# Prolonged Remission Following Refractory Pulmonary Capillaritis in a Young Child

Jodi Gustave[1] and Abigail Strang[2]

[1]Nemours/ AI duPont Hospital for Children
[2]Nemours/Alfred I. duPont Hospital for Children

May 26, 2020

**Abstract**

Diffuse alveolar hemorrhage is a serious disorder where bleeding occurs throughout the alveoli that originates from the pulmonary microvasculature. Pulmonary capillaritis is a common cause of DAH but overall is extremely rare albeit potentially deadly in the pediatric population. PC is typically associated with systemic autoimmune disorders and treatment revolves around control of the cause. Isolated pulmonary capillaritis occurs without an underlying association and is extremely uncommon, particularly in children. Because of this, treatment guidelines do not exist but the urgency of treatment remains due to serious sequelae that may occur, including sudden death. Here, an interesting case is presented involving a toddler with diffuse alveolar hemorrhage due to ANCA-negative isolated pulmonary capillaritis with a strong family history of autoimmune disease. After multiple relapses she is currently in remission following a several year treatment regimen that included rituximab, pulse steroids, IVIG, azathioprine and oral corticosteroids. We would like to acknowledge to Dr. Timothy Vece for his assistance in the final treatment protocol for this patient.

## Prolonged Remission Following Refractory Pulmonary Capillaritis in a Young Child

### Case

A 16 month old female with history of prematurity at 36 weeks gestation presented to the emergency department with a 2 week history of rhinorrhea, congestion, cough, and decreased activity with a recent ED visit for vomiting and diarrhea that had since resolved. There were no reports of obvious blood loss with hematemesis, hematochezia or hemoptysis. She attended daycare where there were multiple sick contacts. Her family history included severe SLE, rheumatoid arthritis and fibromyalgia in her mother and severe SLE and scleroderma in her maternal aunt. A CBC and CMP were obtained as part of her initial work-up and were notable for severe anemia with hemoglobin of 2.9 and a normal CMP. A repeat CBC again demonstrated severe anemia with a hemoglobin of 2.7 and a reticulocyte count of 11.6%. Additional initial lab studies revealed signs of iron deficiency anemia and were otherwise unremarkable. Pertinent findings on her physical exam included a female toddler who was tired-appearing and fussy, a flow murmur, tachycardia, clear lungs, and a soft abdomen.

The patient was admitted to the PICU for pRBC transfusion, further work-up and care. Her initial chest X-ray done on Day 2 of hospital admission showed bilateral diffuse alveolar airspace disease. She was given successive small (5 ml/kg) aliquots of PRBC's. Her chest CT (obtained about 12 days after admission, **Figure 1** ) showed bilateral patchy parenchymal opacities throughout the lungs with most pronounced areas of dense opacification in the periphery. A flexible bronchoscopy was done 13 days after admission and showed bloody secretions in the lower lobes. The cytopathology from the bronchoalveolar lavage fluid showed predominantly red blood cells, macrophages (many hemosiderin- laden), neutrophils and foci of fibrin. Oil-red-O also showed occasional lipid-laden machrophages. All cultures (viral, bacterial, fungal

and mycobacterial) were negative. Lab work-up for autoimmune diseases and other infectious etiology was negative. A left lung biopsy obtained on day 19 of admission showed acute and chronic pulmonary hemorrhage syndrome with features consistent with resolving acute capillaritis (**see Figure 2** ). Within the tissue, there were few EBV-positive cells but EBV infection did not appear to be the cause of pulmonary bleeding. Direct immunofluorescence microscopy showed a granular deposition of IgA and C3 in the alveolar walls.

Throughout her hospital stay, the patient was treated with Bipap and oxygen (for intermittent hypoxia and respiratory distress), diuretics, multiple blood transfusions and oral steroids (prednisone, 2 mg/kg/day). Her hemoglobin levels gradually stabilized and she no longer required respiratory support. She was hospitalized for a total of 23 days and was discharged with a hemoglobin of 8.5, Hct of 35.1, and a reticulocyte count 4.7%. Her discharge medications included prednisone 2 mg/kg/day, ranitidine and iron supplementation. Her CXR prior to discharge showed improved pulmonary opacities.

Following discharge from the hospital she was followed by pulmonology, rheumatology and nephrology due to the IgA deposition noted on lung biopsy. IgA nephropathy was eventually ruled out due to normal kidney function and ultrasound.

At about 2.5 months following her initial admission while continuing oral corticosteroids, a surveillance bronchoscopy showed continued alveolar hemorrhage and the patient was again admitted to the hospital for observation despite a stable Hb and CXR. She was started on methotrexate 0.3 ml SQ weekly and continued prednisone 2 mg/k/day. Other daily medications included ranitidine and atovaqone. Her immune modulators were then changed from methotrexate to mycophenolate mefotil 20 mg/kg twice daily due to the possibility of improved pulmonary penetration and IgA deposition noted on her biopsy. About 2 months later, she had a surveillance bronchoscopy that showed continued lower airway bleeding. Her Hb at that time was stable at 12.3 g/dl, however the decision was made to change her immune modulator to a monthly cyclophosphamide infusion at a dose of 45 mg/kg following a 3 day course of pulse steroids (30 mg/kg/dose). She received 6 total doses of cyclophosphamide. Following the completion of these infusions during which time her prednisone was weaned to 0.5 mg/kg/day, a surveillance CXR showed signs of continued pulmonary hemorrhage that was verified by chest CT. She also had a dip in Hb to 9.8 g/dl and an elevated Reticulocyte count to 5.3% and did not show signs of acute illness.

