CASE REPORT

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Thrombotic microangiopathy in a patient with a poorly controlled human immunodeficiency virus infection – A clinical case

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ABSTRACT

A 56-year-old male with a poorly controlled human immunodeficiency virus infection presents to the emergency room due to anorexia and weight loss. The patient was emaciated, hypertensive and his laboratory tests showed thrombocytopenia, anaemia, an elevated lactate dehydrogenase and an acute kidney injury. The patient was admitted to the Infecciology ward and by the fourth day, as the kidney function did not improve, a Nephrology consultation was requested. We collected a full auto-immune and serological panel and a urinalysis to rule out glomerular pathologies. Two days later, the patient developed a hypertensive emergency associated with an acute respiratory distress, responsive to furosemide and anti-hypertensive medications. The complementary study showed a high LDH, unmeasurable haptoglobin, thrombocytopenia and schizocytes on peripheral blood smear. These findings suggested a thrombotic microangiopathy associated with human immunodeficiency virus infection and so, he restarted antiretroviral therapy. The kidney function deteriorated and, despite starting haemodialysis, the patient died shortly after.

Keywords: acute kidney injury; human immunodeficiency virus infection; thrombotic microangiopathy

INTRODUCTION

Thrombotic microangiopathy (TMA) includes a group of disorders characterized by microangiopathic haemolytic anaemia, thrombocytopenia and microthrombi leading to ischaemic tissue injury, mainly in the brain and kidney. Although considered rare, they are life-threatening conditions that require urgent management. Presenting symptoms may be nonspecific, but laboratory tests usually reveal a specific combination of thrombocytopenia and intravascular haemolytic anaemia with signs of red blood cell fragmentation on the peripheral blood smear.[1] In the differential diagnosis of TMA one must consider a broad spectrum of clinical entities and so the diagnosis can often be challenging. The treatment is usually directed to the underlying cause; however, once the diagnosis is suspected, urgent referral is needed to a specialty service that can provide plasma exchange.

CLINICAL CASE

We present a case of a 56-year-old patient, followed in an Infecciology consultation due to a chronic human immunodeficiency virus (HIV) infection on highly active antiretroviral therapy (HAART) with Dolutegravir, Abacavir and Lamivudine. The patient, however, had poor therapeutic compliance and, on his last consultation, three months before admission, his CD4 count was 52 cells/mm3 (N: >700/mm3) and his viral load was 215000 copies/mL, fulfilling the criteria for Acquired Immunodeficiency Syndrome (AIDS).

In November 2020, the patient presented to the emergency room due to anorexia and weight loss (>10% of his bodyweight (BW)) during the previous six months, associated with nausea and vomiting in the past 2 weeks. He denied any fever, genital, urinary or cardiorespiratory symptoms. Upon arrival, the patient was dehydrated, hypertensive (systolic blood pressure (SBP) of 223mmHg and diastolic Blood Pressure (DBP) of 146mmHg) and emaciated (BW 36Kg). Table 1 displays the initial blood work; it revealed thrombocytopenia, normocytic normochromic anaemia, an elevated lactate dehydrogenase (LDH) and an acute kidney injury (AKI) stage 3. We requested blood and urine cultures to rule out opportunistic agents and, suspecting a prerenal AKI, started isotonic sodium chloride and two units of blood. A kidney ultrasound revealed loss of parenchymal differentiation and excluded obstructive disease. The patient was admitted to the

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Table 1

Initial diagnostic workup.

Biochemistry	Haemogram
SCr 4.1 mg/dL; (Baseline: 1.2 mg/dL) BUN 84mg/dL	**Haemoglobin 9 g/dL** MCV: 93 fL MCH: 33pg
LDH 549U/L	Platelets 44.000/mm3
CRP 6.7mg/dL	Leucocytes 3.5x10^9/L Lymphocytes 0.58x10^9/L
Bilirubin Total/Direct: 0.9/0.5 mg/dL	

SCr – serum creatinine; LDH – Lactate dehydrogenase; CRP – C Reactive Protein; MCV – Mean Corpuscular Volume; MCH – Mean Corpuscular Haemoglobin; BUN – blood urea nitrogen

Infectious Diseases Unit ward and empirically started on Sulfamethoxazole-Trimethoprim and Amphotericin.

