of HIV-TMA. The role of the plasma von Willebrand factor-cleaving metalloprotease in the pathogenesis of HIV-TMA is uncertain because of the paucity of data about the protease level in HIV-TMA cases described in the literature.

CLINICAL AND LABORATORY FEATURES

The clinical spectrum varies from a low grade asymptomatic thrombocytopenia with mild renal insufficiency to a catastrophic illness with gross neurological deficits and renal failure requiring dialysis. In contrast to idiopathic TMA, many of the patients have coexisting AIDS defining illnesses such as *Pneumocystis carinii* pneumonia, Kaposi's sarcoma, cytomegalovirus colitis, or retinitis and cryptococcal meningitis.¹²⁻¹⁹ In a recent review of 93 cases of HIV associated TMA described in the literature, 32 patients had features of HUS and 61 patients were diagnosed with TTP.¹⁹ Of note, in 26 (28%) cases TMA was the first clinical manifestation of HIV infection. While most patients had symptomatic HIV infection at the time of or soon after the diagnosis of TMA, asymptomatic or mild HIV infection (Centers for Disease Control stage I and II) was found in nearly one third of the patients. Patients affected by HUS presented in a more advanced stage of HIV disease and had a mean CD4 count of 70 cells/ μ l (20-400) compared with a mean CD4 count of 142 (0-750) in patients with TTP.

Of note, patients with HIV related TTP seem to present with symptoms and signs quite similar to those of classic TTP. The classic pentad including neurological symptoms was noted in 36 (60%) patients diagnosed with TTP. Additionally, in HIV related TTP central nervous system abnormalities were severe

Box 2: Laboratory features of HIV-TMA

- Anaemia.
- Thrombocytopenia.
- Presence of fragmented red blood cells or schistocytes.
- Raised serum indirect bilirubin and lactate dehydrogenase.
- Raised serum creatinine.
- Microscopic haematuria and proteinuria.
- Lack of laboratory evidence of coagulopathy.

with the frequent presence of seizure, coma, obtundation, and agitation. On the other hand, 22 (68%) out of 32 patients diagnosed with HUS typically presented with haemolytic anaemia, thrombocytopenia, fever, and renal dysfunction. However, the neurological symptoms were noted only in one patient. Although renal involvement was commonly seen in HIV-TMA, it was often limited to haematuria and mild renal insufficiency in patients with TTP. By contrast, patients with HUS had more severe renal dysfunction and higher serum creatinine concentrations. Haemorrhagic diathesis was also seen in both groups, and 34% patients with TTP and 16% patients with HUS had a bleeding episode.¹⁹

Thrombocytopenia, microangiopathic haemolytic anaemia, and increased levels of serum lactate dehydrogenase were common laboratory findings.^{12–19} Patients with TTP had a mean platelet count of $24.6 \times 10^9/l$ (range 1–90) and those with HUS had count of $27.6 \times 10^9/l$ (range 1–120). The peripheral blood smear was used to support the diagnosis of TMA in most cases. The presence of fragmented red blood cells or schistocytes was the most widely reported abnormality on the smear. Bone marrow specimens were obtained in only a fraction of patients with the majority revealing erythroid hyperplasia. In two other small series of HIV-TMA, similar clinical and laboratory abnormalities were observed.^{15–17} However, in another series of 18 HIV related TMA, all patients had a gradual onset of disease in contrast to the sudden onset that is a characteristic of the classical syndrome. They also had less severe thrombocytopenia and less frequent neurological abnormalities.¹⁶

DIAGNOSIS

Thrombocytopenia is frequently seen in HIV infection.^{71–73} The reported incidence varies from 3%–8% of seropositive individuals to 30%–45% in patients with AIDS.^{74–75} Likewise, other clinical features typical of TMA such as anaemia, neurological dysfunction, nephropathy, fever, and raised lactate dehydrogenase levels are also commonly seen in HIV infected patients due to various other causes. Hence, the initial diagnosis of TMA in HIV infected patients may be difficult. Recent studies, however, have required only the presence of microangiopathic haemolytic anaemia and thrombocytopenia without another clinically apparent cause to establish the diagnosis.^{5–11, 76} Examination of the peripheral blood smear, therefore, is essential in making the diagnosis. The diagnosis should be suspected in any patient with HIV infection who presents with a new onset thrombocytopenia and microangiopathic haemolytic anaemia. TMA can also mimic sepsis in HIV infected patients. However, while coagulation abnormalities are typically present in sepsis, they are uncommon in patients with TMA, and if present, usually are not severe.⁷⁷

