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One for the Books: A Most Unusual Case of PAH

Dr. Preston:
Welcome, everyone. I am Ioana Preston, Associate Professor of Medicine at Tufts University School of Medicine in Boston, and the Director of the Pulmonary Hypertension Center at Tufts Medical Center. Today, I will present a most unusual case of pulmonary arterial hypertension.

So this is a man in his sixties with a history of systemic hypertension and presenting with increasing dyspnea on exertion. And he was referred to an outpatient pulmonary clinic for further evaluation of pulmonary hypertension. Now, while later hospitalized for systemic hypertensive urgency, a transthoracic echocardiogram was performed due to the patient's increasing dyspnea. And the TTE revealed a markedly dilated right ventricle and an increased estimated PA systolic pressures of 76 millimeters of mercury. On your right-hand screen, you see a snapshot of his M-mode echocardiogram. And then on the bottom, you will see the function of the right ventricle with the flow showing significant tricuspid regurgitation and a dilated right ventricle.

So the patient was observed to also have lower extremity swelling and a rash over the legs. And he was also complaining of joint pain in the hips, in the knees and feet for four months preceding the current evaluation. Inquiries from the patient's PH team revealed that he had been living principally on a diet of candy and sports drinks. And he had been describing weight loss for the past four to six months.

So on physical examination, we remarked hypertrophy of his gums. On cardiac exam, there was an increased pulmonic component on cardiac auscultation, and he had significant bilateral symmetrical pitting edema three plus. He also had hair loss on the extremities and a diffused petechial lower extremity rash running bilaterally from the mid-calf downwards. The lungs were clear to auscultation and there were no right ventricular heave or impulse, and no jugular venous distension that was appreciated. Now, due to the high estimated PA pressures on the echo and the physical exam, the patient was referred for right heart catheterization. And the results of right heart catheterization and other results showed significantly elevated PA pressures with normal wedge. An autoimmune antibody evaluation that was negative. And the biopsy of the lower extremity rash revealed mild vascular proliferation in the papillary dermis with perivascular hemosiderin deposition and perifollicular erythrocyte extravasation. There was focal fat necrosis. However, there was no evidence of vasculitis.

Now, this table shows the full right heart catheterization data, which revealed mildly elevated systemic pressures, a cardiac output that was on the lower limit, cardiac index below 2.4. Mean RA pressure was normal and PA pressures with a mean of 41 millimeters of mercury and a normal wedge. The calculated pulmonary vascular resistance was almost 700 dynes. Now, after inhaled nitric oxide, you can remark an increase in cardiac index and output, but also a significant decrease in PA pressures with a drop in pulmonary vascular resistance to almost half. And that shows acute vasoresponsiveness to nitric oxide.

So at this point, can you make the call? What do the patient's symptoms and physical data suggest as the cause of his pulmonary arterial hypertension? And what tests or procedures would you order next? Does he have idiopathic or does he have another cause for his PAH?

So clinical findings were suggestive of severe vitamin C deficiency, especially the gum evaluation and the rash, and his history of poor diet and weight loss. Also his autoimmune evaluation was negative and the rheumatology consultation did not believe that his rash was

vasculitic. The patient had no medication exposure that would explain the particular rash or gum hypertrophy. The further blood test showed a significantly decreased vitamin C levels, almost non-detectable, and moderate anemia with a hemoglobin of 8.4 and also decreased iron levels. His vitamin D level was 12, also decreased. So he's got several vitamin deficiency with more importantly, vitamin C that's almost nonexistent. So what is your prescription? How would you treat this type of PAH?

So we started him on high levels of vitamin C and vitamin D daily. And after several months, his lower extremity rash and swelling and dyspnea improved. Vitamin C levels increased to 1.5 after several months, as well as his hemoglobin levels rose to 11.3. A repeat transthoracic echocardiogram revealed a normal right ventricular size and function, and a drop in estimated PA pressures to 29 millimeters of mercury. On the right-hand panel you see the M-mode as well as a sample video of his right ventricular function and improvement in size and systolic function of the right ventricle. Now the left ventricle is normal size and not squished.

So in summary, this case illustrates the potential contribution of dietary vitamin C deficiency in the development of pulmonary arterial hypertension. Patient had a history of several months of malnourishment associated with weight loss, a virtually undetectable vitamin C level, and a right heart catheterization documenting the presence of moderate PAH. PAH in this case resolved following repletion of vitamin C, suggesting that the vitamin C deficiency was the major cause of the pulmonary vascular disease in this case. Now, this case is unique as the patient's PAH resolved with only vitamin C and vitamin D supplementations, and without iron supplementation nor with PAH specific treatment.

So if we think about vitamin C deficiency, which is defined as a serum concentration less than 0.02 milligrams per deciliter, this occurs when vitamin C intake is below critical amount for a prolonged period. And it is associated with features of scurvy, which this patient had, which include failed wound healing, petechial hemorrhages, follicular hyperkeratosis, gum hypertrophy, and bleeding. Vitamin C a multipotent substance integral to the hydroxylation of proline and lysine, which are essential to collagen synthesis and connective tissue integrity. Vitamin C also acts to increase the content of endothelial cell tetrahydrobiopterin, which increases the activity of nitric oxide synthase. And we know this is an enzyme vital to the healthy endothelial function, and in PAH it's deficient or not working well. And maybe this is how the deficiency in this patient acted on causing a reversible pulmonary vascular disease through the nitric oxide synthase that was probably deficient. Also, if we look back at his acute vasoreactivity test with nitric oxide, he responded very well, suggesting that this was the pathway that was deficient in his lungs. So both iron and vitamin C stimulate hypoxia-inducible family of hydroxylases. The deficiency of either leads up to upregulation of hypoxia-inducible family transcription factors, and critical oxidase enzymes, which in turn promotes endothelial dysfunction that predisposes to PAH. In this regard, it is remarkable that in this patient, vitamin C supplementation alone, without iron supplementation, was associated with complete reversal of PAH. Vitamin C may alleviate some of the effects of iron deficiency as well, because it is needed for dietary absorption of iron as well as for maximal uptake of iron from transferrin, which is the whole source of iron for erythropoiesis. The current case highlights the importance of checking vitamin C levels in patients with PAH at risk for vitamin C deficiency and the potential therapeutic role of vitamin C supplementation in patients who are significantly deficient. And with that, I thank you for listening to this very interesting and unique case of PAH.