Thrombocytopenia in Pediatric HIV/AIDS

Suresh Kumar Angurana, Renu Suthar Angurana

From the beginning of the AIDS epidemic, thrombocytopenia has been recognized as one of the main manifestations of the disease (1, 2). Thrombocytopenia in HIV was first described in 1982. Before the introduction of highly active antiretroviral therapy (HAART), the prevalence of thrombocytopenia was reported to be in range between approximately 10% to over 30% (3, 4). However, in the era of HAART, the epidemiology of thrombocytopenia, including frequency, severity, and duration, has not been well characterized especially in pediatric patients.

Thrombocytopenia represents a clinically important outcome among HIV patients for a number of reasons. First, thrombocytopenia is associated with an increase in the risk of serious bleeding, although few fatal bleeding events have been reported (5-7). Second, thrombocytopenia occurs early in HIV disease and is one of the first manifestations of advancing disease (4, 7). Additionally, thrombocytopenia has been linked to decreased survival and other complications of HIV disease, including HIV-dementia (3, 8, 9). Furthermore, treatment of thrombocytopenia may affect treatment of other common conditions in HIV, such as hepatitis C virus (HCV) infection (6, 10). It has been shown that thrombocytopenia is associated with increased morbidity and mortality, accelerated deterioration in CD4 counts and accelerated progression to full-blown AIDS. Thrombocytopenia in HIV can at times be a very challenging illness to treat due to its multifactorial aetiology. One should be aware of all these possibilities so that the necessary investigations are done initially to reach at correct diagnosis.

Although the exact pathogenic mechanism of thrombocytopenia in HIV infections is ill defined, it appears to be multifaceted and heterogenous. Thrombocytopenia in HIV are result of: Increased immune-mediated peripheral destruction of platelets, similar to what seen in classical ITP; impaired platelet production by HIV infected megakaryocytes of bone marrow; as a result of secondary phenomenon in HIV-positive patients, due to hypersplenism, bone marrow infiltration from infections or lymphoma, or myelosuppressive effects of medications (4, 11); increased incidence of diseases such as hepatitis B and C in the HIV-infected patients that can severely hamper thrombopoietin production due to liver damage (10).

The gp120 antibodies directed towards HIV cross-react with the gp IIIa receptor on the platelet. Platelet life span is decreased in HIV-induced idiopathic thrombocytopenic purpura (ITP) and even in HIV patients without ITP. HIV enters the megakaryocytes and platelets via the CXCR4 receptors (12). Once the virus is in the megakaryocyte it starts to cause changes in megakaryocyte morphology and decreased platelet production. The common signs of HIV infection in the bone marrow include: dysplasia in the bone marrow, naked nuclei or bare nuclei, apoptotic megakaryocytes, hypolobation of the nuclei, tendency to form discrete separate nuclear lobules, and clustering of the megakaryocytes. Thus, direct HIV infection of the megakaryocyte lead to apoptosis, dysmegakaryopoiesis, abnormal and dysfunctional production of megakaryocytes and platelets (12).

The occurrence of thrombocytopenia in early and late infection has been proposed to be the result of two separate mechanisms (13, 14). In early phases of infection, thrombocytopenia is thought to be due to immune-mediated platelet destruction and splenic platelet sequestration (7). In AIDS (advanced stages), the predominant mechanism is thought to be decreased platelet production due to direct infection of megakaryocytes in bone marrow by HIV (13, 15). This direct interaction with HIV may explain the observation that severe thrombocytopenia is more common among patients with high viral loads (16). Additionally, autoantibodies may play a prominent role in mucosally infected patients, whereas, immune complexes are more important in parenterally acquired disease (16, 17). The presence of anti-IgG containing immune complexes on the platelet surface may explain many of the immunologic
features of this form of thrombocytopenia (17). The degree of HIV-related thrombocytopenia is generally mild to moderate; however, severe reduction with platelet counts <10,000/µl has been described (14). The incidence of platelet abnormalities appears to increase with progressive immunosuppression. Thrombocytopenia may be the initial manifestation of HIV infection in as many as 10 percent of patients. Therefore, HIV testing is important in the assessment of any patient with newly diagnosed thrombocytopenia.

