Cytomegalovirus Myopericarditis and Hepatitis in an Immunocompetent Adult: Successful Treatment with Oral Valganciclovir

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Abstract

Primary infection by cytomegalovirus (CMV) commonly occurs subclinically or manifested by a self-limited mononucleosis-like syndrome in immunocompetent subjects. Severe clinical pictures are uncommon. We present a case of acute myopericarditis and hepatitis in a previously healthy 32-year-old man with primary CMV infection, assessed by serology and positive pp65 antigenemia. He was successfully treated with a course of oral valganciclovir therapy, with an immediate clinical response and normalization of laboratory tests. The literature on simultaneous presentation of CMV pericarditis and hepatitis in immunocompetent hosts, as well as the role of oral valganciclovir in this clinical setting, is reviewed.

Key words: cytomegalovirus, myopericarditis, hepatitis, immunocompetent, valganciclovir

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Introduction

Cytomegalovirus (CMV) infection is endemic around the globe, with notable differences in the seroprevalence according to geographical region and socioeconomic status. Acquisition of the virus (via saliva, sexual contact, breastfeeding, placental transfer, blood transfusion or transplantation) arises gradually from an early age; overall seroprevalence varies from 40% to 70% of the adult population in developed regions, and it may exceed 90% in specific groups (homosexual subjects) or developing countries (1). Primary CMV infection presents as a symptomatic event in less than 10% of immunocompetent people (1, 2). However, a wide range of presentations have been described in this population, ranging from mononucleosis-like syndrome, to uncommonly severe clinical pictures with multivisceral involvement (such as interstitial pneumonitis, hepatitis, hematologic disorders, or

meningoencephalitis), and it is often associated with significant mortality (2, 3). Cardiovascular complications constitute a very unusual manifestation of CMV infection, with a few cases reported to date in the literature (4-8). Herein, we describe a previously healthy patient who developed acute myopericarditis and hepatitis following primary CMV infection; he responded favourably to a 14-day course of oral valganciclovir.

Case Report

A 32-year-old man presented to the emergency department of a primary care hospital with pleuritic chest pain which radiated to the shoulders lasting for about 48 hours. The patient was a non-smoker with no relevant past medical history; he denied any previous trauma, recent alcohol consumption, or illicit drug abuse. He had never received blood products. A diagnosis of acute myopericarditis was estab-

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Table 1. Relevant Hematological and Blood Chemistry Values on Admission and Subsequent Days

Variable	Day 1	Day 3	Day 4	Day 5	Normal range
White blood cell count	5.67		4.81		$3.40-8.20 \times 10^9/L$
Lymphocyte count	2.83		2.22		$1.05-4.80 \times 10^9/L$
Atypical lymphocyte count	20%		15%		
CK	256	174	148	96	10-190 IU/L
CK-MB	41	24	22	15	5-20 IU/L
Tropononin T	0.23	0.33	0.43	0.53	<0.04 ng/mL
AST	44	228		405	5-45 IU/L
ALT	69	327		653	5-45 IU/L
LDH	258			477	90-230 IU/L
GGT	20	25		32	3-52 IU/L
Total bilirubin	0.52	0.33	0.43	0.30	0.2-1.0 mg/dL
Creatinine	0.99	1.18		1.20	0.3-1.1 mg/dL
Protrombin activity	88		75	60	80-120 %

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK: creatinine kinase; GGT: gamma-glutamyl transpeptidase; LDH: lactic dehydrogenase.

