# Postsplenectomy Cytomegalovirus Mononucleosis is a Distinct Clinicopathologic Syndrome

*Xiang Y. Han, MD, PhD, Beth A. Hellerstedt, MD and Charles A. Koller, MD*

**Abstract:** Lymphocytosis in response to viral infection, such as infectious mononucleosis, rarely exceeds $20 \times 10^9$/L in the adult population. Transfusion-acquired cytomegalovirus (CMV) mononucleosis after trauma-related splenectomy may cause prominent lymphocytosis, but the history and timing usually hint at the diagnosis. We describe a case of severe CMV mononucleosis that was acquired naturally decades after splenectomy. Together with the 2 similar cases that we reported recently, these cases all presented as initial diagnostic challenge because of a remote history of splenectomy, a prolonged febrile illness (~4 weeks), marked lymphocytosis (peak $27.9 \times 10^9$/L), and undetectable or weakened anti-CMV IgM antibody response. The diagnosis was eventually established through detection of circulating CMV antigen or DNA and a year or longer follow-up with serial determination of IgM and IgG antibodies. Two similar cases were also identified in the literature and reviewed. Although the impaired IgM response may confuse the diagnosis, it correlates well with recent studies showing that human blood IgM memory B cells are circulating splenic marginal zone B cells; asplenic or splenectomized individuals, irrespective of the underlying cause, have undetectable IgM memory B cells. Together, these findings suggest that distant or recent postsplenectomy CMV mononucleosis represents a distinct clinicopathologic syndrome resulting from poor control of early viremia because of the lack of both splenic filtration and the typical brisk IgM response. For the practicing clinician, recognizing these features may aid timely diagnosis and treatment.

**Key Indexing Terms:** Cytomegalovirus; Infectious mononucleosis; Splenectomy; IgM response; Marked lymphocytosis. **[Am J Med Sci 2010;339(4):395–399.]**

Cytomegalovirus (CMV) is a ubiquitous large $\beta$-herpesvirus and causes a variety of primary and secondary infections, such as congenital neonatal infections, infectious mononucleosis in healthy individuals, and reactivation in immunocompromised patients.[1] Primary CMV infection manifested as mononucleosis occurs mainly in school age children and is usually subclinical. A recent serosurvey shows that 61% to 73% of German adults, ranged from 20 to more than 60 years old, have detectable CMV antibodies.[2] The same study and one from the United States[3] have also shown that, in some adult patients (18–56 years of age), CMV mononucleosis may present with a prolonged clinical course. CMV is responsible for most of the Epstein Barr virus (EBV)-negative cases of infectious mononucleosis.

CMV mononucleosis after splenectomy has been reported. It typically occurs within 2 to 4 weeks after trauma surgery and multiple blood transfusions, and a marked lymphocytosis is a feature.[4–6] However, the practice of using leukocyte-reduced blood transfusions in the past 2 decades has made this disease rare.[7] Recently, we reported 2 cases of severe CMV mononucleosis that initially presented as a diagnostic dilemma because of a remote history of splenectomy, a prolonged febrile illness, and marked lymphocytosis (peak $27.9 \times 10^9$/L).[8] Both patients were referred to rule out chronic lymphocytic leukemia, and bone marrow examination also noted T-cell receptor (*TCR*)-$\gamma$ gene rearrangements, suggesting monoclonal T-cell proliferation. Because the acute phase had passed, the CMV pp65 antigenemia test, routinely performed in our institution, was negative. Eventually, the diagnosis of CMV mononucleosis was established by demonstrating CMV DNA with polymerase chain reaction (PCR) in a retrieved acute-phase blood DNA sample in 1 case and serial determination of anti-CMV antibodies and exclusion of other causes of infectious mononucleosis, such as EBV, *Toxoplasma*, and other viruses in both cases. Surprisingly, close follow-up also revealed lack of anti-CMV IgM response in 1 case and weakened and delayed response in another, which contrasted with an augmented IgG response in both cases. The poor IgM response was paradoxical to the prominent and prolonged lymphocytosis.

In this study, we extend our experience by describing a similar case of postsplenectomy CMV mononucleosis and reviewing 2 additional cases in the literature. The clinical features of the 5 cases correlate with relevant experimental studies, which led us to the impression that the postsplenectomy CMV mononucleosis represents a distinct clinicopathologic syndrome.

