PH GRAND ROUNDS

A Case of Atypical Hemolytic Uremic Syndrome and Pulmonary Veno-Occlusive Disease

Section Editor
Deborah J. Levine, MD

Mary Jo S. Farmer, MD, PhD
Division of Pulmonary & Critical Care
Assistant Professor of Medicine, Tufts University School of Medicine
Baystate Health System
Springfield, MA

This case was presented by Drs Mary Jo Farmer, Ioana Preston, and Richard Channick at the American Thoracic Society 2016 International Conference in San Francisco, CA.

Presentation: A 56-year-old female was referred for pulmonary evaluation with cough and shortness of breath on exertion. The shortness of breath with exertion had progressed for several months. The cough was of recent onset, about 6 weeks prior to presentation, and described as intermittent, dry, and nonproductive, triggered by exertional dyspnea. The patient denied fever, chills, sputum production, wheezing, hemoptysis, postnasal drip, reflux, seasonal allergies, and sick contacts. There was no history of ankle swelling or blood clots. The patient was a nonsmoker and previously employed as a TSA security officer. She denied use of dietary supplements to enhance weight loss. Prior surgical procedures included 2 unremarkable C-sections and gallbladder removal. There was no family history of pulmonary disease, and the patient's father died at age 62 years due to stomach cancer.

Past medical history was remarkable for atypical hemolytic uremic syndrome diagnosed 4 years prior by kidney biopsy, which revealed thrombotic microangiopathy with severe occlusion, remodeling of the arterial vessels, and widespread double contours of the glomerular vessel walls. ADAMTS13 activity was normal. Atypical hemolytic uremic syndrome (aHUS) panel analyzed at University of Iowa Molecular Otolaryngology Research Laboratory was negative for CFH, CF1, MCP, CFB, C3, THBD, and deletion/duplication of CFHR1-CFHR3 gene. The patient received eculizumab every 2 weeks. Hemolytic uremic syndrome markers stabilized with creatinine 2.5 to 2.7 mg/dL and platelet count 85,000 to 100,000 x 10^9/L without evidence of hemolysis.

Assessment: Physical examination revealed a pleasant female in no apparent distress. Respirations were not labored at rest and breath sounds were clear to auscultation bilaterally. Neck was supple and trachea middle with jugular venous pressure (JVP) estimated at 6 to 7 cm. Cardiovascular exam revealed regular rate and rhythm (RRR), normal point of maximum impulse (PMI), no right ventricular (RV) heave, normal S1, split S2 heard midway from sternum to apex, and a soft systolic murmur at the base. Gastrointestinal (GI) exam revealed a soft, nontender abdomen without hepatosplenomegaly. No peripheral edema, clubbing, or cyanosis noted in the extremities. Skin was warm and dry without rashes.

Spirometry and lung volumes were normal with markedly decreased diffusing capacity of the lungs for carbon monoxide (DLCO) at 26% predicted adjusted for hemoglobin of 13.2. Six-minute walk on room air was 360 meters and desaturation to 87% occurred. Sleep study was unremarkable. Echocardiogram revealed left ventricle (LV) normal size, wall thickness and systolic function with ejection fraction (EF) 55% to 65%, dilated right atrium (RA), markedly dilated RV with moderately reduced systolic function, mild to moderate tricuspid regurgitation (TR), mild mitral regurgitation (MR), trivial pericardial effusion, flattening of the interventricular septum during systole and diastole consistent with RV pressure and volume overload, and estimated pulmonary artery (PA) pressures 80 to 90 mm Hg (echo images); Grade 1 mild diastolic dysfunction with impaired LV relaxation. Ventilation-perfusion (V/Q) was low probability for pulmonary embolism. Chest x-ray showed clear lungs without pleural effusion or pneumonia. Pertinent laboratory values included platelet count 76,000 x 10^9/L, hemoglobin 13.2 g/dL, aspartate aminotransferase (AST) 22 U/L, alanine aminotransferase (ALT) 15 U/L, creatinine 2.2-2.6 mg/dL, HIV negative, international normalized ratio (INR) 1.0, activated partial thromboplastin time (APTT) 29.4 s, N-terminal pro b-type natriuretic peptide (NT-proBNP) 1,633 pg/mL, antinuclear antibody (ANA) positive 1:400 homogeneous pattern, lupus anticoagulant negative, anti-native DNA negative, anti-cardiolipin negative, and complement 50 reduced to 12 L.

