CHEST

Vitamin C Deficiency-Induced Pulmonary Arterial Hypertension

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VIDEO

We report a case of a man in his 60s who developed pulmonary arterial hypertension (PAH) in association with profound vitamin C deficiency. Decreased availability of endothelial nitric oxide and activation of the hypoxia-inducible family of transcription factors, both consequences of vitamin C deficiency, are believed to be mechanisms contributing to the pathogenesis of the pulmonary hypertension. The PAH resolved following vitamin C supplementation. The current case highlights the importance of testing for vitamin C deficiency in patients with PAH in the proper clinical setting.

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KEY WORDS: case report; pulmonary arterial hypertension; respiratory failure

Case Report

A man in his 60s with a history of systemic hypertension and increasing dyspnea on exertion was referred to an outpatient pulmonary clinic for further evaluation of pulmonary hypertension. During a hospitalization for systemic hypertensive urgency, a transthoracic echocardiogram performed for increasing dyspnea revealed a mildly dilated right ventricle and an increased estimated pulmonary artery systolic pressure of 76 mm Hg (Fig 1, Video 1). He also had lower extremity swelling and rash along with joint pain in his hips, knees, and feet for the past 4 months. Further questioning revealed that his diet consisted mainly of candy and sports drinks.

The patient's physical examination was notable for the following: gum hypertrophy; increased P2 on cardiac auscultation; bilateral symmetrical pitting edema; hair loss on extremities; and a diffuse, petechial lower extremity rash bilaterally from mid-calf down. His lungs were clear to auscultation, and no right ventricular heave or jugular venous distention was appreciated.

The patient's right heart catheterization revealed a pulmonary artery pressure of 72/22 mm Hg with a mean pressure of 41 mm Hg (Table 1). He had a normal pulmonary capillary wedge pressure and preserved right atrial pressure with a significant vasodilator response to inhaled nitric oxide. Autoimmune evaluation was negative. Results of a biopsy of the patient's lower extremity rash showed mild vascular proliferation in the papillary dermis with perivascular hemosiderin deposition and perifollicular erythrocyte extravasation. Focal fat necrosis was seen with no evidence of vasculitis. These findings were suggestive of severe vitamin C deficiency; given the patient's negative autoimmune evaluation, rheumatology did not believe his rash was vasculitic, and vascular surgery discounted venous disease. The patient had no medication exposure that would explain petechial rash or gum hypertrophy. He was subsequently found to have a vitamin C level $<$ 0.1 mg/dL (0.2-2 mg/dL), hemoglobin level of 8.4 g/dL (13.5-16 g/dL), iron level of 22 μg/dL (49-181 μg/dL), and 25-OH-vitamin D level of 12 ng/mL (20-100 ng/mL). He was prescribed vitamin C 1 g bid and 1,000

ABBREVIATIONS: PAH = pulmonary arterial hypertension

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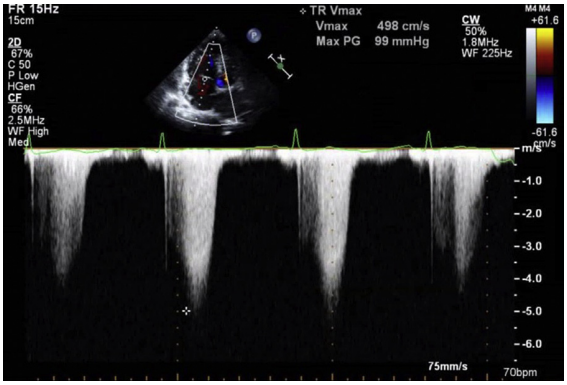

