Case Report

A 17-Year-8-Month Boy with Acute Human Immunodeficiency Virus Infection Presenting with Cardiomyopathy and Creatinine Kinase Elevation: A Case Report

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Acute human immunodeficiency virus (HIV) infection could be challenging to diagnosis due to lack of awareness, unspecific clinical presentations and limited information available. Furthermore, it was rare of acute HIV infection to present with cardiomyopathy. This was a case of 17-year-8-month boy admitted for intermittent fever for 5 days, with accompanying symptoms of sore throat and diarrhea. The clinical course was complicated by massive lower gastrointestinal bleeding, shock and multi-organ failure. The diagnosis of an acute HIV infection was made with a markedly high viral load (>10,000,000 copies /mL), accompanied with myocarditis and acute heart failure. Cytomegalovirus viremia was found. The patient was treated with Ganciclovir along with broad-spectrum antibiotics. His clinical condition improved after treatments. One and a half year later at clinic follow-up, the echocardiography showed normalization of left ventricular systolic function.

Key words: acute HIV infection, cardiomyopathy, acute heart failure, creatinine kinase

Introduction

The discussion of acute human immunodeficiency virus (HIV) infection with cardiomyopathy and acute heart failure was scarce in current literature. In a local HIV cohort study in Taiwan,[1] acute HIV infection with heart disease complication was not even mentioned. In the pre-antiretroviral therapy (ART) era, HIV-associated cardiomyopathy (HIVAC) is an infrequent complication of HIV infection and was known to carry high mortality. To date, there was no native HIVAC case report or case series. Since a local document was lacking, we present a case of a 17-year-8-month old boy diagnosed with acute HIV infection manifesting as cardiomyopathy and acute heart failure.

Case Report

A 17-year-8-month-old boy with intermittent fever for five days presented to a pediatric emergency department (PED) despite

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under treatment with cephalexin by a general physician. He described sore throat, mild dry cough, general muscle soreness, decreased appetite and activity and nausea sensation.

The patient denied any hereditary and congenital disease. He denied any previous systemic illness. He had a normal development. He had neither travel, contact nor cluster history in recent 3 months. He had no known allergy history. After this hospitalization, he was known to have engaged in sexual intercourses with other men without fixed partners.

At PED, vital signs were within normal range except for a low-grade fever up to 37.9 degrees Celsius. Physical examination showed injected throat and enlarged tonsils. Chest radiograph showed bilateral clear lung fields. Urinalysis showed no sign of infection. Laboratory data was listed as Table 1. Abnormal liver function was found.

Streptococcal pharyngitis and infectious mononucleosis were the preferred infection etiology. Thus, the patient was checked for Epstein-Barr virus (EBV) antibodies. However, he refused influenza rapid test. He was discharged from PED with symptomatic treatments. Three days later at clinic follow-up, his intermittent fever persisted, along with new symptoms such as diarrhea and dizziness. He was admitted for treatments.

Multiple tests were done to survey for the infection focus. Serum tests came back negative for group A streptococcal (GAS) antigen. The EBV viral capsid antigen immunoglobulin G (EB-VCA IgG) was positive (ratio > 50 compared to the control; reference: < 9) while the EB-VCA IgM was negative (ratio 4.14 compared to the control; reference: < 9), indicating a previous infection. Hepatitis survey was positive for anti-hepatitis A virus immunoglobulin G (HAV IgG) antibody, suggesting a previous infection. Since the patient was young and acute retroviral syndrome was suspected due to his presentation of fever, pharyngitis, diarrhea and hepatitis, HIV antibody 1+2 Combo test was done and turned back positive. Then, Western blot test was done to confirm his HIV infection.

The patient developed oral mucosa erosion, abdominal pain and bloody diarrhea over ten times a day after hospitalization. Stool routine test showed presence of pus (1+), mucus (1+) and occult blood (4+); but no parasite ova. Ciprofloxacin was initiated on the fourth day of admission to treat infectious diarrhea.