Right heart catheterization (RHC) revealed severe pulmonary arterial hypertension (PAH) with pulmonary artery pressure (PAP) 96/31 (53) mm Hg, pulmonary artery wedge pressure (PAWP) 6 mm Hg, cardiac output (CO) 5.11 L/min, cardiac index (CI) 3.2 L/min, pulmonary vascular resistance (PVR) 9 Wood units. Vasodilator challenge results were reported as follows in

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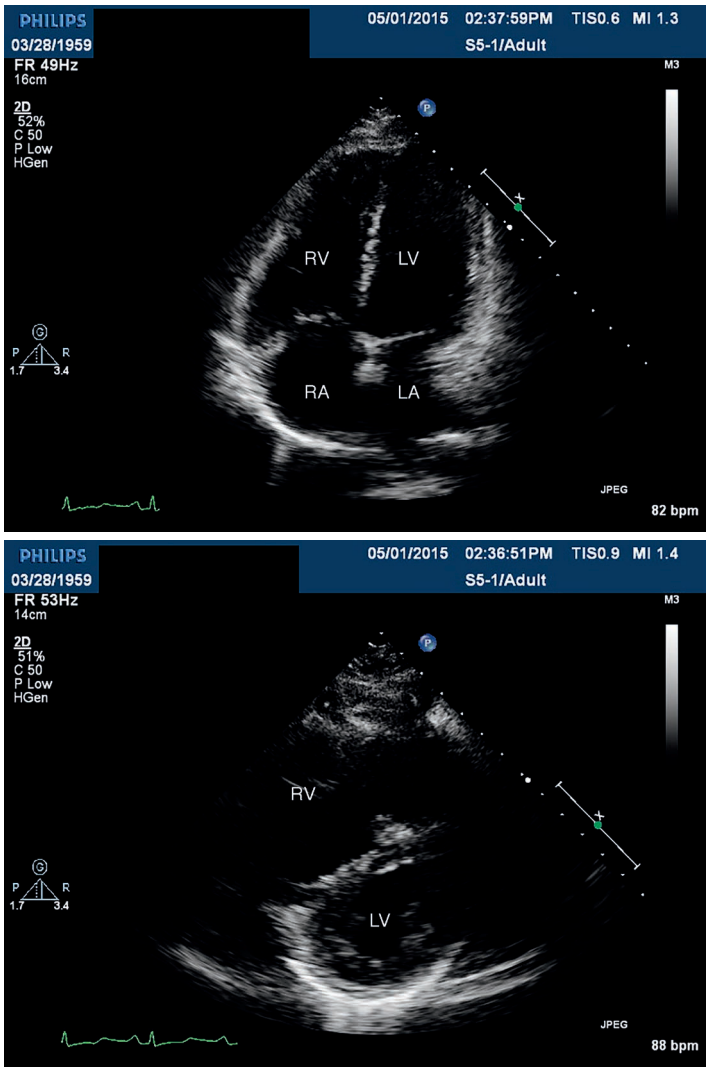
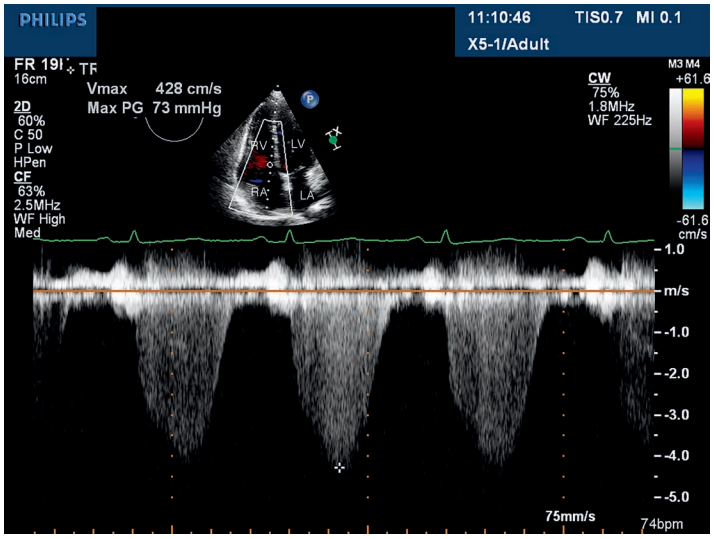
Correspondence: maryjo_farmer@yahoo.com; maryjo.farmer@baystatehealth.org



