Thrombotic thrombocytopenia purpura in HIV patient: A rare case in Malaysia

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SUMMARY

HIV-associated thrombotic thrombocytopenic purpura (TTP) presents unique diagnostic and therapeutic challenges, as its clinical features may overlap with other complications like disseminated intravascular coagulation (DIC), and haemolytic uremic syndrome (HUS). This case report describes a 25-year-old male patient with TTP implicated by HIV. Laboratory findings revealed severe thrombocytopenia and fragmented red blood cells on peripheral blood smear, leading to a diagnosis of TTP. Notably, the patient's HIV viral load was found to be poorly controlled, contributing to the development of TTP. This report emphasises the importance of considering TTP in HIV-positive patients presenting with thrombocytopenia.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening blood disorder due to deficiency of ADAMTS13, which can lead to widespread microvascular thrombi, resulting in multiorgan failure, like the brain and kidney.[1-3] Most of the TTP cases are acquired, where there are autoantibodies against ADAMTS13.[1] It can be idiopathic or associated with autoimmune diseases, pregnancy, drugs or infection like HIV.[1] HIV infection is believed to directly trigger thrombotic thrombocytopenic purpura (TTP), likely by affecting vascular endothelial cells, leading to their dysfunction, localised thrombin formation, and depletion of ADAMTS13.[4] Although TTP is a very rare disease, a study in South Africa found that people with HIV are 15 to 40 times more likely to develop TTP compared to those without HIV, and over 80% of TTP cases in South Africa are found to be HIV-related.[4] TTP tends to occur more frequently in individuals with HIV who have advanced disease, low CD4+ T cell levels, and other coexisting opportunistic infections, with relatively high mortality.[2] Although the availability of antiretroviral therapy (ART) was expected to reduce the occurrence of HIV-associated TTP, current evidence indicates that HIV remains a significant contributor to secondary TTP2.

CASE PRESENTATION

A 25-year-old man initially complained of chronic cough for six months, associated with fevers and constitutional symptoms. On examination, he appeared emaciated and cachectic. Physical findings were unremarkable. The fourth-generation HIV test was reported positive, accompanied by a low CD4 count of 39 cells/mm3 and HIV viral load of 1075251 copies/ml. The tuberculosis workup was negative, and no positive respiratory culture was reported. Chest X-ray showed a clear lung field. He was treated empirically with antimicrobial therapy (Amoxicillin and Clavulanic acid), followed by anti-retroviral therapy consisting of PO tenofovir disoproxil fumarate/emtricitabine (300 mg /200 mg) 1 tablet daily and PO Efavirenz 600mg daily, alongside co-trimoxazole as primary prophylaxis of pneumocystis pneumonia.

One month after discharge, he presented with generalised tonic-clonic seizures for one day, associated with fevers. Upon arrival to the emergency department, he appeared tachypneic and delirious, with a Glasgow Coma Scale (GCS) score of E4V4M5. He was haemodynamically unstable, with blood pressure (BP) of 111/68mmHg, heart rate (HR) of 156bpm, respiratory rate (RR) of 24 per minute, and temperature of 40°C. The physical examination was unremarkable, with absent neurological deficits. Laboratory results depicted pancytopenia, acute kidney injury (AKI), transaminitis, and coagulopathy (Table I). A computer tomography (CT) scan of the brain showed no abnormalities. Lumbar puncture was not performed in the setting of haematological abnormalities. He was empirically started on intravenous ceftriaxone 2g twice daily and intravenous acyclovir 500 mg TDS, treating as presumed meningoencephalitis. Convulsions were controlled with a few antiepileptic agents, like intravenous levetiracetam, on top of phenytoin and phenobarbitone because of status epilepticus. He was subsequently intubated and ventilated for cerebral and airway protection.

Urgent peripheral blood smear demonstrated the presence of schistocytes, indicative of microangiopathic haemolytic anaemia (MAHA) (Table I). In the context of convulsions, fevers, severe thrombocytopenia, AKI, and MAHA, TTP was suspected. Fresh Frozen Plasma Transfusion (FFP) was given promptly. An urgent haematology consult was undertaken and plasma exchange with transfusion support was planned. However, the patient succumbed to his illness before plasma exchange could be initiated. The ADAMTS13 result (the test needs to be outsourced and not offered in our hospital), subsequently confirmed TTP. (Table I)

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Table I: Relevant investigation during the hospitalisation

