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An Unexpected Journey: Thrombotic Thrombocytopenic Purpura Unveiling Hidden HIV Infection

Case reports

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ABSTRACT
According to World Health Organization data from July 2023, human immunodeficiency virus (HIV) remains a global public health issue, having claimed approximately 40 million lives so far, with ongoing transmissions in every country globally. Changes in hematologic parameters, such as anemia or thrombocytopenia, are among the most common complications in people living with HIV/AIDS (PLWHA). These complications arise due to the bone marrow being targeted by the combined effects of HIV infection, inflammatory mediators released in response to the infection, and opportunistic pathogens. HIV-associated thrombotic thrombocytopenic purpura (TTP) is a rare condition that can lead to end-organ ischemia and requires prompt treatment to prevent permanent organ damage.
We present the case of a previously healthy 54-year-old man who presented at the emergency department with profound asthenia and unexplained weight loss of 10 kg over a few weeks. Diagnostic investigations were remarkable for a positive HIV rapid antigen/antibody combination test, severe thrombocytopenia and hemolytic anemia. As HIV-associated TTP was the likely diagnosis, the patient was transferred to the Division of Nephrology for therapeutic plasma exchange (TPE). Monitoring platelet counts and hemoglobin levels in HIV/AIDS patients affected by HIV-associated TTP is essential for assessing disease progression and identifying thrombocytopenia or its related clinical symptoms.

KEYWORDS: HIV-associated thrombotic thrombocytopenic purpura, microangiopathic hemolytic anemia, ADAMTS-13 deficiency, therapeutic plasma exchange, antiretroviral therapy

Introduction

This case report illustrates the diagnosis and treatment of HIV-associated TTP. The prevalence of HIV-associated TTP in HIV-infected individuals has declined in high-income countries, possibly reflecting early initiation of antiretroviral therapy (ART) [1]. By contrast, TTP in low- and middle-income countries remains a significant cause of morbidity and mortality [2]. Since anemia and thrombocytopenia are treatable complications associated with increased mortality among patients suffering from AIDS, clinicians should be aware of these hematologic complications [3].

Case Presentation

A previously healthy 54-year-old man presented to the emergency department of another facility due to profound asthenia developing over weeks, progressive weight loss of approximately 10 kg over the last few weeks and persistent epigastric pain that worsened while eating over the past two months. Before the onset of these symptoms, the patient had no history of epigastric pain or asthenia and did not suffer from any chronic diseases, thus not requiring any medications. He had no known drug allergy.

After emigrating from Algeria, the patient lived alone in a suburban area of Switzerland and worked in the food services industry. He was a non-smoker and did not use alcohol or illicit drugs. On presentation, the ear temperature was 36 °C, pulse 70 beats per minute, blood pressure 118/76 mmHg, and oxygen saturation 99% while breathing ambient air. Physical examination revealed swollen and reddened gums and white lesions of the oral mucosa and tongue consistent with oropharyngeal candidiasis. There was no palpable lymphadenopathy.

Laboratory testing showed severe anemia (hemoglobin 7.6 g/dL), severe thrombocytopenia (platelet count 19 × 10^9/L), leukopenia (WBC 2.5 × 10^9/L), and elevated lactate dehydrogenase (LDH 361 U/L). The peripheral blood smear revealed anisocytosis, poikilocytosis, and schistocytes (approximately 6%), suggesting red blood cell injury from damaged endothelium, as in microangiopathic hemolytic anemia (MAHA). Reticulocyte count was elevated at 120 × 10^9/L, indicating a regenerative anemia. Total bilirubin was elevated at 2.1 mg/dL, with indirect hyperbilirubinemia.

A rapid antigen/antibody combination test for HIV was positive. Confirmatory testing showed HIV-1 infection. Testing for hepatitis B and hepatitis C was negative. Serological testing showed past infections with hepatitis A and Epstein-Barr virus. Screening for CMV revealed positive IgG antibodies with negative IgM antibodies and CMV DNA was undetectable. Serological tests for other common pathogens, including Toxoplasma gondii and Treponema pallidum, were negative.

Contrast-enhanced computed tomography (CT) of the chest and abdomen showed no lymphadenopathy, malignancy, or other abnormalities. Due to persistent epigastric pain, severe anemia, and oropharyngeal candidiasis, an esophagogastroduodenoscopy (EGD) was performed, which showed an ulcerative lesion of the distal esophagus. Given the patient's severe thrombocytopenia, no biopsy of the lesion was performed initially, and daily treatment with pantoprazole was initiated.