Then, patient experienced breakthrough abdominal pain with dyspnea, tachycardia, hypotension, decreased urine output and altered mental status. Hypotension persisted after fluid resuscitation. Dopamine and norepinephrine were initiated as inotropic agents. He was transferred to the pediatric intensive care unit (PICU) for shock management. The laboratory data during resuscitation in PICU was listed in Table 1 and followed chest radiograph was shown as Figure 1. Meropenem, metronidazole and teicoplanin were given as empirical antibiotics to manage this episode of septic shock.

After admission into PICU, electrocardiogram (ECG) showed sinus tachycardia (heart rate up to 180-190 beats per minute) without obvious ST-T changes. The cardiac enzymes and brain natriuretic protein (BNP) were markedly elevated: creatine kinase (CK) 7224 units per liter (U/L), CK-MB isoenzyme (CK-MB) 69.5 nanograms per milliliter (ng/mL), high-sensitive troponin-I 6.817 picograms per milliliter (pg/mL) and BNP 2504 pg/mL. Reduced left ventricular ejection fraction (LVEF, 29.5%) and paradoxical septal motion were identified under the echocardiography; no chamber dilation. Ecchymoses were found over his bilateral thighs. The disseminated intravascular coagulation (DIC) profile was positive for increased level of d-dimer (> 35.2 mg/L) and fibrin degradation product (FDP, 225.7 micrograms per milliliter (μg/mL)). Severe cardiac and/or septic shock leading to multi-organ failure (brain, heart, lung, kidney,

Table 1. Laboratory data at PED and PICU.

Hemogram	PED	PICU	Unit	Reference
White blood cell (WBC)	4.95	17.59	k/μL	3.9 – 10.6
Red blood cell (RBC)	5.06	4.92	M/μL	4.5 – 5.9
Hemoglobin (Hb)	14.9	14.2	g/dL	13.5 – 17.5
Hematocrit (Hct)	44.4	41.7	%	41 – 53
Mean corpuscular volume (MCV)	87.7	84.8	fL	80 – 100
Mean corpuscular hemoglobin	29.4	28.9	pg/cell	26 – 34
Mean corpuscular hemoglobin concentration	33.6	34.1	g/dL	31 – 37
Platelet	87	113	k/μL	150 – 400
Band	0.0	5.2	%	
Lymphocyte	28.0	1.7	%	20 – 56
Monocyte	4.5	2.6	%	4 – 10
Eosinophil	0.0	0.0	%	1 – 5
Basophil	0.0	0.0	%	0 – 1
Neutrophil	66.5	75.7	%	42 – 74
Myelocyte	0.0	5.2	%	
Metamyelocyte	0.0	9.6	%	
Atypical lymphocyte	1.0	0.0	%	
Biochemistry	**PED**	**PICU**	**Unit**	**Reference**
Lactate dehydrogenase (LDH)	N/A	1400	U/L	106 – 211
Aspartate aminotransferase (AST)	68	250	U/L	0 – 38
Alanine aminotransferase (ALT)	50	231	U/L	0 – 40
Blood urea nitrogen (BUN)	N/A	27.4	mg/dL	6 – 21
Creatinine (Cr)	1.1	3.3	mg/dL	1.1 – 1.5
Sodium (Na)	N/A	123	mEq/L	135 – 148
Potassium (K)	N/A	3.7	mEq/L	3.5 – 5.3
Calcium (Ca)	N/A	6.2	mg/dL	8.8 – 10.3
Creatine kinase (CK)	161	N/A	U/L	38 – 160
C-reactive protein (CRP)	13.2	118.7	mg/L	0 – 5
Lactate	N/A	55.85	mg/dL	4.5 – 20

PED: pediatric emergency department, PICU: pediatric intensive care unit, N/A: not tested

