Chronic active Epstein–Barr virus infection manifesting as coronary artery aneurysm and uveitis

Haijuan Xiao1†, Bing Hu1†, Rongmu Luo2, Huili Hu1, Junmei Zhang3, Weiyong Kuang3, Rui Zhang4, Li Li5 and Gang Liu1*

Abstract
Background: Chronic active Epstein–Barr virus (CAEBV) infection is a type of lymphoproliferative disorder characterized by chronic or recurrent infectious mononucleosis (IM)-like symptoms, which can have less-frequent clinical presentations. The prognosis of CAEBV is poor, and hematopoietic stem cell transplantation (HSCT) has been shown to be the only potentially effective treatment. In this article, we present a special CAEBV case of a patient who had no typical IM-like symptoms at the early stage, but manifested with severe and progressive coronary artery aneurysm (CAA), abdominal aortic lesions, and severe uveitis. These manifestations were uncommon features and could only be blocked by HSCT.

Case presentation: A 4-year-old girl with no special medical history complained of decreased vision for 10 months and cough after physical activities for three months. The blurred vision grew rapidly worse within one month, until only light perception remained. She was diagnosed with uveitis and cataract, and received prednisone and ciclosporin A treatment. However, her vision did not improve. Physical examination showed slight hepatosplenomegaly. Ultrasonic cardiogram showed bilateral CAA (5.0 mm and 5.7 mm for inner diameters), and abdominal CT scan revealed a thickened aortic wall, as well as stenosis and dilation of the segmental abdominal aorta. Other significant findings were increased EBV-DNA (3.29 × 10⁴ copies/mL) from peripheral blood, positive EBV antibodies (EBV-CA-IgG, EBV-EA-IgA, and EBV-NA-IgG), and positive EBV-encoded small RNAs found by bone marrow biopsy. Based on her clinical manifestations and evidence for EBV infection, we diagnosed CAEBV. She received allogeneic HSCT, and the cataract operation was performed after HSCT. EBV-DNA could not be detected in peripheral blood after HSCT. Her CAAs did not progress, and uveitis was well controlled. Her vision recovered gradually over the 3 years after HSCT.

Conclusions: We present a rare CAEBV case of a patient who suffered from uncommon and severe cardiovascular and ocular involvement that was relieved by HSCT. Therefore, early recognition and diagnosis of CAEBV are of vital importance to improve its prognosis. In summary, this atypical CAEBV case could help us recognize similar cases more easily, make the right diagnosis as early as possible, and deliver proper and timely treatment.

Keywords: Chronic active Epstein–Barr virus infection (CAEBV), Coronary artery aneurysm (CAA), Coronary artery ectasia (CAE), Lymphoproliferative disorders (LPDs), Uveitis, Hematopoietic stem cell transplantation (HSCT)

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reactivation of EBV could result in various lymphoproliferative disorders (LPDs), including infectious mononucleosis (IM) and hematologic malignancies [2]. Chronic active EBV infection (CAEBV) is a severe disease with high morbidity and mortality, which exhibits a predisposition in East Asian populations. As a type of LPD, the clonal expansion of EBV-infected T or NK cells plays a central role in the disease's pathogenesis. However, the detailed pathogenesis of CAEBV and the mechanism by which EBV induces proliferation of T and NK cells are not known [1]. CAEBV is characterized by chronic or recurrent IM-like symptoms, such as fever, hepatosplenomegaly, lymphadenopathy, and liver dysfunction. However, CAEBV can also have other less frequent clinical presentations, or even fetal complications, such as central nervous system involvement, coronary artery aneurysm (CAA), interstitial pneumonia, digestive tract disorders, uveitis, and hemophagocytic lymphohistiocytosis (HLH) [3]. The prognosis of CAEBV is poor, and a series of therapies has been attempted, including anti-viral agents and immunosuppressors. However, hematopoietic stem cell transplantation (HSCT) has been shown to be the only potentially effective treatment [1].

