Case Reports

Fulminant Cytomegalovirus Myocarditis in an Immunocompetent Host:

Resolution with Oral Valganciclovir

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We report a case of fulminant myocarditis after a primary cytomegalovirus infection, in a previously healthy 72-year-old woman. The infection underwent clinical and immunologic resolution consequent to treatment with oral valganciclovir. In an immunocompetent host, the primary cytomegalovirus infection is usually asymptomatic or manifests itself as a heterophile-negative mononucleosis-like syndrome. Cytomegalovirus myocarditis is uncommon in immunocompetent patients. After presenting our case, we review the literature on cytomegalovirus myocarditis in immunocompetent individuals. ***(Tex Heart Inst J 2014;41(5):523-9)***

Key words: *Antiviral agents/therapeutic use; cytomegalovirus infections/drug therapy; immunocompetence; myocarditis/etiology; valganciclovir*

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We present a rare case of fulminant myocarditis caused by a cytomegalovirus (CMV) infection in an immunocompetent patient—an infection that oral valganciclovir therapy resolved in a dramatic clinical and immunologic manner. Cytomegalovirus infection occurs primarily in the setting of advanced immunosuppression (for example, among human immunodeficiency virus [HIV] patients and organ-transplant recipients) and is typically a reactivation of latent infection. Cytomegalovirus infection in an immunocompetent host is generally asymptomatic; or it might present as a mild, self-limiting, heterophile-negative, mononucleosis-like syndrome. Occasionally, primary CMV infection in immunocompetent hosts can lead to severe organ-specific complications, significant morbidity, and death.[1] In a 2008 review[2] of the medical literature, which examined 290 immunocompetent adults with severe CMV infection, the most frequent sites involved were the gastrointestinal tract (colitis) and the central nervous system (meningitis, encephalitis, and transverse myelitis), followed by the blood (hemolytic anemia and thrombocytopenia), the arterial or venous system (thrombosis), the eyes (uveitis), and the lungs (pneumonitis). In contrast, CMV myocarditis and pericarditis in an immunocompetent host are extremely rare entities: few cases have been reported to date.[3-13] It is quite possible that the true number of CMV myocarditis cases is underreported, because most cases are self limiting and underdiagnosed.

Case Report

In January 2013, a 72-year-old previously healthy white woman was hospitalized for high-grade fevers (2-week history) unresponsive to acetaminophen and for profound weakness, myalgia, headaches, and poor oral intake. She reported no recent contact with sick people or animals, no recent history of travel, no history of blood-product transfusion, and no smoking, alcohol, or recreational drug use. Her medical history was significant for hypothyroidism treated with levothyroxine. Examination at presentation was unexceptional apart from high-grade fevers up to 104 °F.

Her initial laboratory studies showed a white blood cell count of 7.6 $\times 10^3/\mu L$ (normal range, 4–11 $\times 10^3/\mu L$) with a lymphocyte count of 66% (normal range, 20%–53%). Her C-reactive protein level was 11 mg/dL (normal, ≤0.49 mg/dL). Her liver enzymes on admission were elevated: alkaline phosphatase, 201 U/L (normal range, 20–140 U/L); aspartate aminotransferase, 171 U/L (normal range, 5–40 U/L); and alanine aminotransferase, 162 U/L (normal range, 5–40 U/L). Her bilirubin lev-

els were normal. Chest radiography showed bibasilar opacities (Fig. 1A). Urinalysis results were normal. A computed tomogram (CT) of the chest (Fig. 2A), abdomen, and pelvis, and ultrasonograms of the right upper quadrant were also normal. Blood, urine, and respiratory cultures were negative.

Because of the persistent high-grade fevers, there was extensive investigation of possible causes—including an influenza A/B enzyme immunoassay and tests for Epstein-Barr virus, CMV DNA polymerase chain re-