The combination of severe thrombocytopenia and MAHA with signs of hemolysis (elevated LDH, low hemoglobin, presence of schistocytes in the peripheral blood smear, elevated reticulocyte count, low haptoglobin, and indirect hyperbilirubinemia), along with the absence of co-infection with hepatitis B or C, acute liver disease, or malignancy, strongly suggested a presumptive diagnosis of HIV-associated TTP.

Given the need for urgent treatment of TTP with daily therapeutic plasma exchange, the patient was transferred to our facility after receiving 3 units of red blood cell transfusions, with the diagnosis of advanced HIV infection with stomatitis and suspected esophageal candidiasis. Antifungal therapy with fluconazole (200 mg daily) and nystatin oral suspension (500,000 units four times daily) was initiated for two weeks.

Extensive laboratory testing at our facility revealed reduced haptoglobin levels (<0.06 g/L).

A direct Coombs test was negative, excluding immune-mediated hemolysis. Testing for ADAMTS-13 activity showed severe deficiency (7% activity), with a negative inhibitor assay (Bethesda test), thus excluding the presence of autoantibodies to ADAMTS-13 and confirming the diagnosis of HIV-associated TTP due to acquired deficiency.

The HIV-1 viral load was 687,000 copies per milliliter, and lymphocyte subset typing showed severe immunodeficiency with only 64 CD4+ T-cells per microliter. The patient met the criteria for advanced HIV infection due to the CD4+ count being less than 200 cells/µL and the presence of an opportunistic infection (oral candidiasis and suspected esophageal candidiasis).

Daily therapeutic plasma exchange was initiated, using plasma volume exchanges with fresh frozen plasma, for five cycles. Immunosuppression with high-dose corticosteroids was started.

Antiretroviral therapy with a single-tablet regimen containing bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) was initiated. Primary *Pneumocystis jirovecii* pneumonia prophylaxis with trimethoprim/sulfamethoxazole (160 mg/800 mg) three times a week was also started.

Following the first sessions of TPE, the patient reported an improvement in his symptoms, and laboratory tests showed improvement in thrombocytopenia and hemolysis markers. Platelet counts began to rise, and LDH levels decreased. After platelet counts improved to above 50 × 10^9/L, a repeat EGD, including a biopsy of the previously encountered ulcerative lesion of the esophagus, was performed. The pathological examination of the biopsy showed erosive inflammation of the mucosa, and immunohistochemical staining for cytomegalovirus was positive, confirming active CMV esophagitis. Antiviral treatment with valganciclovir (900 mg twice daily) was initiated.

The patient's condition improved with therapeutic plasma exchange, antiretroviral therapy, antiviral therapy for CMV, and high-dose corticosteroids.

Daily monitoring of hematologic parameters showed improvement of the anemia (hemoglobin increased to 10 g/dL), thrombocytopenia (platelets increased to 143 × 10^9/L), and LDH levels decreased to 215 U/L after 14 days of hospitalization.

Discussion

TTP is a rare form of thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and ischemic end-organ damage caused by microvascular platelet-rich thrombi. The condition results from a marked deficiency of ADAMTS13, a von Willebrand factor (VWF)-cleaving protease (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13). Under physiological conditions, endothelial cells release ultra-large von Willebrand factor (ULVWF) multimers into the circulation, allowing ADAMTS-13 to cleave ULVWF into smaller multimers that are less adhesive to platelets. In patients with TTP, the absence or severe deficiency of ADAMTS-13, secondary to immune-mediated (95% of cases) or congenital causes (5% of cases), can be determined. Most cases are immune-mediated: the deficiency is caused by acquired autoantibodies against ADAMTS-13 and can be classified as primary or secondary as a

result of systemic disease, such as HIV infection, systemic lupus erythematosus, antiphospholipid syndrome, or acute pancreatitis [4].

Human immunodeficiency virus type 1 (HIV-1) facilitates viral infection in cells expressing CD4 membrane glycoprotein receptors. Following the binding of HIV-1 to CD4 receptors, a cascade of events is triggered, leading to viral replication. HIV primarily targets CD4+ T cells, macrophages, and dendritic cells but can infect CD8+ T cells, B cells, natural killer (NK) cells, hematopoietic progenitor cells, and platelets [5].

Changes in platelet count are caused by multiple factors in patients affected by HIV and may result from peripheral platelet destruction or decreased platelet production. At the onset of infection, peripheral platelet destruction usually occurs due to the interaction between glycoprotein 120, a glycoprotein expressed on the HIV envelope, and platelet glycoprotein IIIa, a transmembrane receptor expressed by activated platelets. This cross-reactivity leads to platelet lysis in the reticuloendothelial system or early apoptosis, resulting in idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura. A decrease in platelet production generally occurs in more advanced stages of AIDS. Since megakaryocytes express CD4 receptors and the co-receptors necessary for infection, after internalizing HIV, immature megakaryocytes decrease the thrombopoietin c-Mpl receptor expression, disrupting maturation by impairing the signal for colony-forming units of megakaryocytes [3].

