Severe Steroid-resistant Thrombocytopenia Secondary to Cytomegalovirus Infection in an Immunocompetent Adult

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Abstract

Severe thrombocytopenia secondary to cytomegalovirus (CMV) infection is rare in immunocompetent hosts. We describe a case of severe thrombocytopenia secondary to CMV infection in an immunocompetent 30-year-old man who presented with pyrexia and bleeding tendency. A diagnosis of immune thrombocytopenia (ITP) was made following hematological and serological testing, and bone marrow aspiration. Acute CMV infection was confirmed by serological testing, antigenemia, and detection of CMV-DNA. Corticosteroid therapy was ineffective and intravenous immunoglobulin (IVIG) was therefore administered. This resulted in immediate recovery of the platelet count and cessation of nasal bleeding. Early IVIG administration should be considered in steroid-resistant cases.

Key words: cytomegalovirus, severe thrombocytopenia, steroid-resistance, immunocompetent host, intravenous immunoglobulin

(Intern Med 51: 1747-1750, 2012)
(DOI: 10.2169/internalmedicine.51.7193)

Introduction

In immunocompetent adults, cytomegalovirus (CMV) infection is generally asymptomatic or may present as a mononucleosis-like syndrome (1). However, a recent study showed that severe life-threatening complications of CMV infection may be more common in immunocompetent patients than previously thought (2). Several cases of severe thrombocytopenia secondary to CMV infection in immunocompetent adults have been reported (3-8). In almost all of these cases, corticosteroids were administered as a first-line therapy. However, some patients appeared to show only a partial response or no response, and few reports have provided detailed information concerning the response (9). The present report describes the case of an immunocompetent adult who presented with severe thrombocytopenia secondary to CMV infection that was refractory to steroid therapy.

Case Report

The 30-year-old man presented to our hospital with a 10-day history of pyrexia, fatigue, and an oral aphtha. His past medical history was unremarkable, and he was taking no medications. A diagnosis of undetermined viral infection was assigned and he was discharged home. Three days later, he was admitted with continuous nasal bleeding and petechiae.

On clinical examination, the pyrexial (38.7°C) patient had clear consciousness. Continuous right nasal bleeding, oral submucosal hemorrhage, and widespread petechiae were observed. His blood pressure was normal (122/78 mmHg) but the pulse rate was slightly elevated (106/min). No sign of anemia or jaundice was evident in the conjunctiva. Neither the pharynx nor the tonsilla were inflamed, but an aphtha was present on the soft palate. No lymphadenopathy or hepatosplenomegaly was obvious on palpation. Neurological examination was unremarkable.

Laboratory tests on admission revealed a leukocyte count
of 6.2×10³/μL, with 42% neutrophils, 18% lymphocytes, 3% monocytes, and 36.5% atypical lymphocytes (Fig. 1). The hemoglobin concentration was 145 g/L and the platelet count was 0.1×10⁴/μL (normal range 13-36×10⁴). The immature platelet fraction (IPF) was increased to 27.3% (normal range 1.1-6.1) and the platelet-associated IgG (PA-IgG) was elevated. Coagulation tests were normal, and blood chemistry analysis revealed mild liver dysfunction (aspartate aminotransferase 43 IU/L, alanine aminotransferase 61 IU/L, lactate dehydrogenase 353 IU/L, and alkaline phosphatase 236 IU/L). The immunoglobulin level was within normal limits, and thyroid function was normal. A test for antinuclear antibody was negative. Serological tests for hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), and Helicobacter pylori were all negative. Bone marrow aspiration revealed normocellular marrow with an increased number of immature megakaryocytes (Fig. 2). Abdominal ultrasonography revealed slight splenomegaly (12.5×3.4 cm). On the basis of these findings, a presumptive diagnosis of immune thrombocytopenia (ITP) was made (10).

In view of the atypical lymphocytosis, serological investigations were performed to exclude Epstein-Barr virus (EBV) and CMV. Serum IgM and IgG antibodies to CMV were positive (IgM 5.77, normal <0.8) and thus acute CMV infection was suspected. Antibody tests for EBV showed a post-infection pattern. CMV antigenemia was detected using the C7-HRP method. CMV-DNA was found to be positive, with a titer of 310 copies/10⁶ cells in whole blood according to the quantitative polymerase chain amplification (PCR) method. On the basis of these findings, a clinical diagnosis of acute CMV infection with ITP was made.

