Viral-Associated Immune Thrombocytopenic Purpura

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Chronic immune thrombocytopenic purpura (CITP) is a diagnosis of exclusion that occurs either de novo or secondary to other underlying disorders. Chronic infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are now well-characterized causes of CITP. Between 6% and 15% of patients infected with HIV may develop thrombocytopenia. Patients with CITP with risk factors for HIV infection should be screened for the virus. Treatment of HIV-related CITP should be directed toward antiviral therapy with highly active antiretroviral therapy (HAART) regimens. Hepatitis C viral infection can also be associated with chronic thrombocytopenia, even in the absence of overt liver disease. While HCV-related thrombocytopenia is typically less severe than primary CITP, affected patients are at greater risk of major bleeding. Sustained suppression of HCV virus with interferon-ribavirin therapy can improve platelet counts. Screening for HCV infection should be considered in patients with ITP with risk factors for infection, from regions with high rates of infection or in patients with unexplained mild elevations of liver enzymes.

Chronic immune thrombocytopenic purpura (CITP) is characterized by accelerated platelet destruction and variably impaired platelet production resulting in thrombocytopenia. CITP has been classified either as a primary autoimmune disorder (idiopathic thrombocytopenic purpura) or as secondary to a number of underlying disorders. Common conditions associated with secondary CITP include lymphoproliferative disorders and other autoimmune collagen vascular diseases. CITP is also associated with certain chronic infections. While the association between human immunodeficiency virus (HIV) infection and immune thrombocytopenia has been well known for over 20 years, recent studies have suggested that infection with Helicobacter pylori or hepatitis C virus (HCV) may be an even more frequent cause of chronic thrombocytopenia.

The relationship between these chronic infections and the development of immune-mediated thrombocytopenia represents a largely unexplored paradigm in which the host response to an infectious agent results in a loss of immune self-regulation. The pathophysiology of infection-related ITP involves diverse immunologic pathways as well as non-immune mechanisms that accelerate platelet destruction and/or decrease platelet production. A diagnosis of CITP associated with these chronic infections must include consideration of other potential causes of thrombocytopenia. For example, thrombocytopenia with HCV infection can also result from the hepatic cirrhosis leading to portal hypertension with splenic platelet sequestration and/or decreased hepatic production of thrombopoietin. However, the relationship between the infectious agent itself and the development of thrombocytopenia is clearly demonstrated by the improvements in platelet counts that follows successful treatment of the underlying infection. Therefore, the diagnostic and therapeutic algorithm for managing infection-related ITP can differ significantly from that of primary, i.e., idiopathic, thrombocytopenic purpura.

Human Immunodeficiency Virus

Background

An association between the acquired immunodeficiency syndrome (AIDS) and CITP was described before the human immunodeficiency virus (HIV) had been isolated and characterized. HIV infects CD4 thymic lymphocytes, monocytes, macrophages and megakaryocytes. Although a number of different mechanisms have been reported by which HIV infection can produce thrombocytopenia, the ability of effective antiretroviral therapy to improve platelet counts demonstrates the relationship between viral replication and expression of viral-related proteins and the host response to platelets.

Epidemiology

Thrombocytopenia was first associated with the acquired immune deficiency syndrome before the discovery of the HIV. Prior to the use of highly active antiretroviral therapy (HAART), HIV-associated thrombocytopenia (HIV-CITP, platelet count < 150 × 10^9/L) was identified in approximately 5% to 30% of patients infected with HIV-1. Thrombocytopenia is more prevalent in patients with advanced HIV infection defined as a CD4-lymphocyte count of < 200/μL, clinical AIDS, and among intravenous drug abus-
In the Multicenter AIDS Cohort Study of 1611 HIV-seropositive homosexual and bisexual men a platelet count of < 150 × 10^9/L was reported in 6.7% of HIV-seropositive men.\(^2,3\) The incidence of thrombocytopenia was only 2.8% in men with CD4 lymphocyte counts greater than 700/μL, but rose to 10.8% in those with CD4 lymphocyte counts of less than 200/μL.\(^2\) A review of 1004 patients who were HIV antibody positive seen in two HIV/AIDS clinics identified platelet counts of < 150 × 10^9/L on at least one determination in 110 (11%) patients, 42 (4.2%) patients had platelet counts of < 100 × 10^9/L and 15 (1.5%) had a platelet count of < 50 × 10^9/L.\(^3\) Thrombocytopenia was more prevalent in patients with a clinical diagnosis of AIDS (21.2%) and a CD4 lymphocyte count of less than 200/μL (20%).\(^3\)