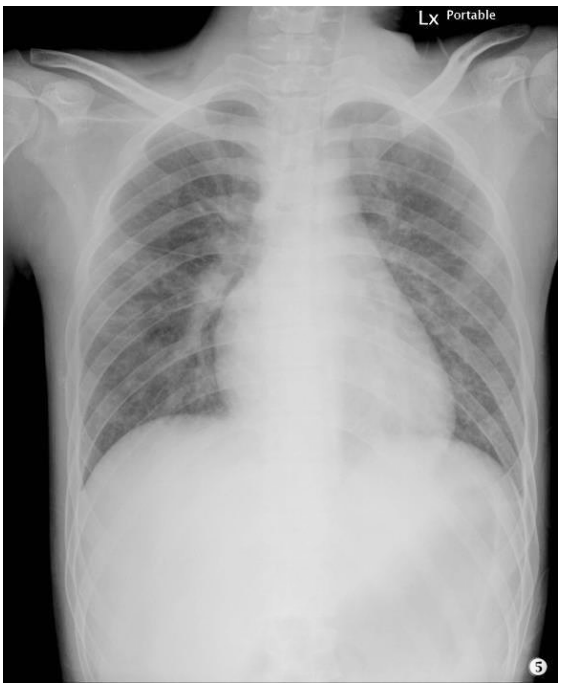


Fig. 1 Chest radiograph upon pediatric intensive care unit admission.

coagulation system) was the most likely explanation. On the fifth day of admission, he was intubated for respiratory failure and transferred to medical ICU (MICU).

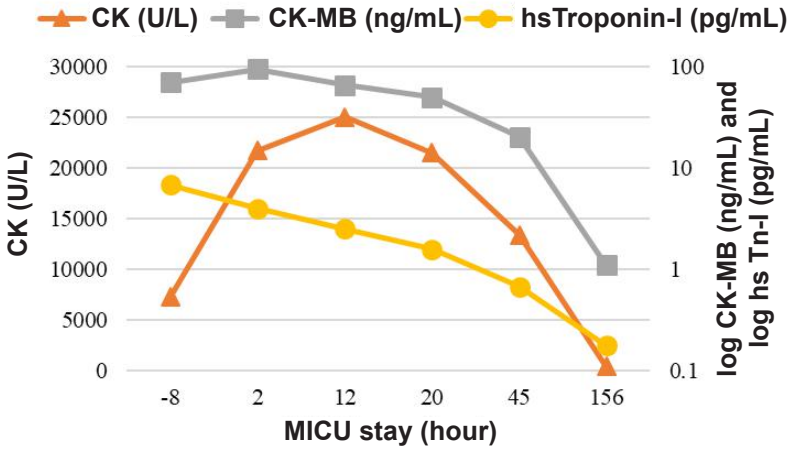
The pulse contour cardiac output monitoring (PiCCO), presented in Table 2, showed a fair cardiac index (CI) with decreased systemic vascular resistance index (SVRI) under the effects of high-dose vasopressors and inotropic agents. The consulted cardiologist suggested that the patient's markedly elevated CK level was related to rhabdomyolysis in addition to myocardial damage, and rhabdomyolysis could worsen the existing hypoperfusion-related acute kidney injury. Continuous venovenous hemofiltration (CVVH) was initiated to manage persistent shock with

anuria. Broad-spectrum antibiotics with levofloxacin, imipenem/cilastatin, teicoplanin and fluconazole were empirically administered. Then, his fever and shock status gradually resolved. The CK level peaked at 25,027 U/L on the sixth day of admission, then declined.

The prior Western blot confirmatory test was indeterminate, since Env and Pol antigen bands were absent. Only Gag p24/25 antigen was detected. The HIV viral load was > 10,000,000 copies per milliliter (cp/mL) and the lymphocyte with cluster of differentiation 4 receptor ($CD4^+$) count was 33 cells /uL only. According to Fiebig Stage Classifications, the patient may be in an acute HIV infection. On the sixth day of admission, the patient began receiving combination antiretroviral therapy (cART) with abacavir 600 mg/lamivudine 300 mg/dolutegravir 50 mg (Triumeq®). Trimethoprim/sulfamethoxazole (TMP/SMX) was given as prophylaxis for Pneumocystis jirovecii pneumonia infection.

