PH GRAND ROUNDS

Eisenmenger Syndrome: When Less Is More

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Presentation: A 61-year-old woman with Eisenmenger syndrome due to an unrepaired truncus arteriosus (type 2) and a history of atrial fibrillation complicated by a cerebrovascular accident presented to an outside hospital with one week of worsening exertional shortness of breath, cough, and chills after recent airplane travel to the Philippines. She had been managed at our pulmonary hypertension center for 5 years and treated with sildenafil as well as warfarin for her history of atrial fibrillation. Evaluation at the outside hospital included a chest radiograph showing a left lower lobe infiltrate. She was started on a continuous heparin infusion for possible pulmonary embolism, as her international normalized ratio was subtherapeutic at 1.6. She was also started on ceftriaxone and doxycycline before transfer to our tertiary care center for further management.

Physical examination at the time of her arrival revealed a chronically ill–appearing woman with increased work of breathing. She was normotensive, tachycardic, and resting pulse oximetry saturation was 84% to 85% on 5 liters of supplemental oxygen; at baseline she used 2 liters of supplemental oxygen with oxygen saturations in the mid-80s. Auscultation revealed decreased breath sounds bilaterally with diffuse expiratory wheezing, a loud S2, and a III/VI systolic murmur heard loudest at the left upper sternal border. Extremities had decreased pulses bilaterally, clubbing of all digits, and 1+ edema to the mid-shins.

Prior Medical History: The patient was diagnosed with truncus arteriosus after presenting with tachypnea at a few days of life. It was recommended that she undergo heart surgery, but her parents declined due to lack of surgical expertise in their hometown. The patient had multiple hospitalizations during infancy and childhood for congestive heart failure but eventually improved, likely due to the development of pulmonary vascular disease. She survived a pregnancy and delivery at 28 years of age in the Philippines. Since then she reported progressive dyspnea, perioral and digital cyanosis, and fatigue. She was diagnosed with paroxysmal atrial fibrillation and started on warfarin. In 2010 she had dysmenorrhea for which she underwent a uterine biopsy and suffered a cerebrovascular accident when warfarin was held perioperatively. She has mild residual left hand and arm weakness.

In 2013 she underwent diagnostic cardiac catheterization showing a pulmonary artery pressure (PAP) of 145/61 mm Hg with a mean of 95 mm Hg and an indexed pulmonary vascular resistance (PVRi) of 58 Wood units per meter squared of body surface area. Supplemental oxygen resulted in a decrease in PVRi to 23 Wood units per meter squared and the addition of inhaled nitric oxide (iNO) reduced the PVRi to 14.4 Wood units per meter squared. She also was noted to have a single coronary artery arising from the anterior aspect of the left sinus of Valsalva. She was started on oral sildenafil 20 milligrams 3 times daily with significant improvement

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in symptoms and decreased cyanosis. She was then started on ambrisentan 5 milligrams orally once daily with development of pedal edema and abdominal bloating. The ambrisentan was discontinued and supplemental oxygen was started. Her 6-minute walk test (on room air) after 3 months of treatment demonstrated desaturation from 80% at rest to as low as 57% with ambulation after 2 minutes of walking. After one year of treatment she remained functionally impaired, again walking for only 2 minutes but with resting oxygen saturation of 87% falling to only 68% with ambulation.

Hospital Course: The patient was admitted to the cardiac intensive care unit and continued on anticoagulation and antibiotics. Chemistries and arterial blood gas showed an acute-on-chronic respiratory acidosis. Coagulation studies showed subtherapeutic international normalized ratio and partial thromboplastin times, and complete blood count showed an elevated white blood cell count to 10,000/uL with a hemoglobin of 18.3 g/dL and a hematocrit of 55.9%. Respiratory pathogen PCR panel was positive for respiratory syncytial virus. A chest radiograph showed moderately enlarged central pulmonary arteries but did not reveal an acute cardiopulmonary process. Transthoracic echocardiogram demonstrated unrepaired truncus arteriosus and a large, unrestrictive perimembranous ventricular septal defect with bidirectional flow, a dilated right ventricle with severe hypertrophy and mild to moderately reduced systolic function, flattening of the interventricular septum throughout the cardiac cycle, right atrial dilation, an estimated right ventricular systolic pressure of at least 98 mm Hg, normal left ventricular size and systolic function, a thickened truncal valve with a peak gradient of 21 mm Hg, and no other valvular disease. Lower extremity venous Doppler ultrasounds were negative for deep venous thrombosis. CT angiogram chest showed no pulmonary embolism but did show centrilobular ground glass opacities, worse in the right lung, and near collapse of the left lower lobe with superior segment sparing.