A review of the medical records of 36,515 patients infected with HIV who were participants in the Multistate Adult and Adolescent Spectrum of Disease Project reported a 1-year incidence of thrombocytopenia of 3.7%, defined as a platelet count of less than 50 × 10^9/L.\(^3\) The incidence and severity of thrombocytopenia was associated with the stage of disease with an incidence of 1.7% among patients with HIV infection, but not clinical or immunologic AIDS, 3.1% among persons with immunologic AIDS (CD4 lymphocytes < 200/μL) and 8.7% in patients with clinical AIDS.\(^3\) By logistic regression analysis, clinical AIDS, CD4 lymphocyte count of < 200/μL, age > 45 years, intravenous drug use, lymphoma and/or anemia was associated with a platelet count < 50 × 10^9/L.\(^4\)

An increased incidence and severity of thrombocytopenia in HIV-infected intravenous drug users compared to HIV-infected homosexuals has been reported.\(^4,5\) Mientjes et al\(^5\) reported a platelet count of < 150 × 10^9/L in 29 of 182 (15.9%) homosexual HIV-infected men compared with 38 of 181 (21%) HIV-infected intravenous drug users. None of the homosexual men had a platelet count of < 50 × 10^9/L, while 6 (3.3%) of intravenous drug users had a count of < 50 × 10^9/L.\(^5\) These differences may be explained, in part, by the higher incidence of co-infection with hepatitis C and underlying liver disease in HIV-infected intravenous drug users.\(^6\)

In a prospective multicenter cohort study of 738 HIV-infected hemophilia patients, the incidence over time of HIV-related conditions was determined in 130 children and 193 adults.\(^7\) The 10-year cumulative incidence of thrombocytopenia (platelets < 100 × 10^9/L) after seroconversion was 43% ± 7% in adults and 27% ± 6% in children.\(^7\) The mean CD4 counts were significantly higher in children (514 ± 61 cells/μL) than adults (260 ± 24 cells/μL) with thrombocytopenia (P = .0004).\(^7\)

Most data have been obtained prior to the widespread use of HAART in patients with early HIV-infection. There are few data on the current prevalence of thrombocytopenia in patients under active antiviral treatment. However, recent prospective data from the Women’s Interagency HIV study has documented a reduction in the incidence of anemia and neutropenia in HIV-infected women on HAART therapy.\(^8,9\) This is in accord with the impression that there has been a similar reduction in the incidence of thrombocytopenia, especially platelet counts < 50 × 10^9/L in compliant patients.

**Pathophysiology**

Multiple mechanisms may contribute to the development of CITP in the HIV-infected patient and these have recently been reviewed.\(^10\) Proposed mechanisms include accelerated platelet clearance due to immune complex disease,\(^10,12\) and antiplatelet glycoprotein antibodies\(^13,14\) and/or anti-HIV antibodies that crossreact with platelet membrane glycoproteins (antigenic mimicry).\(^15,16\) The ability of the HIV-1 to rapidly mutate may facilitate both its ability to escape immune surveillance and to mimic host antigens. Direct infection of megakaryocytes results in defective platelet production and megakaryocytic apoptosis.\(^17,18\) In this regards it is surprising that only a small percentage of patients infected with HIV develop clinically significant thrombocytopenia.

Epidemiologic studies suggest that the pathogenesis of thrombocytopenia is partially dependent on disease burden. HIV-associated thrombocytopenia developing early after infection more often resembles classical ITP in which thrombocytopenia is mediated primarily by peripheral destruction, whereas thrombocytopenia in patients with immunologic AIDS (CD4 lymphocytes < 200/μL) is attributable predominately to decreased platelet production and ineffective hematopoiesis.\(^19,20\) While platelet counts may improve with antiretroviral therapy in both patient populations, patients with advanced disease are less likely to respond to classic primary CITP therapy such as splenectomy, corticosteroids, intravenous immunoglobulin or anti-RhD.\(^19,20\)