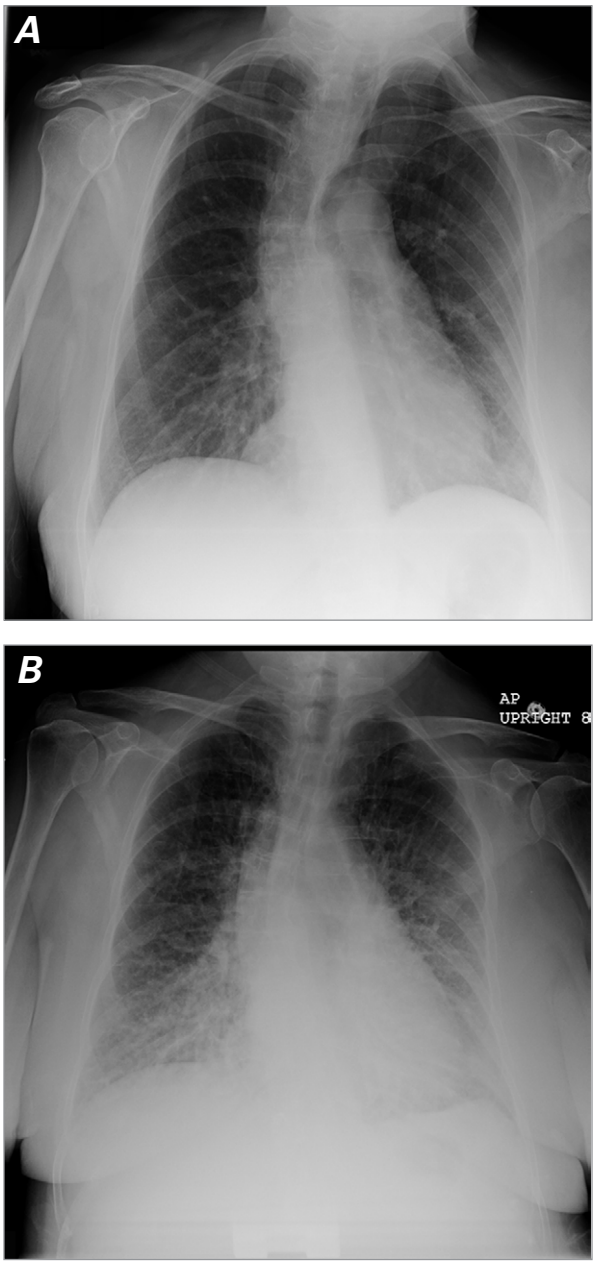

***Fig. 1 A**) Chest radiograph on admission shows bibasilar opacities. **B**) Chest radiograph within 48 hours after the initiation of oral valganciclovir shows prominent interstitial markings and hilar congestion, suggesting pulmonary edema and small bilateral pulmonary effusions.*