Echocardiograms 1 and 2: Apical 4-chamber view and parasternal short axis view depicting severe right ventricular dilation, small left ventricle, normal left ventricular wall thickness, and flattening of the interventricular septum during systole and diastole consistent with RV pressure and volume overload. *Courtesy of William Hiser, MD, Director, Cardiac Stress Lab Baystate Cardiology, Springfield, MA.*



Echocardiogram 3: Continuous wave spectral Doppler demonstrating severe pulmonary hypertension. *Courtesy of William Hiser, MD, Director, Cardiac Stress Lab, Baystate Cardiology, Springfield, MA.*

Table 1. The patient did not meet the strict definition of a positive vasoreactivity challenge test in that the mean PAP did not decrease to a value <40 mm Hg.

On the basis of RHC data and following a discussion of available treatment options with the patient and spouse, treatment for idiopathic PAH was begun with tadalafil 20 mg once daily and ambrisentan 5 mg once daily. Tadalafil had to be discontinued within 1 week due to severe gastroesophageal reflux disease, nausea, and vomiting. Two days later, the patient noticed increased weight gain and diuretics were increased. Several days later, the patient developed nonproductive cough and oxygen desaturation to 60% on room air. High-resolution chest computed tomography (CT) (Figure 1) was reviewed with radiology and revealed findings consistent with pulmonary veno-occlusive disease (PVOD) including moderate bilateral layering pleural effusions, adjacent bilateral compressive atelectasis, right middle lobe subpleural pulmonary nodules, scattered ground glass opacities, mild interstitial thickening, and mildly enlarged subcarinal lymph nodes. Ambrisentan was discontinued with prompt improvement in oxygenation. Sildenafil 10 mg twice daily and prednisone were started, while aggressive diuresis was continued. Pleural effusions and cough resolved and room air oxygen saturation improved to 95%. Patient continued to require 2 L/min supplemental oxygen with exertion. The patient was referred for lung transplant evaluation to a tertiary pulmonary hypertension (PH) center; however, after further discussion with her spouse, she decided she was not interested in proceeding with this option. In addition, there was concern at the tertiary center that her renal disease would increase the risk for postoperative transplant complication.

Prednisone dose was tapered then increased again due to worsening dyspnea. Patient traveled to Florida with sildenafil increased to 10 mg 3 times daily, prednisone 15 to 20 mg daily, and Lasix 40 mg twice daily. Patient noticed an increase in fluid retention, increased weight, and return of nonproductive cough at the end of the Florida trip with

Table 1: VASODILATOR CHALLENGE (rest, then 5-minute intervals with inhaled nitric oxide at 40 ppm)

	Rest	5 min	10 min	15 min
HR bpm	102	89	86	85
SBP mm Hg	131/77	124/79	117/75	133/71
PAP (mean) mm Hg	95/35 (60)	80/36 (47)	75/25 (44)	75/30 (44)
PCWP mm Hg	6	7	7	5
CO/CI (TD) L/min	5.1/3.2	4.8/	4.4/	4.7/

sildenafil at 20/10/10 mg and intermittent use of portable oxygen concentrator for travel toward the end of the trip. Patient was admitted with chest x-ray demonstrating small bilateral pleural effusions and basilar atelectasis, NT-proBNP 34,804 pg/mL and creatinine (Cr) 3.0 mg/dL. Laboratory parameters normalized with institution of continuous supplemental oxygen, prednisone 5 to 10 mg daily, sildenafil 20/10/10 mg, and diuretics. The patient was subsequently weaned off prednisone at her request due to concern for side effects such as immunosuppression, weight gain, and bone loss.

Repeat echocardiogram around 6 months compared to prior echocardiogram showed a decrease in pulmonary artery systolic pressure (PASP) to 60-65 mm Hg, mildly dilated RA, normal RV size, mild to moderate RV hypertrophy, moderate RV hypokinesis, LV normal size wall thickness, systolic function with EF 55% to 65%, and no pericardial effusion. Six-minute walk was approximately 341 meters around this time.