Initial studies of HIV-CITP suggested an immune complex mechanism was responsible for the thrombocytopenia, wherein platelets were cleared from the circulation as “innocent bystanders.”\(^10,12,13\) More recent studies have shown that these immune complexes contain antibodies that crossreact with both HIV and platelet glycoproteins.\(^10,14,16\) These antibodies also crossreacted with sequences on HIV nef, gag, env and pol proteins.\(^10,14,16\) Similar crossreactivity between HIV viral proteins and platelet glycoproteins has been reported.\(^15\) In the studies of Bettlaieb and co-workers immunoglobulin in platelet eluates bound to epitopes common to platelet GPIIb and HIV GP160.\(^15\)

Studies of platelet kinetics have demonstrated that HIV-CITP is frequently associated with decreased platelet production.\(^16,17\) Megakaryocytes express the CD4 receptor and co-receptors necessary for HIV infection. Cytopathic infection of HIV of the megakaryocyte has been demonstrated and is the postulated primary mechanism for impaired platelet poiesis.\(^10,18\)
Clinical manifestations

HIV-seropositive patients can develop thrombocytopenia several years before the development of overt AIDS, and the early disease is clinically indistinguishable from classical ITP. However, the clinical picture of HIV-CITP is often mild, with only a minority of patients having platelet counts of less than 50 × 10^9/L. Major bleeding is rare and only a few cases of fatal hemorrhage have been reported. There has been greater variability in patients with hemophilia A. For example, Finazzi and co-workers documented thrombocytopenia (platelets <100 × 10^9/L) in 14 of 124 (11%) hemophiliacs, only one of whom had a major hemorrhage. In contrast, Ragni and colleagues reported a platelet count of < 100 × 10^9/L in 30/87 (34.5%) hemophiliac patients, with 11 (13%) having a platelet count < 50 × 10^9/L. Nine of the 11 patients (82%) had major bleeding complications and 3 suffered fatal hemorrhage.

Severe thrombocytopenia in patients with advanced HIV infection is frequently associated with additional cytopenias. In a study of 52 HIV-infected intravenous drug users with thrombocytopenia, 4 patients (8%) with advanced HIV infection had a hypocellular bone marrow examination and pancytopenia. HIV-infected drug users were also more likely to have antibodies to both hepatitis B and C and to have abnormal liver function studies. The role of immune-mediated platelet destruction versus bone marrow failure in patients with advanced HIV disease is still uncertain.

Treatment

HIV-CITP is generally responsive to therapeutic interventions used in classical ITP. Therapy with prednisone produces a major hematologic response (platelet count > 100 × 10^9/L) in over half of all patients, although only a minority will maintain platelets > 50 × 10^9/L after cessation of steroids. Notwithstanding, initial anxiety regarding the use of corticosteroids in HIV-infected, immune-suppressed patients, no deleterious effect of short-term treatment with prednisone has become evident. However, long-term treatment with corticosteroids should still be avoided and other co-infections such as tuberculosis, cytomegalic virus or hepatitis C should be excluded before initiating treatment with corticosteroids. Intravenous immunoglobulin (IVIg) and anti-RhD are equally effective in increasing platelet counts acutely in severely affected patients, but a crossover study clearly demonstrated a longer duration of response with the latter agent.

Splenectomy has proven to be safe and effective in refractory patients with HIV-TP. After splenectomy, there is a transient increase in the peripheral blood CD4 lymphocyte count, which reflects redistribution from the splenic pool into the circulation rather than an improvement in the patient’s immunologic status.

HIV-related hematologic cytopenias have been shown to correlate with plasma viral load. Effective anti-retroviral therapies have resulted in improvement in several HIV-related cytopenias, including HIV-CITP. Zidovudine monotherapy increased platelet counts in 60% to 70% of patients with HIV-CITP. While other antiretroviral drugs have been shown to improve hematologic parameters in patients with advanced HIV infection, their efficacy as monotherapy for the management of HIV-CITP is less well documented. Use of HAART in both de novo and zidovudine-refractory HIV-CITP has induced sustained platelet responses in association with effective viral suppression.