lished on the basis of clinical history, presence of pericardial friction rub on physical examination, and moderate elevation of myocardial necrosis markers; symptomatic treatment with salicylic acid was subsequently initiated. Nevertheless, the patient referred himself to our institution five days later because of persistence of symptoms. He also complained of asthenia, cephalgia, myalgias and diffuse arthralgias. Recent drug history did not include exposure to β -lactam antibiotics. On admission his blood pressure was 105/66 mmHg, pulse rate 62 beats per minute, respiratory rate 21 breaths per minute, and temperature 36.6°C. The physical examination was unremarkable except for a three-component pericardial friction rub on thoracic auscultation, accompanied by a single, subcentimetric, asymptomatic right cervical lymphadenopathy. Neither rash nor splenomegaly was detected. Routine serum testing revealed relative lymphocytosis of over 50.0% (white blood cell count, $5.67 \times 10^9/L$; lymphocyte count, $2.83 \times 10^9/L$), associated to a moderate elevation of serum cardiac troponin T (0.23 ng/mL; cutoff value, < 0.04); other laboratory investigations, including liver function tests, initially remained within normal values. Laboratory data on admission at our institution are summarized in Table 1. Twelve-lead electrocardiogram showed sinus rhythm with incomplete right bundle-branch block, similar to previous studies. Chest X-ray was normal. Over the following 96 hours the serum myocardial enzyme levels continued to rise to a maximum of 0.53 ng/mL for troponin T (Table 1). Diagnosis of acute myopericarditis was confirmed as assessed by the association of clinical history with both auscultatory and laboratory findings. The patient was admitted to the hospital and treatment with high doses of salicylic acid was continued. Trans-thoracic echocardiogram revealed normal left ventricle function with no findings suggestive of pericardial effusion or cardiac tamponade. In the course of

the following days, the patient's general condition deteriorated with nausea, vomiting, right hypochondralgia, and marked asthenia. Liver function tests showed: aspartate aminotransferase (AST), 678 IU/L (normal range, 5-45); alanine aminotransferase (ALT), 1,178 IU/L (normal range, 5-45); gamma-glutamyl transpeptidase (GGT), 112 IU/L (normal range, 3-52); lactic dehydrogenase (LDH), 498 IU/L (normal range, 90-230); and prothrombin activity, 48% (normal range, 80-120 %). Total bilirubin, alkaline phosphatase, and creatinine levels, were within normal limits. There was no evidence of hepatic encephalopathy. Abdominal ultrasonography showed no relevant findings. An extensive serological screening was performed with the aim to identify any possible viral cause of hepatitis: hepatitis B surface antigen, anti-hepatitis B core antigen immunoglobulin (Ig) M and IgG, hepatitis C virus IgG, hepatitis A virus IgM and IgG, *Toxoplasma gondii* IgM, human immunodeficiency virus (HIV)-1 and -2 total IgG, and Epstein-Barr anti-capsid viral antigen (VCA) IgM, were all negative. We ruled out other potential causes of acute hepatitis, including drug-induced or autoimmune hepatitis, hereditary hemochromatosis, Wilson's disease, or α 1-antitrypsin deficiency. CMV-specific IgM titer (by enzyme-linked immunosorbent assay) was strongly positive (96.3), associated with undetectable CMV IgG values (<0.5); pp65 antigenemia (by immunofluorescent assay in peripheral blood leukocytes) was also performed, showing more than 10 positive cells per 2×10^5 leukocytes. The patient was diagnosed with acute myopericarditis and hepatitis due to primary CMV infection. In view of his stable clinical condition, we started specific antiviral treatment with oral valganciclovir (900 mg q 12 hours for 2 weeks) in association with oral salicylic acid (1.8 g q 8 hours). In the subsequent days the patient's general condition showed an obvious clinical improvement, with rapid

Figure 1. Clinical and laboratory evolution and effect of valganciclovir therapy.

resolution of asthenia, nausea and hypochondalgia. The pericardial friction rub disappeared within one week after starting the treatment. Progressive normalization of both liver function indices and serum myocardial enzymes following valganciclovir introduction is shown in Fig. 1. The patient underwent a second echocardiographic examination previous to discharge, with no evidence of clinically relevant myocardial or pericardial disease. CMV antigenemia assay became negative within 14 days of treatment. Four months after discharge, he remains asymptomatic without evidence of recurrent pericardial or liver disease. All laboratory values are within normal ranges (ALT, 37 IU/L; AST, 25 IU/L; GGT, 17 IU/L; CK, 64 IU/L; troponin T, <0.04 ng/mL), and convalescent CMV IgG titer rose from 0.49 to 9.10.