Ill-defined opacities were seen on serial chest radiographs and the patient developed hemosputum, massive bloody stool and generalized vesicles and bullae eruption on his trunk and extremities during the MICU stay. Tests for Mycoplasma pneumoniae IgM, adenovirus antigen, influenza A, influenza B, parainfluenza-1, parainfluenza-2 and parainfluenza-3 all came back negative. Serologic tests for cytomegalovirus (CMV), herpes simplex virus (HSV) and varicella zoster virus (VZV) were done and deoxyribonucleic acid (DNA) of CMV were tested. CMV DNAemia was found. Since the patient had presentations of cardiomyopathy, suspicious pneumonitis and colitis, a CMV disease was considered. Therefore, Ganciclovir was started.

Levofloxacin, imipenem/cilastatin and fluconazole were discontinued after fourteen days. CVVH was switched to hemodialysis after vasopressors and inotropes were tapered off. Then, renal replacement therapy was discontinued since his urine output was adequate under diuretics treatment. Cardiac enzymes (Fig. 2) and liver enzymes gradually decreased to normal range. On the nineteenth day of admission, he was extubated and transferred to ordinary ward. Then, the patient was discharged with stable condition. Ganciclovir was changed to oral form Valganciclovir, which was given for another two months, and Triumeq was continued in the outpatient department. Follow-up echocardiography one and a half year later revealed normalized left



MICU stay (hour)	-8	2	12	20	45	156
CK (U/L)	7,224	21,698	25,027	21,456	13,377	406
CK-MB (ng/mL)	69.5	93.6	65.5	49.5	20.2	1.1
hsTroponin-I (pg/mL)	6.817	3.992	2.494	1.577	0.673	0.176

Fig. 2 Cardiac enzyme levels. CK: creatine kinase, CK-MB: creatine kinase-MB isoenzyme, MICU: medical intensive care unit.

Table 2. PiCCO data (2017/04/25 – 04/28).

Time	CI	SVRI	ITBVI	EVLWI	BW	D	NE	V	Do
	L/min/m^2	DSm^2/cm^5	mL/m^2	mL/kg	kg	mcg/kg/min	mcg/min	U/min	mcg/kg/min
4/25 17:42	5.21	1152	878	8.4	64.9	20.54	16.44	0.03	5.14
4/26 09:18	3.01	2102	844	13.6	67.1	N/A	16.44	0.02	2.98
4/26 17:09	3.37	1638	877	10.8	N/A	N/A	16.44	0.01	2.98
4/27 10:15	4.19	1279	1701	7.3	67.4	N/A	4.27	N/A	2.97
4/27 17:21	4.50	1367	993	14.8	67.5	N/A	4.27	N/A	2.97
4/28 02:06	4.26	1540	975	16.0	N/A	N/A	4.27	N/A	2.96

PiCCO: pulse-induced contour cardiac output, CI: cardiac index, SVRI: systemic vascular resistance index, ITBVI: intrathoracic blood volume index, EVLWI: extravascular lung water index, BW: body weight, D: dopamine, NE: norepinephrine, V: vasopressin, Do: dobutamine, N/A: not applicable

ventricular systolic function (LVEF, 63%) without regional wall motion abnormality.

Discussion

We have reported a case of acute HIV infection with a presentation of profound septic shock with multi-organ involvements and acute heart failure. Pertinent infection workup was positive for CMV antibodies, CMV viremia and HIV viremia; no specific bacteria were isolated. Bibhuti B. Das[2] in 2014 mentioned that myocarditis was a common cause of acute-onset systolic heart failure in children. The pathogenesis of myocarditis was caused by viral infections, post-viral immune-mediated response, or both. We hypothesized a combined pathophysiological mechanism in our patient, mediated either by infections, immune responses and septic cardiomyopathy. Currently, there is a lack of formal diagnostic criteria for septic cardiomyopathy.[3,4] Furthermore, our patient did not receive an endomyocardial biopsy to provide a final diagnosis. In our patient, his heart failure seemed to be related, directly and indirectly, to the acute HIV infection. Hence, we will discuss about HIV-associated cardiomyopathy (HIVAC) in detail.

