Acute Cytomegalovirus Infection Complicated by Vascular Thrombosis: A Case Report

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We present a case report of a previously healthy adult with cytomegalovirus infection that was complicated by extensive mesenteric arterial and venous thrombosis. To our knowledge, this is the first reported case of this syndrome in an immunocompetent individual who had no predisposing risk factors for thrombosis, and it demonstrates the propensity for cytomegalovirus to be involved in vascular disease.

Cytomegalovirus (CMV) is a double-stranded DNA virus that belongs to the herpesvirus family. Infection with this virus is common, with seropositivity rates ranging from 40% to 100%, depending on the population surveyed [1]. Like other members of the herpesvirus family, CMV has the capacity to remain latent in tissue after acute infection occurs [2]. Initial infection with CMV can be asymptomatic and may go unrecognized, but acute disease may occur and may commonly present as Monospot-negative infectious mononucleosis in the otherwise healthy adult host [3]. In an immunocompromised patient, the presentation of acute CMV infection may be different, with CMV causing such life-threatening conditions as pneumonitis, hepatitis, retinitis, colitis, or encephalitis [4].

CMV-induced vasculopathy and thrombosis have been reported, but they are rare conditions. The few published reports on these conditions focus either on immunocompromised transplant recipients who are receiving high-dose immunosuppressive agents or on HIV-infected patients [5–11]. We present a case report of a previously healthy, immunocompetent, middle-aged man who had acute CMV infection that was complicated by extensive vasculitis and thrombosis of the hepatoportal veins and mesenteric arteries in addition to splenic infarction. This is one of the very few case reports that describe an immunocompetent individual with such a syndrome caused by CMV, and to our knowledge, it is the only one in which no other risk factors for thrombosis were present.

Case report. A 50-year-old previously healthy man who had no history of vasculitis or thromboembolic disease presented with a 2-day history of worsening abdominal pain. He had a temperature of 38.9°C (102°F), and he had rigors and diaphoresis. Initial laboratory tests revealed normal values for complete blood count, blood urea nitrogen, creatinine, serum electrolyte, lipase, and amylase levels. Transaminase and bilirubin levels were also in the normal range, and the lactate dehydrogenase level was mildly elevated to 274 IU/L. The erythrocyte sedimentation rate was 58 mm/h, blood culture results showed no growth, and urinalysis findings were negative for protein. The results of serological tests for hepatitis A, B, and C were negative.

An abdominal CT scan obtained at the time of admission showed a large, wedge-shaped, hypodense lesion in the spleen, consistent with acute infarction. A subsequently obtained abdominal arteriogram showed probable dissection (vs. thrombosis) of the distal celiac artery axis, with possible dissection of the common hepatic artery and compression of the proximal splenic artery lumen, as a result of either dissection or pressure from the false lumen of the common hepatic artery. The distal splenic artery and the left gastric artery were normal in appearance. Unusual reconstitution of the splenic artery by pancreatic-duodenal to dorsal-pancreatic flow was noted. In addition, the jejunal branches of the superior mesenteric artery were found to have an irregular caliber, and many of the vessels had an unusual beaded appearance.

Evaluation of vasculitis revealed normal complement levels, and test results were negative for antinuclear antibodies, perinuclear antineutrophil cytoplasmic antibodies, and cytoplasmic antineutrophil cytoplasmic antibodies. A hypercoagulable state was considered, but prothrombin time, partial thromboplastin time, protein C and protein S activity, homocysteine levels, and antithrombin III levels were normal. Results of tests for anticardiolipin antibodies, lupus anticoagulant, factor V Leiden, and prothrombin 20210 were negative.

On the ninth day after admission, the patient’s abdominal pain had progressed and his fever persisted; an abdominal CT scan was subsequently obtained and revealed extension of the splenic infarct. The patient underwent exploratory laparotomy and splenectomy. During surgery, 80%–90% of the spleen was found to be infarcted with extensive necrosis. The pathological...
report revealed a spleen that weighed 275 g and that contained a wedge-shaped, 8.2-cm infarct. The splenic parenchyma showed an extensive infarct. Inflammatory cells adjacent to the necrosis had nuclear and, sometimes, cytoplasmic inclusion bodies, which were consistent with CMV. The splenic hilar vessels showed organizing thrombus and rare endothelial cells with viral inclusion bodies. No true vasculitis was seen.

The results of monoclonal antibody staining for the presence of CMV were also positive (figure 1). Serological testing showed that CMV IgM and IgG levels were elevated to 2.46 UA/mL (normal level, <0.90 UA/mL) and 8.0 UA/mL (normal level, <6.0 UA/mL), respectively. CMV PP65 antigen was detectable at a level of 1 cell per 200,000 cells. The results of HIV ELISA and CMV culture of auffy coat sample were negative. Post-operatively, the patient had defervescence. He was treated with an initial course of iv ganciclovir, followed by a 2-week course of oral ganciclovir, 500 mg given t.i.d.

Approximately 6 weeks after the initial episode, the patient again developed diffuse abdominal pain and tightness that localized to the epigastrium. His liver now spanned 14.5 cm by percussion and was palpable 10 cm below the right costal margin. A CT scan of the abdomen showed extensive portal vein thrombosis that extended both into the superior mesenteric vein and intrahepatically out to the peripheral branches of the portal vein. The patient was admitted to the University of Michigan Hospital (Ann Arbor).

