Clinical Analysis of Chronic Active EBV Infection with Coronary Artery Dilatation and Matched Case-control Study

Ang Wei
Beijing Children's Hospital
https://orcid.org/0000-0002-7046-2417

Honghao Ma
Beijing Children's Hospital

Liping Zhang
Beijing Children's Hospital

Zhigang Li
Beijing Children's Hospital

Yitong Guan
Beijing Children's Hospital

Qing Zhang
Beijing Children's Hospital

Dong Wang
Beijing Children's Hospital

Hongyun Lian
Beijing Children's Hospital

Rui Zhang
Beijing Children's Hospital

Tianyou Wang ( wangtianyou@bch.com.cn )
Beijing Children's Hospital

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Abstract

Objective To investigate the clinical characteristics, treatment, prognosis, and risk factors of chronic active EBV infection (CAEBV) associated with coronary artery dilatation (CAD) in children.

Methods Children with CAEBV associated with CAD hospitalized in Beijing Children's Hospital, Capital Medical University, from March 2016 to December 2019 were analyzed. At the same time, children with CAEBV without CAD were selected as the control group, matched by sex, age, treatment and admission time. The clinical manifestations, laboratory and ultrasonic examinations, treatment and prognosis of the children were collected in both groups.

Results There were 10 children with CAEBV combined with CAD, accounting for 8.9% (10/112) of CAEBV patients at the same period, which including 6 males and 4 females, with onset age of 6.05 (2.8-14.3) years. The median follow-up time was 20 (6-48) months. All the patients had high copies of EBV-DNA in whole blood 1.18x10^7±1.90x10^5-3.96x10^7 copies/mL and plasma 1.81x10^6±1.54x10^5-1.76x10^6 copies/mL, and the Epstein-Barr virus encoded small RNA in biopsy was all positive. Among the 10 children, 8 had bilateral CAD, with 2 patients unilateral. After diagnosis, 7 children were treated with L-DEP chemotherapy in our hospital. After chemotherapy, four patients accepted allo-genetic Hematopoietic Stem Cell Transplantation (HSCT). The others were waiting for HSCT. By the end of the follow-up, CAD had returned to normal in 3 patients, and the time from diagnosis of CAD to recovery was 21 (18-68) d. The level of LDH, serum ferritin, TNF-α and IL-10 had statistically significant difference between the two groups (P=0.009, 0.008, 0.026 and 0.030). There were no significant differences in survival rate between the two groups (P=0.416).

Conclusion The incidence of CAEBV with CAD was low. CAEBV with CAD did not influence the prognosis. Patients with CAEBV had high LDH, serum ferritin, TNF-α and IL-10 in the early onset were prone to have CAD.

1 Introduction

Epstein-Barr virus (EBV) belongs to the gamma–herpesvirus family, which consists of double-stranded DNA viruses. The primary infection mainly invades B lymphocytes, which can cause infectious mononucleosis (IM) and EBV-associated hemophagocytic lymphohistiocytosis (HLH). EBV can also occasionally infect T lymphocytes and/or natural killer (NK) cells, resulting in EBV-driven T/NK cell lymphoproliferative diseases, such as chronic active EBV infection (CAEBV)[1-2]. CAEBV is characterized by fever, lymphadenectasis, hepatosplenomegaly and abnormal hemogram. But CAEBV combined with coronary artery dilatation (CAD) is rarely reported, and it is easy to be misdiagnosed as Kawasaki disease at the initial stage of diagnosis. Here, we report 10 cases of pediatric patients diagnosed with CAD secondary to CAEBV.

2 Patients And Methods

2.1 Patients

From March 2016 to December 2019, 10 children suffering from CAEBV combined with CAD were enrolled in this study. All these patients fulfilled the diagnostic guidelines. Data were retrospectively reviewed for the clinical manifestations, laboratory findings, age at the onset, and therapy. We performed a retrospective matched case-control study (1:2) to identify the risk factors for CAEBV combined with CAD in the pediatric population. The criteria for selecting control patients were: (1) hospitalization in the same year. (2) comparable age stratication, and (3) same gender.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Beijing Children's Hospital, Capital Medical University (2020-k-021). All patients' parents signed informed consent.

