Chemotherapy Improved Pulmonary Arterial Hypertension in a Patient with Chronic-Active Epstein-Barr Virus Infection

Satoshi Akagi, MD, Takashi Miki, MD, Yasuhisa Sando, MD, Nobuharu Fujii, MD, Toshihiro Sarashina, MD, Kazufumi Nakamura, MD and Hiroshi Ito, MD

Summary

Chronic-active Epstein-Barr virus infection (CAEBV) is a rare disease that can lead to pulmonary arterial hypertension (PAH). However, the treatment for CAEBV-associated PAH has not been established. We discuss a case of improved pulmonary hypertension after chemotherapy in a patient with CAEBV-associated PAH. A 44-year-old man was admitted to our hospital because of an abnormal electrocardiogram and liver dysfunction detected by annual medical examination. Echocardiography showed a dilated right ventricle and an estimated right ventricular systolic pressure of 92 mmHg. Right heart catheterization revealed a mean pulmonary arterial pressure of 45 mmHg and pulmonary vascular resistance of 9.8 Wood units. Laboratory examination showed granular lymphocytes and 91% natural killer cells in lymphocyte subsets in peripheral blood. We diagnosed the patient as having CAEBV-associated PAH. After two cycles of chemotherapy without PAH-specific drugs, echocardiography showed improvement in the dilated right ventricle and an estimated right ventricular systolic pressure of 59 mmHg. Right heart catheterization revealed a mean pulmonary arterial pressure of 27 mmHg and pulmonary vascular resistance of 2.4 Wood units. Chemotherapy may improve pulmonary hypertension in patients with CAEBV-associated PAH.

Key words: Pulmonary hypertension, Natural killer cells

Epstein-Barr virus (EBV) is a ubiquitous virus in humans, and primary infection with EBV is usually asymptomatic. However, in some patients, acute EBV infection is symptomatic and is known as infectious mononucleosis. The clinical manifestations are caused by a cytotoxic T-lymphocyte response against polyclonal proliferation of EBV-infected B cells. Although most EBV remains latent in B cells, chronically-EBV-infected T cells or natural killer (NK) cells cause chronic-active EBV infection (CAEBV). CAEBV is a disease with high mortality and life-threatening complications such as virus-associated hemophagocytic syndrome, malignant lymphoma, disseminated intravascular coagulation, interstitial pneumonia, liver failure, cardiovascular disease, and pulmonary arterial hypertension (PAH). CAEBV-associated PAH is very rare, and is reported predominantly in East-Asian countries. However, the treatment for CAEBV-associated PAH is not established. We report here a case of improved pulmonary hypertension after chemotherapy in a patient with CAEBV-associated PAH.

Case Report

A 44-year-old man began to experience exertional breathlessness 8 months before visiting a hospital. Abnormal electrocardiography and liver dysfunction were detected by annual medical examination, and he was admitted to our hospital with heart failure graded as New York Heart Association functional class II. Cardiovascular examination revealed increased P2 intensity. His lung fields were clear, and the remainder of the physical examination was unremarkable. His heart rate was 83 bpm, blood pressure was 127/96 mmHg, and SpO2 was 97% on room air. Chest radiography revealed pulmonary arterial dilatation and cardiomegaly (Figure 1A), and electrocardiography revealed right ventricular hypertrophy (Figure 1B). Echocardiography showed a dilated right atrium and ventricle (Figure 1C) and an estimated right ventricular systolic pressure of 92 mmHg. Right heart catheterization revealed a mean pulmonary arterial pressure of 45 mmHg, pulmonary arterial wedge pressure of 6 mmHg, and pulmonary vascular resistance of 9.8 Wood units. We diagnosed PAH and pursued a diagnosis of the underlying etiology. Lung perfusion scintigraphy showed no evidence of pulmonary thromboembolism, spirometry showed normal pulmonary function, and chest computed tomography showed no evidence of lung disease. Abdominal computed tomography and abdominal ultrasonography showed hepatomegaly and...
Figure 1. Imaging findings in a patient with CAEBV-associated PAH. A: Chest radiographs at diagnosis. B: Electrocardiogram at diagnosis. C: Echocardiography at diagnosis. D: Chest radiographs after chemotherapy. E: Electrocardiogram after chemotherapy. F: Echocardiography after chemotherapy.