TREATMENT

The mainstay of treatment of HIV-TMA is plasma exchange, similar to that of idiopathic TMA. Treatment with anti-retroviral agents may be an effective treatment for HIV-TMA as it can decrease HIV mediated endothelial damage. Use of antiretroviral agents in relapsing HIV-TMA has been associated with remission, and they should be considered in the chronic management of these patients.⁷⁸

Box 3: Differential diagnosis of TMA

- Disseminated intravascular coagulation.
- Severe vasculitis.
- Sepsis (bacterial, viral, fungal, or rickettsial).
- Eclampsia.
- HELLP syndrome.
- Malignant hypertension.
- Catastrophic antiphospholipid syndrome.

Plasma therapy

To date a relatively small number of HIV-TMA cases have been reported, therefore, the precise role of plasma infusion and/or exchange as well as the long term outcome in these patients are not well known. However, based on the cases described in the literature, plasma therapy (fresh frozen plasma, cryodepleted plasma, or solvent detergent treated plasma), as either plasma infusion or exchange, appears to be an effective treatment in HIV-TMA. The superiority of plasma exchange over plasma infusion in idiopathic TMA was shown almost a decade ago, and this therapy should be considered as the standard treatment in patients with HIV-TMA as well.³ The effectiveness of plasmapheresis is thought to be the result of either removal of a harmful plasma component or the replacement of a deficient component.

Prompt response to the plasma exchange is evidenced by an increase in platelet count, improvement of anaemia, and normalisation of peripheral blood smear. Exchange should be performed daily with the goal of exchanging 1 to 1.5 times the plasma volume (40–60 ml/kg) with each procedure. Neurological improvement occurs most rapidly, often within hours to days.¹¹ The serum lactate dehydrogenase level falls by 50% within three days in responders and platelet count begins to rise in a mean of five days, though normalisation may take several weeks.¹¹ Impaired renal function is generally the last to improve. Plasma exchange should be continued until neurological symptoms have resolved, and both a normal serum lactate dehydrogenase and platelet count have been maintained for three days. A shorter duration of therapy risks immediate and occasionally fatal relapse.

Among 100 cases of HIV-TMA reported in the literature, plasma exchange and/or plasma infusion was used in 86 cases. A complete response to treatment was reported in 41 (41%) cases.¹⁶ In a separate review of 28 of those 100 cases, 81% of the patients were treated with plasma exchange. Nineteen per cent only received infusion with fresh frozen plasma.¹⁸ Twenty five per cent of these patients who received plasma exchange died of their disease compared with 33% patients who only received plasma infusion. However, in a series of 18 HIV-TMA patients, a low response to plasma therapy appropriate for TMA was seen. Fifteen of 18 patients received plasma therapy. Eight patients received plasma exchange along with plasma infusion, five patients only received plasma infusion, and none of them had a complete response.¹⁶ In a series of 14 patients with HIV-TMA, three of 14 patients died of progressive disease within the first 24 hours of diagnosis, but no patient died of progressive TMA after 48 hours of institution of plasma exchange in addition to other therapy.¹⁷ Hence, a rapid diagnosis and institution of plasmapheresis is crucial for a favourable outcome.

Other therapies

The precise role of corticosteroids, splenectomy, and anti-platelet agents in patients with HIV-TMA is unknown. In a review of 28 cases of HIV-TMA, 23 patients (74%) received at least one form of additional treatment in addition to plasma therapy: prednisone (20 patients), antiplatelet agents such as aspirin and dipyridamole (15 patients), vincristine (seven patients), and intravenous gammaglobulin (two patients).¹⁸

Box 4: Management of HIV-TMA

- Plasmapheresis and/or plasma infusion should be performed promptly.
- Use of corticosteroids should be individualised.
- Splenectomy should be reserved for those patients who are refractory to plasma therapy.
- Antiplatelet agents should be avoided as haemorrhagic diathesis commonly observed in HIV-TMA patients.
- Antiretroviral therapy is an important component of the management.
- Haemodialysis should be considered in patients with severe renal dysfunction.