2.2 Diagnostic criteria

Inclusion criteria of diagnosing CAEBV in this study were as follows: (1) Persistent or recurrent infectious mononucleosis (IM)-like symptoms for > 3 months, such as fever, persistent hepatitis, lymphadenopathy, hepatosplenomegaly, hydroa vacciniforme, and hypersensitivity to mosquito bites; (2) EBV antibodies (EBV-CA and EBV-EA) were detected in tissues or peripheral blood samples or Epstein-Barr virus encoded small RNA (EBER) positive cells in tissues or EBV-DNA in plasma and whole blood >10^5 copies/ml; (3) No identifiable underlying immunological abnormalities[3-4]. Patients should fulfill all the three criteria.

The diagnostic criteria of HLH were according to the HLH-04 criteria proposed by the International histiocyte society[5].

CAD was defined as an abnormal coronary dilatation (segmental or diffuse) > 1.5 times of the reference normal value either in the same artery or in other adjacent normal arteries. The normal range of Chinese children's coronary arteries referred to the published paper by Du[6]. The internal diameter of the coronary arteries was measured by transthoracic echocardiography and assessed using the z-score (http://zscore.chboston.org/).

2.3 Therapeutic regimens[7]

(1) The first step was using L-DEP regimen to reduce the number of EBV copies and EBV infected T and/or Nk cells. L-DEP included: 2000 U/m^2 PEG-asparaginase on day 5, doxorubicin 25 mg/m^2 on day 1, etoposide 100 mg/m^2 on day 1, 8 and 15, methylprednisolone 15 mg/kg/day (days 1–3), 2 mg/kg/day (days 4–7) and 1 mg/kg/day (days 8–14) followed by gradual tapering the following week.

(2) In the second step, after 2 cycles of chemotherapy, patients accepted the allo-HSCT. The L-DEP regimen could be repeated in patients who did not receive allo-HSCT for various reasons, with a maximum of four courses.

2.4 Statistical Analysis
The results of statistical were expressed as the median (range). Statistical analysis was performed by using IBM SPSS Statistics 24 software (IBM, USA). Skewed distribution data are presented as median (quartile). Independent-samples T test was used to test for differences of quantitative variables. The Kolmogorov-Smirnov test was used to verify the overall survival rate, and the log-rank test was used to compare the survival rate between different groups. P < 0.05 was considered significant difference.

3 Results

3.1 General patient information

Ten cases of CAEBV combined with CAD were enrolled in this study, accounting for 8.9% (10/112) of CAEBV in the same period. The median age of disease onset was 6.1 (2.8–14.3) years. The ratio of males to females was 1.5:1 (Table 1). In all, 7 patients were defined as having T-cell type and 3 patients were defined as having NK-cell type.

Table 1

| Pt | Sex | Onset age (years) | Final diagnosis | Treatment | Time of CAD recovered | Duration of follow-up (month) | Result |
|----|-----|------------------|----------------|-----------|-----------------------|-------------------------------|--------|
| 1 F | 10.5 | CAEBV            | L-DEP          | non-recovered | 8.0                  | Alive                         |        |
| 2 M | 6.3  | CAEBV            | Abandon        | non-recovered | 12.0                | Alive                         |        |
| 3 M | 12.2 | CAEBV/HLH        | Abandon        | non-recovered | 13.0                | Alive                         |        |
| 4 F | 5.8  | CAEBV            | Abandon        | non-recovered | 27.0                | Alive                         |        |
| 5 M | 14.3 | CAEBV            | L-DEP          | 18d        | 28.0                | Alive                         |        |
| 6 M | 3.2  | CAEBV            | L-DEP, HSCT    | 68d        | 28.0                | Alive                         |        |
| 7 M | 7.6  | CAEBV            | L-DEP, HSCT    | non-recovered | 6.0                  | Dead                          |        |
| 8 F | 4.3  | CAEBV            | L-DEP, HSCT    | non-recovered | 48.0                | Alive                         |        |
| 9 F | 2.8  | CAEBV/HLH        | L-DEP          | non-recovered | 8.0                  | Alive                         |        |
| 10 M | 5.0 | CAEBV/HLH        | L-DEP, HSCT    | 21d        | 30.0                | Alive                         |        |

Note: Pt: patient, CAEBV: chronic active Epstein–Barr virus infection; HLH: hemophagocytic lymphohistiocytosis; CAD: coronary artery dilatation; L-DEP: PEG-Aspegaspargase, doxorubicin, etoposide and methylprednisolone; Time of CAD recovered: the time from discovery of CAD to recovery.