Figure 2. Imaging findings in a patient with CAEBV-associated PAH. A: Abdominal computed tomographic images at diagnosis. B: Positron emission tomography-computed tomographic images at diagnosis.

splenomegaly (Figure 2A). Laboratory examination showed thrombocytopenia, liver dysfunction, and an increased brain natriuretic peptide level (347 pg/dL) and increased granular lymphocyte count. EBV-related antibody titers were as follows; anti-VCA IgG 1280x, anti-VCA IgM < 10x, and anti-EBV nuclear antigens 40x. The EBV DNA level was 7.9 x 10^5 copies/mL. T cell subsets in peripheral blood were as follows; clusters of differentiation (CD)56+: 41.79%, CD4+: 4.26%, CD8+: 2.86%, and CD19+: 1.58%. Positron emission tomography-computed tomography revealed high glucose uptake in the left maxilla, right supraclavicular lymph node, mediastinal lymph node, liver, and spleen (Figure 2B). Based on positron emission tomography-computed tomographic findings, we performed targeted biopsies of the bone marrow and liver to facilitate determining a definitive diagnosis. Immunohistochemical examination showed that CD3-positive cells were increased compared with CD20-positive cells, and a
subset of CD56-positive cells were EBV-encoded small ribonucleic acid-positive cells. These findings indicated NK-cell type CAEBV. Based on these cumulative findings, we diagnosed CAEBV-associated PAH. We initiated chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP). After two cycles of CHOP, the patient’s cardiomegaly improved on chest radiography (Figure 1D), and the signs of right ventricular hypertrophy diminished on the electrocardiogram (Figure 1E). Echocardiography showed improvement of the dilated right ventricle (Figure 1F) and an estimated right ventricular systolic pressure of 59 mmHg. Right heart catheterization revealed a mean pulmonary arterial pressure of 27 mmHg, pulmonary arterial wedge pressure of 15 mmHg, and pulmonary vascular resistance of 2.4 Wood units. Although we added two additional CHOP cycles, the effect was transient, and we decided to perform allogeneic peripheral blood stem cell transplantation. However, the patient died of septic shock and multiple organ failure 1 month after the transplantation.

Discussion

To the best of our knowledge, ours is the first report of improved pulmonary hypertension after chemotherapy in CAEBV-associated PAH.

Cardiovascular complications are common in both adult and pediatric patients with CAEBV. However, the complication of PAH is rare in patients with CAEBV. Luo, et al. studied the clinical characteristics and the features of adult CAEBV. In 28 patients with CAEBV, 4 patients developed PAH. The clinical classification of pulmonary hypertension includes 5 groups according to their clinical presentation and pathological findings. CAEBV-associated PAH belongs to group 5, which is defined as pulmonary hypertension with unclear and/or multifunctional mechanisms. The diagnosis of CAEBV-associated PAH is difficult; however, identifying this complication is important in patients with CAEBV. Confirming CAEBV is also important in patients with PAH with liver dysfunction and atypical lymphocytes in hematological examination.

The treatment strategy for CAEBV-associated PAH remains undefined. Two detailed cases were reported previously. Hashimoto, et al. reported the first case of CAEBV-associated PAH in a 45-year-old man in 2011. The patient was diagnosed with CAEBV-associated PAH, and chemotherapy was started. Although the patient showed marked depression of the EBV DNA in his peripheral blood after chemotherapy, the PAH did not improve. The patient was started on sildenafil followed by epoprostenol; however, he died suddenly to right heart failure and PAH. Fukuda, et al. reported CAEBV-associated PAH in an 11-year-old boy in 2015. The patient was first diagnosed with idiopathic PAH and was treated with sildenafil, bosentan, and beraprost, which decreased the systolic pulmonary arterial pressure on echocardiography. Subsequently, the patient developed liver dysfunction, and was then diagnosed with CAEBV-associated PAH. Although chemotherapy and peripheral blood stem cell transplantation were performed, the PAH did not improve. The patient died of septic shock and multiple organ failure.

The latest guidelines recommend initial combination therapy for PAH (Group 1 of pulmonary hypertension clinical classification). Initial combination therapy involves multiple PAH-specific drugs concomitantly, early in therapy before confirming the clinical response to a single medication. This strategy contributes to improved hemodynamics, exercise capacity, and survival. We did not use PAH-specific drugs to treat the PAH in our patient because we believed that CAEBV was the main cause of the PAH, and that treatment for CAEBV would improve the PAH. Although chemotherapy decreased our patient’s pulmonary arterial pressure, combination chemotherapy and therapy with PAH-specific drugs might have improved the PAH even more. However, PAH-specific drugs were not recommended for Group 5 of the pulmonary hypertension clinical classification including CAEBV-associated PAH. Therefore, higher numbers of similar patients are needed to establish an effective strategy to treat CAEBV-associated PAH.