Clonal proliferation of EBV-infected T or NK cells implies that CAEBV has a malignant nature. However, CAEBV is a chronic disease, and patients may remain in a stable condition for years without effective treatment [4]. Overt malignant lymphoma occurs after a long course of disease. Some researchers propose that CAEBV is a continuous spectrum ranging from a smoldering phase to overt lymphoma [4]. It is commonly believed that hosts with normal immune functions possess the ability to recognize EBV-infected T and NK cells, and CAEBV patients are thus thought to have some defects in immunological function that cause inefficient recognition and/or killing of EBV-infected cells [1]. However, CAEBV patients have not been found to have obvious immunodeficiency until the present day [5]. Nevertheless, it should be noted that some immunocompromised patients have accompanying EBV infections, and their clinical manifestations are analogous to CAEBV [6]. The mutations of several genes, including SH2D1A, XIAP, CD27, CD70, MAGT1, and PRKCD, are shown to cause hosts to be susceptible to chronic or even fetal EBV infections [7]. Therefore, genetic testing is necessary to distinguish CAEBV from these primary immunodeficiency diseases (PIDs).

Coronary artery ectasia (CAE) is an uncommon cardiovascular disorder that is defined as localized or diffuse dilatation of the coronary lumen. CAA describes local dilatation in the coronary lumen that is 1.5-fold greater than in normal adjacent segments [8]. CAA could be seen in various disorders, including atherosclerosis, systemic inflammatory vasculitis (e.g., Kawasaki disease, Behcet's disease), hereditary collagen defects (e.g., Marfan syndrome), infectious diseases (e.g., bacteria, mycobacteria), and congenital malformations [9]. Uveitis describes inflammation of the uvea, which contains the iris, ciliary body, and choroid. As intraocular inflammation can affect surrounding tissues, clinical uveitis may comprise inflammation of the retina, optic disc, and vitreous [10]. Uveitis may be the result of infectious (e.g., human herpes virus, tuberculosis, syphilis), non-infectious (mostly autoimmune or autoinflammatory), or masquerade (e.g., lymphoma) causes [11]. In this article, we will introduce a special CAEBV case of a patient who had no typical IM-like symptoms at the early stage, but whose illness manifested as uveitis, cataract, and cardiovascular involvement (CAA).

Case presentation
In July 2016, a 4-year-old girl was admitted to our department complaining of decreased vision and cough after physical activities. Ten months before hospitalization, she suffered from blurred vision, which grew rapidly worse within one month, until only light perception remained. In her local hospital, she was diagnosed with uveitis and cataract, and received prednisone, ciclosporin A, and local symptomatic treatment. The ocular lesions did not further exacerbate. Three months before hospitalization, the girl began to cough after exercise, with no fevers or other symptoms. Examinations showed normal blood routines and biochemical indicators, as well as a slightly increased erythrocyte sedimentation rate (ESR, 29 mm/h). There were no positive findings from the pulmonary CT scan or electrocardiogram, while an ultrasonic cardiogram showed bilateral CAs, hypertrophic interventricular septum and left ventricular wall, and mitral and aortic valve insufficiency. Other significant findings were increased EBV-DNA (3.29 × 10^4 copies/mL) in the peripheral blood, and positive EBV antibodies (EBV-CA-IgG, EBV-EA-IgA, and EBV-NA-IgG). She was given aspirin and ganciclovir, and the cough subsided. This patient did not suffer from recurrent infections, having no other medical history and no family history of PID. She had an elder sister (17 years old), who was healthy with no known diseases. Physical examination showed vision loss (only light perception remaining), systolic murmur at the apex, and slight hepatosplenomegaly.

The examinations after hospitalization showed generally normal brain MRI manifestations, and similar results for ophthalmic tests and the ultrasonic cardiogram as before (inner diameters of left and right coronary arteries: 5.0 mm and 5.7 mm respectively). The pulmonary CT scan showed extensive parenchymal and interstitial lesions of the lungs bilaterally (Fig. 1a), and abdominal
CT scan revealed a thickened aortic wall, as well as stenosis and dilation of the segmental abdominal aorta (Fig. 1b). There were no apparent abnormal findings in other vessels. Blood EBV-DNA and EBV antibodies were still positive, but autoantibodies were negative. There was no evidence for other infections, including other human herpes viruses [such as herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and human herpes virus 8 (HHV-8)], human immunodeficiency virus (HIV), tuberculosis, toxoplasmosis, and syphilis. The immunoglobulin and complement levels were within normal range. Lymphocyte subgroups showed an increased percentage of CD3+ T cells and a decreased percentage of B cells and NK cells. The proportion of CD4+ T cells increased, and the ratio of CD4+ T to CD8+ T cells was also elevated (Table 1). A bone marrow smear was near normal, while bone marrow biopsy showed much infiltration of lymphoid cells, which had mildly irregular nuclei (Fig. 2a). Positive CD3/CD5/CD7/CD2 (partially)/TIA-1/GrB (sparsely)/ki67 (80%) and negative CD20/CD56 were revealed by immunohistochemistry, and the presence of EBV-encoded small RNAs (EBERs) was shown by in-situ hybridization (Fig. 2b). We did not find significant pathogenic genes by whole-exome sequencing (WES).

