Thrombocytopenia: Proposed Mechanisms and Treatment in Human Immunodeficiency Virus Infection*

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ABSTRACT

Thrombocytopenia (TC) is noted in three to nine percent of patients who are seropositive for human immunodeficiency virus (HIV). Causes of this may be immune, infectious, platelet destruction, or underproduction. Thrombocytopenia associated with HIV will be seen with increasing frequency. Corticosteroids and splenectomy are the usual therapeutic approaches. Intravenous gammaglobulin and antiviral agents may be indicated and useful in some patients.

Introduction

Thrombocytopenia (TC) is associated with a variety of etiologies. These include increased utilization or destruction, decreased bone marrow production, immune mechanisms, adverse drug effects, and infectious agents. The mechanisms whereby each of these causes thrombocytopenia is multifactorial. For instance, some drugs have a specific toxic suppression of megakaryocytes or their precursors: examples in this category include gold and alcohol, while others form haptens and cause immune thrombocytopenia. Quinidine, quinine, and possibly heparin are related to the interaction of the drug and chemicals on the cell surface or membrane which results in immunologic responses either to the drug as a hapten or formation of immune complexes which become absorbed on the platelet surface, resulting in aggregation or subsequent reticuloendothelial system removal of the platelet. Infectious agents can result in decreased platelets because of direct involvement and suppression of megakaryocytes as in viral diseases, particularly Epstein-Barr virus, invasion of cells by obligate intracellular parasites, such as histoplasmosis or toxoplasmosis, or secondary to extensive infection and blockage of vessels, as in some mycotic infections and infectious vasculitides such as pseudomonas pneumonia.

Human immunodeficiency virus (HIV) is associated with TC in approximately three to nine percent of patients with symptoms. It is possible that the decreased thrombocytes seen in HIV infection may be related to infection of the megakaryocytes, although direct invasion of megakaryocytes and/or receptor sites for HIV have not been demonstrated. Indirect evidence, including the clinical efficacy of zidovu-

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dine, suggests this hypothesis. Other HIV TC may be related to concurrent infections or therapy. The purpose of this review is to examine TC associated with HIV infection, to attempt to elucidate the pathogenesis of this thrombocytopenia, and to propose and evaluate therapy for HIV TC.

Methods

There are many methods used in studying thrombocytopenia. These include measurement of platelet associated antibodies, specific antibodies for specific platelet antigens, glycoproteins or other components of the platelet membrane, radio labeled, fluorescent labeled and enzyme linked assays as well as quantitative and qualitative methods.

Immune thrombocytopenia purpura (ITP) may be divided into acute or chronic types. Using specific and sensitive assays, current methodology indicates that approximately 90 to 95 percent of all patients with ITP have demonstrable antibodies against one or the other platelet antigens. These platelet antigens may be directed against PLA1, PLE1, human leukocyte antigens (HLA) or various glycoprotein antigens (e.g., GpIIb/IIIa or GpiIb). Those patients that have antibodies specifically directed against glycoprotein antigens may have severe clinical manifestations of hemorrhage because of the interference of the action of the glycoproteins with their appropriate receptor sites resulting in the lack of platelet function.

Results

Diagnosis of HIV associated TC includes the presence of HIV seropositivity and thrombocytopenia of less than 130,000 platelets per ml. Thrombocytopenia may be seen either as an isolated entity or associated with other hemalogic abnormalities; TC may be mild, moderate, or severe.

Approximately three to nine percent of all patients seropositive for HIV are noted to have TC. In those instances where a search has been made for antibodies, there have been only a few instances of specific platelet antigen antibodies. The majority of the results are non-specific and may reflect measuring only circulating immune complexes or total platelet immunoglobulin. Another mechanism for HIV TC has been proposed as an hypothesis. That is the suppression and/or destruction of platelet precursors by the HIV itself. No direct proof of this exists although treatment success with zidovudine has been reported.

The treatment for HIV TC includes observation and clinical intervention when the platelet count is sufficiently low and/or purpuric signs or hemorrhagic symptoms appear. Treatments, including use of glucocorticoids, intravenous gammaglobulin, splenectomy, immunosuppressives, interferon, Rh immune globulin, plasma exchange, danazol, or zidovudine, have been recommended.

Intravenous gammaglobulin infused once every two weeks has been reported by Bussel and Haimi to result in correction of platelet counts in patients who were seropositive for HIV and had TC. The best responses were seen in patients who did not have opportunistic infections. A study by Gernsheimer and coworkers revealed that approximately 92 percent of patients treated with prednisone had a three-fold increase in platelet count. Prednisone treatment did not alter platelet survival time, however. In the same study, six out of 10 patients had a significant rise in platelet counts following splenectomy despite the fact that platelet production was unchanged and they could not demonstrate indium labeled platelet localization in the liver. The total platelet localization as measured by radio labeled indium decreased
Treatment of Human Immunodeficiency Virus-Thrombocytopenia

Determine:
- Cause, if possible
- If therapeutic intervention is needed

Treatment modalities:
- Corticosteroids
- Immunosuppressives
- Splenectomy
- I.V. gammaglobulin
- I.V. anti Rh globulin
- Other:
  - Plasma exchange
  - Zidovudine
  - Danazol
  - Platelet transfusions

Figure 1.

by more than half after successful splenectomy in both the liver and the spleen.

Therapy with antiviral agents, including zidovudine, has been described as effective in patients with TC and infections of HIV. Oksenhendler and co-workers demonstrated that zidovudine given for 12 weeks at 250 mg every six hours or 500 mg every eight hours resulted in a statistically significant increase in 29 patients of the 34 who completed the study. The effectiveness of zidovudine, a known effective antiviral drug, is taken as indirect evidence that HIV itself may play a role in the pathogenesis of this disorder by somehow invading the megakaryocytes or its precursor.

Discussion

Thrombocytopenia associated with HIV infection appears in large part to be secondary to immune mechanisms. As many as 10 percent of the patients who are seropositive for HIV will have TC as a significant part of their clinical presentation. Treatment of TC in patients infected with HIV is pursued in the same way as the treatment for ITP in general. That is, corticosteroids are effective in approximately 90 percent of the patients usually for short periods of time. Immunosuppressives may be useful therapy. Intravenous gammaglobulin has been demonstrated to be beneficial in a majority of the patients. The use of the antiviral agent zidovudine indicates that there may also be a component of direct or indirect infection related to the HIV organism itself. As in other patients who have immune thrombocytopenia, the use of platelet transfusions should be avoided whenever possible. The specifics of the cause of HIV related TC should be sought and treated appropriately where possible. Additional information as to the pathogenesis, natural history, and outcome of therapy in patients with HIV associated TC is still unfolding.

Conclusion

Infections of HIV continue to increase. Thrombocytopenia may be noted in as many as 10 percent of HIV seropositive intravenous drug abusers. Thrombocytopenia has been reported during primary infection and correlates with the presence of CD4 low lymphocyte counts. The causes of HIV related TC may be nonspecific or specific immune mechanisms, concurrent infections, suppression by treatment or possibly direct invasion of megakaryocytes or precursors. Multiple therapeutic approaches may be useful. Corticosteroids and/or splenectomy are the accepted treatments as in other ITP. Antiviral agents (e.g., zidovudine) may be useful. Because of the co-existing disease in these patients, an effective nontoxic treatment modality should be pursued.

Acknowledgments

Recognition and thanks are extended to Ms. Maxine Goldstein for her secretarial assistance.

References