Responses to zidovudine and HAART may be more limited in HIV-infected intravenous drug users, possibly reflecting the impact of associated liver disease and infection with HCV. In a prospective placebo-controlled, double-blind, randomized trial, 12 of 14 zidovudine-refractory HIV-infected intravenous drug users with elevated serum alanine aminotransferase suggestive of underlying liver disease who were treated with interferon-alpha (IFN-α) had a statistically significant increase in their platelet counts by week 4 of therapy. Similar responses to IFN-α therapy alone have been reported in HIV-seronegative patients infected with HCV. An unblended open label trial of IFN-α in a cohort of predominately homosexual men documented responses in 9 of 16 patients, with responses occurring as early as 2 weeks after the initiation of treatment. Such rapid responses preclude the possibility that improvement in the platelet count is due solely to suppression of concomitant HCV infection. There are no reported studies on the association of Helicobacter pylori infection and thrombocytopenia in patients infected with HIV.

HCV Infection

Background

Hepatitis C (HCV) is the most common blood borne chronic viral infection in the United States. The 3rd National Health and Nutrition Examination Survey (NHANES III) estimated that nearly 3.2 million persons in the general population of the United States are infected with HCV. Worldwide, an estimated 145 million individuals (2.2% of the world’s population) are infected. A significant proportion of HCV-infected individuals are unaware of their illness and, therefore, many only present to their physicians when they develop overt symptoms. In addition to cirrhotic liver disease, HCV is associated with the development of a variety of immune diseases and lymphoma.
Epidemiology

Six cross-sectional studies have reported serologic evidence of HCV infection in 159 of 799 (20%) patients with a clinical diagnosis of CITP (Table 1). In the largest series published to date, HCV antibodies were identified in 76 (30%) of 250 patients fulfilling the ASH guideline criteria for CITP.37 There were significant differences in demographic characteristics of patients with HCV-positive compared with HCV-negative CITP. Patients positive for HCV were older (54.9 ± 8 years vs 40.3 ± 8 years, P < .001), and the incidence was distributed equally between sexes compared with the female predominance in HCV-negative CITP.

Pockros et al retrospectively identified 7 ITP cases among 3440 new HCV patients seen over a 56-month period. They estimated that the prevalence of CITP among their HCV patients was much greater than would be expected by chance (P < .00001).41 Even in the presence of active liver disease, patients with HCV infection present with lower platelet counts when compared with patients with hepatitis B (HBV) or alcoholic liver disease.31,42 Nagamine et al found a platelet count of < 150 × 10^9/L in 151 of 368 patients (41.0%) with chronic HCV infection compared with 3 of 17 patients with chronic HBV infection.43 The prevalence of HCV-positive CITP patients in the cohort studies may be indirectly related to the background prevalence HCV reported in the general populations studied.30,31,38

Pathophysiology

A variety of pathogenic mechanisms have been implicated in CITP related to chronic HCV infection. The binding to and possible infection of platelets and megakaryocytes by HCV has been reported. High affinity binding of HCV to platelet membrane with subsequent binding of anti-HCV antibody might lead to phagocytosis of platelets through an “innocent bystander” mechanism.43 Nonimmune mechanisms might also contribute to chronic thrombocytopenia in patients with HCV infection and associated liver disease, including sequestration of platelets in the enlarged spleen secondary to portal hypertension (hyper-splenism) and inadequate production of thrombopoietin.45,46

Dysregulation of the host immune system triggering the production of autoantibodies against platelet glycoproteins has also been postulated.41,42 There have been conflicting data reported with respect to the presence of specific antibodies in platelet eluates from patients with HCV-related ITP.31,42,47,48 In the latter report, 66% of patients infected with HCV had detectable anti-platelet glycoprotein antibodies. However, their presence did not correlate with the patients’ platelet counts. A similar frequency of anti-platelet glycoprotein antibodies was found in patients with alcoholic cirrhosis, indicating these antibodies were not specific for HCV infection.45

Clinical manifestations

In one study of HCV-associated thrombocytopenia from Japan, platelet counts in patients who were HCV positive were lower than in patients who were HCV negative (26 ± 9 vs 49 ± 30 × 10^9/L, respectively; P < .02). Conversely, in the American series, patients who were HCV positive had less severe thrombocytopenia, defined as a platelet count ≤ 10 × 10^9/L (4% vs 46% for ITP, P = .001). However, 56 (74%) had a platelet count ≤ 50 × 10^9/L. Symptoms and signs of thrombocytopenia were less frequent in HCV-positive CITP, but major bleeding was more frequent (25% vs 10%, P = .0059). Serum cryoglobulins and anticardiolipin antibodies were more frequent in HCV-positive ITP (90% and 62%, respectively) than in HCV-negative CITP (7% and 15%, respectively, P = .001 compared with HCV-positive ITP). In studies from France and China, the characteristics of ITP in patients who were HCV positive did not differ from those without positive serology. However, the French study evaluated only patients with platelet counts ≤ 25 × 10^9/L.