Investigation	Normal Range	Pre-admission (First follow-up in clinic)	Day 1 (of admission)	Day 2 (of admission)
Hb, g/L	13-17	7.8	5.8	5.6
MCV (fl)	83-101	73	65	63
White Cell Count, 109/L	4-10	5.1	0.2	0.1
Platelet ,109/L	150-410	170	23	30
Reticulocyte Count, %	0.5-2.1		0.1	
Urea, mmol/L	3.1-8.2	2.4	19.8	17.8
Serum creatinine, mmol/L	62-115	64	264	238
Total bilirubin, umol/L	<21	7.3	9.6	10.6
Albumin, g/L	31-48	38	34	25
ALT, U/L	10-49	17	61	50
AST, U/L	<34	-	239	257
LDH, U/L	120-246	-	-	1422
pH	7.35-7.45	-	7.25	6.98
HCO3, mmol/L	18-23	-	11.4	8.9
Serum lactate, mmol/L	0.5-2.0	-	3.7	11.2
INR	0.82-1.03	-	1.45	1.81
APT, seconds	22-31	-	42.7	45.3
PT, seconds	9.4-11	-	14.6	17.9
CRP, mg/L	<10	-	93.4	140
Fibrinogen, g/L	1.85-4.27		2.85	-
Serum Ferritin, pmol/ml	48-708			3471.2
Triglycerides, mmol/l	<1.7			2.38
Sputum MTB C+S		No Growth		
Sputum AFB		Negative		
Serum parvovirus IgM			Negative	
Serum Cryptococcal Antigen			Negative	
Serum Toxoplasma IgM and IgG			Non-reactive	
G6PD			Normal	
Blood culture			Nil growth	
Blood fungal culture			Nil growth	
Full blood picture			presence of spherocytes and fragmented cells, suggestive of haemolysis	
ADAMTS13			Activity – 35% (40-130) Inhibitor – 22.5U/ml (Positive : >15U/ml) Inhibitor is positive at 22.5u/ml.	

Table II: Studies of patients with HIV associated TTP

Studies	Sample Size	Results
Muriel Meiring et al.[4]	40 patients	- Only 50% of TTP with HIV infected patients presented with autoantibodies to ADAMTS13. - HIV-positive persons who were not on combination antiretroviral therapy treatment (cART) seemed to have slightly lower ADAMTS13 levels than those who were on cART, although the levels were still in the normal range. - HIV-positive persons who were not on cART also presented with high amounts of autoantibodies against ADAMTS13.
Karen Gunther et al.5	20 patients	- 6 (30%) patients had activity of ADAMTS13 within the normal range. - Of the patients with reduced activity, 8 showed no evidence of an inhibitor.
Masoet et al.[8]	52 cases (41 is HIV infected)	- 90.2% of HIV-infected patients with TTP only received plasma infusion with good clinical response.
Novitzky, N. et al.[9]	44 patients (21 is HIV infected)	- HIV infected patients responded to FFP faster than HIV negative patients, and none of them required apheresis.

DISCUSSION

We described a case of TTP complicating HIV. Of note, TTP is rare, with a rate of nearly 0.0001% per year.[2] TTP is suspected in the presence of fever, thrombocytopenia, MAHA, neurological symptoms, and renal involvement.[3] A peripheral blood smear may reveal schistocytes, which are fragmented red blood cells, further supporting the diagnosis.[3] To confirm TTP, the ADAMTS13 activity assay is conducted, confirming the deficiency of the ADAMTS13 enzyme.[3] A Level of ADAMTS13 less than 10 IU/dL usually indicates severe TTP.[3] Additionally, testing for ADAMTS13 inhibitors can identify the presence of autoantibodies against this enzyme.[3] Of note, people living with HIV (PLHIV) were 40 times more likely to acquire TTP compared to those who had no HIV.[2] There are literatures reported that amongst the PLHIV afflicted with TTP, the ADAMTS13 level can be within near normal range with the presence of ADAMTS13 inhibitor (Refer to Table II).[4,5] On the contrary, our patient has fulfilled the pentad of TTP, ADAMTS13 level was not severely deficient, and there was presence of ADAMTS13 inhibitor.

It is crucial to exclude other opportunistic infections in this case. The patient had a negative tuberculosis workup prior to the current admission. Investigations on this admission, including serum parvovirus serology, serum cryptococcal antigen, serum toxoplasmosis serology, blood cultures, and blood fungal cultures, were all unremarkable. However, a lumbar puncture could not be performed due to severe thrombocytopenia, limiting our ability to rule out meningitis. Opportunistic infections remain a possible trigger for TTP, but based on the available investigations, no positive cultures were identified. Hemophagocytic syndrome was also considered as part of the differential diagnosis. The patient had an H Score of 164 (excluding bone marrow aspiration), indicating a 40-54% probability of hemophagocytic syndrome. However, the clinical presentation was consistent with the classical pentad, which was more suggestive of TTP.