The patient was initially treated with iNO at 10 ppm and inhaled iloprost 5 micrograms every 4 hours. She was maintained on her home dose of sildenafil to achieve pulmonary vasodilation and continued on ceftriaxone and doxycycline for presumed community-acquired pneumonia. Her oxygen saturations continued to deteriorate, ranging from 50% to 70% on maximum noninvasive support. She was started on a combination of intravenous dobutamine and phenylephrine for improved pulmonary blood flow and systemic blood pressure support. Her antimicrobial coverage was broadened to vancomycin and meropenem, but her oxygen saturations did not improve. She had several episodes of melena and hematochezia with hemoglobin levels falling to 10 to 11 g/dL. Imaging of the gastrointestinal tract with an esophagogastroduodenoscopy was thought to be too high risk. Her hemoglobin goal was increased to 16 g/dL in an attempt to increase her oxygen carrying capacity and she received a total of 7 units of packed red blood cells over 10 days. This resulted in a significant improvement in her clinical status. She was also diuresed with intermittent doses of intravenous furosemide. She was progressively weaned from the iNO, iloprost, and inotropic support and transitioned from high-flow nasal cannula supplemental oxygen to 3 liters of supplemental oxygen with saturations in the mid to high 80s. She was discharged from the hospital after one month in the intensive care unit on sildenafil 20 milligrams 3 times daily as she was intolerant of higher dosing due to intermittent hypotension, warfarin, and 2 to 3 liters of supplemental oxygen.

Six months following this hospitalization she underwent repeat cardiac catheterization. On room air her PAP was 142/53 mm Hg with a mean of 85 mm Hg and a PVRi of 28.4 Wood units per meter squared. She is awaiting initiation of macitentan and has been advised to undergo evaluation for heart and lung transplantation.

Discussion: Truncus arteriosus (TA) is a rare form of cyanotic congenital heart disease (CHD), affecting 1 in 10,000 live births and accounting for approximately 1% of congenital heart lesions.[1] TA occurs due to failure of the development of the conus arteriosus, which normally separates the primitive truncal valve into the aortic and pulmonary valves. In the absence of a conus arteriosus and spiral septum, there is a nonrestrictive outflow ventricular septal defect with blood ejected from both ventricles across a common truncal valve into the truncus arteriosus. The pulmonary arteries then emerge in a series of ways, either from the ascending aorta as a common trunk (type 1) or less often arising separately from the ascending truncus (type 2). The natural history of unrepaired TA is dismal, with death in early infancy usually secondary to heart failure and a survival of only 15% at one year of age. Those patients who survive to young adulthood will unequivocally develop pulmonary arterial hypertension (PAH),[2] with subsequent mortality attributed to complications of pulmonary vascular disease and infective endocarditis.[3]

Uncorrected CHD frequently results in PAH, the most severe form of which is Eisenmenger syndrome (ES). Unrepaired systemic-to-pulmonary communications cause pulmonary vascular remodeling secondary to nonrestrictive increases in pulmonary blood flow and PAP.[4] Over time, as pulmonary arterial resistance exceeds that of the systemic vasculature, the shunt direction reverses resulting in predominant right-to-left flow and oxygen-unresponsive hypoxemia. This stage, identified as ES, represents a disease state in which pulmonary hypertension is largely irreversible and cardiac lesions are inoperable.[5] Although the prevalence of ES is not known, historical data estimate that approximately 11% of patients with CHD with known left-to-right shunts develop ES.[6] Although natural history studies of ES patients have demonstrated a wide spectrum of variability, survival overall is thought to be superior to other forms of PAH, with approximately 95% survival at 5 years and 56% at 20 years following ES diagnosis.[7]

The majority of patients with ES survive to adulthood. Their clinical course, however, is complicated by the development of a unique constellation of

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multisystem disease that does not occur in idiopathic PAH (IPAH) including coagulopathy, erythrocytosis, hyperviscosity, renal dysfunction, pulmonary hemorrhage/hemoptysis, endocarditis, and brain abscesses.[8] Though our patient has a history of menorrhagia and ischemic stroke in the setting of atrial fibrillation, she has otherwise been without other multisystem sequelae of ES. It is important to note that this complex profile includes both a tendency toward bleeding and clot formation, with proximal pulmonary artery thrombosis observed in 21% to 29%, and distal pulmonary artery thrombosis observed in 43%, of patients with ES.[9,10] Women and patients with lower oxygen saturations were noted to be at increased risk for pulmonary embolism. While most clinicians recommend anticoagulation for ES patents who have experienced a pulmonary embolism, there are no data to support routine prophylactic anticoagulation in this patient subset as it has not been shown to impact long-term survival.[11] The risk of hemoptysis and absence of a consensus international normalized ratio target range for ES patients add to the complexity of routinely anticoagulating these patients.