Based on her clinical manifestations, increased EBV-DNA, positive EBV antibodies, and the pathological results of the bone marrow biopsy, we diagnosed the patient with CAEBV. She received allogeneic HSCT (allo-HSCT) in another hospital. The EBV-DNA in the peripheral blood could not be detected after HSCT. Compared with before HSCT, the percentage of CD4+ T cells and the ratio of CD4+ T to CD8+ T cells both decreased after HSCT (Table 1). The cataract operation was performed after HSCT. Her CAAs did not progress, and uveitis was well controlled. The patient’s vision recovered gradually over the 3 years after HSCT.

Table 1 Lymphocyte subsets before and 1 year after HSCT

| Lymphocyte Subsets          | Before HSCT | 1 year after HSCT | Reference valuesa |
|-----------------------------|-------------|-------------------|-------------------|
| CD3+ T lymphocytes (%)      | 91.4        | 85.7              | 55–82             |
| CD3+CD4+ T lymphocytes (%)  | 74.5        | 36.0              | 27–57             |
| CD3+CD8+ T lymphocytes (%)  | 15.4        | 41.0              | 14–33             |
| CD4/CD8                     | 4.8         | 0.9b              | 1.1–2             |
| CD19+ B lymphocytes (%)     | 5.1         | 2.1               | 9–29              |
| CD16+CD56+ NK cells (%)     | 1.5         | 10.2              | 7–40              |

a Reference values used in Beijing Children’s Hospital
b The value of another test at the same time was 1.25

Discussion and conclusions

This is a rare CAEBV case of a patient who suffered from cardiovascular and ocular involvement. This patient showed severe and progressive CAAs and abdominal aortic lesions, which could only be blocked by HSCT. Uveitis
was also controlled, and vision recovered gradually after HSCT. She did not have typical IM-like symptoms at the early stage, and slight hepatosplenomegaly did not occur until the very late stage. Therefore, early recognition and diagnosis of CAEBV are of vital importance to improve the prognosis of patients like the case described.

There have been several reports about CAEBV-associated cardiovascular diseases, including CAA, aortic aneurysms, myocarditis, pericardial effusion, and others, among which CAA and myocarditis are the major complications resulting in a poor prognosis [12, 13]. In Table 2, we summarize 20 CAEBV patients with coronary artery lesions reported in the literature, including 11 females and 9 males. There were 19 cases who had detailed descriptions about clinical features. The age at onset of CAEBV was between 2 years old and 16 years old, and 16 patients had symptoms at less than 10 years old. Eighteen patients had IM-like symptoms during the disease course. CAE, or even CAA, was found nearly simultaneously with CAEBV diagnosis in 12 cases, while these were found about 2–9 years after diagnosis in seven patients. Coronary lesions were described in detail in 13 patients: there were eight cases with bilateral CAE, four cases with left CAE, and one with right CAE only. The most severe coronary diameter was 8.2 mm. Only seven cases suffered from concomitant vascular lesions in the major branches of aorta. Three patients with pericardial effusion and two patients with pulmonary arterial hypertension (PAH) were noted, but no myocarditis was reported. Other organ lesions included pneumonia, nephritis, gastrointestinal diseases, and skin lesions. EBV-infected cell types were revealed in 12 cases: including 10 patients with infected T cells, one with infected NK cells, and one with infected γδT cells. Seventeen patients showed evidence for EBV infections, and all of them had positive EBV-DNA or EBERs. However, it should be noted that EBV antibodies were negative in one patient. As for the therapy, HSCT were not performed in 12 cases, among which eight patients died for various reasons. Six patients experienced HSCT: two patients were alive, and three patients died.