An abdominal venogram revealed portal, splenic, and superior and inferior mesenteric venous thrombosis. The patient underwent mechanical and local tissue plasminogen activator thrombolysis. This was followed by insertion of a catheter into the superior mesenteric vein, for infusion of tissue plasminogen activator, and insertion of a catheter into the main portal vein, for infusion of heparin. The next day, further mechanical and chemical thrombolysis was performed, and it resulted in

**Figure 1.** Cytomegalovirus (CMV) infection detected in the spleen. *Left,* One large cell shows nuclear and cytoplasmic inclusions from CMV (hematoxylin and eosin; original magnification, ×1000). *Right,* Immunohistochemical staining with antibodies against CMV shows reactivity of the nuclear inclusions in 2 cells (original magnification, ×400). Immunohistochemistry was performed on paraffin-embedded splenic tissue by use of a monoclonal antibody against an immediate-early antigen of CMV (clone 8B1.2, catalog number MAB810; 1:100 dilution; Chemicon International) with protease digestion and avidin-biotin-peroxidase detection.
marked improvement in the hepatoporal venous flow and creation of numerous patent portal venous branches. Abdominal ultrasound confirmed patency of the portal venous flow 2 days later, and the patient’s abdominal pain decreased.

Anticoagulation with coumarin therapy was initiated, and it was complicated by subcapsular hepatic therapy, which eventually resolved. The patient was treated with a second course of iv ganciclovir for 10 days, followed by oral ganciclovir, 1 g given t.i.d. for 3 months. The patient remained asymptomatic after discontinuation of ganciclovir therapy. Of interest, during the time that the patient was receiving oral ganciclovir, his wife developed a viral syndrome that was thought, on the basis of a positive test result for IgM, to be due to acute CMV infection.

Discussion. Vasculopathy with thrombosis is a rare presentation of CMV infection that is primarily reported in transplant patients following high-dose immunosuppressive therapy regimens and in HIV-infected patients [5–11]. Microscopic examination of the vessels involved typically shows evidence of perivascular inflammation plus endothelial and smooth muscle wall proliferation with thrombosis [7]. One of the early cases, reported in 1987 by Min et al. [5], involved a 36-year-old woman who died of disseminated CMV infection after receiving a heart transplant. Autopsy revealed widespread coronary arterial thrombosis. Two years later, McDonald et al. [6] reviewed 102 cardiac transplant patients and found that 16% of them had accelerated allograft vasculopathy. He also observed that 62% of the patients who were CMV seropositive showed evidence of coronary vascular thrombosis, compared with only 25% of those who were CMV seronegative. Another group of investigators in Finland reviewed the pathological findings for 104 endomyocardial biopsy specimens obtained 12–24 months after cardiac transplantation; they found that patients with CMV infection had a higher rate of perivascular inflammation and increased intimal thickness [7].

Approximately 7% of orthotopic liver transplant recipients develop hepatic artery thrombosis, which is a major cause of morbidity and graft loss. Recent studies have indicated that hepatic artery thrombosis is 5 times more likely to occur in patients who are CMV seropositive [8]. Although most reported cases of CMV infection–associated thrombosis have involved arteries, there are also case reports of unexplained venous thrombosis in kidney and bone marrow transplant recipients, as well as in HIV-infected patients who are coinfected with CMV [9–11].

In the nonimmunocompromised host with CMV, vasculitis with thrombosis appears to be extremely rare. We identified 3 previous cases reported in the literature. Two 31-year-old women with apparently active CMV disease developed hepatic vein thrombosis [12, 13], but both patients were taking oral contraceptive pills, which predispose patients to thrombosis. A 4-month-old girl with acute CMV infection also developed portal vein thrombosis, but she had protein C and protein S deficiency, which very likely contributed to thrombosis in this patient [14].

Several mechanisms have been proposed as causes of the CMV-induced vascular changes that result in perivascular inflammation and thrombosis. There is evidence that IE84, a viral immediate-early protein, binds to and inhibits the p53 tumor-suppressor gene product. This results in enhanced vascular smooth muscle cell proliferation, inhibition of cell loss through apoptosis, or both [15].

CMV infection is also known to lead to elevation of both platelet-derived growth factor and transforming growth factor–β. These growth factors can cause vascular cell wall proliferation [16]. It has been shown that CMV infection can also cause vascular cell activation and expression of adhesion proteins leading to increased platelet and leukocyte adhesion. This proinflammatory effect can cause changes that alter the anticoagulant environment of the vascular endothelium so that it favors coagulation [17]. Finally, CMV has also been shown to increase the levels of IL-1β, IL-6, TNF-α, and other cytokines that have inflammatory properties [18, 19]. Therefore, CMV infection, as a result of either one or a combination of these mechanisms, can induce vascular changes that may trigger a cascade of events that lead to inflammation and thrombosis [20].

Regardless of what the causative mechanism is, there is growing evidence that CMV infection may induce vascular damage with associated thrombosis that may be life-threatening. The patient who we describe, who had both venous and arterial clotting, is one of the very few otherwise healthy hosts in whom this syndrome has been reported. The extensive vascular involvement and thrombosis noted in this patient appear to have been induced by CMV infection. Acute CMV infection was confirmed by IgM and IgG serological tests, tests for CMV antigenemia, presence of CMV nuclear inclusion bodies in the splenic parenchyma and hilar vessels, and monoclonal antibody staining of the spleen for the presence of CMV. In addition, no other predisposing factors for this syndrome were found, despite an extensive search for other causes of vasculitis and thrombosis. Therefore, the ubiquitous CMV is a rare but potentially significant cause of arterial and venous thrombosis in otherwise healthy individuals as well as in immunocompromised hosts.

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References