Figure 1 – *Pretreatment pulmonary artery systolic pressure estimate.*

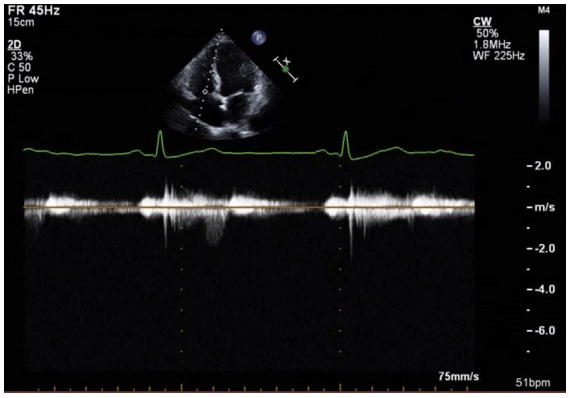

Figure 2 – *Post-treatment pulmonary artery systolic pressure estimate.*

units of vitamin D_3 daily. Over 5 months, the patient's lower extremity rash and swelling and dyspnea improved. His vitamin C level increased to 1.5 mg/dL, hemoglobin rose to 11.3 g/dL, and a repeat transthoracic echocardiogram revealed normal right ventricular size and function with a drop in estimated pulmonary artery systolic pressure to 29 mm Hg (Fig 2, Video 2).

Discussion

The current case illustrates the potential contribution of dietary vitamin C deficiency to the development of PAH. The 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 resolved following repletion of vitamin C, suggesting vitamin C deficiency as the major cause of PAH. To the best of our knowledge, there are only a few previously reported cases of vitamin C deficiency-induced PAH in the adult population. This case is unique in that the patient's PAH resolved with vitamin C supplementation alone without iron supplementation or PAH-specific treatment; in the other cases, the latter two therapies were used.[1,2]

Vitamin C deficiency is defined as a serum concentration < 0.2 mg/dL, and it occurs when vitamin C intake is below a critical amount (10 mg/d) for a prolonged period. It is associated with features of scurvy, which include failed wound healing, petechial hemorrhages, follicular hyperkeratosis, gum hypertrophy, and bleeding.[3]

Vitamin C is a multipotent substance integral to the hydroxylation of proline and lysine, which is essential to collagen synthesis and connective tissue integrity. Vitamin C also acts to increase the content of

TABLE 1] Data From the Study Patient's Right Heart Catheterization

Condition	Rest	After Inhaled Nitric Oxide 20 ppm
Heart rate, beats/min	72	70
Arterial pressure, mm Hg	159/98	…
Arterial oxygen saturation (room air)	99%	99%
RA oxygen saturation	61%	…
PA oxygen saturation	58%	71%
Cardiac output (thermodilution), L/min	3.5	4.3
Cardiac index, L/min/m^2	2.2	2.7
Mean RA pressure, mm Hg	5	…
PA pressure (systolic/diastolic), mean, mm Hg	72/22 (41)	47/13 (28)
Mean PA wedge, mm Hg	11	11
Pulmonary vascular resistance, dyn · s/cm^5	694	316

PA = pulmonary artery; ppm = parts per million; RA = right atrial.

endothelial cell tetrahydrobiopterin, which increases the activity of nitric oxide synthase, a function vital to healthy endothelial function.[4,5]

Both iron and vitamin C stimulate hypoxia-inducible family hydroxylases; deficiency of either leads to upregulation of hypoxia-inducible family transcription factors and critical oxidase enzymes, which in turn promotes endothelial dysfunction that predisposes to PAH.[6-8] In this regard, it is remarkable that in the study patient, vitamin C supplementation alone, without iron supplementation, was associated with reversal of PAH. Accordingly, vitamin C may alleviate some of the effects of iron deficiency as well. Vitamin C is needed for dietary absorption of iron as well as for maximal uptake of iron from transferrin, the sole source of iron for erythropoiesis.[9] Experimental animal models have shown the effectiveness of vitamin C and other antioxidants in blunting PAH development and progression, but these factors have not been adequately studied in humans.[10]

The current case highlights the importance of checking vitamin C levels in patients with PAH at risk for vitamin C deficiency, as well as the potential therapeutic role of vitamin C supplementation in patients who are deficient. Whether vitamin C supplementation, as with iron supplementation,[5,11] could be helpful in a broader population of patients with PAH remains to be determined.

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