Despite the consequences of chronic cyanotic heart disease enumerated above, ES patients were historically thought to have slower disease progression and overall improved survival compared to their IPAH counterparts.[12] This was thought to be secondary to a "training effect" on right ventricular function in the setting of long-standing right ventricular hypertension and the inherent benefit of a right-to-left shunt in relieving these elevated right ventricular pressures. This survival advantage in ES patients, however, is challenged by more recent data from REVEAL (Registry to Evaluate Early and Long-Term PAH Disease), which demonstrated higher systemic blood flow, lower mean right atrial pressure, higher mean PAP, higher pulmonary vascular resistance index, and lower systemic arterial saturations at rest in ES patients compared to those with IPAH, and also found no difference in 4- or 7-year survival between these patient cohorts. Within the ES cohort, superior 6-minute walk time, lower mean right atrial pressure and brain natriuretic peptide level, and more acute pulmonary vasoreactivity was associated with a survival advantage.[13] These data highlight the unique hemodynamic profile of ES patients which, despite similar pulmonary vascular histopathologic changes to patients with IPAH, complicates empirical extrapolation of IPAH therapies to the ES population.

Investigation of targeted PAH agents for ES has been limited partly due to concern for increased right-to-left shunting and worsened hypoxemia in the context of systemic vasodilation precipitated by these agents. BREATHE-5, the first placebo-controlled study in ES, demonstrated that bosentan significantly improved 6-minute walk distance and reduced PVRi without worsening oxygen saturation.[14] Long-term analysis of the data also highlighted the dynamic nature of ES as PVRi increased in the placebo arm and improvements in functional status persisted beyond the end of the bosentan treatment window.[15] Treatment with sildenafil improved pulmonary hemodynamics (reduced systolic and mean PAPs, lower pulmonary vascular resistance, and improved pulmonary arterial saturation) in ES patients.[16] Subsequent studies also demonstrated a significant improvement in quality of life and functional capacity in ES patients treated with sildenafil.[17] The newly updated American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of Adults with Congenital Heart Disease offers lesion-specific guidance for initiation of PAH treatment in ES, with bosentan as a Class I indication for ES secondary to an atrial or ventricular septal defect and combination therapy of bosentan and/or sildenafil as a Class IIa recommendation for all forms of symptomatic ES.[18] Although small in size, additional studies have shown improvement in exercise capacity in ES patients treated with ambrisentan and macitentan.[19,20]

As the studies above demonstrate, ES patients often respond favorably to advanced PAH therapies despite long-standing pulmonary vascular disease. This may be due, in part, to maintenance of pulmonary vasoreactivity in ES patients that was also seen in our case presentation patient.[21,22] Although our patient was a notable outlier given her survival to an advanced age with unoperated TA, it is intriguing to hypothesize that her improved survival was, in part, due to retained plasticity of her pulmonary vasculature. Although most prior studies, including REVEAL, have demonstrated poor vasodilatory response testing in the ES population (8% vs 22% in iPAH),[13] a few studies have shown that approximately 20% to 30% of ES patients respond to nitric oxide inhalation (defined as a 20% reduction in PVR); they have improved survival (90% vs 40% at 10 years) and freedom from treatment with prostacyclin-based therapy or heart-lung transplantation compared to their ES counterparts that are "nonresponders."[23] It is important to note that the definition of a responder in this study was not as strict as those proposed by Sitbon et al (reduction in mean PAP of ≥10 mm Hg, reaching an absolute value of mean PAP ≤40 mm Hg, with unchanged or increased cardiac output) and adopted by the ACC/AHA and European Society of Cardiology for pulmonary hypertension.[24,25] This finding, however, highlights the benefit of early testing of the reactivity of the pulmonary vasculature in ES patients to provide a tailored approach to care. Further work remains in defining the unique anatomic, hemodynamic, and clinical characteristics that exist even within the ES population and defining the optimal treatment approach for this complex subset of PAH patients.

Teaching Points

1. ES is a complication of CHD associated with unrepaired systemic to pulmonary shunts that result in increased PAP and eventual reversal of the shunt direction.
2. Patients with ES may develop unique multisystem disease including coagulopathy, erythrocytosis, hyperviscosity, renal dysfunction, pulmonary hemorrhage/hemoptysis, endocarditis, and brain abscess that is not characteristic of other forms of pulmonary hypertension.