3.2 Clinical manifestations and laboratory examination

In the early stages of the disease, all patients presented with various degrees of hepatomegaly, eight patients (80%) had different degrees of splenomegaly, seven patients (70%) had fever and fever duration was 1 (0.5-6) months. 5 patients (50%) developed skin rashes, which were mainly red papule or maculopapule without itching, occurring predominantly on the torso. 5 patients (50%) had lymphadenopathy, 4 of which were located in the cervical region as well as 1 was located in the bilateral axilla. Before admission, all the children had no symptoms of Kawasaki disease (KD), such as red eyes, red lips, red bayberry tongue, limb swelling, molting, and so on. Two patients were admitted to the hospital as ‘incomplete Kawasaki disease’ (case 6 and 7). And the other 8 cases were admitted to the hospital for fever or hepatosplenomegaly.

After admission, laboratory examinations showed 7 patients (case 1, 3, 5, 6, 7, 9 and 10) had varying degrees of hematocytopenia. Five patients (case 2, 3, 5, 9 and 10) had high triglyceride level (> 3 mmol/L), 3 patients (case 5, 6, 10) had high serum ferritin level (> 500 ug/L), 3 patients (case 2, 6 and 10) had higher sCD25 level (> 6400 ng/L), 2 patients (case 1 and 9) had lower NK cell activity (< 15.11%) and 2 patients (case 9 and 10) had hemophagocytic phenomenon in bone marrow smear. The EBV antibody spectrum of all children indicated reactivation of previous infection. EBER had been tested positive in all 10 cases. Biopsy were performed in the bone marrow (8 cases), lymph node (2 cases) and liver (1 case) respectively. Serological and PCR tests for other pathogens were negative (such as herpes zoster virus, hepatitis B virus, cytomegalovirus, bacteria and parasites). All exon genetic examination and bone marrow cell flow cytometry were normal. Other laboratory examination results of 10 patients are summarized in Table 2.
3.3 Cardiac complications

The date of echocardiography of coronary shows in Table 3. Of the 10 patients, 8 had bilateral CAD (80%) and 2 had left CAD (20%) (Fig. 1). The z-score of left coronary was 4.125 (2.76–9.28) and right coronary was 5.275 (0.99–9.63). No obvious abnormal blood flow signal was found in the coronary artery. The ECG showed abnormal ST-T voltage indication in 1 patient (case 3), prolonged PR (0.19 s) in 3 patients (case 2, 5, 7) and T wave inversion in 1 patient (case 1).

Table 3

| Pt | Affected branch | LCA Diameter (mm) | RCA Diameter (mm) | Body surface area (m²) | Z score (Left/Right) | Shape of vessel |
|----|----------------|------------------|------------------|------------------------|---------------------|----------------|
|    | main | bifurcation | Anterior descending branch | circumflex | orifices | proximal | middle | distal |      |      |              |
| 1  | LCA/RCA | 4.9–5.7 | 6.4 | 3.0–3.5 | 3.4 | 5.0 | 5.1–5.9 | 5.3–6.1 | 3.5 | 1.030 | 5.91/8.87 | Aneurysms |
| 2  | LCA/RCA | 3.5 | - | 3.2 | 2.7 | 4.2 | 3.9 | 3.4 | 2.5 | 0.605 | 2.84/6.01 | Aneurysm |
| 3  | LCA | 4.0–4.5 | - | 2.7 | 2.7 | - | 3.0 | - | 2.1 | 1.210 | 2.76/0.99 | Dilated |
| 4  | LCA/RCA | 4.6 | - | 3.0 | 3.3 | - | 2.9–3.5 | 2.2 | 2.2 | 0.748 | 4.79/4.02 | Aneurysm |
| 5  | LCA/RCA | 4.8 | - | 3.6 | 3.1 | - | 3.8 | 2.6 | 2.6 | 1.250 | 3.23/2.77 | Aneurysm |
| 6  | LCA/RCA | 3.9–5.8 | 4.5 | 3.6 | 2.2 | - | 2.7–4.9 | 3.2–3.7 | 2.5–3.3 | 0.525 | 9.28/9.63 | Aneurysms |
| 7  | LCA/RCA | 5.2–5.6 | 6.2 | 3.5 | 4.4–5.7 | 5.4 | 5.0–5.8 | 5.3 | 2.7 | 0.870 | 6.48/9.59 | Aneurysms |
| 8  | LCA/RCA | 4.5 | - | 2.8 | 2.3 | 4.9 | 5.7 | 2.3–3.3 | 2.3–3.3 | 0.835 | 4.14/9.56 | Aneurysms |
| 9  | LCA/RCA | 3.4 | - | 2.2 | 2 | 2.9 | 3.3 | 4.9–5.9 | 2.3 | 0.556 | 2.85/4.54 | Aneurysm |
| 10 | LCA | 4.2 | - | 3.6 | 2.6 | - | 2.8 | 2.5 | 1.9 | 0.695 | 4.11/2.30 | Aneurysm |