There are limited studies available in pediatric population regarding frequency, severity, and duration of HIV-related thrombocytopenia. Initial study by Ellaurie et al (18) found that thrombocytopenia occurs in 13% of children with symptomatic HIV infection. They described clinical and laboratory course of 19 children infected with HIV with thrombocytopenia. Levels of antiplatelet antibodies were increased in 80% of the children and circulating immune complexes were found in 74%. Spontaneous remission of thrombocytopenia occurred in three of the 19 subjects. They concluded that thrombocytopenia in children with HIV disease is due to immune mechanisms and is a major cause of morbidity and mortality, high-dose IV gamma-globulin and/or corticosteroids were temporarily effective in increasing the platelet count and reducing bleeding in about half of thrombocytopenic patients; the ability to respond to therapy correlates with improved survival (18).

Recently, Kumar et al (19) studied the clinical profile of HIV associated thrombocytopenia, co-relation between thrombocytopenia and immune status and the effect of the anti-retroviral therapy (ART) on platelet count in pediatric population. Thirty four children (19.6%) out of 173 had thrombocytopenia. The platelet counts ranged between 4000 to 140000/µl. No specific co-relation could be made out between CD4 count and platelet count. The mortality was higher in thrombocytopenic children on ART as compared to children on ART with normal platelet count. Amongst the live children, the platelet counts normalized within 3 months of ART. Thrombocytopenia in HIV infected may be an incidental finding in some children. Thrombocytopenia was found to be a poor prognostic factor and no specific co-relation to immune status was seen (19). Severe thrombocytopenia (platelets <50 000/µl) was most common among patients in the 'symptomatic, not AIDS' category of HIV disease. Among antiretroviral naive patients, the majority of patients with severe thrombocytopenia had CD4 counts <200/µl (14). This was consistent with the observation that thrombocytopenia occurs in early phases of infection, and may thus affect HIV patients before beginning HAART (4, 7, 15). Among patients on treatment who developed severe thrombocytopenia, the majority had CD4 counts <200/µl. However, among all patients with severe thrombocytopenia, approximately 70% had viral load of >30,000 copies/ml (14). Hence, HAART, by lowering viral load, should also mitigate thrombocytopenia. In the pre-HAART era, use of Zidovudine was reported to improve platelet counts among HIV patients (20). Recently, many studies have reported improvements in platelet count with HAART (21, 22). However, other studies have not shown a similar effect. In a study by Miguez and colleagues (23), thrombocytopenia was found to persist in 70% of cases despite receiving HAART. A case-control study by Burbano and colleagues (24) reported that 30-40% of patients with thrombocytopenia experienced partial or no resolution of thrombocytopenia even after treatment with combination therapy. They found a strong association between HCV co-infection and thrombocytopenia, likely explains why thrombocytopenia did not resolve with effective HIV treatment in some patients. The thrombocytopenia related to HCV has been attributed to cirrhosis and portal hypertension causing splenic sequestration of platelets, although other factors may also contribute. Advanced liver disease results in reduced liver production of thrombopoietin (6). This mechanism may not be responsible in pediatric patients.

The most important biomarkers of disease stage and progression in patients with HIV infection are the CD4 count and HIV RNA concentration (25, 26). However, there are other factors that can influence or predict the prognosis (27). Hematological abnormalities, such as anemia, neutropenia, and thrombocytopenia, are commonly observed in patients infected with HIV (25). For this reason the total lymphocyte count, white blood cell count, platelet count, and hemoglobin concentration have been proposed as alternative markers of the disease, especially for developing countries where financial resources are limited (28). Nevertheless, the majority of these markers have not been adopted into routine practice because of their supposedly poor correlation with disease progression (25).

Thrombocytopenia is an important manifestation of HIV/AIDS, predominant mechanisms being immune mediated platelet destruction in early stages and decreased platelet production in late stages of the disease.
Thrombocytopenia is a poor prognostic factor with no specific correlation to immune status. Therefore, HIV testing is important in the assessment of any patient with newly diagnosed thrombocytopenia so as to diagnose these patients earlier rather than missing the diagnosis when they present with thrombocytopenia. So it is up to astute pediatricians to suspect and screen for HIV infections in children with thrombocytopenia, even if other clinical manifestations of HIV/AIDS are absent.

References