Severe Thrombocytopenia Associated with HIV-1 Infection: Sustained Response to Zidovudine-Based cART

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Introduction

Thrombocytopenia in association with human immunodeficiency virus (HIV) infection was described in the medical literature even before the term HIV was coined.[1] The authors linked thrombocytopenia to disorders of immune regulation in young men who had sex with men. Thrombocytopenia can be found at any stage during the course of illness with its prevalence ranging from 10-30% for mild thrombocytopenia (< 1.50 x 10^9/L), to 1.5-9% for severe thrombocytopenia (< 50 x 10^9/L).[2,3]

The mechanism producing thrombocytopenia in HIV infection is multifactorial with evidence implicating both the direct and indirect role played by HIV in decreasing platelet turnover and immune-mediated peripheral destruction of platelets. How HIV alters the internal milieu of the bone marrow resulting in ineffective thrombopoiesis is still a mystery. In-vitro studies of megakaryocytes show quantitative and qualitative abnormalities in patients with HIV infection,[4,5] while the peripheral destruction has been attributed to molecular mimicry of immunodominant epitopes of these mutating strains.[6]

The past decade has transformed our understanding of HIV and acquired immune deficiency syndrome (AIDS) and offered a better perspective into its natural history. With the introduction of aggressive combination antiretroviral therapy (cART or highly active antiretroviral therapy, HAART) and continued research towards better therapeutic options, survival in individuals with this once dreaded infection has increased considerably. We report a case of HIV-associated thrombocytopenia who presented with severe bleeding despite being on cART for a considerable period of time.

Case Report

A 35-year-old female presented to the emergency department with complains of menorrhagia, bleeding from the gums, and bruises of three weeks duration over her lower extremities. She was diagnosed with HIV-1 infection four years prior and had been on cART (stavudine, lamivudine, nevirapine) since diagnosis. Her complete hemogram revealed a reduced platelet count of 8 x 10^9/L. She was transfused with platelet concentrate and was admitted for further management.

Her detailed medical history was unremarkable except for a viral flu-like, febrile illness four years prior, during which she was diagnosed with HIV-1. The possibility of horizontal transmission was deduced, since her husband indulged in high-risk behavior and was infected with the same strain. Physical examinations revealed

multiple petechial and purpuric lesions, varying in size between 0.2 to 0.8 cm, localized predominantly to the extensor compartment of the lower limbs bilaterally, extending up to the knees with a few discrete patches over the abdomen. She was asymptomatic with respect to HIV infection and any related opportunistic infection.

Baseline renal and liver functions tests were normal. Her coagulation profile was unremarkable except for prolonged bleeding time (8 min; 32 sec). HbSAg titres and anti-HCV antibody titres were negative. Bone marrow examination revealed megakaryocytic thrombocytopenia. Her absolute CD4 count was 356/mcl and viral load was 10,200 copies/ml.

The patient was started on oral prednisolone 60 mg/day after explaining the potential risks, since the option of intravenous immunoglobulin was declined due to monetary constraints. Additional units of platelet concentrate were transfused until the second day post-admission and were abandoned when active bleeding stopped. Simultaneously, her cART regimen was revamped and she was started on zidovudine, lamivudine, and indinavir. Her platelet count improved in the following days with no evidence of any further bleeding. By the fifth day post-admission, the platelet count was 8 x 10^9/L and she was discharged on the seventh day with a platelet count of greater than 10 x 10^9/L.

The patient was followed weekly with an intention to titrate the dose of prednisolone appropriately. By the end of week 6, she maintained a platelet count of greater than 20 x 10^9/L on 10 mg prednisolone every other day. Her viral load decreased to less than 200 copies/ml and prednisolone was stopped. She maintained complete remission throughout the course of a 6-month follow-up period with platelet counts of greater than 20 x 10^9/L and HIV-RNA copies suppressed to less than 200/ml.

Discussion

The mainstay in the treatment of HIV-associated thrombocytopenia is combination antiretroviral therapy (cART).[7] Life-threatening bleeding is treated with a short course of anti-RhD or intravenous immunoglobulin. Rapid response with dramatic increases in platelet counts is seen albeit short-lived, necessitating repeat administration of these agents to maintain platelet counts in the near normal range.[8,9] Corticosteroids have been tried as a cost-effective modality, but its inability to sustain remission after tapering and the risk of opportunistic infections on continuous use have precluded its widespread use.

Thrombocytopenia of less than 10 x 10^9/L is uncommon in HIV infection, especially in the setting of aggressive treatment with cART. Our patient, who received cART at the outset, had a benign clinical course with suppression of plasma viremia to undetectable levels. The striking feature of this acute presentation was the simultaneous increase in plasma viremia which coincided with severe reduction in platelet count, implying thrombocytopenia may be primarily a manifestation of the active driving force behind this disease-viral replication. Interrupting cART is known to increase the risk of thrombocytopenia.[10] Factors contributing to the decline in platelets after interrupting antiretroviral therapy may include activation of coagulation pathways or HIV-1 replication. However, this possibility was ruled out in our patient since she had regular follow-up and strictly adhered to her treatment regimen. Whether this sudden burst in replication is an early manifestation of drug resistance is debatable.

The observed response seen after initiation of corticosteroid therapy confirms that anti-HIV antibodies played a role in destruction of platelets similar to the mechanism seen in settings of autoimmune

thrombocytopenic purpura.[11] The sustained response manifested as elevated platelet counts for a prolonged period even after the withdrawal of steroids confirms the multi-factorial etiology of HIV-associated thrombocytopenia and implies a role for active viral replication as the etiology of low platelets.

In severe thrombocytopenia, elevated platelet counts are well documented in treatment-naïve as well as ART-experienced individuals after the introduction of cART. Studies have confirmed the efficacy of cART in this regard.[7,12] For decades, zidovudine has been an integral component of cART in severe thrombocytopenia, with its efficacy attributed to suppression of viral load, thereby attenuating the infection of megakaryocytes. Its ability to increase platelet production is thought to play an important role.[13-15]

Plasma viremia in our patient, after the introduction of zidovudine and protease inhibitor to the cART regimen, was suppressed and undetectable after six weeks. Corticosteroids were withdrawn by the end of six weeks. The favorable response beyond six weeks is attributed to the clinical efficacy of modified cART. Although the exact mechanism of action cannot be elucidated, suppression of plasma viremia quantified by serial measurements and corresponding clinical outcome suggest that efficacy of cART in reducing the viral load played an important role.

In an era where our understanding of HIV infection has gone beyond the molecular levels, thrombocytopenia associated with HIV remains elusive. Ongoing research in this field might help understand this condition better. Until concrete evidence is available, it is wise to implement zidovudine-based cART in patients with mild to moderate thrombocytopenia and reserve corticosteroids for life threatening bleeding not responding to intravenous immunoglobulin therapy.

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