Cytomegalovirus Infection as Cause of Severe Thrombocytopenia in a Nonimmunosuppressed Patient

V.R.	Valder R.	Arruda ^a
C.L.	Cláudio L.	Rossi ^b
E.	Eliaana	Nogueira ^a
J.M.	Joyce M.	Annicchino-Bizzacchi ^a
F.F.	Fernando F.	Costa ^a
S.C.B.	Sandra C.B.	Costa ^a

^aDepartment of Clinical Medicine and ^bDepartment of Clinical Pathology, Faculty of Medicine, State University of Campinas, Brazil

Valder R. Arruda, MD, Hematology-Hemotherapy Center, State University of Campinas, CP 6198, BR-13081-970 Campinas, SP (Brazil), Fax+55 19 239 31 81/239 31 14

Autoimmune thrombocytopenic purpura (AITP) is characterized by the development of antibodies against platelet membrane proteins which results in their phagocytosis and destruction by the monocyte-macrophage system [1]. The production of platelet autoantibodies may occur as an idiopathic pathogenesis or in conjunction with other autoimmune diseases, cancer, drugs or various infections and may result in secondary autoimmune thrombocytopenia [2, 3]. Viral infections affecting megakaryocytes or platelets which result in a clinical picture of AITP are commonly associated with a self-limited course although a chronic evolution is now recognized in HIV infection [2-5]. Thrombocytopenia has been described in acquired and congenital infections by cytomegalovirus (CMV) but the mechanism of the decrease in the platelet number could be similar to that of AITP or that of myelo-suppression of hematopoietic progenitor cells [3]. Healthy adults rarely manifest clinical infections by CMV although there are a few cases of association between CMV infection and secondary AITP [6-10]. Here we describe the case of a nonimmunosuppressed adult with severe thrombocytopenia related to a subclinical CMV infection in which total resolution of the condition was achieved only after specific antiviral therapy.

A 34-year-old man was admitted to the outpatient clinic with a 7-day history of an abrupt onset of petechiae in the lower extremities. On admission, he was in a healthy condition without fever, and had no lymphadenopathy or hepatosplenomegaly. He reported that he had suffered from transitory fever and generalized fatigue 3 weeks previously. No medication was used at the time and the resolution was spontaneous. The laboratory findings included a platelet count of $12 \times 10^9/l$, hemoglobin of 13.8 g/dl, hematocrit of 46.2%, red blood cell counts of $5.63 \times 10^{12}/l$, and a reticulocyte count of 2.4%. The white blood cell count was $11.5 \times 10^9/l$ and inspection of the blood smear revealed 24% polymorphonuclear leukocytes, 4% eosinophils, 4% monocytes, and 68% lymphocytes, most of them with atypical

forms. A bone marrow study revealed an increase in the number and size of megakaryocytes with many young forms which is compatible with a peripheral destruction or consumption of platelets. The coagulation tests, including activated partial thromboplastin time, prothrombin time, and thrombin time were normal as were the Russell's viper venom time and the kaolin clotting time performed in order to identify antiphospholipid antibodies. The erythrocyte sedimentation rate was 6 mm/h (Westergren). No abnormalities were found upon hepatic or renal evaluation. A test for antinuclear antibody and rheumatoid factor was negative. Serologic analyses were negative for hepatitis A, B, and C virus, human immunodeficiency virus, and EBV. CMV-specific antibodies IgM and IgG were detected by antibody capture enzyme-linked immunosorbent assay (ELISA) using commercial kits ETI-CITOK-M and ETI-CITOK-G, respectively (Sorin Biomedica, Italy). Concerning IgM detection serum samples with absorbance values higher than or equal to the cutoff value were considered positive and for IgG those serum samples higher than 5 AU/ml. Simultaneously, the detection of CMV DNA was carried out in urine and blood samples by nested PCR, as previously described using primers described by Demmler et al. [11]. The treatment, which lasted 12 weeks, consisted of prednisone at 1-2 mg/kg/day with a nonsustained partial response in platelet counts. During this period, the tests to detect CMV IgG and IgM and CMV DNA were repeated with persistently positive results. On the basis of these data, we decided to stop the immunosuppression with cortico-steroids and start treatment with intravenous ganciclovir (5 mg/kg i.v., twice a day) for 21 days. No severe side effect was registered. A gradual increase in the platelet count was observed during the first 3 weeks of treatment with this drug. A transient reduction in hemoglobin levels and in the leukocyte and platelet counts was observed during the last week of ganciclovir infusion but there was a complete recovery after drug cessation (fig. 1). The CMV DNA detection was negative at the end of the ganciclovir therapy a finding which agreed with the increased platelet counts. On the other hand, CMV IgM

KARGER

E-Mail karger@karger.ch Fax + 41 61 306 12 34 <http://www.karger.ch>

© 1997 S. Karger AG, Basel 0001-5792/97/0984-0228\$15.00/0

This article is also accessible online at: <http://BioMedNet.com/karger>

■ ■ ■ ■

Fig. 1. Platelet counts, CMV DNA and CMV IgM in a patient with CMV infection during the treatment with prednisone (12 weeks) and ganciclovir (21 days). CMV DNA was detected from diagnosis until the end of ganciclovir therapy.