HIV-associated cardiomyopathy (HIVAC) was first reported in New England Journal of Medicine in 1986, manifesting as marked four-chamber dilatation, myofibrillar loss and focal myocarditis seen on postmortem examination.[5] The condition was associated recurrent opportunistic infections. In the pre-ART era, the clinical features of HIVAC were predominantly symptomatic dilated cardiomyopathy (DCM) with reduced ejection fraction, and the extent of DCM was correlated to the severity of immunosuppression.[6] In the post-ART era, HIV patients treated with ART were found to have increased risk of coronary artery disease, dyslipidemia and diastolic dysfunction.[7]

Cardiomyopathy with cardiac dysfunction during an acute HIV infection was seldom discussed. According to an HIV cohort study in Taiwan,[1] the common symptoms in a primary HIV infection included fever, pharyngitis and myalgia and the most severe condition was documented as aseptic meningitis; manifestation of common cardiac dysfunctions, such as arrhythmia, myocardial infarction and heart failure, was not mentioned. Relevant literature was also scarce. F. Fath-Ordoubadi et al[8] described the first case of patient presenting with echocardiographic DCM during the seroconversion phase of an acute HIV infection in 1997, indicating the HIV itself may be a cardiotropic virus. The patient had a $CD4^+$ count of 850 cells/uL, while the HIV RNA viral load was not mentioned. S Schneider et al[9] reported a 22-year-old woman, who was admitted for fever and infection of unknown cause with multiorgan involvement, developed ventricu-

lar fibrillation and myocarditis manifested in cardiac magnetic resonance imaging (CMRI). She had a negative HIV-1/2 enzyme immunoassay (EIA) initially, which was later turned positive while the Western blot remained negative. After mechanic support, her cardiac systolic function gradually returned to normal. Later a primary HIV infection was confirmed by positive nucleic acid test (NAT), with an HIV RNA viral load of 1.8 x 106 copies/mL and a $CD4^+$ count of 318 cells/uL. This case illustrated that the cardiomyopathy during an acute HIV infection could resolve without the intervention of ART.

Dan Kiselnik et al.[10] reported a 46-year-old Caucasian man who was admitted for acute onset of chest pain, diffuse muscle pain and four extremities weakness, and he was later diagnosed as having an HIV infection. ECG showed elevated ST segment over the anterolateral leads with reciprocal ST-T depression over the inferior leads, while the coronary angiography showed normal coronary arteries. Laboratory workup revealed CK 14549 U/mL and troponin-T 0.21 ng/mL and the CMRI findings were consistent with myocardial inflammation. The diagnosis of myocarditis with skeletal muscle myopathy was made. Albeit a normal echocardiogram on admission, a moderately decreased left ventricular systolic function and dilatation and akinesia of right ventricle were found on followed echocardiographic study during hospitalization. HIV serology test was positive for enzyme-linked immunosorbent assay (ELISA) and an HIV infection was confirmed by Western blot. His HIV RNA viral load was 16000 copies/ml, and the $CD4^+$ count was 264/uL. The authors postulated the HIV infection may be the cause of myocarditis in the reported patient since no other specific pathogens were identified.

The patient in our case had some similarities and differences when compared to the three aforementioned cases from literature review. Firstly, the patients in our case and in the first and second cases were having a proved acute HIV infection, while the patient in the third case had an HIV infection with unspecified state. The first case was in the seroconversion stage and the second case had positive ELISA, negative Western blot and positive NAT, all suggested of an acute infection.