The diagnostic logic of CAEBV-associated PAH is important as well as treatment of CAEBV-associated PAH. When we detect pulmonary hypertension, it is important to examine major etiologies such as PAH, pulmonary hypertension due to left heart failure, pulmonary hypertension due to lung diseases and CTEPH. If these etiologies are not applicable, we need to examine rare etiologies including CAEBV. CAEBV can be defined according to proposed diagnostic guidelines as follows: 1) a severe progressive illness of > 6 month duration usually with fever, lymphadenopathy, and splenomegaly that either begin as a primary EBV infection or is associated with high titers of IgG antibody to EBV-VCA and with little or no antibody to EBNA, or markedly elevated EBV DNA in the blood; 2) elevated EBV DNA, RNA or proteins in affected tissues; and 3) the absence of any other immunosuppressive condition. If these definitions are met, CAEBV-associated with PAH can be diagnosed. When we detect pulmonary hypertension in patients who are already known to be CAEBV, it is also necessary to exclude pulmonary hypertension caused by major etiologies such as PAH, pulmonary hypertension due to left heart failure, pulmonary hypertension due to lung diseases and CTEPH. If these etiologies are excluded, CAEBV-associated with PAH can be diagnosed.

The underlying pathological mechanism for CAEBV-associated PAH is unknown. One possible mechanism is that EBV causes pulmonary arteritis, which leads to pulmonary arterial remodeling. A second possible mechanism is that chronic EBV infection in T cells and NK cells induces high levels of inflammatory cytokines such as IL-6, which leads to inflammatory changes in pulmonary arteries. Indeed, serum IL-6 level is correlated with right ventricular function and worse clinical outcomes in patients with PAH. Blocking the IL-6 pathway might be a treatment option in patients with CAEBV-associated PAH. Indeed, an IL-6 receptor antagonist improved pulmonary hypertension in an animal study. Furthermore, a clinical trial on the safety and efficacy of treatment of an IL-6 receptor antagonist (Tocilizumab) in patients with PAH is ongoing.
In conclusion, we have reported a case of improved pulmonary hypertension after chemotherapy in a patient with CAEBV-associated PAH. Although the treatment strategy has not been confirmed, chemotherapy may improve pulmonary hypertension in patients with CAEBV-associated PAH.

Acknowledgments

We thank Jane Charbonneau, DVM, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Disclosure

Conflicts of interest: None.

References

1. Luo L, Wang H, Fan H, Xie J, Qiu Z, Li T. The clinical characteristics and the features of immunophenotype of peripheral lymphocytes of adult onset chronic active Epstein-Barr virus disease at a Tertiary Care Hospital in Beijing. Medicine (Baltimore) 2018; 97: e9854.
2. Fukuda Y, Momoi N, Akaishi M, et al. Pulmonary arterial hypertension associated with chronic active Epstein-Barr virus infection. Pediatr Int 2015; 57: 731-4.
3. Hashimoto T, Sakata Y, Fukushima K, et al. Pulmonary arterial hypertension associated with chronic active Epstein-Barr virus infection. Intern Med 2011; 50: 119-24.
4. Arai A. Advances in the study of chronic active Epstein-Barr virus infection: Clinical features under the 2016 WHO Classification and Mechanisms of Development. Front Pediatr 2019; 7: 14.
5. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT), Eur Heart J 2016; 57: 67-119.
6. Galie N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015; 373: 834-44.
7. Okano M, Kawa K, Kimura H, et al. Proposed guidelines for diagnosing chronic active Epstein-Barr virus infection. Am J Hematol 2005; 80: 64-9.
8. Cracowski JL, Chabot F, Labarere J, et al. Proinflammatory cytokine levels are linked to death in pulmonary arterial hypertension. Eur Respir J 2014; 43: 915-7.
9. Tamura Y, Phan C, Tu L, et al. Ectopic upregulation of membrane-bound IL6R drives vascular remodeling in pulmonary arterial hypertension. J Clin Invest 2018; 128: 1956-70.
10. Hernandez-Sanchez J, Harlow L, Church C, et al. Clinical trial protocol for TRANSFORM-UK: A therapeutic open-label study of tocilizumab in the treatment of pulmonary arterial hypertension. Pulm Circ 2018; 8: 2045893217735820.