The potential mechanism of CAA in CAEBV patients has not yet been discovered. The pathological results showed lymphoid vasculitis, and two mechanisms were considered to play a central role in the onset and progression of cardiovascular lesions in CAEBV: EBV-infected T or NK lymphocyte infiltration and injuries in the myocardium and vessel walls, and EBV-induced high levels of pro- and anti-inflammatory cytokines resulting in inflammatory responses [12, 14, 15]. As for the pathogenesis of CAE or CAA, the activation of matrix-degrading enzymes (especially matrix metalloproteinases [MMPs]) and enzymatic degradation of the extracellular matrix (ECM) of the media are considered to be the most critical molecular events, which ultimately lead to excessive expansive arterial remodeling [9, 16]. This process is mediated via several factors, including increased levels of inflammatory mediators [e.g., vascular endothelial growth factor (VEGF), adhesion molecules], and induction of nitric oxide (NO) and its metabolite, which could trigger MMP formation [9, 16]. These factors have also been shown to play an important role in the pathogenesis of CAA in Kawasaki disease (the most common cause of CAA in childhood), but their functions in CAEBV still need to be further elucidated [17–19]. It has been noted that CAA frequently occurs in association with more widespread vascular abnormalities, including aneurysms in the thoracic and abdominal aorta, as well as in the pulmonary and iliac arteries [20]. Our patient also suffered from segmental dilation of the abdominal aorta.

The reports of CAEBV-associated uveitis are rare, and the exact mechanisms are not fully understood. Infectious uveitis could arise from local infection, but is more
| Pt | Sex | Onset age (years) | IM-like symptoms | Coronary artery lesions | Other cardiovascular complications | Other organ manifestations |
|----|-----|------------------|------------------|-------------------------|----------------------------------|--------------------------|
|    |     |                  |                  |                         | Large-vessel arteritis           | Gastrointestinal tract, hypersensitivity to mosquito bites, hydroa vacciniforme |
|    |     |                  |                  |                         | Myocarditis                      |                          |
|    |     |                  |                  |                         | Others                           |                          |
|    |     |                  |                  |                         |                                   |                          |
| 1  | M   | 4                | L, H             | 4                       | NA                               | No                       | Interstitial pneumonitis, Sjögren syndrome |
|    |     |                  |                  |                         | NA                               |                          |
|    |     |                  |                  |                         | NA                               |                          |
| 2  | F   | 5                | L, H             | 5                       | NA                               | No                       |                          |
|    |     |                  |                  |                         | NA                               |                          |
|    |     |                  |                  |                         | NA                               |                          |
| 3  | M   | 2                | F, L, H          | 2                       | NA                               | No                       |                          |
|    |     |                  |                  |                         | NA                               |                          |
|    |     |                  |                  |                         | NA                               |                          |
| 4  | F   | 6                | F, L, H          | 6                       | NA                               | Abdominal aortic aneurysm |                          |
|    |     |                  |                  |                         | NA                               | No                       |                          |
|    |     |                  |                  |                         | NA                               |                          |
| 5  | F   | 5                | F, H             | 5                       | No                               | Dilation of the sinus of Valsalva |                          |
|    |     |                  |                  |                         | No                               | No                       |                          |
|    |     |                  |                  |                         | No                               |                          |
| 6  | F   | 2                | F, H             | 4                       | No                               | Dilation of the sinus of Valsalva |                          |
|    |     |                  |                  |                         | No                               | No                       |                          |
|    |     |                  |                  |                         | No                               |                          |
| 7  | M   | 5                | F, H             | 8                       | No                               | Dilation of bilateral common carotid and subclavian arteries, abdominal aorta and major branches, and bilateral common iliac arteries |                          |
|    |     |                  |                  |                         | No                               |                          |
|    |     |                  |                  |                         | No                               |                          |
| 8  | M   | 6                | F, H             | 10                      | No                               | Dilation of bilateral common carotid and subclavian arteries, abdominal aorta and major branches, and bilateral common iliac arteries |                          |
|    |     |                  |                  |                         | No                               |                          |
|    |     |                  |                  |                         | No                               |                          |
| 9  | F   | 9                | F, H             | 18                      | No                               | Dilation of bilateral common carotid and subclavian arteries, abdominal aorta and major branches, and bilateral common iliac arteries |                          |
|    |     |                  |                  |                         | No                               |                          |
|    |     |                  |                  |                         | No                               |                          |
| 10 | M   | 11               | H                | 14                      | No                               | Dilation of bilateral common carotid and subclavian arteries, abdominal aorta and major branches, and bilateral common iliac arteries |                          |
|    |     |                  |                  |                         | No                               |                          |
|    |     |                  |                  |                         | No                               |                          |
| 11 | F   | 10               | F, H             | 10                      | No                               | Dilation of bilateral common carotid and subclavian arteries, abdominal aorta and major branches, and bilateral common iliac arteries |                          |
|    |     |                  |                  |                         | No                               |                          |
|    |     |                  |                  |                         | No                               |                          |
| 12 | M   | 2                | F, H, L          | 2                       | No                               | Dilation of bilateral common carotid and subclavian arteries, abdominal aorta and major branches, and bilateral common iliac arteries |                          |
|    |     |                  |                  |                         | No                               |                          |
|    |     |                  |                  |                         | No                               |                          |
| 13 | F   | 7                | F, H, L          | 7                       | No                               | Dilation of bilateral common carotid and subclavian arteries, abdominal aorta and major branches, and bilateral common iliac arteries |                          |
|    |     |                  |                  |                         | No                               |                          |
|    |     |                  |                  |                         | No                               |                          |
| 14 | M   | 2                | F, H, L          | 2                       | No                               | Dilation of bilateral common carotid and subclavian arteries, abdominal aorta and major branches, and bilateral common iliac arteries |                          |
|    |     |                  |                  |                         | No                               |                          |
|    |     |                  |                  |                         | No                               |                          |
| 15 | F   | 5                | F, H             | 5                       | No                               | Dilation of bilateral common carotid and subclavian arteries, abdominal aorta and major branches, and bilateral common iliac arteries |                          |
|    |     |                  |                  |                         | No                               |                          |
|    |     |                  |                  |                         | No                               |                          |