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3. Although patients with ES are at high risk for pulmonary artery thrombosis, prophylactic anticoagulation has not been shown to improve survival and is not recommended as part of routine care.
4. Retained pulmonary vasoreactivity occurs in 20% to 30% of ES patients and is associated with improved survival.
5. Evidence for targeted pulmonary hypertension therapy in ES is emerging. Bosentan and sildenafil are recommended treatments for ES in the new ACC/AHA 2018 Guideline for the Management of Adults with Congenital Heart Disease.

References

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39(12):1890-1900.
2. Berman EB, Barst RJ. Eisenmenger's syndrome: current management. *Prog Cardiovasc Dis*. 2002;45(2):129-138.
3. Allen H, Driscoll D, Shaddy R, Feltes T, eds. *Moss and Adams' Heart Disease in Infants, Children, and Adolescents, 7th ed*. Philadelphia, PA: Lippincott, Williams and Wilkins; 2008. Vol 1:917.
4. Fratz S, Geiger R, Kresse H, et al. Pulmonary blood pressure, not flow, is associated with net endothelin-1 production in the lungs of patients with congenital heart disease and normal pulmonary vascular resistance. *J Thorac Cardiovasc Surg*. 2003;126(6):1724-1729.
5. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. *Br Med J*. 1958;2(5099):755-762.
6. Duffels MG, Engelfriet PM, Berger RM, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. *Int J Cardiol*. 2007;120(2):198-204.
7. Clarkson PM, Frye RL, DuShane JW, Burchell HB, Wood EH, Weidman WH. Prognosis for patients with ventricular septal defect and severe pulmonary vascular obstructive disease. *Circulation*. 1968;38(1):129-135.
8. Kaemmerer H, Mebus S, Schulze-Neick I, et al. The adult patient with eisenmenger syndrome: a medical update after dana point part I: epidemiology, clinical aspects and diagnostic options. *Curr Cardiol Rev*. 2010;6(4):343-355.
9. Silversides CK, Granton JT, Konen E, Hart MA, Webb GD, Therrien J. Pulmonary thrombosis in adults with Eisenmenger syndrome. *J Am Coll Cardiol*. 2003;42(11):1982-1987.
10. Perloff JK, Hart EM, Greaves SM, Miner PD, Child JS. Proximal pulmonary arterial and intrapulmonary radiologic features of Eisenmenger syndrome and primary pulmonary hypertension. *Am J Cardiol*. 2003;92(2):182-187.
11. Sandoval J, Santos LE, Cordova J, et al. Does anticoagulation in Eisenmenger syndrome impact long term survival? *Congenit Heart Dis*. 2012;7(3):268-276.
12. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant*. 1996;15(1 Pt 1):100-105.
13. Barst RJ, Ivy DD, Foreman AJ, McGoon MD, Rosenzweig EB. Four- and seven-year outcomes of patients with congenital heart disease-associated pulmonary arterial hypertension (from the REVEAL Registry). *Am J Cardiol*. 2014;113(1):147-155.
14. Galie N, Beghetti M, Gatzoulis MA, et al; Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation*. 2006;114(1):48-54.
15. Gatzoulis MA, Beghetti M, Galie N, et al; BREATHE-5 investigators. Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study. *Int J Cardiol*. 2008;127(1):27-32.
16. Chau EM, Fan KY, Chow WH. Effects of chronic sildenafil in patients with Eisenmenger syndrome versus idiopathic pulmonary arterial hypertension. *Int J Cardiol*. 2007;120(3):301-305.
17. Tay EL, Papaphylactou M, Diller GP, et al. Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy. *Int J Cardiol*. 2011;149(3):372-376.
18. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018 Aug 10. [Epub ahead of print]
19. Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB. Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. *Am J Cardiol*. 2011;107(9):1381-1385.
20. Herbert S, Gin-Sing W, Howard L, Tulloh RMR. Early experience of macitentan for pulmonary arterial hypertension in adult congenital heart disease. *Heart Lung Circ*. 2017;26(10):1113-1116.
21. Budts W, Van Pelt N, Gillyns H, Gewillig M, Van de Werf F, Janssens S. Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome. *Heart*. 2001;86(5):553-558.
22. D'Alto M, Romeo E, Argiento P, et al. Pulmonary vasoreactivity predicts long-term outcome in patients with Eisenmenger syndrome receiving bosentan therapy. *Heart*. 2010;96(18):1475-1479.
23. Post MC, Janssens S, Van de Werf F, Budts W. Responsiveness to inhaled nitric oxide is a predictor for mid-term survival in adult patients with congenital heart defects and pulmonary hypertension. *Eur Heart J*. 2004;25(18):1651-1656.
24. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary hypertension. *Circulation*. 2005;111(23):3105-3111.
25. Galie N, Hoeper MM, Humbert M, et al; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2009;30(20):2493-2537.

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