Given the clinical context, we believe the TTP in this patient is related to HIV infection. Several mechanisms have been suggested for how HIV contributes to the development of TTP. It is proposed that endothelial dysfunction directly implicated by HIV can be the major driver of microvascular disease, resulting in inappropriate activation of the immune system and hypercoagulopathy.[3] Interestingly, underlying endotheliitis is present in both ART-naïve and ART-virally suppressed PLHIV3. On the other hand, HIV may directly induce chronic inflammation, promoting an autoimmune response against ADAMTS13 enzyme.[3] Its deficiency undermines the cleavage of vWF, leaving the hyperadhesive vWF unfolded in the micro-vessels and forming platelet thrombi.[3] Additionally, opportunistic infections (including cytomegalovirus, Hepatitis C, Kaposi sarcoma, Mycobacterium tuberculosis, etc) could provoke an immune response that affects both the endothelium and the coagulation system, thereby contributing to the development of TTP.[3] Another secondary trigger for HIV-related TTP is that HIV-associated complement activation poses a threat by developing immunothrombosis and mediating loss of endothelial cell integrity.[3]

There is a clinical overlap among TTP, Haemolytic Uremic Syndrome (HUS), and disseminated intravascular coagulation (DIC). In our case, the diagnosis is in favour of TTP, supported by low ADAMST13 and the presence of its inhibitor. Low ADAMTS13 activity and the presence of autoantibodies against ADAMTS13 further support a diagnosis of TTP. Conversely, DIC typically presents with a bleeding tendency and does not commonly exhibit neurological manifestations. It is less likely DIC in this patient as the initial INR was less than 1.5 and the fibrinogen level is not low. Both conditions may share similarities including anaemia and thrombocytopenia. However, rapid-onset DIC causes prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (aPTT), low fibrinogen levels, and elevated D-dimer.[6] Importantly, the ADAMTS13 level in DIVC is unaffected. HUS was unlikely because there was no severe renal dysfunction and absence of diarrhoea from history. Louw et al., study demonstrated that there was only 1 patient in their study who had severe renal dysfunction.[2]

Considered as a medical emergency, TTP requires immediate intervention to halt its progress and prevent death. A valuable clinical tool called the PLASMIC Score is useful to predict the likelihood of TTP and guide further management, whilst awaiting ADAMTS13 results.[3] Each criterion in the score is assigned 1 point, and in our patient's case, the PLASMIC score was 6, strongly suggestive of TTP. The sensitivity and specificity of PLASMIC score of ≥ 6 are 85% and 89%, respectively.[7] A PLASMIC score < 6 is less sensitive to exclude TTP and the need for therapeutic plasma exchange.[7]

The mainstay treatment for TTP is plasma exchange, with the primary aim to remove autoantibodies against ADAMTS13 and replenish functional ADAMTS13.[3] Infusion of FFP alone at a dose of 30 ml/kg/day may be helpful to dilute ultra-large VWF and supply ADAMTS13.[2] There are also several studies have demonstrated that fresh frozen plasma, when used alone, can effectively treat TTP without the need for plasma exchange (Refer to Table II).[8,9] In contrast, for this patient, he did not respond to Fresh Frozen Plasma transfusion alone. Other treatment modalities include corticosteroids and rituximab, an anti-CD20 monoclonal antibody, which helps suppress the production of autoantibodies3. However, rituximab is usually used for refractory and immune/idiopathic TTP rather than secondary TTP, which is likely to be in this patient.[1] Additionally, Caplacizumab has been approved for the treatment of immune-mediated TTP (iTTP). It is an anti-VWF nanobody that prevents VWF-mediated platelet aggregation.[3] Despite its clinical use, studies on Caplacizumab are still limited[3], and to the best of our knowledge, we are not aware of any study for PLHIV. Overall, engagement in a multidisciplinary team including neurologist, haematologist, intensivist, infectious diseases physician, and pathologist limits adverse events and improves outcomes.

CONCLUSIONS

Despite significant advancements in therapy, HIV-associated TTP continues to pose a diagnostic challenge. It is of paramount importance to maintain a high index of suspicion for TTP. Early recognition and prompt treatment can be lifesaving and significantly reduce mortality rates. Further research is necessary to optimise treatment protocols for this specific subset of patients.

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