Pulmonary Alveolar Proteinosis in Association with Secondary Hemophagocytic Lymphohistiocytosis

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Pulmonary alveolar proteinosis (PAP) is a rare diffuse lung disease in the pediatric population. There are currently few cases documenting hemophagocytic lymphohistiocytosis as a cause for secondary PAP. We describe an ex-preterm child with secondary hemophagocytic lymphohistiocytosis, complicated by PAP and hypoxemic respiratory failure. *(J Pediatr 2017;183:191-5).*

Pulmonary alveolar proteinosis (PAP) is a rare disorder, characterized by excessive accumulation of surfactant lipids and protein in the alveolar spaces with resultant impairment in gas exchange.[1] It has mostly been documented in adults with rare occurrence in pediatric patients.[1] PAP can be classified into 3 categories: autoimmune, congenital (genetic), and secondary.[1] Autoimmune PAP accounts for 90% of PAP cases and is attributed to neutralizing antibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF), which lead to defects in alveolar macrophage function with impaired catabolism and clearance of surfactant.[1,2] Congenital PAP in infants and children represents <2% of cases and is caused by mutations in genes encoding surfactant proteins B or C (*SFTPB* or *SFTPC*), adenosine triphosphate-binding cassette protein (*ABCA3*), or GM-CSF receptors (*CSF2RA* or *CSF2RB*).[1,2] In cases of mutations in *SFTPB, SFTPC*, or *ABCA3*, patients may also present with other clinical or histology phenotypes (ie, chronic pneumonitis of infancy, desquamative interstitial pneumonia, or nonspecific interstitial pneumonia), whereas those with mutations in *CSF2RA* or *CSF2RB* primarily present with PAP.[3] Generally, the age of onset and clinical presentation may vary based on etiology of congenital PAP (depending on whether the defect is in surfactant production vs surfactant clearance).[3] Secondary PAP accounts for 7%-10% of cases and is associated with a variety of diseases (including hematologic disorders, immunodeficiency, lysinuric protein intolerance, and toxic inhalants) that cause a reduction in alveolar macrophage number or function, leading to decreased pulmonary clearance of surfactant.[1] PAP because of hemophagocytic lymphohistiocytosis (HLH) is extremely rare but plausible because PAP involves dysfunction of alveolar macrophages which are cells within the histiocyte spectrum.[4]

We explore here the complex clinical challenges involved in diagnosis and management of a young girl with a rare presentation of secondary HLH complicated by secondary PAP and severe respiratory failure.

Case Report

A 21-month-old girl with complex medical history including prematurity (28 weeks gestation), previous methicillin-resistant *Staphylococcus aureus* endocarditis, cleft lip/palate status-post repair, global developmental delay, chronic lung disease with baseline oxygen dependence, tracheostomy, and gastrostomy status who initially presented with rash, fevers, and increased oxygen requirement, was transferred to our hospital following a month-long admission at another institution where she had continuous fevers of unknown origin despite comprehensive workup and multiple antibiotic courses. She was placed on mechanical ventilation prior to transfer because of worsening respiratory distress. Her previous neonatal intensive care unit course was notable for severe chronic lung disease with prolonged ventilator dependence leading to tracheostomy placement. On admission to our hospital, physical examination revealed dysmorphic facies, mild barrel-shaped chest, diffuse bilateral coarse lung crackles, peeling erythematous rash on extremities and abdomen, and palpable left inguinal lymph nodes. Extensive infectious workup was negative, except for positive tracheostomy cultures (*Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*),

CT	Computed tomography
EBV	Epstein-Barr virus
ECMO	Extracorporeal membrane oxygenation
FiO_2	Fraction of inspired oxygen
FUO	Fever of unknown origin
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HLH	Hemophagocytic lymphohistiocytosis
LCH	Langerhans cell histiocytosis
MAS	Macrophage activation syndrome
NK	Natural killer cell
PAP	Pulmonary alveolar proteinosis
WLL	Whole lung lavage

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which were treated with antibiotics. Chest computed tomography (CT) scan at previous institution showed bibasilar airspace disease with widespread mosaic attenuation and a T6 vertebral body compression deformity, characteristic of vertebra plana often associated with Langerhans cell histiocytosis (LCH). Further radiologic testing for LCH included skeletal imaging, which was negative for any osteolytic lesions. Basic immunologic and rheumatologic workups were negative with no evidence of arthritis. Echocardiogram was negative for endocarditis with normal heart structure. She was also treated with a 6-week course of vancomycin and cefepime for presumed T6 vertebral osteomyelitis.