## CASE REPORT

The patient was a 34-year-old man who had a medical history of splenectomy at teenage because of idiopathic thrombocytopenic purpura. Since then, he had been in good health, and he had visited his physician regularly. He developed a sudden onset of fever up to 39.5°C, headache, myalgias, arthralgias, and night sweats; after failing to respond to 2 courses of oral antibiotics, he was hospitalized elsewhere for the illness. Admission physical examination documented the fever and disclosed a grade 2/6 holosystolic murmur heard loudest at the apex. Blood cultures were negative, and a transesophageal echocardiogram showed mitral valve prolapse and regurgitation without any evidence of endocarditis. A computed tomographic scan revealed several cervical lymph nodes, up to 14 mm in size, and a possible accessory spleen at the prior surgical site. A prominent leukocytosis with marked absolute lymphocytosis was observed (Figure 1), which led to a flow cytometric analysis of the peripheral blood 14 days after onset of illness, revealing proliferation of large granular lymphocytes (LGL) with an unusual T-cell phenotype, because of the loss of CD5 and CD7 markers, and increased natural killer (NK) cells with expression of CD56 and CD16. The CD4 to CD8 ratio was inverted. Because the white blood cell count (WBC) continued to rise and reached a peak of $33.8 \times 10^9$/L with an absolute

*From the Department of Laboratory Medicine (XYH), The University of Texas M. D. Anderson Cancer Center, Houston, Texas; Texas Oncology PA (BAH), Austin, Texas; and Department of Leukemia (CAK), The University of Texas M. D. Anderson Cancer Center, Houston, Texas.*

*Submitted November 12, 2009; accepted in revised form December 9, 2009.*

*Correspondence: X. Y. Han, MD, PhD, Department of Laboratory Medicine, Unit 84, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030 (E-mail: xhan@mdanderson.org).*

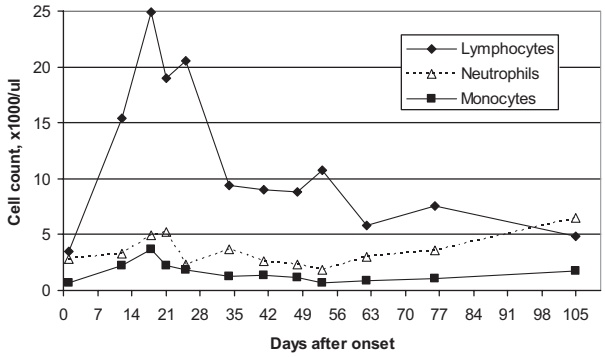


FIGURE 1. Prominent lymphocytosis in CMV mononucleosis after remote splenectomy.

lymphocyte count of 24.9 $\times$ $10^9$/L (day 18 after onset; Figure 1), the patient was referred to our institution with a diagnosis of possible T-cell acute lymphoblastic leukemia.

When seen at our institution, initial laboratory examination (day 21 after onset) revealed a WBC of 27.5 $\times$ $10^9$/L, including 19.0 $\times$ $10^9$ lymphocytes/L and 2.2 $\times$ $10^9$ monocytes/L, and elevated transaminases [alanine transaminase, 270 IU/L (normal range 7–56 IU/L); aspartate transaminase, 155 IU/L (normal range, 15–46 IU/L)] and lactate dehydrogenase [1505 IU/L (normal range, 313–618 IU/L)]. A bone marrow biopsy and aspirate showed trilineage hematopoiesis with an increase in $CD3^+$, $CD8^+$ cytotoxic T-cells/LGL (~68% of lymphocytes), with 50% of the $CD8^+$ cells showing expression of TCR V-$\beta$ 5.1. *TCR* $\beta$ gene rearrangements were also demonstrated by PCR, suggesting monoclonal or oligoclonal T-cell proliferation. Together, these findings indicated a possible T-cell lymphoproliferative process.

Viral etiologies were also sought to explain the clinical and laboratory findings. Although the tests for hepatitis B and C viruses, HIV, and HTLV I/II were negative, and the anti-EBV antibodies represented past infection, a CMV pp65 antigenemia test (21 days after onset of illness) was positive for 2 cells/$10^6$ WBC, consistent with acute CMV infection in the clinical context. With improvement of the constitutional symptoms 25 days after onset, the patient was followed up closely without anti-CMV treatment, and his lymphocytosis declined remarkably in the following month (Figure 1). A follow-up CMV antigenemia test (53 days after onset) was negative.