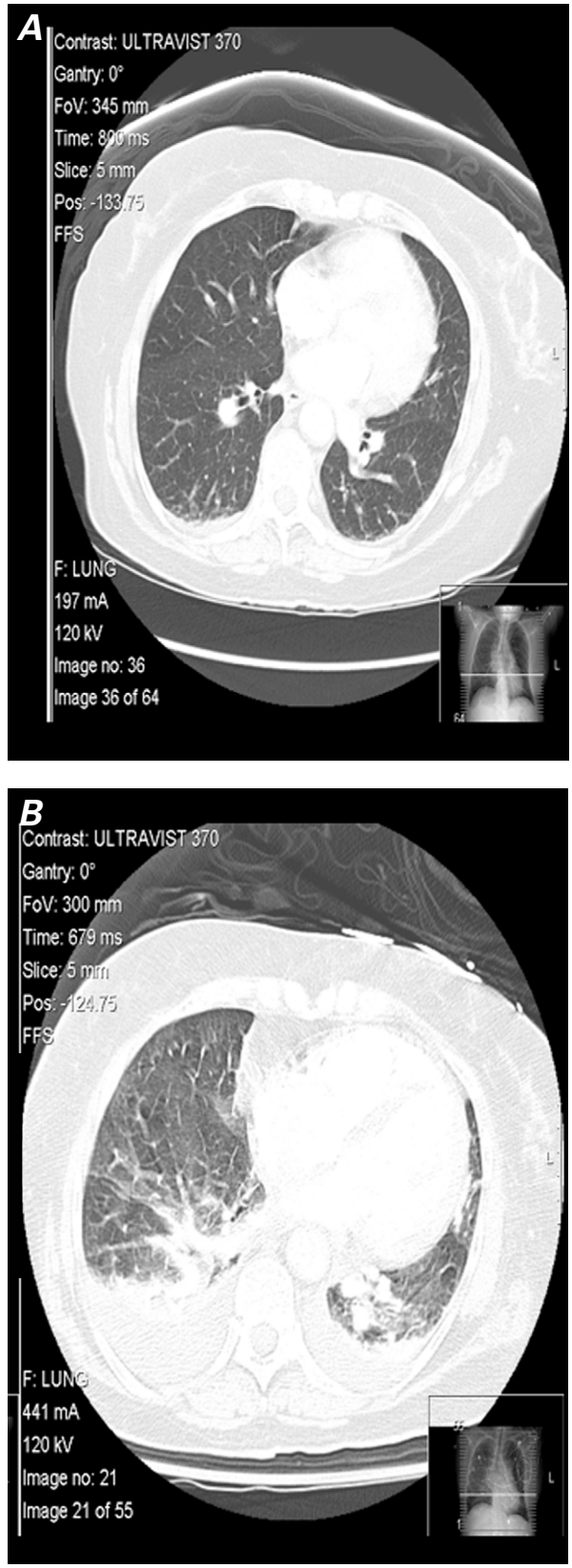

***Fig. 2 A**) Computed tomogram of chest on admission shows no significant abnormality. **B**) Computed tomographic angiogram of chest shows substantial hilar congestion, cardiomegaly, and bilateral moderate-sized pleural effusions.*

action (PCR), parvovirus B19 antibodies, anaplasma phagocytophilia antibodies, hepatitis B virus, hepatitis C virus, HIV, and rheumatic diseases. All the tests were negative, except for a CMV immunoglobulin M (IgM) titer that was strongly positive at 1.75 (index value, <0.9) with a normal CMV IgG titer of 0.6 (index value, <0.8), which suggested an acute CMV infection. A CMV DNA quantitative PCR assay revealed 13,100 viral copies/mL (>1,000 copies/mL is high).

After diagnosis, the patient was started on oral valganciclovir. Within 48 hours after initiation of treatment, despite decreased viral counts, the patient developed sudden-onset shortness of breath and was noted to be febrile (temperature, 102 °F), tachycardic (heart rate, 142 beats/min and regular), tachypneic (respiratory rate, 32 breaths/min), hypotensive (blood pressure, 72/54 mmHg), and hypoxemic (SaO_2, 68% on room air). Cardiovascular examination revealed distended jugular veins and an S_3 gallop. Lung auscultation revealed bibasilar rales. A chest radiograph showed prominent interstitial markings and hilar congestion that suggested pulmonary edema and small bilateral pulmonary effusions (Fig. 1B). A CT angiogram confirmed pulmonary interstitial edema with moderate-sized bilateral pleural effusions and showed significant cardiomegaly, when compared with the CT scan performed on admission (Fig. 2B). An electrocardiogram (ECG) showed sinus tachycardia and previously existing left bundle branch block (Fig. 3). There was also mild elevation in cardiac troponin T to 0.36 ng/mL (normal, <0.03 ng/mL), with normal creatine kinase levels. The patient's brain natriuretic peptide level was elevated at 1,537 pg/mL (normal, <100 pg/mL). Echocardiography showed severe global hypokinesis with a left ventricular ejection fraction (LVEF) of 0.25, and tissue Doppler imaging was consistent with diastolic dysfunction. The diagnosis of CMV-induced fulminant myocarditis was made on the basis of the acute clinical presentation and serologic evidence of infection.

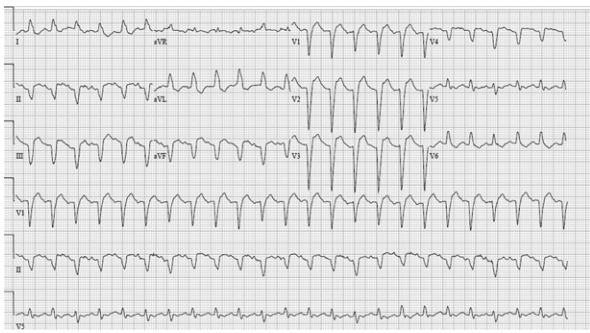

Fig. 3 *Electrocardiogram shows sinus tachycardia at 144 beats/min and previously existing left bundle branch block.*

The new-onset congestive heart failure was treated with intravenous diuretic and inotropic agents; the patient had improved hemodynamic results without the need of a mechanical circulatory support device. Treatment with oral valganciclovir was continued. During the next 2 weeks, the patient made steady progress and was weaned from the intravenous medications. Repeat CMV DNA quantitative PCR showed a level of 6,200 viral copies/mL, which further decreased to 200–1,000 copies/mL (qualitatively positive but below limits of quantization) at the time of the patient's discharge from the hospital. Echocardiography a week later showed an LVEF of greater than 0.55 with no regional wall-motion abnormalities (Table I). The patient was discharged from the hospital on oral valganciclovir for a