Prednisolone 85 mg per day (1 mg per kilogram body weight per day) was initiated on admission. However, no increase in the platelet count was observed. Although the IPF showed a gradual decrease from day 10 of admission, the platelet count remained at 1×10⁹/L, and both the nasal bleeding and the atypical lymphocytosis persisted. On day 13 of admission, a five-day course of intravenous gamma-immunoglobulin (IVIG) was begun at a dose of 0.4 g/kg/day. As a result, the platelet count immediately recovered, the atypical lymphocytosis was resolved, and the nasal bleeding ceased. By day 69 of admission, CMV-DNA was no longer detectable. The prednisolone was gradually withdrawn and then stopped on day 46 of admission with no recurrence of the thrombocytopenia (Fig. 3).

**Discussion**

The current patient presented with severe thrombocytopenia and acute CMV infection. The latter was confirmed by serological testing, detection of antigenemia, and detection of CMV-DNA in whole blood using PCR. In immunocompromised adults, the clinical course of a CMV infection may be severe, particularly in HIV patients (11, 12) and in transplant recipients treated with immunosuppressants (13, 14). However, no signs of immunosuppression were evident in the present case. CMV infection in an immunocompetent host is usually asymptomatic and detected retrospectively (5). However, a systematic review by Rafailidis et al. revealed that severe life-threatening complications of CMV infection may be more common in immunocompetent patients than previously thought, and several reports have described severe complications of CMV infection, such as colitis, meningoencephalitis, pneumonitis,
uveitis, hematological disorders, and thrombosis of the venous or arterial vascular systems (2). DiMaggio et al. suggested that CMV infection may result in severe, and refractory ITP, and that PCR should be used to test for CMV if there is any clinical suspicion of the infection (15).

Epidemiological studies have shown an inverse correlation between the prevalence of anti-CMV antibody in a given population and the socioeconomic-development status of the respective country (16, 17). Other studies have reported a recent decrease in the prevalence of the anti-CMV antibody, particularly in young adults (18, 19). Consequently, the number of cases of acute CMV infection in immunocompetent adults appears to be increasing, along with an increase in the incidence of severe complications. Thus, the possibility of acute CMV infection should be considered in all patients who present in the primary care or hospital setting with fever, fatigue or other mononucleosis-like symptoms.

Although thrombocytopenia is a recognized complication of acute CMV infection, the underlying mechanism is unclear. This results in the use of a wide range of treatments (20). Several mechanisms for the association between CMV infection and thrombocytopenia have been proposed and these fall into two categories: the production of auto-anti-platelet antibodies (e.g., CMV-related thrombocytopenia), and direct cytotoxicity to bone marrow progenitor cells or leukocytes and stromal bone marrow cells that results in decreased platelet production (e.g., CMV-induced thrombocytopenia) (21). The presence of anti-platelet autoantibodies is a hallmark for the diagnosis of ITP. Therefore the detection of platelet-associated anti-GPIIb/IIIa antibody and the measurement of anti-GPIIb/IIIa antibody-producing B cell frequency are useful to identify ITP (22).

In this regard, although there is no direct evidence for involvement of anti-platelet antibodies in the platelet destruction in the present patient, PA-IgG was positive, the IPF was very high, and an increased number of immature megakaryocytes was detected in the bone marrow, findings which are suggestive of autoimmune mechanism for thrombocytopenia.

Steroid-resistant cases, as in the present patient, are rare, and approximately 80 to 95% of severe ITP patients respond to the steroid therapy (23, 24). Although a few previous cases appeared to have been worsened by treatment with steroids (15), corticosteroids were the main and effective treatment for CMV-related thrombocytopenia (20). Some authors recommend a short trial of corticosteroids as a first-line therapy, with subsequent IVIG in refractory cases with severe bleeding (9, 24, 25). In the present case, administration of IVIG was very effective, resulting in the immediate return of a normal platelet count along with the improvement of atypical lymphocytosis (Fig. 3). However the high CMV-DNA level, as assessed by PCR assay of whole blood, was still sustained at that point, and we confirmed its improvement after 10 days. Although several studies have demonstrated that whole blood detection of CMV-DNA improves sensitivity compared with plasma detection of that (26-28). Very recently, a large prospective study comparing the use of whole blood versus plasma in monitoring
therapeutic response to CMV infection revealed that enhanced detection of viremia using a whole blood real-time PCR does not necessarily predict recurrence of CMV disease (29). Thus, the timing difference between the improvement of atypical lymphocytosis and sustained CMV-DNA level may be explained in part by the use of whole blood for detection of CMV-DNA, resulting in the overestimation of viral load.

In conclusion, the present report describes the case of an immunocompetent adult with severe thrombocytopenia secondary to acute CMV infection that was refractory to corticosteroid therapy. Since the prevalence of CMV infection with severe complications appears to be increasing, CMV infection should be in the differential diagnosis in all patients presenting with mononucleosis-like symptoms.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
We thank Dr. Tatsuo Ichinohe for valuable suggestions. We are also very grateful to the members of the Division of Haematology and Oncology, Department of Internal Medicine, Saga University for helpful discussions.

References