By the fourth day, the patient was clinically stable, despite maintaining AKI and anaemia. A urinalysis revealed an active urinary sediment and sub-nephrotic proteinuria (albumin to creatinine ratio (ACR) 1357mg/g), which motivated a Nephrology consultation. On our examination the patient was pale, hypertensive (SBP 200mmHg), with preserved urine output (2000cc/24h) and no signs of hypervolemia. This presentation suggested a nephritic syndrome and we requested a complete autoimmune and serological study.

Two days later, the patient developed acute respiratory distress, associated with global respiratory insufficiency, requiring high-flow oxygen. The patient was polypneic, hypertensive (SBP 210mmHg/DBP 120mmHg), with basal crackles on pulmonary auscultation and a urine output of 82cc/hour. A transthoracic echocardiography was performed, showing good systolic function and no valve dysfunction, virtually ruling out a cardiac cause and suggesting a hypertensive pulmonary oedema. We started high-dose intravenous furosemide and nitrates to lower blood pressure and non-invasive ventilation (NIV) to control hypoxaemia. Although he improved clinically, the patient remained with an uncontrolled hypertension.

Table 2 exposes the diagnostic workup, available by the eighth day on the ward. These results were compatible with a TMA diagnosis: high LDH, very low haptoglobin level and schizocytes on peripheral blood smear (PBS). The positive Coombs test would argue against this hypothesis as the cause of intravascular haemolysis; we discussed the findings with Clinical Pathology and considered them to be secondary to HIV infection. A kidney biopsy could have been useful in this situation, because of the valuable diagnostic and prognostic information. However, since the patient was clinically unstable (hypertensive and with high-oxygen demands), had sustained thrombocytopenia and given the fact that this was not a life-saving procedure, we decided against performing a biopsy. After processing all the results and excluding the most frequent conditions leading to TMA, we interpreted this case as an Acquired Immunodeficiency Syndrome (AIDS)-related TMA: besides explaining the clinical and laboratory findings, this relates to the poorly controlled HIV infection. Hypertensive associated-TMA would be another very important differential diagnosis: the clinical features of these two entities usually overlap, which made distinguishing between these two entities very difficult; however,

Table 2

Immunologic and infectious diagnostic workup.

Immunology	
Anti-DsDNA	NEGATIVE
Antinuclear antibodies	NEGATIVE
Anti-pyruvate dehydrogenase autoantibodies	NEGATIVE
ANCA	NEGATIVE
C3/C4	NORMAL
Cryoglobulins	NORMAL
ADAMTS13 level/activity	NORMAL/ 74%
Blood and urine	
IGRA	NEGATIVE
BK virus	NEGATIVE
Urine culture	NEGATIVE
Blood culture	NEGATIVE
HIV viral load	22300copies/mL
Hepatitis B Virus (HBV)	IMMUNE
Hepatitis C Virus (HCV)	NEGATIVE
Biochemistry	
Haptoglobin	<0.07g/L
LDH	388U/L
Bilirubin Total/Direct	0.4/0.3mg/dL
Serum iron	48ug/dL
Ferritin	776ng/mL
Vitamin B12 and Folate	NORMAL
SCr	3.81mg/dL
Erythrocyte Sedimentation Rate	9mm/h
Haemogram	
Haemoglobin	7.9mg/dL
RPI	6.11
Platelets	85.000/mm3
Peripheral blood smear	4 schyzocytes/field
Leucocytes	3.4x10^9/L
CD4 Lymphocytes	25/mm3

Anti-DsDNA – anti double stranded DNA antibodies; ANCA – Anti-neutrophil cytoplasmic autoantibody; IGRA – Interferon gamma release assay; LDH – Lactate Dehydrogenase, SCr – serum creatinine; RPI – Reticulocyte Production Index

the absence of improvement after blood pressure control would argue against this hypothesis.