The patient was recently admitted to her local medical center with increasing supplemental oxygen requirements, a self-reported 5-pound weight gain, moderate to large bilateral pleural effusions, and increased serum Cr to the 3.2 to 3.5 mg/dL range. Ultrasound-guided thoracentesis, chest tube drainage, hi-flow supplemental oxygen, restarting prednisone, and escalation of diuretics were instituted; however, the patient's renal function and respiratory status did not improve. The patient was transferred to the tertiary PH center for further evaluation and treatment including a trial of inotropes and possible dialysis. Unfortunately, the serum creatinine rose to 5.0 mg/dL and the patient expired shortly thereafter from RV failure.

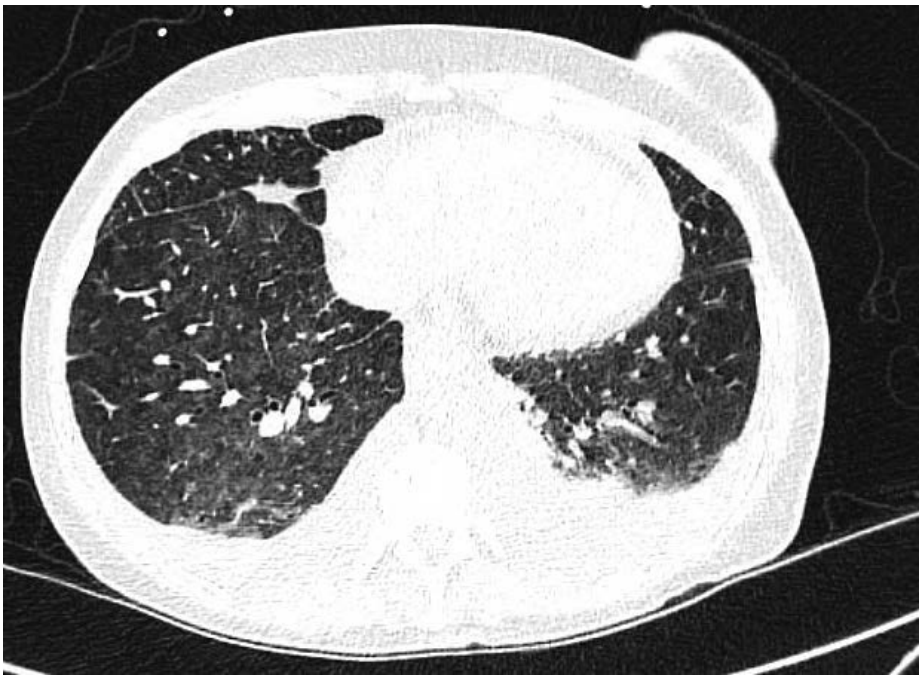


Figure 1: Chest CT – PVOD Findings.
Moderate bilateral layering pleural effusions, adjacent bilateral compressive atelectasis, right middle lobe subpleural pulmonary nodules, scattered ground glass opacities, mild interstitial thickening, and mildly enlarged subcarinal lymph nodes (latter finding present on another cross section).

Discussion: The hemolytic uremic syndrome (HUS) is characterized by nonimmune hemolytic anemia, thrombocytopenia, and renal impairment. Approximately 10% of cases of HUS are classified as atypical since they are caused by neither Shiga-like toxin nor Streptococci. Atypical hemolytic uremic syndrome (aHUS), unlike typical HUS, is not due to bacteria but rather to an idiopathic or genetic cause that promotes uncontrolled activation of the complement system and dysregulation of the alternative complement pathway leading to hemolytic anemia, thrombocytopenia, and renal impairment. Atypical hemolytic uremic syndrome is classified as familial (20%) or sporadic. Triggers for the sporadic form include infection with HIV, cancer, organ transplantation, pregnancy, use of anticancer drugs, immunotherapeutic agents (cyclosporine, tacrolimus), and antiplatelet agents (ticlopidine, clopidogrel). Individuals with familial aHUS frequently relapse even after complete recovery from the presenting episode. Mutations are reported in the genes of 3 proteins that regulate the alternative complement pathway: Factor H, membrane cofactor protein, and Factor I. Although aHUS secondary to a Factor H mutation is relatively rare, aHUS usually presents with younger onset and a more severe course, the majority culminating with end-stage renal failure. Prognosis is poor with death rates as high as 25% and progression to end-stage renal disease in 50% to 80% of patients. The lesions of HUS and aHUS are characterized by thickening of arterioles and capillaries, endothelial swelling and detachment, and subendothelial accumulation of proteins and cell debris. There is widening of the subendothelial space with obstruction of vessel lumina by platelet thrombi. Hemolysis occurs and fragmented or distorted erythrocytes are found in