Discussion

In most of the immunocompetent adults, primary CMV infection constitutes an asymptomatic episode or typically runs a self-limited, mononucleosis-like clinical picture (1). The potential role of CMV, either via reactivation of latent infection or via primary acquisition, may be considered into the differential diagnosis of prolonged, unexplained, relapsing febrile syndrome associated with diverse non-specific symptoms (such as asthenia, arthralgia, or sweating) (2, 3). Evidence of cardiovascular events, mainly acute pericarditis or myopericarditis, following CMV infection has been rarely reported in immunocompetent hosts without any identifiable risk factor (4-9). However, it has been suggested that this association may remain underdiagnosed due to its usually non-severe evolution (5). Most of the previous reports have dealt with CMV pericarditis as an incidental electrocardiographic finding during the course of a typical mononucleosis-like syndrome (3, 7). However, severe com-

plications associated with acute myopericarditis, such as hemodynamically significant cardiac tamponade or acute heart failure, have been reported in this setting (4, 6, 8). In a series of 115 hospitalized non-immunocompromised adults with proved or presumed diagnosis of primary CMV infection, Bonnet et al included only two cases of pericarditis (1.7% of the entire cohort), diagnosed as a fortuitous finding during routine echocardiogram (3). In a prospective clinical trial of subxiphoid pericardial biopsy in 57 adults with large pericardial effusions, Campbell et al found five patients with CMV pericardial disease (four of them with CMV culture-proven diagnosis in pericardium or pericardial fluid, and one case diagnosed retrospectively by serologic testing) (8). Predisposing factors for the development of CMV infection were present in three of the five cases (rheumatoid arthritis treated with prednisone, chronic renal failure, and congenital heart disease, respectively).

Liver function test abnormalities are frequently reported in immunocompetent adults with clinically relevant primary CMV infection, occurring in up to 90% of cases (1, 3). Sub-clinical, mild to moderate elevation of circulating level of transaminases, that rarely exceeds 5-fold above normal, constitutes the most frequently observed laboratory alteration, affecting alanine aminotransferase more than aspartate aminotransferase (3, 9). Increases in alkaline phosphatase or total bilirubin levels are uncommon. These findings are usually self-limited, with progressive normalization of transaminase levels after a few weeks (1, 3). However, unusual clinical patterns with severe cholestatic course, granulomatous hepatitis, or acute hepatocellular failure, have been rarely described (10, 11).

The data regarding the need for specific antiviral therapy in non-immunocompromised subjects with severe CMV infection, are rather conflicting (3, 9). The clinical improve-

ment observed in some uncontrolled case reports may be related to the usually self-limiting course of the disease; however, some authors have advocated a relatively short course of parenteral ganciclovir in order to reduce the symptomatic phase of the infection (11, 12). Although the role of oral valganciclovir in the management of CMV disease in high-risk seropositive transplant patients has been well established (13), its usefulness in non-immunocompromised subjects remains unclear. No definitive conclusions can be drawn about the indication of such therapy from the few experiences reported in this clinical setting (14, 15). In the present patient, the progressive character of liver function deterioration associated with mild coagulopathy, with normal bilirubin levels and no signs of encephalopathy, prompted us to introduce specific treatment with valganciclovir. To the best of our knowledge, this is the first case of CMV myopericarditis and hepatitis successfully treated with oral valganciclovir in an immunocompetent host. However, any pre-

sumed benefit derived from specific antiviral therapy must be weighed against its potential toxicity and the risk of selection of resistant viral strains after long-term courses of treatment (3).

A review of the English language literature revealed only three previous, well documented cases reporting simultaneous acute myopericarditis and hepatitis associated to primary CMV infection in an immunocompetent subject (5, 9, 10). Remarkably, no predisposing factors resulting in increased susceptibility to CMV disease were present in the present patient. In conclusion, the possibility of primary CMV implication should be considered in cases of simultaneous development of acute myopericarditis and hepatitis, even in the absence of apparent risk factors for immunosuppression. The present case illustrates that oral treatment with oral valganciclovir may be beneficial in such patients. However, more clinical experience is necessary to evaluate the potential role of this specific antiviral therapy in this setting.

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