The treatment of AIDS-related TMA is based essentially on the control of the HIV infection. Plasmapheresis should also be considered, especially when there is central nervous system involvement or severe kidney impairment. In our patient there was a late recognition of the presence of acute TMA; since the patient maintained a stable kidney function and good urine output, our option was to restart HAART – this was done by the ninth day. Plasma exchange was not performed. Nonetheless, HAART often takes several weeks to produce its benefits: the patient clinical status deteriorated and he showed no signs of serological response for the following weeks (no fall in viraemia and no improvement in CD4 counts). Despite all efforts, kidney function deteriorated and, by the 20th day on the ward, we started haemodialysis. Clinical status complicated in the following days, due to a multi-drug resistant bacteraemia, eventually leading to his death.

DISCUSSION

TMA is the most common microvascular injury associated with chronic HIV infection.[1] Since the introduction of HAART the incidence of HIV-related TMA is decreasing, with a reported incidence of 1.4% pre-HAART and very few cases reported during HAART era.[2] This type of lesion usually affects male patients with AIDS criteria (especially when CD4 counts fall above 100 cells/mm3)[3] and patients with AIDS-associated diseases such as *Pneumocystis Carinii* pneumonia, CMV retinitis and cryptococcal meningitis.[1,4] The pathogenesis of this disease is still poorly understood, although it is widely accepted that endothelial damage is a key feature of TMA. Endothelial damage can be caused directly by viral invasion as evidenced by the expression of HIV-1 P24 antigen/chemokine receptors CXCR4 in endothelial cells or indirectly by the action of cytokines/HIV-associated proteins such as TaT and gp 120 on endothelial cells.[5,6] Complete deficiency of the vWF-cleaving protease ADAMTS13 has also been reported in HIV-associated TMA due to the development of IgG autoantibodies, although this is considered a very rare occurrence.[6,7] Other factors include drugs (valacyclovir, tenofovir, fluconazole, and clofazimine), malignancies, and direct vascular injury by other infectious agents. Various inflammatory cytokines such as tumour necrosis factor-α and interleukin-1 are found to be raised, and there is evidence of enhanced apoptosis of microvascular endothelial cells in these patients.[6] The clinical and laboratorial findings are similar to other diseases presenting with TMA: intravascular haemolytic anaemia (low haptoglobin, high LDH and schizocytes on PBS), acute kidney injury and low platelet count.

The differential diagnosis for TMA with kidney involvement is extensive; therefore a concise laboratory work and auto-immune panel are vital. One of these diagnoses is thrombotic thrombocytopenic purpura (TTP), which presents with haemolytic anaemia, low platelet count, AKI and occasionally with fever and neurologic symptoms. This diagnosis was excluded by measuring the ADAMTS13 level (absolute and activity) that was normal (Table 2). Although less frequent, other auto-immune diseases such as systemic vasculitis and connective tissue autoimmune diseases may have this kind of clinical and laboratory presentation, but were promptly excluded by a negative auto-immune panel. Atypical haemolytic uremic syndrome (aHUS) associated with dysregulation of the complement alternate pathway could also be considered. We were not able to perform a full genetic workup of the genes encoding the regulatory proteins of the complement alternate pathway; however the presence of HIV with AIDS criteria pointed towards a secondary aetiology. Finally, sepsis (bacterial, viral, fungal) or chronic viral infections such as hepatitis B virus (HBV), hepatitis C virus (HCV) and BK virus, may cause TMA with frequent kidney involvement; however, the serological panel showed no signs of these infections. As the most frequent causes of TMA with kidney involvement were excluded, a diagnosis of HIV-related TMA was made, supported by the associated clinical diagnosis of AIDS. A kidney biopsy, although not mandatory, could have been useful for confirmation of the TMA as cause of the AKI; the clinical condition of our patient (poorly cooperative, with severe hypertension and thrombocytopenia) prevented its performance.

The treatment of AIDS-related TMA resides in HIV infection control: prompt initiation of antiretroviral therapy is the key for clinical success.[1,7,8] However, because HAART takes several weeks to produce an effect on CD4 counts and viraemia, supportive strategies, such as plasma exchange, must be considered and may be important to control the inflammatory response.