TABLE I. Relevant Laboratory and Imaging Data on Admission and Subsequent Days

Variable	Normal Range	Day 1	Day 3 (Antiviral Started)	Day 5	Day 7	Day 14
WBC ($\times 10^3/\mu L$)	4–11	7.6	5.5	9.4	6.5	4.5
CMV viremia (copies/mL)	<1,000	—	13,100	6,700	2,600	200–1,000
Creatine kinase (U/L)	24–173	—	—	129	42	—
Troponin T (ng/mL)	<0.03	—	—	0.36	0.15	—
BNP (pg/mL)	0–99	—	—	1,537	—	301
ALP (U/L)	32–122	201	181	160	—	—
AST (U/L)	10–50	171	147	91	—	—
ALT (U/L)	10–50	162	141	101	—	—
Total bilirubin (mg/dL)	0.2–1	0.5	0.5	0.4	—	—
LVEF	—	—	—	0.25	—	0.55

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; CMV = cytomegalovirus; LVEF = left ventricular ejection fraction; WBC = white blood cell count

TABLE II. Reported Cases of CMV Myocarditis in Immunocompetent Hosts

Reference	Age, Sex, and History	Signs and Symptoms	Laboratory Findings	Imaging	Diagnosis	Treatment	Course
Wilson RS, et al.[3] (1972)	60, F, scarlet fever in childhood	3 wk fever, tachycardia, SOB at rest, and paroxysmal nocturnal dyspnea. Exam: +JVD, bibasilar rales, and gallop	Four-fold increase in complement-fixing CMV ab titer; CMV ag in urine negative; sinus tachycardia, LBBB, and LVH	Catheterization: significantly elevated left- and right-sided filling pressures	CMV myocarditis	Failed supportive HF therapy; cytosine arabinoside for 5 d	Viral titers and HF resolved; cardiomegaly, mitral insufficiency, and LBBB persisted
Waris E, et al.[4] (1972)	43, F, none	1 wk fatigue, SOB, and lower-extremity swelling. Exam: +JVD, pansystolic murmur over precordium, and hepatomegaly	Four-fold increase in complement-fixing CMV ab titer, CMV ag in urine, abnormal LFTs; initial sinus rhythm with T-wave inversion in leads II, III, aVF, and V_1 through V_5; later, paroxysmal atrial fibrillation and transient 2nd-degree atrioventricular block	Chest radiograph: cardiomegaly and pulmonary congestion	Fatal CMV myocarditis, hepatitis, encephalitis, and adrenal insufficiency	HF therapy and prednisone	Died at 7 mo. Autopsy (heart): diffuse inflammatory infiltrate, enlarged muscle fibers with halos, and inclusion-like bodies consistent with CMV myocarditis
Wink K and Schmitz H[5] (1980)	31, M, none	1 wk fever, tachycardia, SOB on exertion, and lower-extremity swelling	+IgM CMV titers, CMV ag in urine, and 4-fold increase in complement-fixing ab titer; sinus tachycardia, LAD, and T-wave inversion in leads I, II, aVL, and V_2 through V_6	Echo: cardiomegaly and RWMA	CMV myocarditis	Supportive therapy	Complete resolution at 3 wk
Dietz AJ Jr[6] (1981)	21, M, bronchitis, measles, mumps, and rubella in childhood	2 d fever, SOB on minimal exertion, palpitations, and sharp precordial chest pain. Exam: tachycardia, tachypnea, axillary lymphadenopathy, pericardial friction rub, and hepatosplenomegaly	+IgM CMV titers; urine and buccal smear cultures +CMV, elevated CK, and abnormal LFTs; sinus tachycardia, T-wave inversions in leads I and aVL, and biphasic T waves in leads V_3 through V_6	Echo: normal LVEF and no effusion	CMV myopericarditis, hepatitis, and hemolytic anemia	Supportive therapy and aspirin	Complete resolution at 4 wk
Biton A and Herman J[7] (1989)	29, M, none	1 wk fever, SOB on exertion, palpitations, and pleuritic chest pain. Exam: tachycardia, normal heart and lung sounds, and no pericardial friction rub	Abnormal LFTs and 4-fold rise in IgM CMV titers; sinus tachycardia, and T-wave inversion in leads II, III, aVF, and V_2 through V_6	Echo: normal LVEF and small pericardial effusion	CMV myopericarditis and hepatitis	Supportive therapy	Complete resolution within a few weeks
McCormack JG, et al.[8] (1998)	31, M, none	Fever, cough, SOB, palpitations, abdominal pain, and jaundice. Exam: tachycardia, hypotension, +JVD, bibasilar rales, S_3 gallop, and tender hepatomegaly	+IgM CMV EIA titers, elevated WBC count, and abnormal LFTs; atrial fibrillation at 170 beats/min	Echo: global hypokinesis and LVEF of 0.36	CMV myocarditis and hepatitis	HF therapy and intravenous ganciclovir for 14 d	Complete resolution at 2 wk