30

Time (weeks)

indicated a slow but continuous decrease of the values until 2 months after the disappearance of CMV DNA. The CMV IgG ranged from 100 to 150 AU/ml during the follow-up. The patient remained asymptomatic and no further therapy was required for the last 7 months of follow-up. CMV infection is common and generally benign, often remaining asymptomatic in nonimmunosuppressed adults [3-5]. Hemolytic anemia with a chronic evolution has also been associated with CMV infection in nonimmunosuppressed persons [12]. To our knowledge only five cases of thrombocytopenia associated with CMV infection in healthy individuals have been reported and in all of them the response to prednisone and splenectomy was disappointing [6-10]. The mechanism leading to a decrease in platelet numbers in these cases may involve the

production of multiple autoantibodies or the suppression of the hematopoiesis of human progenitor cells by CMV [2, 3, 13]. In this report, we have described an unusual case of severe thrombocytopenia related to CMV infection in a nonimmunosuppressed patient in whom the response to specific antiviral therapy was followed by a platelet count improvement. We clearly showed the correlation between CMV DNA detection and thrombocytopenia. This result illustrates that in spite of being a rare event, the detection of a CMV infection in patients with AITP makes possible a correct diagnosis and the application of specific therapy. Recently, van Spronsen and

Breed [10] also described a similar case and the response to ganciclovir was successful. These findings raise important questions as to the rationale for CMV detection during the diagnosis of AITP. Peripheral blood analysis and CMV IgM antibody detection allow a positive diagnosis of active CMV infection in most cases but not in immuno-suppressed patients such as those with AIDS [14]. The detection of CMV DNA could improve the etiologic diagnosis and virus replication is not expected in the cells from blood or bone marrow of the normal population [15]. A study of a large number of patients with AITP, especially those with refractory disease, would be interesting to test the hypothesis of the disease being mediated by CMV infection.

Thrombocytopenia in a Healthy Patient due to CMV Infection
Acta Haematol 1997;98:228-230 229

References

- Karpatkin S: Autoimmune thrombocytopenia purpura. *Semin Hematol* 1985;22:260-288.
- Kaplan C, Morinet F, Cartron J: Virus-induced autoimmune thrombocytopenia and neutropenia. *Semin Hematol* 1992;29:34-44.
- von Laer D, Meyer-Koenig U, Serr A, Finke J, Kanz L, Fauser AA, Neumann-Haefelin D, Brugger W, Hufert FT: Detection of cytomegalovirus DNA in CD34+ cells from blood and bone marrow. *Blood* 1995;86:4086-4090.
- Zucker-Franklin D: The effect of viral infections on platelet and megakaryocytes. *Semin Hematol* 1994;31:329-337.
- Grundy JE: Virologic and pathogenic aspects of cytomegalovirus infection. *Rev Infect Dis* 1990;12(suppl7):711-719.
- Chanarin I, Walford DM: Thrombocytopenia in cytomegalovirus mononucleosis. *Lancet* 1973;ii:238-239.
- Fiala M, Kattlove H: Cytomegalovirus mononucleosis with severe thrombocytopenia. *Ann Intern Med* 1973;79:450-451.
- Harris AL, Meyer RJ, Brody EA: Cytomegalovirus-induced thrombocytopenia and hemolysis in an adult. *Ann Intern Med* 1975;83:670-671.
- Eisenberg MJ, Kaplan B: Cytomegalovirus-induced thrombocytopenia in an immunocompetent adult. *West J Med* 1993;58:525-526.

van Spronsen DJ, Breed WPM: Cytomegalovirus-induced thrombocytopenia and hemolysis in an immunocompetent adult. *Br J Haematol* 1996;92:218-220.

Demmler GJ, Buffone GJ, Schimbor CM, May RA: Detection of cytomegalovirus in urine from newborn by using polymerase chain reaction DNA amplification. *J Infect Dis* 1988; 158: 1177-1184.

Horwitz CA, Skradski K, Reece E, Lewis FB, Schwartz B, Kelly R, Polesky H: Haemolytic anaemia in previously healthy adult patients with CMV infections: Report of two cases and an evaluation of subclinical haemolysis in CMV mononucleosis. *Scand J Haematol* 1984; 33:35-42.

Simmons P, Kaushansky K, Torok-Storb B: Mechanisms of cytomegalovirus-mediated myelosuppression: Perturbation of stromal cell function versus direct infection of myeloid cells. *Proc Natl Acad Sci USA* 1990;87:1386-1391.

Lazzarotto T, Dal Monte P, Boccuni MC, Ripalti A, Landini NV: Lack of correlation between virus detection and serologic tests for diagnosis of active cytomegalovirus infection in patients with AIDS. *J Clin Microbiol* 1992; 30:1027-1029.

Smith KL, Kulski JK, Cobain T, Dunstan RA: Detection of cytomegalovirus in blood donors by the polymerase chain reaction. *Transfusion* 1993;33:497-503.

230

Arruda/Rossi/Nogueira/Annicchino-Bizzacchi/Costa/Costa