Secondly, the patients in our case and in the first and third cases all had proved decreased left ventricular systolic dysfunction (ejection fraction 29.5% in our patient, 35% in the first case and not revealed in the third case), while the second case presented with ventricular fibrillation and myocarditis shown on CMRI. Only the patient in the first case had documented dilated cardiomyopathy, and CMRI was utilized in both second and third cases to reveal myocardial inflammation.

Thirdly, both patients in our case and the third case had a marked CK elevation and an HIV-associated myopathy was pointed out by the authors. Many proposed pathophysiologies were listed, including rhabdomyolysis, polymyositis, drug-induced myopathy, inflammatory myopathy and HIV-associated polymyositis.[10] Rhabdomyolysis was also previously documented in cases of streptococcal toxic shock syndrome.[11-13] Eleni Geladari et al[14] in 2018 reported a 59-year-old man with influenza type A myocarditis and rhabdomyolysis. Hence, we believed severe sepsis and certain viral infections could possibly lead to rhabdomyolysis. Since muscle biopsy was not performed in our case and the third case, the etiology of myopathy could not be further clarified.

Fourthly, patients in our case and the second and third cases all had high HIV RNA viral load, of which was not disclosed in the first case. The phenomenon linked to a theory that higher HIV viral loads lead to stronger inflammatory reactions and thus more severe immunosuppression, as seen in a previous local cohort study.[1] But it stayed unclear which factor (e.g. age, ethnicity, comorbidity and HIV

subtypes) would play a role in more extensive viral replication. Furthermore, our patient had a strikingly high viral load and a profoundly low $CD4^+$ count, making this case even more noteworthy.

Fifthly, the second case and our case included laboratory results of cardiomyopathy workup, which was absent in the first and third cases. The serologic CMV markers were positive in our case and the patient was put on Ganciclovir treatment. However, due to the absence of pathologic evidence, CMV infection with multiorgan involvements (DNAemia, heart, lung and colon) was only a clinical diagnosis. Authors of above case reports all commented that an HIV screening in line with other viral studies may be considered for all patients with unexplained myocarditis.

Lastly, in the second case, the patient's heart function gradually improved before the intervention of ART. Similarly, in our case, the patient's CK level peaked before ART was started. Therefore, whether the cardiomyopathy in acute HIV infection is self-limited and whether ART could fasten the healing process of myocardial inflammation, both remained questionable. On the other hand, the fact of that ART lowered the incidence of HIVAC was already well documented in previous literature.[15] Since early ART initiation was proved to reduce onward transmissions,[16] both AIDS-related and non-AIDS related serious events and death,[17] it is imperative to early start ART on patients who were not yet on treatments.

There were some limitations regarding the diagnosis of cardiomyopathy in our case. The most important of all, a myocardial biopsy was not done. Moreover, coronary angiography was not performed to exclude ischemia or other congenital anomalies. Lastly, although echocardiography was repeated one and a half year later, there was no time-to-time follow-up to correlate with the trend of HIV viral loads and $CD4^+$ counts.

In summary, long-term HIV infection was found to be associated with DCM in pre-ART era. On the other hand, an acute HIV infection could possibly, although rarely, manifest as myocarditis and acute heart failure, as presented in our case and above literature review. HIVAC can present as DCM, arrhythmias, myocarditis and heart failure. Cardiac enzymes, echocardiography, electrocardiogram and cardiac magnetic resonance imaging can be utilized for diagnosis. It is crucial to identify concomitant causes of cardiomyopathy that may require specific managements, such as coronary artery disease, opportunistic infections and cardiotoxic drugs. There was no standardized therapy for HIVAC, but organ support may be indicated in severe cases. Previous literature postulated that HIV may be a cardiotropic virus and a higher HIV viral load probably leads to a stronger inflammatory response and thus a detrimental consequence of cardiomyopathy.[8]

By reporting this 17-year-8-month boy whose acute HIV infection manifested itself as cardiomyopathy and acute heart failure, we aim to draw attention to these atypical presentations and possible life-threatening conditions in an acute HIV infection and hope to acquire more nationwide database on this issue.

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