Table continued on next page.

TABLE II (continued)**.** Reported Cases of CMV Myocarditis in Immunocompetent Hosts

Reference	Age, Sex, and History	Signs and Symptoms	Laboratory Findings	Imaging	Diagnosis	Treatment	Course
Zubiaurre L, et al.[9] (2007)	36, M, none	Fever, and chest pain radiating to shoulders	+IgM CMV titers, abnormal LFTs, and elevated CK, CK-MB fraction, and Tn-T; diffuse ST elevation	Not reported	CMV myopericarditis and hepatitis	Supportive therapy and aspirin	Complete resolution within a few days
Fernández-Ruiz M, et al.[10] (2008)	32, M, none	2 d pleuritic chest pain. Exam: pericardial friction rub	+IgM CMV EIA titers, +pp65 antigenemia, abnormal LFTs, and elevated CK, CK-MB fraction, and Tn-T; sinus tachycardia and incomplete RBBB	Echo: normal LVEF and no pericardial effusion	CMV myopericarditis and hepatitis	Initially, high-dose aspirin; for worsening LFTs and abdominal symptoms, oral valganciclovir started	Complete resolution at 2 wk
Baumgratz JF, et al.[11] (2010)	38, M, none	6 wk fever, malaise, and neck lymph node swelling; 1 wk SOB and palpitations. Exam: tachycardia, hypotension, +JVD, bibasilar rales, and S_3 gallop	+IgM CMV EIA titers and +CMV PCR. Endomyocardial biopsy: inflammation, edema, and mononuclear infiltrate; sinus tachycardia and nonspecific ST-T changes	Echo: LVEF of 0.40	CMV myocarditis and cardiogenic shock	Oral ganciclovir for total 21 d, pulse-dose intravenous methylprednisolone for 5 d, then oral steroid taper for 21 d	Complete resolution at 3 wk
Roubille C, et al.[12] (2010)	35, M, none	1 wk severe headaches, asthenia, and polymyalgia	+IgM CMV titers, elevated CRP, and normal cardiac enzymes; sinus rhythm	Echo: LVEF of 0.50 and RWMA; CMR: lateral hypokinesis, LVEF of 0.35, and delayed subepicardial enhancement in lateral wall	CMV myocarditis	Supportive therapy	Complete resolution at 2 wk
Vanstechelman F and Vandekerckhove H[13] (2012)	29, M, none	Fatigue, myalgia, chest pain, dizziness, and interscapular pain	+IgM CMV titers, elevated Tn-I, and abnormal LFTs; diffuse ST elevations	CMR: delayed subepicardial gadolinium enhancement in inferior and posterolateral wall of left ventricle; normal LVEF and pericardial effusion	CMV myopericarditis and hepatitis	Supportive therapy and aspirin for 6 wk	Complete resolution
Current case	72, F, hypothyroidism	High-grade fevers, profound weakness, myalgias, headaches, and poor oral intake. Exam: temperature 102 °F, tachycardia, hypotension, +JVD, bibasilar rales, and S_3 gallop	+IgM CMV titers, +CMV DNA PCR, elevated Tn-T, and abnormal LFTs; sinus rhythm, old LBBB	Echo: LVEF of 0.25 and diffuse hypokinesis	CMV fulminant myocarditis and hepatitis	Oral valganciclovir for total 21 d and HF therapy	Complete resolution at 3 wk

+ = positive; ab = antibody; ag = antigen; CK = creatine kinase; CMR = cardiac magnetic resonance; CMV = cytomegalovirus; CRP = C-reactive protein; ECG = electrocardiogram; Echo = echocardiogram; EIA = enzyme immunoassay; Exam = examination; F = female; HF = heart failure; Ig = immunoglobulin; JVD = jugular venous distention; LAD = left-axis deviation; LBBB = left bundle branch block; LFT = liver function test results; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; M = male; PCR = polymerase chain reaction; RBBB = right bundle branch block; RWMA = regional wall-motion abnormalities; SOB = shortness of breath; Tn = troponin; WBC = white blood cell count

total course of 21 days and on metoprolol succinate for 6 months. She remained asymptomatic at her 6-month follow-up visit and was monitored thereafter by outside providers.