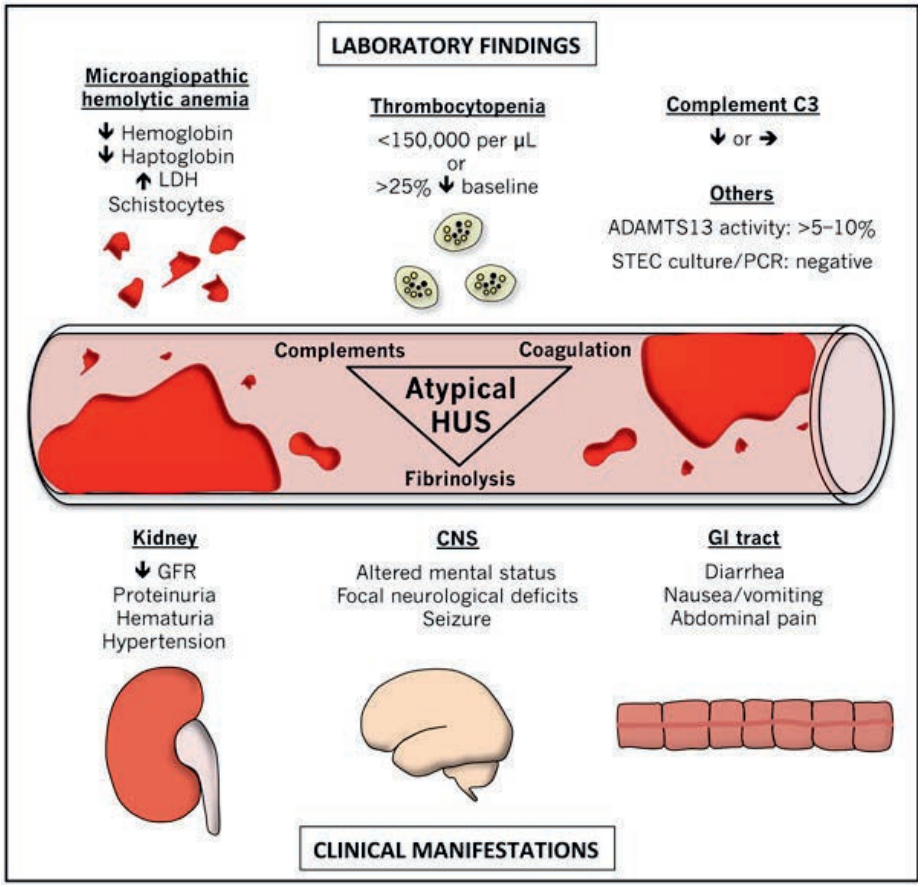


Figure 2: Atypical HUS. Laboratory findings and clinical manifestations. www.benthamopen.com.