**Table 2 Clinical manifestations and prognosis of previously reported CAEBV patients with coronary artery lesions**

- **Pt**: Patient ID
- **Sex**: Gender (M: Male, F: Female)
- **Onset age (years)**: Age at onset
- **IM-like symptoms**: IM-like symptoms
- **Coronary artery lesions**: Coronary artery lesions
- **Occurrence age (years)**: Age at occurrence
- **Affected branch**: Affected branch
- **Coronary diameter**: Coronary diameter
- **Other cardiovascular complications**: Other cardiovascular complications
- **Large-vessel arteritis**: Large-vessel arteritis
- **Myocarditis**: Myocarditis
- **Others**: Other complications
- **Other organ manifestations**: Other organ manifestations

**Notes:**
- NA: Not applicable
- LCA: Left coronary artery
- RCA: Right coronary artery
- LAD: Left anterior descending artery
- LCX: Left circumflex artery
- LMCA: Left main coronary artery
### Table 2 (continued)

| Pt | Sex | Onset age (years) | IM-like symptoms | Coronary artery lesions | Other cardiovascular complications | Other organ manifestations |
|----|-----|-------------------|------------------|-------------------------|----------------------------------|---------------------------|
|    |     |                   |                  |                         | Large-vessel arteritis           |                           |
|    |     |                   |                  |                         | Myocarditis                      |                           |
|    |     |                   |                  |                         | Others                           |                           |
|    |     |                   |                  |                         |                                  |                           |
| 16 | M   | 6                 | F, H             | 8                       | NA                               | No                        |
| 17 | F   | NA                | NA               | NA                      | No                               | No                        |
| 18 | F   | 16                | F, H, L          | 16                      | RCA (multiple stenoses and dilation) | No                        |
| 19 | F   | 6                 | F, H, L          | 6                       | LMCA, RCA                        | No                        |
| 20 | M   | 5                 | NA               | 9                       | LAD, RCA                         | No                        |