Chronic viral infections such as HIV, hepatitis, and CMV can cause secondary TTP [6]. Although the exact pathogenesis of HIV-associated TTP is still unclear, endothelial dysfunction and activation of the immune system are presumed to be pivotal for its development. HIV proteins, along with transactivators of transcription (Tat), negative factors (Nef), and membrane glycoproteins, damage endothelial cells, initiating cell dysfunction and apoptosis. Furthermore, biomarkers of inappropriate endothelial cell activation and dysfunction are upregulated in HIV infection, resulting in excessive release and accumulation of von Willebrand factor (VWF), a coagulation factor produced and secreted by the endothelium. This accumulation produces ultra-large VWF (ULVWF) multimers that accumulate further in TTP. These infections may directly activate and damage the endothelium, subsequently releasing ULVWF multimers and initiating the microthromboses seen in TTP [6].

The primary driver of microvascular disease is then to be addressed in the endothelial dysfunction, directly impacted by HIV proteins on endothelial cells. Endothelial dysfunction has emerged as a central mechanism linking HIV infection with chronic inflammation, immune activation, and the development of atherosclerosis. Although HIV does not replicate actively within endothelial cells, its deleterious effects are mediated through both viral proteins and inflammatory factors secreted by infected immune cells. Notably, viral components such as gp120 and Tat are released into the perivascular milieu, while Nef may be transferred directly to endothelial cells. These proteins exert profound effects on endothelial homeostasis, promoting increased permeability, cellular apoptosis, oxidative stress, pro-inflammatory cytokine production, and enhanced expression of adhesion molecules – culminating in widespread endothelial activation and dysfunction [11]. This leads to a relative deficiency of ADAMTS-13, activation of the complement system and platelets, recruitment of leukocytes, and, ultimately, the formation of microthrombi [7].

Louwa S. et al. demonstrated that inflammation, endothelial dysfunction, and complement activation contribute to the pathogenesis of HIV-TTP. They observed significantly elevated levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), indicating a strong inflammatory response. Endothelial dysfunction was evident through increased soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1). Complement activation was suggested by decreased C3 and C4 levels and elevated complement factor H (CFH),

which may reflect compensatory anti-inflammatory mechanisms. The levels of ADAMTS-13 were consistently markedly reduced, with all patients having detectable ADAMTS-13 autoantibodies, though their clinical relevance remains uncertain. As ADAMTS-13 activity has been variably reduced in previous studies, it is unclear whether its deficiency is the primary cause of HIV-TTP or a result of acute consumption. These findings suggest that HIV-TTP shares features with a TTP-like syndrome driven by immune dysregulation, where complement activation and endothelial dysfunction may play pivotal roles, potentially requiring an additional insult for clinical manifestation. In contrast, in this case report, no ADAMTS-13 autoantibodies were detectable, highlighting the heterogeneity of HIV-TTP and the need for further investigation into its pathophysiology [8].

Early guidelines for diagnosing congenital or immune-mediated TTP established a pentad of clinical criteria consisting of fever, hemolytic anemia, cutaneous purpura or other bleeding due to thrombocytopenia, impaired mental status, and renal dysfunction [9]. Currently, the classic pentad appears in fewer than 10% of cases. The most common clinical findings are severe thrombocytopenia (<30 × 10^9/L) and microangiopathic hemolytic anemia (with schistocytes seen on the blood smear), both associated with their relative symptoms such as cutaneous and mucosal bleeding, weakness, and dyspnea, as described in this clinical case [10].

TTP is a diagnosis of exclusion, and it is crucial to rule out other possible thrombotic microangiopathies (TMA), most importantly disseminated intravascular coagulation (DIC), as the distinction can be difficult due to overlapping clinical symptoms and laboratory results. In this patient, laboratory findings showed elevated D-dimer (1.78 mg/L) with no significant changes in fibrinogen (3.7 g/L), activated partial thromboplastin time (aPTT 26 seconds), or international normalized ratio (INR 1.0). Therefore, DIC was less likely, given that the fibrinogen and aPTT values were normal.

The treatment of HIV-associated TTP relies on two key components: managing TTP through TPE and addressing the HIV infection with antiretroviral therapy. Therapeutic plasma exchange aims to remove and dilute ULVWF multimers, autoantibodies, and inflammatory cytokines while supplementing ADAMTS-13. To guide plasma therapy, therapeutic monitoring should include monitoring complete and differential blood cell counts, lactate dehydrogenase levels, and electrolytes such as calcium, magnesium, and phosphate to exclude metabolic abnormalities associated with plasma therapy and citrate anticoagulation (if used). Therapeutic targets include a persistent downward trend of LDH levels (ideally <450 U/L) and the normalization of platelet count, which should be sustained above 150 × 10^9/L for at least two days [6]. Given that HIV can cause thrombocytopenia through various mechanisms other than HIV-associated TTP, achieving a normal platelet count in HIV-infected patients may be challenging. Therefore, LDH levels may be a more appropriate target for monitoring treatment efficacy.