She then began a new long-term treatment regimen that included rituximab infusions of 500 mg/m2 on days 0 and 14 and at 6 months, IV solumedrol at a dose of 30 mg/kg IV (weekly for the first 3 months, then bi-weekly for 3 months, then monthly for 2 months) and IVIG at 2 grams monthly for 3 months. Following that, she was then given oral azathioprine (approx. 2 mg/kg) for 3 years and her oral steroids were slowly weaned. About 10 months after starting the second phase, she was admitted to the hospital for a week for multifocal pneumonia, gastroenteritis and relapse in her capillaritis. Her Hb at that time dropped to 8.4 and was 9.8 g/dl prior to discharge. At the time of that illness, she was getting azathioprine daily and her steroids had been weaned to 2.5 ml every other day. During the admission and following discharge, an antibiotic course was completed, her azathioprine continued at 2 mg/ kg/day and her steroid dose was increased back to 2 mg/ kg/ day. Her subsequent lab testing at hospital follow up revealed a Hb of 13.1 g/dl. Her prednisone dose was gradually weaned again to a final dose of 1 ml every other day and her azathioprine dose was continued at 2 mg/kg/ day. After about 2 years of continued therapy following the clinical relapse, her Hb has remained in the normal range. She had a subsequent surveillance bronchoscopy that did not show evidence of alveolar hemorrhage. Since that time, she is not receiving medications and is an active 6 year old.

**Discussion:**

Pulmonary hemorrhage in children can be insidious or can present acutely as an acute life-threatening event (1). The bleeding may be diffuse (alveolar) or focal (2). Diffuse alveolar hemorrhage (DAH) is a rare but potentially life threatening condition in children. (2). DAH occurs as a result of injury to the small vessels (capillaries, arterioles and venules) of the pulmonary circulation (3). Idiopathic pulmonary hemosiderosis

(IPH) is a diagnosis of exclusion and includes diffuse infiltrates, anemia and alveolar hemosiderin-laden macrophages of unknown cause (3). Various hypotheses have been proposed to explain the pathophysiology of IPH including allergic, environmental, genetic and/or auto-immune processes (4). The differential diagnosis in time has expanded to include pulmonary capillaritis (PC) and idiopathic hemorrhage of infancy (AIPH). Pulmonary capillaritis was first described in the 1950's and is thought to be an immune mediated disorder that targets cytoplasmic components of neutrophils. It is an inflammatory process involving capillaries and may present in isolation or as part of a disorder (1). DAH with pulmonary capillaritis can have many causes, with underlying defects in the alveolar-capillary bed, immune mediated lung injury or environmental and genetic factors (3). Autoimmune disorders that are associated with pulmonary capillaritis include Wegener's granulomatosis, microscopic polyantiitis, Goodpasture's Syndrome, and Systemic Lupus Erythematosis (SLE). There are also associated drugs that include propylthiouracil, retinoid acid and phenytoin (3).

In order to identify pulmonary capillaritis and differentiate it from IPH, a lung biopsy is required. It is important to differentiate the two in order to guide treatment. Isolated pulmonary capillaritis is a rare disorder with poorly understood etiology (1). Our patient with isolated PC was very interesting in the she had strong family history of autoimmune disease, particularly in females on her maternal side, however her rheumatologic work-up was negative. There is very sparse literature available regarding management of pediatric patients with PC, particularly refractory cases such as our patient. In 2004, a case series was published by Fullmer, et al (2) that identified 8 pediatric patients with pulmonary capillaritis, ranging in age from 1.5 to 12 years of age. Final diagnoses varied and one patient was diagnosed with isolated pulmonary capillaritis. Interestingly, this patient appeared more recalcitrant than many others with underlying disorders. Many of the other patients were reported as "resolved" following pulse and oral steroids. Other treatments included IVIG, cyclophosphamide, hydroxychloroquine and azathioprine. There was also a case report published in 2015 that described a 45 year old male with isolated pauciimmune PC who failed cyclophosphamide and was then successfully treated with rituximab (5). Our patient had 2 known relapses in her course, one thought to be infection- related (acute pneumonia) and one without notable underlying cause, however she did not initially receive IV pulse steroids, as treatment options were not well published. She currently remains in remission following a combination of rituximab, pulse steroids and IVIG, followed by maintenance therapy with azathioprine and an oral corticosteroid taper and a total treatment time of about 3.5 years with these medications.

Since pulmonary capillaritis and particularly isolated PC is such a rare disorder in children, publication of cases is vital in order to begin to detect a pattern of successful therapies.

References:

1. Parris D, van Niekerk A, Jeevarathnum, AC et al. An approach to pulmonary hemorrhage in children. S Afr Respir J. 2017; 23(3):63-70.
2. Fullmer JJ, Langston C, Dishop M et al. Pulmonary capillaritis in children: a review of eight cases with comparison to other alveolar hemorrhage syndromes. J Pediatr. 2005; 146(3):376-81
3. Susarla SC and Fan LL. Diffuse alveolar hemorrhage syndromes in children. Curr Opin Pediatr. 2007;19:314-320.
4. Taytard J, Nathan N, deBlic J et al. New insights into pediatric idiopathic pulmonary hemosiderosis: the French RespiRare cohort. Orphanet Jurnal of Rare Disease. 2013;8:161.
5. Thompson G, Specks U and Cartin-Ceba R. Isolated pauciimmune pulmonary capillaritis successfully treated with rituximab. Chest. 2015;147(4):e134-e136.