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Selected Reports

Reversible Pulmonary Hypertension Associated With Vitamin C Deficiency

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We describe the case of a 40-year-old female patient who developed severe pulmonary hypertension and life-threatening right-sided heart failure in association with dietary scurvy and iron deficiency. Supplementation with oral vitamin C and iron very likely contributed to her complete cure. Scurvy-associated pulmonary arterial hypertension could result from impaired availability of endothelial nitric oxide, but inappropriate activation of the hypoxia-inducible family (HIF) of transcription factors could play an even more important role. HIF coordinates the body's responses to hypoxia, and its activity is regulated by oxygen-dependent prolyl hydroxylases, which need vitamin C and iron as cofactors. Deficiency of these cofactors could lead to uncontrolled HIF activity and pulmonary vasoconstriction responsive to vitamin C and iron administration.

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Abbreviations: HIF = hypoxia-inducible family

A 40-year-old woman was admitted due to anemia, increasing breathlessness, and subcutaneous bleeding. Aside from mild asthma and food allergies, she had been well until 18 months previously, when tender red-bluish nodules, ecchymoses, and palpable purpura first appeared on her legs. The skin changes had escaped diagnosis despite extensive studies, including repeated skin biopsies. On admission, the patient had large subcutaneous hematomas on her legs but was in no acute distress. BP was 115/75 mm Hg, heart rate 105 beats/min, and oxygen saturation 100% on ambient air. Her height was 182 cm, and weight was 81 kg. A 12-lead ECG showed flattening of the T waves in the right precordial leads. Chest radiographs were considered normal. Blood hemoglobin level was 74 g/L, but the laboratory tests were otherwise nonrevealing. The patient was hospitalized for further investigation.

Diagnostic tests in hospital failed to disclose the cause of her bleeding tendency. Yet another skin biopsy specimen showed only subepidermal hemosiderin, with extravasated RBCs, lymphocytes, and some fibrosis, but no signs of vasculitis. Indicative of iron deficiency and/or subacute blood loss, serum iron level was 5.4 μM (reference range, 9-34 μM), transferrin saturation 10% (reference range, 17%-52%), and transferrin receptor concentration, 7.0 mg/L (reference range, 1.9-4.4 mg/L). A bone marrow aspirate showed reduced but not totally absent stainable iron. The patient was given 5 units of packed RBCs altogether and treatment with oral iron was started later. Because of a vague clinical suspicion of vasculitis, treatment with oral prednisone was initiated. Within a few days, the patient became increasingly dyspneic and the oxygen saturation dropped from 99% to 77% to 80% on ambient air. Echocardiography (Fig 1, Table 1, Videos 1-3) showed a dilated and poorly contracting right ventricle, tricuspid regurgitation with a peak jet velocity of 3.5 m/s, an eccentrically deformed left ventricle, pericardial effusion, and flow from right to left atrium through open foramen ovale. Pulmonary CT scan angiography revealed dilatation of the pulmonary artery but no signs of pulmonary embolism. A confirmatory ventilation-perfusion lung scan was also normal. Right-sided heart catheterization, with the patient breathing room air, revealed severe precapillary pulmonary hypertension, right ventricular failure, and a large right-to-left shunt (Table 1). A nonformal vasodilatory test was done by infusing epoprostenol at doses of 1 and 5 ng/kg/min. At baseline, with the patient now breathing oxygen, pulmonary artery pressure measured 84/39 mm Hg (mean, 52 mm Hg), and finger oxygen saturation was 82%. At 5 ng/kg/min of epoprostenol, pulmonary artery pressure dropped to 53/36 mm Hg (mean, 42 mm Hg), and oxygen saturation rose to 95%. The response was interpreted as suggestive of pulmonary vasodilation unloading the right side of the heart and leading to less shunt flow through the foramen ovale.

The possibility of dietary scurvy was first entertained at the precatheterization clinical examination. It appeared that because of proven and presumed food allergies, the patient's diet had been deficient of fruits and vegetables for several years. Supplementation with oral vitamin C, 1 g/d, was started after catheterization, along with sildenafil, 20 mg tid. The patient experienced relief of dyspnea and normalization of oxygen saturation within 48 h, and a control echocardiography 1 week later (Table 1) showed no signs of pulmonary hypertension. Plasma vitamin C, the sample taken at catheterization, was undetectable (<10 μM; reference range, 20-80 μM). The patient was