However, the individual benefit of these modalities in achieving remission is not known. Corticosteroids have frequently been used in idiopathic TMA with variable response rate.^{4 79} In general, they are of little benefit of their own, and routine use of corticosteroid should be avoided in patients with HIV-TMA who often present with advanced HIV infection.^{2 3} Splenectomy is mainly confined to refractory TMA cases.^{4 11 80} A patient with HIV-TMA refractory to plasma exchange had a permanent remission of his TMA and a survival of 38 months after splenectomy.¹⁷ Therefore, splenectomy may have a role in the management of those patients who are refractory to large volume plasma exchanges. Antiplatelet agents such as aspirin, dipyridamole, and sulfapyrazone have not been convincingly shown to increase the response to plasma exchange and may promote bleeding in the setting of severe thrombocytopenia.^{2 4 5} Hence their use as first line therapy cannot be recommended. Lastly, there are several anecdotal reports of success with multiple other treatments in TMA such as azathioprine, cyclophosphamide, cyclosporin, and intravenous gammaglobulin. However, the role of these agents in HIV-TMA patients who often have profound immunosuppression is unknown.^{43 76 77}

Platelet transfusion

Platelet transfusions have been reported to exacerbate TMA. Cases of TMA with acute deterioration and death have been reported after platelet transfusion.^{4 81} Therefore, all patients who are receiving platelet transfusion either because of bleeding or undergoing invasive procedures should be carefully monitored for signs and symptoms of clinical deterioration.

PROGNOSIS AND SURVIVAL

The relapse rate appears to be less frequent in HIV related TMA compared with idiopathic TMA; however, the overall prognosis is less favourable.^{18 19 78} Among 61 reviewed cases of HIV associated TTP, 33 (51%) patients achieved a complete response, four (6%) patients had partial response (14), and 28 (43%) patients died. On the other hand, of total 32 cases of HUS, 10 (31%) patients achieved a complete response, two patients (6%) had a partial response, and 20 (63%) patients died of their disease. Thus, the prognosis appears to be worse in HUS patients.¹⁹ In one series of HIV-TMA, however, many patients survived for weeks or months without plasma therapy, in contrast to the nearly universal rapid mortality in untreated patients with classical TMA and some patients had spontaneous improvement without specific therapy.¹⁶

The long term prognosis of HIV-TMA probably depends on the stage of HIV infection. The mortality of patients with symptomatic HIV infection (Centers for Disease Control stage IV) is three times higher (39%) than mortality of patients with asymptomatic HIV infection (Centers for Disease Control stages II and III, 13%).¹⁸ In the vast majority of patients, life expectancy rarely exceeded one year after the diagnosis. Similarly, in another series of nine patients with

Box 5: Key messages

- Thrombotic microangiopathy (TMA) is a clinical syndrome associated with multiple inciting events and is increasingly seen in HIV infected patients.
- HIV infection both directly and indirectly, by predisposing to malignancy, opportunistic infection, and exposure to various drugs has been implicated in the pathogenesis of HIV-TMA.
- Endothelial cell injury appears to be the primary event leading to platelet aggregation.
- Early diagnosis may be difficult as other clinical features typical of TMA such as anaemia, thrombocytopenia, neurological dysfunction, nephropathy, fever, and raised lactate dehydrogenase levels are also commonly seen in HIV infected patients due to various other causes.
- The diagnosis should be suspected in any HIV infected patient with new onset thrombocytopenia and microangiopathic haemolytic anaemia.
- TMA can be the initial presenting symptom of HIV infection and HIV testing may be considered in patients presenting with TMA.
- Plasma therapy (plasma exchange and/or infusion) appears to be efficacious and a rapid institution of therapy is crucial for a favourable outcome.
- The overall prognosis is less favorable for HIV-TMA than for idiopathic TMA and appears to be related to profound immunodeficiency.
- The recent data after the use highly active retroviral treatment is unavailable and current prognosis is therefore uncertain.

HIV-TMA, seven patients died of TMA with or without sepsis within three months. Among these nine patients, eight belonged to Centers for Disease Control group IV.¹⁵ This indicates that the poor prognosis in HIV-TMA is likely related to severe immunodeficiency. Most of the literature in HIV-TMA was written before the availability of effective antiretroviral therapy. In the past decade, however, the advent of highly active antiretroviral therapy has dramatically improved the overall prognosis of HIV infected patients.⁸² This improved prognosis has been associated with a significant reduction in various AIDS associated complications. At the present time it is not known whether this decline in morbidity and mortality among HIV infected patients with advanced immune depletion would also translate into an improvement in the prognosis of HIV-TMA. Future investigation is warranted to address this issue.

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