The precise role of plasma infusion and/or exchange in HIV-related TMA is still up for debate, because randomized clinical trials lack in this population, given the lower incidence in the post-HAART era. Some reports suggest that plasma therapy (fresh frozen plasma, cryo-depleted plasma, or solvent detergent-treated plasma), as either plasma infusion or exchange, appears to be an effective treatment in HIV-TMA as a result of either removal of a harmful plasma component or the replacement of a deficient component.[6,9] However, its role should not be overemphasized. Indeed, case series of patients with TMA in the pre-HAART era report an exceedingly high mortality, despite plasma exchange. For instance, Gervasoni et al.[2] reported a mortality of 76% for HIV patients with TMA (13 out of 17, died within 90 days of diagnosis); similarly, Bachmeyer et al.[10] reported an 89% mortality (8 out of 9 patients). Several cases of HIV-associated TMA resistant to plasma therapy are reported in the literature, that responded only to the initiation of HAART[11]. In a revision published in the Journal of Clinical Apheresis, Brecher et al.[7], concludes that the treatment of the underlying HIV infection (e.g., with HAART) appears to be the cornerstone of therapy and that plasma exchange, although frequently used in this condition, has not been proven effective. The authors also add that, as most cases have no demonstrable inhibitor, there is little rationale for the use of plasma exchange; in the absence of definitive trials, plasma exchange cannot be considered a standard of care for HIV-TMA.[11]

Our patient presented with classic clinical and laboratorial findings of TMA, which should have alerted us sooner to the diagnosis and encouraged us to initiate plasmapheresis, pending the establishment of a definitive diagnosis. Although controversial, after establishing the diagnosis of HIV-associated TMA, plasmapheresis should have been considered and could have been beneficial, given the severe kidney impairment, the delay between HAART initiation and clinical benefits and the inefficiency of the applied supportive measures in controlling tissue damage and inflammation.

However, the most critical aspect of treatment is the prompt control of HIV replication with HAART. With the advent of HAART, the overall prognosis of HIV patients has dramatically improved, with a significant reduction in progression to AIDS and in various AIDS-associated complications. The long-term prognosis of HIV-TMA depends on the stage of HIV infection: mortality in patients with symptomatic HIV infection (Centre for Disease Control stage IV) is three times higher (39%) than mortality in patients with asymptomatic HIV infection (Center for Disease Control stages II and III, 13%).[6,9] In the vast majority of stage IV patients, life expectancy rarely exceeds one year after the diagnosis, indicating that the poor prognosis of these patients is probably related to severe immunodeficiency.[6,9]

This case highlights the importance of precocious clinical suspicion and treatment initiation in immediate and long-term prognosis of patients presenting with a TMA. Most of the studies regarding HIV-related TMA are clinical reports and systemic reviews from the era before HAART and, therefore, a revision of the epidemiology, treatment and prognosis is mandatory.[9]

LEARNING POINTS

1. Thrombotic microangiopathy should be suspected in a patient with laboratorial evidence of intravascular haemolytic anaemia: low haptoglobin levels, high LDH, schizocytes on peripheral blood smear, high unconjugated bilirubin and thrombocytopenia.

2. HIV infection-related TMA is a rare entity in HAART era. For this reason, before making a diagnosis, one must first exclude the most frequent causes with TMA with kidney involvement, such as thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, systemic vasculitis, connective tissue auto-immune diseases and chronic viral infections.

3. HIV infection-related TMA usually presents in male patients with advanced disease (AIDS), especially when CD4 counts fall below 100/mm3. It usually presents with TMA, acute kidney Injury and recurrent hypertensive emergencies.

4. The mainstay of the treatment is the control of the HIV infection by inhibiting viral replication. Plasma therapy can be an effective adjunctive therapy, especially when there is central nervous system involvement and severe kidney impairment.

5. The overall prognosis of these patients is poor and is directly related with the degree of immunodeficiency. In the vast majority of patients, life expectancy rarely exceeds one year after the diagnosis.

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