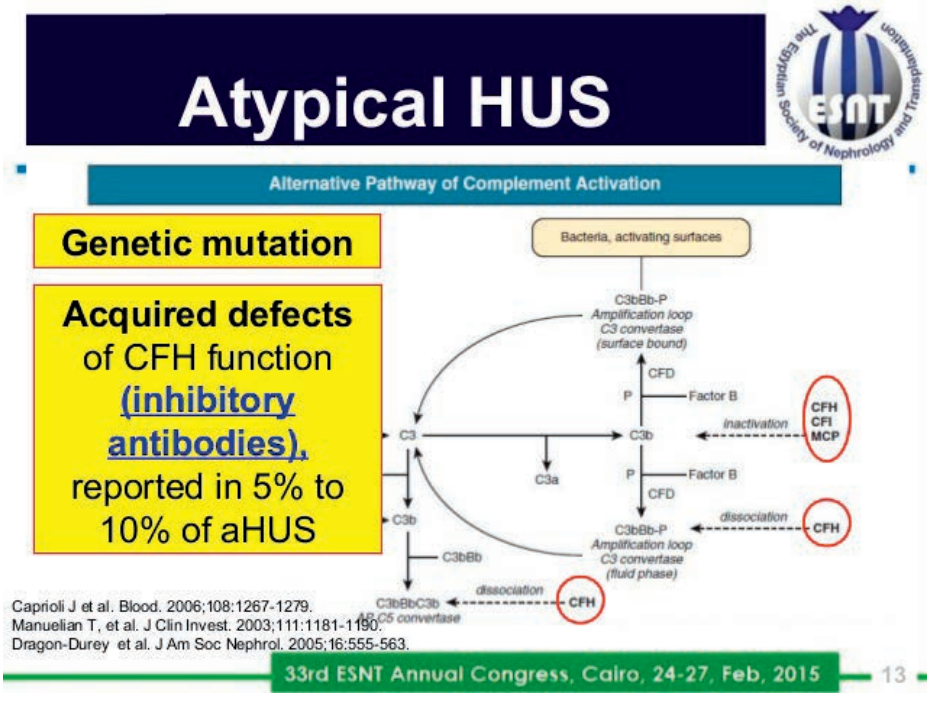


Figure 3: Atypical HUS. Alternative pathway of complement activation. www.slideshare.net.

blood smears. Lesions typically affect the kidney, mainly glomeruli and arterioles, although the brain, heart, lungs, GI tract, and pancreas may be involved. Diagnosis of aHUS requires the exclusion of other associated diseases, a lack of criteria for typical HUS, and a lack of criteria for thrombotic thrombocytopenic purpura determined with serum ADAMTS13 activity (Figures 2 and 3). Plasma infusion or exchange has been done to reduce mortality. Markers of renal failure and red blood cells, hemoglobin, and platelet count are checked on a regular basis. Alternatively, eculizumab (Soliris) is the first therapy approved for treatment of aHUS to inhibit complement-mediated microangiopathy.

Pulmonary veno-occlusive disease is a rare condition classified as a subgroup of World Health Organization Group 1 PAH. The pathologic hallmark is extensive and diffuse occlusion of pulmonary veins due to smooth muscle hypertrophy and collagen matrix deposition (fibrous tissue). It is a fibroproliferative disease primarily affecting small pulmonary veins. Most cases of PVOD are idiopathic and pathogenesis is unknown and likely multifactorial. Pulmonary veno-occlusive disease may represent a common aberrant response to an inciting event of endothelial injury that leads to widespread fibrosis of pulmonary venules. Families with multiple siblings affected by PVOD have been identified, suggesting a possible genetic basis for the disease.

Although PAH has been associated with autoimmune disorders characterized by thrombotic angiopathy, this appears to be the first case of aHUS and PVOD occurring together in an adult female. The mechanisms underlying the association between aHUS and PVOD are not clear, although one explanation may involve inflammatory mediators and microangiopathic thrombosis affecting both the kidneys and pulmonary vasculature.

Atypical HUS affects the vascular endothelial cell causing endothelial cell damage, leukocyte and platelet activation, widespread inflammation, and multiple thromboses in small blood vessels. Pulmonary veno-occlusive disease on the other hand is character-

ized by pulmonary arteriolar, venular, and lymphatic inflammation and remodeling with consequent increased PVR and a typical radiologic appearance. The mechanisms underlying the association between aHUS and PVOD are not clear and present areas for further study. One possible explanation might be inflammatory mediators and microangiopathic thrombosis affecting both the kidneys and pulmonary vasculature.

Eculizumab (Soliris) is the first therapy approved for treatment of aHUS to inhibit complement-mediated microangiopathy by blocking terminal complement activation. A question raised by this case is whether terminal complement activation in the pulmonary vasculature is mediated by eculizumab. Lung transplant was discussed; however, the patient was hesitant to proceed without better understanding any potential interaction between aHUS and the transplanted lung.

Teaching Points

1. Atypical hemolytic uremic syndrome affects the vascular endothelium and has been associated with pulmonary vascular disease.
2. Pulmonary veno-occlusive disease must be considered when worsening shortness of breath and signs of fluid overload develop on pulmonary vasodilator therapy.
3. Eculizumab (Soliris) is the first therapy approved for treatment of aHUS to inhibit complement-mediated microangiopathy by blocking terminal complement activation. A question raised by this case is whether terminal complement activation in the pulmonary vasculature is mediated by eculizumab with the expectation of slowing or preventing the development of pulmonary vascular disease.

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