Severe Adenovirus Pneumonia Associated With Hemophagocytic Lymphohistiocytosis With Coronary Involvement

Infection-associated hemophagocytic lymphohistiocytosis (HLH) is being increasingly observed in children with severe adenoviral pneumonia in recent reports [1,2]. However, coronary involvement in viral infection associated HLH is rare and most of the previous literature documents cases of Epstein-Barr virus (EBV) associated HLH with coronary involvement [3]. Herein, we report a severe adenovirus-associated HLH with coronary involvement.

This previously healthy 2-year-old boy presented with two weeks history of a febrile illness associated with cold and cough, which was being treated on outpateint basis. He was admitted with us for fever and increasing respiratory rates. His upper respiratory Biofire (rapid respiratory polymerase chain reaction test) was positive for adenovirus. Blood and urine cultures were sterile. He was treated with broncho-dilators and intravenous fluids. However, his fever still persisted. Echocardiography was done on day-5 post admission, which showed significant coronary artery dilatation. The child did not have any clinical features of Kawasaki disease. The child received 2 g/kg intravenous immunoglobulin (IVIG) but developed respiratory distress the next day, and was shifted to the pediatric intensive care unit (PICU).

The patient received heated, humidified high-flow oxygen by nasal cannula (HHHFNC). On auscultation, there was impaired note and bronchial breathing on left lower lobe area. Per abdominal examination revealed hepatosplenomegaly. Chest *X*-ray showed dense consolidation in left lower zone and his C-reactive protein (57 mg/dL) and procalcitonin (31 ng/mL) were high. Patient was treated with injection vancomycin and meropenem. Echocardiography done two days after being shifted to PICU showed dilated left main coronary artery (LMCA) and left anterior descending artery (LAD) with mild mitral regurgitation (MR) and mild left ventricle (LV) systolic dysfunction. The child was started on high dose aspirin and injection methylprednisolone.

As the fever still persisted, work-up to rule out HLH was done, and it showed bicytopenia, hyperferrtinemia and hypertriglyceridemia. Tratment with injection anakinra was started for the child at a dose of 100 mg/day subcutaneously, as the child had not responded to IVIG and methyl-prednisolone.

On fourth day of anakinra, repeat echocardiography showed LVEF 62%, proximal LAD aneurysm with a small thrombus inside, and injection clopidogrel was added to the treatment. His HLH markers started showing improvement but the child continued to remain febrile and HHHFNC dependent (**Table I)**. Anakinra was continued and steroids were changed to intravenous hydrocortisone. The child was not hemodynamically compromised. The patient became afebrile on day 6 of anakinra. High-resolution computed tomography (HRCT) thorax showed near complete collapse/consolidation of left lung, with patchy consolidation in right upper and lower lobes.

After one week of treatment with anakinra, the dose was reduced. The child remained afebrile and he was weaned off HHHFNC after two weeks. Anakinra was stopped after day 10. Whole exome sequencing did not reveal any genetic evidence of primary HLH. Repeat investigations showed decreasing levels of triglycerides, ferritin and aspartate aminotransferase, and rising total leukocyte and platelets.

Table I Trend of Hemophagocytic Lymphohistiocytosis Markers in the Index Child with Adenovirus Pneumonia

Date	*Hemoglobin (g/dL)*	*Total leukocyte count ($\times 10^9$/L)*	*Platelet count ($\times 10^9$/L)*	*Ferritin (µg/L)*	*Fibrinogen (mg/dL)*	*Triglyceride (mg/dL)*	*AST (IU/L)*
Day 1	9.0	3.2	100	4960	-	754	426
Day 6 Anakinra	9.5	3.2	200	2440	-	686	213
Day 9 Anakinra	8.8	3.7	306	757	-	1053	50
Day 11	7.4	9.5	510	317	212	279	28
Day 17	7.9	10.9	480	97	327	67	36

AST: aspartate aminotransferase.

Follow-up echocardiography showed small aneurysm in proximal LAD with possible thrombus in it.

The child was gradually weaned off steroids, and his antibiotics were stopped after a week. The patient was discharged one month post admission. Currently, child is doing well and remains on aspirin since the last six months post discharge.

Adenoviral infections are known to cause secondary HLH, but there is no publication documenting coronary involvement in such cases. On the other hand, EBV-associated secondary HLH has been found to occur with cardiac complications, including coronary involve-ment [3]. In the first published pediatric cases of EB virus associated secondary HLH complicated by coronary artery dilatation [3], the patient also fulfilled the criteria for Kawasaki disease, which was not seen in our patient.

We preferred ankanira over etoposide due to lower sepsis risk and absence of hematological toxicity. There is previous literature documenting use of anakinra as a first line agent in secondary HLH, even in non-rheumatic causes [4,5]. Our observations also suggest that anakinra may be considered for treatment in secondary HLH instead of etoposide with/without dexamethasone. However, in our case, child became afebrile on D6 of anakinra; although, previous literature shows that the average time for anakinra response is within 1-2 days [6].

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REFERENCES

1. Bradley JS, Byington CL, Shah SS, et al. The management of Community-acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis.2011:53:e25-76.
2. Chen HL, Chiou SS, Hsiao HP, et al. Respiratory adenoviral infections in children: a study of hospitalized cases in southern Taiwan in 2001–2002. J Trop Pediatr. 2004;50:279-84.
3. Kato S, Yoshimura K, Tanabe Y, et al. A child with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis complicated by coronary artery lesion mimicking kawasaki disease. J Pediatr Hematol Oncol. 2013;35:317-9.
4. Eloseily EM, Weiser P, Crayne CB, et al. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. Arth Rheumatol. 2020;72:326-34.
5. Rajasekaran S, Kruse K, Kovey K, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children. Pediatr Critic Care Med. 2014;15:401-8.
6. Baverez C, Grall M, Gerfaud-Valentin M, et al. Anakinra for the treatment of hemophagocytic lymphohistiocytosis: 21 cases. J Clin Med. 2022;11:5799.