Note: Pt: patient, LCA left coronary artery, RCA right coronary artery, - didn’t do the test

Echocardiography showed normal left ventricular ejection fraction range 62–79% and left ventricular shortening fraction range 32–46%. Three patients had mild mitral and aortic valve regurgitation (case 1, 3, 8). 3 patients had mild tricuspid regurgitation (case 3, 5, 7). Echocardiography and chest x-ray showed mild pericardial effusion in 4 patients (case 3, 5, 6, 8). No cardiac autopsy was obtained.
3.4 Diagnosis, treatment and prognosis

All the children met the diagnostic criteria of CAEBV, and 3 of them were complicated with HLH (case 3,9,10). Of the 10 patients, 3 patients gave up treatment due to their own reasons (case 2,3,4). The remaining 7 patients received L-DEP protocol. Allo-HSCT was performed for 4 patients (case 6,7,8,10). The other 3 patients were still under chemotherapy (case 1,5,9).

The last follow-up was July 1, 2020 and the median follow-up time was 20 (6–48) months. For 3 patients (case 5.6.10) who underwent treatment, the lumen of the coronary arteries regressed to normal size, and the echogenecity of the arterial walls reduced normally. The time from discovery of CAD to return to normal was 21 (18–68) days, including 2 patients CAD recofered after chemotherapy and 1 patient after HSCT. One patient (case 7) died of severe infection related to HSCT. There were no signicant changes in the coronary artery of the remaining 3 patients. At the last follow-up, no patients died of bleeding, thrombus and/or pericardial tamponade caused by ruptured coronary artery aneurysms (Table 1).

3.5 Comparison of CAEBV with and without CAD

We compared the characteristics of CAEBV patients with and without CAD (Table 4). The level of LDH, SF, TNF-α and IL-10 of CAEBV was relatively higher in patients with CAD compared with that of those without CAD (P = 0.009, 0.008, 0.026 and 0.030). The incidence of lymphadenopathy, hepatosplenomegaly and the EBV copy number did not differ between patients with and without CAD (P = 0.625, 4.565, 0.093, 0.284 and 0.992). There was no signicant difference in the rate of survival between the two groups (90.0% VS. 95.0%, log-rank test, P = 0.631) (Fig. 2).

### Table 4

|                         | Case group (n = 10) | Control group (n = 20) | P Value |
|-------------------------|--------------------|------------------------|---------|
| Course of disease (d)   | 70.57              | 86.31                  | 0.693   |
| Lymphadenopathy         | 5                  | 13                     | 0.625   |
| Hepatomegaly            | 10                 | 13                     | 4.565   |
| Splenomegaly            | 8                  | 15                     | 0.933   |
| WBC (x10^9/L)           | 5.03 (1.49–9.91)   | 4.82 (1.13–12.98)      | 0.205   |
| ANC (x10^9/L)           | 2.66 (0.42–5.11)   | 1.74 (0.36–7.89)       | 0.472   |
| Hb (g/L)                | 106.00 (73.00–131.00) | 105.00 (21.00–341.00) | 1.000   |
| PLT (x10^9/L)           | 137.00 (30.00–422.00) | 187.00 (21.00–341.00) | 0.890   |
| ALT (U/L)               | 230.70 (22.80–1928.00) | 109.85 (19.30–695.00) | 0.090   |
| AST (U/L)               | 124.80 (12.20–1806.00) | 46.50 (9.90–662.90) | 0.450   |
| TG (mmol/L)             | 2.91 (1.20–5.24)   | 1.71 (0.66–5.71)       | 0.797   |
| Fib (g/L)               | 2.12 (1.35–3.11)   | 1.29 (0.90–3.35)       | 0.890   |
| CK-MB (U/L)             | 21.00 (10.00–33.00) | 17.50 (6.00–45.00)     | 0.598   |
| LDH (U/L)               | 433.500 (226.00–9934.00) | 219.50 (201.00–1393.00) | 0.009   |
| CD4+/CD8+               | 0.75 (0.02–2.03)   | 2.31 (0.73–7.95)       | 0.049   |
| SF (ug/L)               | 162.3 (27.80–91893.20) | 156.05 (24.70–17043.00) | 0.008   |
| sCD25 (ng/L)            | 3848.40 (1504.00–23684.00) | 9282.20 (1500.00–40623.00) | 0.080   |
| EBV (plasma) (Copies/mL) | 1.81 (0.15–176.00) x10^4 | 2.65 (0.15–755.00) x10^4 | 0.284   |
| EBV (whole blood) (Copies/mL) | 1.18 (0.02–3.96) x10^7 | 0.17 (0.016–3.97) x10^7 | 0.992   |
| NK cell activity(%)     | 15.30 (12.84–20.52) | 14.52 (10.82–50.80)    | 0.282   |
| IFN-γ (ng/L)            | 13.68 (3.41–790.41) | 76.29 (0.00–769.91)    | 0.585   |
| TNF-α (ng/L)            | 2.66 (0.00–525.62) | 2.37 (0.00–244.33)     | 0.026   |
| IL-6 (ng/L)             | 14.24 (4.98–2500.00) | 31.64 (0.00–2500.00)   | 0.384   |
| IL-10 (ng/L)            | 5.14 (1.79–270.01) | 6.14 (1.93–75.72)      | 0.030   |