Discussion

To the best of our knowledge, this is the 3rd reported case of severe fulminant CMV myocarditis treated with valganciclovir therapy that resulted in complete resolution of symptoms. A comprehensive review of the English-language medical literature yielded 16 reported cases of CMV myocarditis in immunocompetent individuals,[3-13] including our case and 4 cases from the review by Eddleston and colleagues.[1] There were 6 women and 10 men. The mean age of the patients was 36 ± 14 years. These cases are summarized in detail in Table II.

In a retrospective population-based study[14] to identify (by means of in situ hybridization and PCR technology) a viral cause in myocardial autopsy specimens of 40 patients who died of myocarditis, the most common viral nucleic acid identified in 15 of 40 of the specimens (38%) was CMV DNA. Fourteen of these 15 patients with CMV DNA were immunocompetent, which raised the possibility of CMV as an agent of fatal myocarditis in such hosts.

The presentation of CMV myocarditis in immunocompetent hosts can range from asymptomatic ECG or echocardiographic changes[12] to symptoms of cardiac dysfunction—including heart failure, cardiogenic shock, intractable arrhythmias, and death.[1,4,8,11] If the CMV infection is associated with pericarditis, patients might also report pleuritic chest pain and manifest pericardial friction rub on auscultation, diffuse ST elevations on ECG, and pericardial effusion on echocardiography.[6,7,9,10,13] Classically, a prolonged viral prodrome is typical before the development of cardiac symptoms, as seen in our patient.

In our patient, a presumptive diagnosis of CMV myocarditis was made on the basis of high CMV IgM titers and a positive CMV DNA quantitative PCR assay, along with the patient's cardiac biomarker elevation and abnormal echocardiogram. Although the gold standard for diagnosing myocarditis has for almost 3 decades been an endomyocardial biopsy that shows lymphocyte infiltrate and myocardial necrosis in accordance with the Dallas criteria,[15] endomyocardial biopsy has low sensitivity because of the patchy nature of the disease, sampling error, and intraobserver variability in interpretation.[16] Molecular techniques such as in situ hybridization and PCR amplification have improved the sensitivity of viral genome detection in biopsy specimens remarkably.[14] The CMV antigen can also be detected in urine.[4,5] Cardiovascular magnetic resonance (CMR) has emerged as a valuable noninvasive tool in diagnosing myocarditis with 76% sensitivity, 95.5% specificity, and 85% accuracy.[17] Neither endomyocardial biopsy nor CMR was performed in our patient, because she experienced expedited clinical improvement of her heart-failure symptoms and echocardiographic resolution of her left ventricular dysfunction with valganciclovir therapy.

Although the treatment of CMV myocarditis with antiviral agents is well established in immunosuppressed populations,[18] the potential side effects of valganciclovir therapy—including bone marrow suppression, renal toxicity, teratogenicity, carcinogenicity, and permanent infertility—render its use debatable in immunocompetent individuals. Nine of the 16 cases of CMV myocarditis in immunocompetent individuals were self-limited, resulting in complete recovery without antiviral therapy.[1,3,5-7,9,10,12,13] In the presented case and in 2 previously reported cases with documented severe left ventricular dysfunction, the antiviral therapy led to a complete resolution of symptoms.[8,11] On the other hand, 4 of 16 patients with CMV myocarditis who had multiorgan involvement did not receive antiviral therapy and died.[1,4] Even though half of the cases of CMV infection in an immunocompetent host are mild and self-limiting (with complete recovery), the benefits of valganciclovir therapy might outweigh the risks when one considers the high mortality rate in patients with fulminant myocarditis, severe myocardial dysfunction, and multiorgan involvement.

In conclusion, CMV should always be considered a potential causative agent of severe myocarditis, even in an immunocompetent host. If the patient tests positive, prompt initiation of antiviral therapy might improve the chances of recovery, especially in patients with cardiac dysfunction and evidence of multisystem involvement.

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