Regression of kaposiform lymphangiomatosis and chronic disseminated intravascular coagulation after inhaled budesonide-formoterol treatment

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Abbreviations:

KLA	kaposiform lymphangiomatosis
mTOR	mammalian target of rapamycin
FDP	fibrin-fibrinogen degradation product
MRI	magnetic resonance imaging

KLA	kaposiform lymphangiomatosis
CT,	computed tomography

To the Editor:

Kaposiform lymphangiomatosis (KLA) is a rare disease classified as a subtype of lymphatic malformations. It affects multiple organs, including the mediastinum, lungs, bones, spleen, and soft tissues and is often associated with thrombocytopenia and coagulopathy. Currently, no treatments have been established for this disease. It is often a progressive disease with poor prognosis.[1-4]

A previously healthy 10-year-old male was found to be thrombocytopenic (70 000/μL) in a preoperative examination for acute appendicitis and was diagnosed with immune thrombocytopenia by a local physician. Additionally, abnormal infiltrates were observed on his chest radiographs. One year later, his platelet count decreased to 30 000/μL. After an additional 6 months, hemoptysis was observed, leading to the patient's referral to our department at the age of 12 years. At the initial visit, laboratory investigation indicated an oxygen saturation of 95% on room air, platelet count 43 000/μL, and an elevated level of fibrin-fibrinogen degradation product (FDP) (26.6 μg /mL). The pulmonary function test indicated a percentage-predicted vital capacity of 66.8%, and the percentage-predicted forced expiratory volume in 1 s was 80.9%. Magnetic resonance imaging (MRI) showed that lesions with high signal intensity on both T1- and T2-weighted images ascended through the peritracheal region and extended to the extrapulmonary regions involving the subcutaneous neck. It extended caudally into the pelvic cavity (Fig. 1A and B). Chest computed tomography (CT) revealed a diffusely spread, low-density area in the mediastinum. Thickening of the interlobular septal wall and pleura were also observed. (Fig. 1C and D). A lung biopsy was not able to be performed due to chronic disseminated intravascular coagulation. Subcutaneous tissue and neck lymph nodes were biopsied instead of the lungs. Pathological examination revealed dilated lymphatic channels in the fatty connective tissue (Fig. 1E), which lead to the diagnosis of diffuse pulmonary lymphangiomatosis. A multimodal treatment regimen consisting of interferon-alpha, thalidomide, and propranolol was ineffective (Fig. 2). Propranolol was discontinued due to frequent and recurrent asthma-like attacks, which are considered as the adverse effects. Subsequently, fluticasone followed by inhaled budesonide-formoterol was administered to control the asthma-like attacks. After 1 year and 2 months of inhaled combined budesonide-formoterol (1 280 μg of budesonide and 36 ug of formoterol), the platelet count suddenly increased from 28 000 to 43 000/μL during a month without any triggers at the age of 20 years. Surprisingly, during the following 3 months, platelet counts and FDP levels rapidly returned to their normal ranges. The pathology was re-evaluated, and a focal cluster of D2-40 positive spindle cells was observed, leading to a final diagnosis of KLA (Fig. 1F). The respiratory function gradually recovered. The MRI findings also improved, but slight deterioration was observed after the inhalation dose was reduced. Seventeen years after the onset of respiratory symptoms, the patient rarely complained of dyspnea or bleeding while receiving inhaled budesonide-formoterol therapy.

KLA is a progressive disease that worsens over time, and respiratory failure is the primary cause of death. Approximately 20% of patients survive for 7 years after the onset of respiratory symptoms[1]. Previous reports have indicated that various medical treatments, including corticosteroids, vinblastine, interferon-alpha, doxycycline, thalidomide, and octreotide, as well as surgical interventions such as pleurodesis, chest tube ligation, and tumor resection, have been temporizing[1-4]. Activation of the RAS/PI3K/mTOR signaling pathway has been observed in KLA tissues[5]. Although sirolimus, an mTOR inhibitor, has been reported to be effective[6], its efficacy rate is insufficient, with 58.3% of patients achieving partial response, 25% experiencing stable disease, and 16.7% showing disease progression[7]. Recent case reports have shown its effectiveness in treating sirolimus-resistant patients with either the PIK3CA inhibitor, alpelisib, for somatic *PIK3CA*mutations[8] or the MEK inhibitor trametinib for somatic*NRAS* p.Q61R mutations[9,10]. Corticosteroids are used for their anti-inflammatory effects and typically administered systemically. Previous reports have shown only transient improvements in coagulation abnormalities, imaging findings, and pulmonary function tests even with systemic administration[10,11]. No reports have indicated the efficacy and long-term improvements induced by corticosteroid-beta-2 receptor agonist inhalation therapy, as observed in the present case. The mechanism

underlying the improvement in coagulopathy and regression of abnormal mediastinal soft tissue and lung parenchyma remains unknown.