| Pt | Sex | Onset age (years) | IM-like symptoms | EBV status | EBV copies (in PB)/EBRs | Abnormal EBV antibodies | Therapies— HSCT | Prognosis | Reports |
|----|-----|-------------------|------------------|------------|------------------------|------------------------|----------------|-----------|---------|
|    |     |                   |                  | Cell type   | EBV copies (in PB)/EBRs | Abnormal EBV antibodies |                |           |         |
|    |     |                   |                  |            |                        |                         |                |           |         |
| 1  | M   | 4                 | L, H             | T          | EBERs (+)              | Yes                     | No             | Died (streptococcus pneumoniae) within 36 months from onset | Nakagawa et al. [25] |
| 2  | F   | 5                 | L, H             | T          | EBERs (+)              | Yes                     | No             | Died (respiratory failure) within 13 months from onset | Nakagawa et al. [25] |
| 3  | M   | 2                 | F, L, H          | NA         | EBV-DNA in cardiac tissues | Yes                   | No             | Died within 5 years from onset | Kikuta et al. [26] |
| 4  | F   | 6                 | F, L, H          | NA         | EBV-DNA in cardiac and aortic tissues | Yes | No | Died within 5 years from onset | Kikuta et al. [26] |
| 5  | F   | 5                 | F, H             | NA         | EBV-DNA in cardiac tissues | Yes | No | Died within 5 years from onset | Kikuta et al. [26] |
| 6  | F   | 2                 | F, H             | NK         | 3 x 10^4 copies/mL     | No                      | Yes            | Alive and disease free | Muneuchi et al. [12] |
| 7  | M   | 5                 | F, H             | T          | 3 x 10^4 copies/mL     | Yes                     | Yes            | Died at 14 years | Muneuchi et al. [12] |
| 8  | M   | 6                 | F, H             | T          | 5 x 10^4 copies/mL     | Yes                     | Yes            | Alive and disease free | Muneuchi et al. [12] |
| 9  | F   | 9                 | F, H             | γδT        | 9 x 10^4 copies/mL     | Yes                     | No             | Died at 18 years | Muneuchi et al. [12] |
| 10 | M   | 11                | H                | NA         | 8.2 x 10^4 copies/μg DNA | Yes | Yes | Died (septic shock and multiple organ failure) within 13 days after transplantation | Fukuda et al. [27] |
| 11 | F   | 10                | F, H             | T          | EBERs (+)              | Yes                     | No             | Died (respiratory failure due to diffuse alveolar damage) | Murakami et al. [28] |
| 12 | M   | 2                 | F, H, L          | T          | EBV-DNA in PBMC        | Yes                     | NA             | Died (failure of umbilical cord blood transplantation) | Kikuta et al. [29] |
| 13 | F   | 7                 | F, H, L          | T          | EBV-DNA in pericardial effusion | Yes | Yes | Died (failure of umbilical cord blood transplantation) | Toubo et al. [30] |
| 14 | M   | 2                 | F, H, L          | T          | NA                     | Yes                     | No             | NA         | Kobayashi et al. [31] |
| 15 | F   | 5                 | F, H             | T          | EBERs (+)              | Yes                     | No             | Died (acute respiratory failure) within 13 months from onset | Nakagawa et al. [14] |
| Pt | Sex | Onset age (years) | IM-like symptoms | Cell type | EBV copies (in PB)/EBERs | Abnormal EBV antibodies | Therapies—HSCT | Prognosis | Reports |
|----|-----|------------------|-----------------|-----------|----------------------|-----------------------|-----------------|-----------|---------|
| 16 | M   | 6                | F, H            | T         | NA                   | Yes                   | NA              | NA        | Ohga et al. [32] |
| 17 | F   | NA               | NA              | NA        | NA                   | NA                    | Yes             | NA        | Nishimura et al. [33] |
| 18 | F   | 16               | F, H, L         | NA        | 2.8 x 10^4 copies/mL | NA                    | No              | NA        | Jiang et al. [34] |
| 19 | F   | 6                | F, H, L         | NA        | 3.72 x 10^7 copies/mL| NA                    | No              | NA        | Xie et al. [35] |
| 20 | M   | 5                | NA              | NA        | 4.53 x 10^9 copies/mL in plasma, EBERs (+) | Yes                   | No              | NA        | Ba et al. [36] |