Her fevers persisted, prompting workup for HLH which met 7 out of 8 HLH-2004 diagnostic criteria, except for normal natural killer (NK) cell function (**Table I**). Inguinal lymph node biopsy showed extensive reactive CD1a-negative histiocytosis and focal erythrophagocytosis suggestive of HLH/macrophage activating syndrome (MAS) with no evidence of lymphoma, LCH, or lymphoproliferative disease. There was no family history of HLH or lung disease. Genetic testing for HLH (which included evaluation for the *SLC7A7* mutation associated with lysinuric protein intolerance) was negative. Bone marrow biopsy was normocellular for age with full maturation of all 3 cell lines and increased histiocytes. Flow cytometry was negative for leukemia and lymphoma. Viral causes of secondary HLH were ruled out with negative serum viral polymerase chain reaction testing for Epstein-Barr virus (EBV), cytomegalovirus, adenovirus, and human herpes virus 6. While still undergoing workup for her fevers of unknown origin, she eventually developed acute respiratory distress syndrome, which was successfully treated with methylprednisolone (2 mg/kg/day), followed by transfer to a chronic rehabilitation facility where her ventilator support and steroids were quickly weaned.

Four months after hospital discharge, she was readmitted with fevers, rash, diarrhea, and respiratory distress. During this admission, she developed central line-associated *Serratia marcescens* bacteremia and was effectively treated with antibiotics and line removal, but her fevers persisted with negative infectious workup, so methylprednisolone (2 mg/kg/day) was restarted for secondary HLH. High-dose intravenous corticosteroids (10 mg/kg/day) were given for 3 days with brief decreased oxygen requirement (from fraction of inspired oxygen [FiO_2] 1.0 to 0.65), before returning back to previous settings because of persistent desaturations. Chest radiograph showed diffuse bilateral lung disease (**Figure**, A). Repeat chest CT scan showed extensive ground glass opacities with crazy paving pattern (**Figure**, B). Lung biopsy revealed histopathology consistent with PAP including diffuse alveolar filling with abundant proteinosis material and positive periodic acid-Schiff stain (**Figure**, D-F). Further microscopic analysis of lung parenchyma showed mild interstitial inflammation and fibrosis along with alveolar enlargement and distension suggestive of chronic lobular remodeling. Genetic and autoimmune testing for PAP were negative, leading to a diagnosis of secondary PAP, likely because of secondary HLH. Repeat laboratory testing met 4 out of 8 HLH-2004 diagnostic criteria (**Table II**). Chromosome microarray was normal without clear evidence of a unifying genetic syndrome for her congenital abnormalities.

Her respiratory status continued to deteriorate with arterial partial pressure of carbon dioxide ($PaCO_2$) 61-76 torr, requiring high ventilatory support (including positive end expiratory pressure 10, FiO_2 0.8-0.9) despite airway clearance therapies and diuretics. After much discussion, the patient was treated with bilateral whole lung lavage (WLL) while placed on veno-venous extracorporeal membrane oxygenation (ECMO) and received a total of 6 WLL procedures over the course of 18 days. Each WLL was performed with a flexible bronchoscope instilling warmed normal saline into each subsegment of the tracheobronchial tree followed by suctioning. Initial effluent fluid was white and very thick, but subsequent WLLs achieved clearer fluid return. Serial chest radiography showed gradual improvement in lung aeration. (**Figure**, A and C). After completing WLL, she was treated with 8 weeks of etoposide and steroids as per modified HLH protocol with successful transition from full ventilator support to only oxygen via tracheostomy collar (FiO_2 0.35) before discharge to rehabilitation facility.

Table I. Assessing the diagnostic criteria for HLH during patient's first hospital admission

Diagnostic criteria for HLH (diagnostic if has HLH mutation or if 5 out of 8 criteria are met)[5]	First admission to our hospital
1. Fever	39°C-40°C
2. Splenomegaly	Present
3. Cytopenia (2 of 3 cell lineages)	
Hemoglobin < 9g/dL	6.9 g/dL
Platelets < 100 000/mL	38 000/mL
ANC < 1000/mL	3600/ ml
4. Hypertriglyceridemia (fasting ≥ 265 mg/dL) or hypofibrinogenemia (≤150 mg/dL)	293 mg/dL 120 mg/dL
5. Hemophagocytosis	Present in bone marrow biopsy and lymph node biopsy
6. Low or absent NK cell activity	Normal
7. Ferritinemia ≥ 500 ng/mL	28 167 ng/mL
8. Soluble IL-2Rα (sCD25) ≥ 2400 U/mL (or per local reference laboratory)*	Elevated (11 289 U/mL)
Additional molecular diagnostic testing	No pathogenic mutations for primary HLH

ANC, absolute neutrophil count; *IL*, interleukin.
*Cincinnati Children's Hospital reference laboratory diagnostic criteria: soluble IL-2Rα > 2126 U/mL.