Note: WBC: white blood cell; ANC: neutrophil; Hb: hemoglobin; PLT: platelet; ALT: alanine transaminase; AST: aspartate transaminase; TG: triglyceride; Fib: fibrinogen; CK-MB: creatine kinase MB; LDH: lactate dehydrogenase; SF: serum ferritin; EBV: Epstein-Barr virus; IFN-γ: Interferon-γ; TNF-α: tumor necrosis factor-α; IL: interleukin.

4 Discussion
As a γ-herpesvirus, EBV is mainly transmitted through saliva. It is generally prevalent in East Asia, but rarely in other regions. The report of EBV infection with CAD is relatively rare. Until now, only 25 cases have been reported. Among them, 16 cases were IM combined with CAD [10–12], 3 cases were EBV-HLH combined with CAD [13–14]. All the 25 patients were children and equally split between male and female (male-female ratio of 1.08). Of the 25 patients, 4 had bilateral CAD (16%), 14 had right CAD (56%), and 7 had left CAD (28%). The majority of CAD in IM patients were the right coronary artery (81.2%), however, in EBV-HLH and CAEBV patients were left (100%). In this study, we described the characteristics of 10 CAEBV patients with CAD and found that the majority of CAD implicated left. Consistent with previous reports, there was no gender difference or specificity in the age of onset. As for patients infected with EBV combined with CAD, the cardiac structure might be abnormal, but the cardiac function could be normal.

The mechanism of EBV infection leading to CAD is unclear, which may be related to the following factors. EBV antigenic determinants on the cell surface of cytotoxic T cell (CTL), such as latent membrane protein (LMP) -1 [15], could be changed when CTL infected by EBV. LMP-1 can significantly increase the production of vascular endothelial growth factor (VEGF) in vivo [16]. VEGF can increase the permeability of retinal capillary veins and venules by inducing the production of related zymogen activators, resulting in vascular wall destruction and vascular involvement [17]. EBV can also activate the Janus kinase-signal transducer and transcriptional activator (JAK-STAT) pathway, which leads to the transcription of angiogenic genes. This can promote cell migration, invasion and angiogenesis in an autocrine and paracrine manner. However, excessive growth and persistent stimulation related to pathological angiogenesis lead to basement membrane defects and uneven pericyte coverage of these vessels [18]. In addition, Dogan [19], and Ariza [20] had found that EBV can produce deoxyuridine triphosphatase in the process of replication, which can increase the level of interleukin (IL)-6 in vivo, and IL-6 can lead to vascular endothelial damage, resulting in CAD. Tumor necrosis factor (TNF)-α binds to the corresponding receptors on LMP-1, which leads to the activation of intracellular PKC and PKA, then they can bind to and active nuclear factor (NF)-κB. Studies have demonstrated that NF-kB can lead to the degradation of extracellular matrix in the arterial wall, promote an inflammatory response, and accelerate the occurrence of hemangioma [21].