NA not available, F fever, H hepatosplenomegaly, L lymphadenopathy, LAD left anterior descending artery, LCA left coronary artery, LCX left circumflex artery, LMCA left main coronary artery, RCA right coronary artery, PAH pulmonary arterial hypertension, PB peripheral blood, PBMC peripheral blood mononuclear cell
commonly due to hematogenous spread of pathogens to the uvea [10]. The pathogenic antigens are presented to the leukocytes within the eye that are activated against infectious agents, and the release of chemokines could further attract leukocytes to the inflammation sites [21]. Therefore, uveitis occurs as collateral damage from immune responses and is the result of the breach of the blood-retinal barrier that occurs due to the inflammatory cascade [10, 21]. Wong et al. [22] described three CAEBV patients whose ocular involvement ranged from anterior uveitis to a severe panuveitis with cataract, vitritis, macular edema, and optic disc swelling. The onset age of three reported patients was between 15 years old and 30 years old, and they suffered from uveitis almost simultaneously with the CAEBV diagnosis or nearly 2 years after the diagnosis. Although their ocular lesions were relieved for a while by glucocorticoid and/or acyclovir therapies, the uveitis could relapse repeatedly [22]. Morishima et al. [36] reported a 7-year-old girl with CAEBV and associated uveitis who exhibited bilateral granulomatous iridocyclitis, mild vitritis, optic disk swelling, and left facial nerve palsy nearly 2 years after the diagnosis of CAEBV. Treatment with topical steroids, systemic interleukin-2, and splenectomy relieved the symptoms [23]. There have been no reports about the direct relationship between CAEBV and cataracts. However, cataract development is common among children with uveitis and is strongly related to the extent of inflammation recurrences [24]. Therefore, we believe the cataract of our patient may be secondary to her uveitis. She received a cataract operation after the HSCT, after which her vision recovered gradually.

In summary, this atypical CAEBV case with CAA and uveitis could help us recognize similar cases more easily, make the right diagnosis as early as possible, and deliver proper and timely treatment.

Abbreviations
allo-HSCT: Allogeneic HSCT; CAA: Coronary artery aneurysm; CAE: Coronary artery ectasia; CAEBV: Chronic active Epstein–Barr virus infection; CMV: Cytomegalovirus; EBERs: EBV-encoded small RNAs; ECM: Extracellular matrix; HHV-8: Human herpes virus 8; HIV: Human immunodeficiency virus; HLH: Hemophagocytic lymphohistiocytosis; HSCT: Hematopoietic stem-cell transplantation; HSV: Herpes simplex virus; IM: Infectious mononucleosis; LPDs: Lymphoproliferative disorders; NO: Nitric oxide; PAH: Pulmonary arterial hypertension; PIDs: Primary immunodeficiency diseases; MMPs: Matrix metalloproteinases; VEGF: Vascular endothelial growth factor; VZV: Varicella zoster virus; WES: Whole-exome sequencing.

Acknowledgements
All the authors thank the patient and her parents for the support.

Authors’ contributions
HX conceived the study and drafted the main manuscript. BH provided the clinical details of this case. RL provided detailed information about allo-HSCT. HH helped in the process of literature review. JZ, WK, RZ and LL helped in the collection of clinical details and the process of diagnosis and treatment. GL supervised the overall study. All authors read and approved the final version of the manuscript.

Funding
The study was supported by The Special Fund of the Pediatric Medical Coordinated Development Center of Beijing Hospitals Authority (No. XTZD20180501), and Beijing Hospitals Authority “Dengfeng” Talent Training Plan (DFL 20181201).

Availability of data and materials
All the data and materials used in this report are included in the manuscript.

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Beijing Children’s Hospital, Capital Medical University, and performed according to the Declaration of Helsinki. Written informed consents were obtained from the parents of the recipient.

Consent for publication
Written informed consents were obtained from the parents of the recipient for publication.

Competing interests
The authors declared that they had no competing interest.

Author details
1 Department of Infectious Diseases, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China. 2 Department of Hematology and Oncology, Affiliated Bayi Children’s Hospital, The Seventh Medical Center of PLA General Hospital, Beijing, China. 3 Department of Rheumatology, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China. 4 Hematology Oncology Center, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China. 5 Department of Ophthalmology, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China.

Received: 15 April 2020 Accepted: 1 September 2020
Published online: 29 October 2020

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