This case is a significant example of the prognosis of KLA and gathering more cases using this treatment is crucial.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Croteau SE, Kozakewich HPW, Perez-Atayde AR, et al. Kaposiform Lymphangiomatosis: A Distinct Aggressive Lymphatic Anomaly.*Journal of Pediatrics* . Feb 2014;164(2):383-388.

2. McDaniel CG, Adams DM, Steele KE, et al. Kaposiform lymphangiomatosis: Diagnosis, pathogenesis, and treatment. *Pediatr Blood Cancer* . Apr 2023;70(4):e30219.

3. Ozeki M, Fujino A, Matsuoka K, Nosaka S, Kuroda T, Fukao T. Clinical Features and Prognosis of Generalized Lymphatic Anomaly, Kaposiform Lymphangiomatosis, and Gorham-Stout Disease. *Pediatr Blood Cancer* . May 2016;63(5):832-8.

4. Ozeki M, Fukao T. Generalized Lymphatic Anomaly and Gorham-Stout Disease: Overview and Recent Insights. *Advances in Wound Care* . Jun 2019;8(6):230-245.

5. Barclay SF, Inman KW, Luks VL, et al. A somatic activating NRAS variant associated with kaposiform lymphangiomatosis. *Genetics in Medicine* . Jul 2019;21(7):1517-1524.

6. Wang Z, Li K, Yao W, Dong K, Xiao X, Zheng S. Successful treatment of kaposiform lymphangiomatosis with sirolimus. *Pediatr Blood Cancer* . Jul 2015;62(7):1291-3.

7. Zhou JY, Yang KY, Chen SY, Ji Y. Sirolimus in the treatment of kaposiform lymphangiomatosis. *Orphanet Journal of Rare Diseases* . Jun 2021;16(1)260.

8. Grenier JM, Borst AJ, Sheppard SE, et al. Pathogenic variants in PIK3CA are associated with clinical phenotypes of kaposiform lymphangiomatosis, generalized lymphatic anomaly, and central conducting lymphatic anomaly. *Pediatr Blood Cancer* . May 17 2023:e30419.

9. Foster JB, Li D, March ME, et al. Kaposiform lymphangiomatosis effectively treated with MEK inhibition. *EMBO Mol Med* . Oct 07 2020;12(10):e12324.

10. Chowers G, Abebe-Campino G, Golan H, et al. Treatment of severe Kaposiform lymphangiomatosis positive for NRAS mutation by MEK inhibition. *Pediatric Research* . 2022 Mar 2022;

11. Anthony MD, Swilling A, Jiwani ZM, et al. Multidisciplinary Multiagent Treatment of Complex Lymphatic Anomalies with Severe Bone Disease: A Single-Site Experience. *Lymphatic Research and Biology* . Apr 2022;20(2):118-124.

Legend list

FIGURE 1

Coronal magnetic resonance imaging (MRI), computed tomography (CT) images, and histopathological studies for a patient with KLA.

1. Short-T1 inversion recovery (STIR) imaging of the chest in a 10-year-old male at the time of diagnosis showed significant mediastinal thickening that ascended through the peritracheal region and extended

into both shoulders and the subcutaneous neck. It extended caudally from the aorta to the abdominal cavity (white arrows).

2. T2 images at the age of 27 years showed high-intensity areas within the mediastinum to the pulmonary hilum, and bronchovascular bundles were decreased.
3. Axial chest computed tomography (CT) of the pulmonary window revealed a diffusely spread low-density area in the mediastinum.
4. An axial chest CT scan in the mediastinal window shows variable thickening of the peri-bronchial wall (yellow arrows), interlobular septal wall (white arrows), and pleura (blue arrows). Continuity is observed through the bilateral pulmonary hila to the diffuse bronchovascular bundle thickening.
5. Microscopic findings of biopsied lymph nodes demonstrated dilated lymphatic channels in the fatty connective tissue with hematoxylin and eosin staining.
6. Microscopic findings of biopsied lymph nodes demonstrated clustered spindle cells that stained positive for D2-40.

FIGURE 2

The clinical course and treatment

The upper panel shows the changes in platelet count (red) and fibrin-fibrinogen degradation products (FDP) (blue) during the treatment course. The lower panel shows the results of the pulmonary function tests, including the percent predicted vital capacity (solid line) and percent predicted forced expiratory volume in 1 s (dotted line). Inhaled corticosteroids are shown in yellow. Budesonide-formoterol contains 160 μg of budesonide and 4.5 μg of formoterol per inhalation. Four inhalations per day were initiated, and improvements in coagulopathy and pulmonary function were observed after eight inhalations. When the dose was reduced to two inhalations per day, the MRI findings worsened; therefore, the dose was maintained at four inhalations per day.