This retrospective observational study showed several important findings. The level of TNF-α and IL-10 of CAEBV was relatively higher in patients with CAD compared with those without. As mentioned above, TNF-α and IL-6 can lead to vascular endothelial damage, resulting in CAD. Therefore, CAEBV patients with high level of TNF-α and IL-6 should be paid more attention to in case of secondary CAD. At the same time, our study also found that CD4+/CD8+ was lower in CAEBV patients combined with CAD, suggesting that the disorder of T cell immune function may also be one of the main causes of CAD, especially when CD4+ T decreases or CD8+ T increases. In addition, the patients with high ferritin in the early stage of CAEBV should also be watched out for the possibility of secondary CAD.

Coronary artery dilatation, especially coronary artery aneurysm, is most common in KD in childhood, and it is one of the characteristics of KD [22]. EBV infection combined with CAD and KD have many similarities in clinical manifestations, such as fever, cervical lymphadenopathy, rash and so on, which makes them difficult to distinguish. Of the 10 patients, 2 (20%) were misdiagnosed as atypical KD at the early stage of the disorder. However, these patients didn’t have conjunctival congestion, bayberry tongue, fingertip scleroderma, molting, and elevated platelets, suggesting that the diagnosis of KD was irrational. The treatment and prognosis between CAEBV combined with CAD and KD are significantly different, so the differential diagnosis of these two diseases is necessary. For the patients with fever more than 2 weeks, accompanied by hepatosplenomegaly, elevated transaminase and coronary artery dilatation, but without other typical manifestations of KD, the possibility of EBV infection should be highly suspected. The detection of EBV antibody and EBV-DNA should be completed as soon as possible, and bone marrow or lymph node biopsy should be performed if necessary. CAEBV patients have poor prognosis and some of them have rapid progress. Therefore, once the diagnosis of CAEBV is confirmed, chemotherapy and succeeding HSCT should be performed as soon as possible.

The incidence of EBV infection with CAD is low. Previous studies have found that the incidence of IM with CAD is 4.4% [8]. However, no incidence of EBV-HLH with CAD has been reported. This study found that the incidence of CAEBV complicated with CAD was 8.9%. Previously reported, 14 cases (56%) returned to normal, including 13 cases of IM combined with CAD and 1 case of CAEBV combined with CAD. In this study, 3 cases of coronary artery returned to normal, accounting for 30.0% of CAEBV with CAD, and no patients died of CAD-related complications. EBV infection combined with CAD does not affect the prognosis of the primary disease, so controlling the primary disease and eliminating EBV infection are the key point of the treatment. Previous studies have found that if EBV infection in the body could not be cleared or effectively controlled, CAD was difficult to return to normal [23]. CAD should be examined by echocardiography regularly to monitor their dynamic changes. Also, doctor should be alert whether CAD is complicated with abnormal cardiac function.

5 Conclusions

The incidence of CAEBV with CAD was low. CAEBV with CAD did not influence the prognosis. Patients with CAEBV had high LDH, serum ferritin, TNF-α and IL-10 in the early onset were prone to have CAD. There were some shortcomings in this study: the number of patients was small, and the mechanism of CAD secondary to EBV infection still needed to be further studied.

List Of Abbreviations

EBV Epstein-Barr virus
IM infectious mononucleosis
HLH hemophagocytic lymphohistiocytosis
CAEBV chronic active Epstein–Barr virus infection
CAD coronary artery dilatation
EBER Epstein-Barr virus encoded small RNA
L-DEP PEG-Aspegaspargase, doxorubicin, etoposide and methylprednisolone
LVEF left ventricular ejection fraction
LVSF left ventricular shortening fraction
CTL cytotoxic T cell
LMP latent membrane protein
VEGF vascular endothelial growth factor
JAK-STAT Janus kinase-signal transducer and activator of transcriptions
IL interleukin
NF-κB nuclear factor κB
HSCT Hematopoietic Stem Cell Transplantation
KD Kawasaki disease

**Declarations**

**Ethics approval and consent to participate:**
This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Beijing Children's Hospital, Capital Medical University (2020-k-021).

**Consent for publication:**
All authors have read and approved the final manuscript. All parents signed informed consent forms and approved the final manuscript.

**Availability of data and materials:**
The data that support the findings of this study are available on request from the corresponding author.

**Competing interests:**
No

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**Authors' contributions:**
Ang Wei, Honghao Ma Writing - original draft
Liping Zhang, Zhigang Li Writing - review & editing
Li Zhang, Yitong Guan, Dong Wang Data curation
Hongyun Lian, Qing Zhang Formal analysis
Tianyou Wang, Rui Zhang Project administration

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