Table 1. Prevalence of hepatitis C virus (HCV) infection in adult patients with chronic immune thrombocytopenia (CITP).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Total number</th>
<th>Number of infected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivetti et al (1996)</td>
<td>33</td>
<td>12 (36)</td>
</tr>
<tr>
<td>Garcia-Suarez et al (2000)</td>
<td>51</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Sakuraya et al (2002)</td>
<td>79</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Rajan et al (2005)</td>
<td>250</td>
<td>76 (30)</td>
</tr>
<tr>
<td>Total</td>
<td>799</td>
<td>159 (20)</td>
</tr>
</tbody>
</table>

*Seven patients of this series had an associated autoimmune disorder. Study only included patients with platelet counts of less than 25 × 10^9/L.

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of 7 (57%) patients treated with prednisone responded, but 6 developed elevated hepatic transaminases of greater than twice pretreatment levels while on therapy and all 6 had a documented increase in HCV viral load. Two patients developed elevated serum bilirubin levels, with 1 patient developing overt jaundice. Treatment with either intravenous immunoglobulin (IVIG) or anti-RhD Ig has proven to be effective in increasing platelet counts in both the HCV-seropositive and -seronegative patients.30,31 Approximately half of adult CITP patients with HCV treated with INF-α therapy responded with a rise in platelet count.30,3147 Four of 5 HCV-positive patients treated with interferon-alpha (IFN-α) responded with increased platelet counts.41,47 Responders to IFN-α could be distinguished from the non-responder by a decrease in HCV quantitative RNA, hepatic transaminases and cryoglobulins.47 In the report of Garcia-Suarez et al each of 6 HCV patients treated with IFN-α responded with a significant increase in platelet count.30 Iga et al reported significant increases in the platelet counts of 12 HCV infected patients who were complete responders to interferon alpha (IFN-α) treatment, but no improvement in the platelet counts of 11 patients who failed IFN-α therapy assessed by viral load.51

In a recent Phase II study, eltrombopag, an oral thrombopoietin receptor agonist, increased platelet counts in the majority of patients with cirrhosis associated with HCV infection to >100 × 10^9/L and allowed for effective IFN-based therapy.52 Response was dose-dependent, with 9/17 (53%) responding to 30 mg/day, 15/19 (79%) to 50 mg/day and 20/21 (95%) to 75 mg/day. None of the 17 patients treated with placebo increased platelet counts to >100 × 10^9/L.52 For the patients whose platelet counts reached a prespecified threshold to initiate antiviral therapy, 12 weeks of therapy was completed by 36%, 53% and 65% of patients receiving 30 mg, 50 mg, and 75 mg of eltrombopag, respectively, and by 6% of patients receiving the placebo.52

**Summary**

Infection with HCV appears to be a frequent cause of thrombocytopenia and has relevant clinical implications. Therefore, we would recommend screening all patients presenting with chronic thrombocytopenia with risk factors (multiple sex partners, intravenous drug abuse, blood transfusion recipients) or with a high background prevalence of infection in the general population for the presence of HCV, as a different treatment strategy should be employed. Treatment with corticosteroids should be avoided as long as possible, because it can increase the viral load and worsen liver damage. If possible, treatment should be directed at the HCV infection. In patients without clinically evident liver disease, treatment with IFN-α combination therapy should be considered. Thrombopoietin receptor agonists may prove effective in preventing IFN-α suppression of platelet production, therefore, preventing treatment interruption and IFN-α dose reduction that can result in a reduction in the efficacy of antiviral therapy. Improvements in platelet count should parallel a reciprocal suppression of viral load and eradication of HCV infection should result in remission of the thrombocytopenia.

**Disclosures**

Conflict-of-interest declaration: The author is a consultant for Glaxo Smith Kline and Amgen and has received research funding from them; he is a consultant and member of the speakers’ bureau for Baxter. Off-label drug use: None disclosed.

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are common in hepatitis C infection, irrespective of the presence of thrombocytopenia. Eur J Haematol. 2006;77:513-517.