The role of additional treatments in managing HIV-associated TTP remains uncertain. Immunosuppressive therapies, such as corticosteroids, are utilized to mitigate inflammation-associated endothelitis. Corticosteroids are commonly used for their efficacy in treating inflammation and autoimmune conditions. They target various stages of the inflammatory process, making them valuable for reducing inflammation in these cases [7].

Among the various treatment options, we considered caplacizumab, which is a nanobody that inhibits the interaction between ULVWF multimers, explicitly targeting the A1 domain of VWF and the glycoprotein Ib receptor on platelets. The inhibition of VWF-platelet interaction by caplacizumab leads to a rapid reduction in platelet adhesion and aggregation, lowering the risk of thrombotic events. This action is particularly beneficial in patients with TTP, where rapid intervention is crucial to prevent organ damage due to microvascular thrombosis. However, although caplacizumab is

approved for the treatment of TTP in both acquired and congenital forms of the disease, no large-scale studies have explored its effectiveness specifically in HIV-associated TTP [9]. Additionally, the limitations of the use of caplacizumab include high costs and the risk of minor bleeding events. Due to the known erosive lesion of the esophagus at risk for bleeding events and the rapid improvement in the patient's clinical state and thrombocytopenia in this case, no adjunctive therapy with caplacizumab was initiated.

Managing clinical remission, defined as a sustained clinical response longer than 30 days after the final plasma exchange, presents a significant challenge due to the unpredictable nature of relapse, often manifesting one or two years following the initial episode. To mitigate this risk, Rituximab, an anti-CD20 monoclonal antibody, is prescribed in patients with low ADAMTS-13 activity. However, instances of relapse have been reported as late as 20 years post-initial episode, necessitating careful consideration of treatment implications. These include potential adverse effects such as infusion reactions (including severe cases resulting in death), reactivation of hepatitis B, pulmonary fibrosis, and progressive multifocal leukoencephalopathy [10].

In this patient, given the absence of inhibitors to ADAMTS-13 and the improvement in ADAMTS-13 activity during follow-up (from 7% to 75%), rituximab was not initiated.

Monitoring of ADAMTS-13 activity during treatment and follow-up is essential. In this patient, ADAMTS-13 activity improved significantly after treatment, correlating with the clinical response. Regular monitoring can help in early detection of potential relapses and guide the need for additional therapies.

Prognosis in HIV-associated TTP depends on prompt diagnosis and initiation of therapy. With timely treatment, the mortality rate has significantly decreased. Long-term management includes continued antiretroviral therapy to maintain viral suppression and immune reconstitution, which may reduce the risk of TTP relapse. Regular follow-up with hematologic assessments is necessary to monitor for potential relapses.

Conclusion

This case highlights the importance of considering HIV-associated TTP in patients presenting with severe thrombocytopenia and microangiopathic hemolytic anemia, especially in the context of a new HIV diagnosis. Prompt recognition and treatment with therapeutic plasma exchange, corticosteroids, and initiation of antiretroviral therapy are crucial for improving patient outcomes. Monitoring of ADAMTS-13 activity and hematologic parameters during treatment and follow-up is essential for assessing response and preventing relapses. Clinicians should remain vigilant for opportunistic infections that may trigger TTP and manage them appropriately. This case underscores the need for a multidisciplinary approach in the management of complex cases involving HIV and hematologic complications.

Follow-Up

The patient's condition improved after five cycles of TPE and treatment with glucocorticoids. After discharge from the hospital, the patient underwent an ophthalmologic evaluation, which ruled out complications due to cytomegalovirus or other opportunistic infections.

During the hematologic follow-up visit one month after discharge from the hospital, the patient regained his usual weight of 72 kg and reported no more epigastric pain. Laboratory testing showed hemoglobin levels 116 g/L, platelets 127 × 10^9/L, and leukocytes 6.8 × 10^9/L, allowing for a faster

tapering of the glucocorticoid treatment. Additionally, ADAMTS-13 activity improved significantly, showing 75% activity.

The patient remained clinically stable at subsequent follow-up visits, with sustained viral suppression on antiretroviral therapy and improving CD4+ counts. Regular monitoring for potential relapse of TTP was planned, including periodic assessment of ADAMTS-13 activity and hematologic parameters.

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