However, the total anti-CMV antibodies by the latex agglutination method (BD Microbiology Systems, Sparks, MD) were negative repeatedly at 25 and 53 days after onset. By day 62, an enzyme immunoassay for the anti-CMV IgM and IgG antibodies (Diamedix, Miami, FL) was weakly positive for IgM (index 1.96, cutoff 0.90) but strong for IgG (index 7.90, cutoff 0.90). These results, therefore, confirmed CMV mononucleosis. At 1-year follow-up, the patient's lymphocyte count was 5.6 $\times$ $10^9$/L, with essentially normal blood chemistry. The anti-CMV IgM turned negative, but IgG remained strong (index 8.79) along with affinity maturation. Throughout the course, the patient's neutrophil counts remained normal, but monocyte counts were moderately elevated (peak 3.7 $\times$ $10^9$/L; Figure 1).

## Literature Review and Discussion

A primary function of the spleen is to filter senescent red cells and particulate substances in the bloodstream. As such, it is a major site for primary immunological response to blood-borne antigens. CMV is a blood-borne pathogen as indicated by the presence of viremia during its primary infection and reactivation. For eusplenic patients with CMV mononucleosis, leukocytosis occurs infrequently (4%–14% of cases), and the absolute lymphocyte count remains normal to mildly elevated ($<8 \times 10^9$/L) despite common relative lymphocytosis.[2,3] Splenomegaly can be detected by ultrasound examination in 83% of cases.[2] This feature, along with reported cases of spontaneous splenic rupture with identification of CMV inclusions in the spleen,[9] suggests that the spleen is a replication site of and, hence, early immunity against CMV mononucleosis. Furthermore, primary CMV infection elicits early strong IgM response,[10] being positive diagnostically in more than 99% of cases and strongly positive in 62% to 64%.[2,3] Typically, the anti-CMV IgM rises from being weakly positive several days after onset to strongly positive in a few weeks.[3,11]

It is well known that asplenic or splenectomized individuals are prone to life-threatening infections by encapsulated bacteria. They also mount poor antibody response to bacterial polysaccharide vaccines, and study shows that it is the IgM response that is impaired, not IgG.[12] Recent data further suggest that this is because of the lack of IgM memory B cells.[13] Two additional studies corroborate such IgM defect after splenectomy by showing that human blood IgM memory B cells are circulating splenic marginal zone B cells harboring a prediversified immunoglobulin repertoire[14] and that asplenic or splenectomized individuals, regardless of the underlying causes, have undetectable IgM memory B cells.[15]

Our case was worrisome because of prolonged fever and marked lymphocytosis (mostly LGL and NK cells). It was difficult to connect this picture clinically with his remote history of splenectomy. Historically, multiple blood transfusions after trauma-related splenectomy may cause severe CMV mononucleosis within 2 to 4 weeks with an unusually high lymphocytosis.[4–6] However, this disease is now much less common with the practice of leukocyte-reduced red cell transfusion. Besides, the immediate history of trauma surgery and transfusion usually render the diagnostic clues. Our patient's surgery was remote, and he had received no transfusions.

Although it is common to see increases of LGL and NK cells in usual CMV mononucleosis,[16] typical levels are far below the numbers seen in our case. In addition, our patient's LGL were also aberrant in view of the loss of CD5 and CD7 expressions. More perplexingly, *TCR* gene rearrangements were also found, hinting clonal T-cell proliferation. Fortunately, the CMV pp65 antigenemia test was most helpful in reaching a presumptive diagnosis on referral to our institution. We routinely use antigenemia to monitor CMV reactivation in our stem cell recipients and in patients with leukemia and lymphoma.[17,18] This test has a turnaround time of several hours and is highly specific. Over the years, we have also found it useful to diagnose primary CMV infection.[11] With the current case included, there are at least 9 reported cases of primary CMV infection diagnosed by antigenemia test, and positive cells can be detected from 3 to 32 days after onset of illness.[11,19,20] The presence of 2 cells/$10^6$ WBC at 21 days after onset in our case was probably at the tail of antigenemia (viremia), following the peak of lymphocytosis at 18 days after onset. Earlier tests may have detected more positive cells.[11]

The anti-CMV IgM response in our patient was delayed and weakened on repeated testing. This feature is paradoxical to the marked and year-long proliferation of T cells and B cells and the strong IgG antibody response. As discussed above, this defect is well explained by the loss of splenic IgM memory B cells as a consequence of splenectomy. Without adequate IgM,