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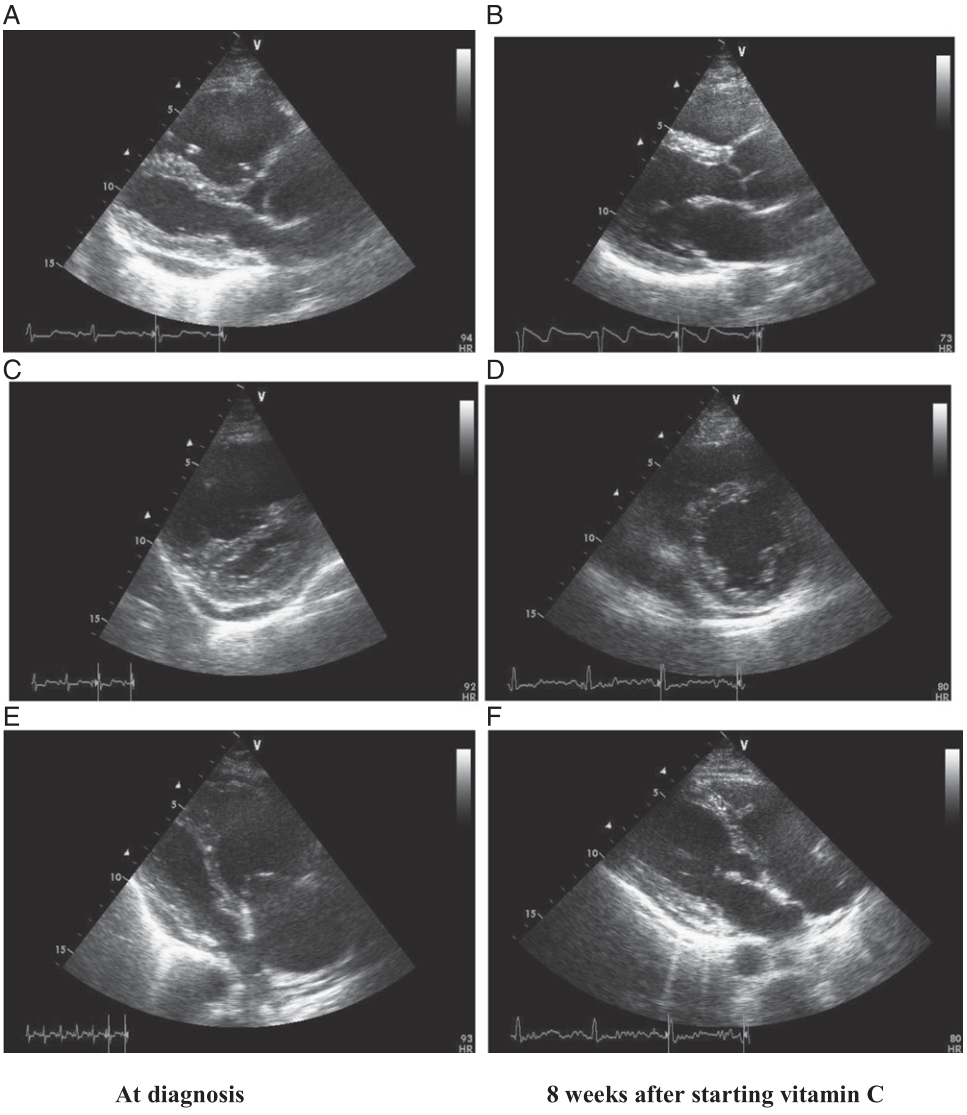

FIGURE 1. Diastolic images of the heart at diagnosis of pulmonary hypertension (left) and during vitamin C supplementation (right). A and B, Long axis. C and D, Short axis. E and F, Apical four-chamber planes. Note the dilated right side of the heart and the severely flattened left ventricle before treatment and the full normalization of findings after vitamin C supplementation. HR = heart rate.

discharged in a much improved condition on vitamin C, oral iron, sildenafil, and rapidly tapering doses of prednisone. Sildenafil was discontinued after 3 weeks of administration. A complete reexamination was performed 8 weeks after starting vitamin C (5 weeks off sildenafil). The patient reported normal exercise capacity and had normal concentrations of blood hemoglobin (140 g/L) and plasma vitamin C (50 μM). Findings at catheterization and echocardiography (Fig 1, Table 1, Videos 3-6) showed that the pulmonary artery pressure, flow, and resistance were completely normal, as was right-sided heart function.

DISCUSSION

The patient had pulmonary hypertension associated with vitamin C deficiency and clinical scurvy. A causal relation is likely because no other cause was identified and pulmonary hemodynamics were completely normalized during vitamin C supplementation. Sildenafil no doubt contributed to the early improvement but is unlikely to explain the cure because it was discontinued several weeks before the second catheterization. The patient's iron deficiency was not severe (there was stainable tissue iron in bone marrow) but may still have played some contributory role.

The rapid normalization of pulmonary artery pressure and the observed response to epoprostenol suggest that the main mechanism of pulmonary hypertension was vasoconstriction. There are at least two possible pathways for the involvement of vitamin C in this case. First, vitamin C increases the synthesis and availability of endothelial nitric oxide and has vasodilatory capacity even in the absence of its deficiency.[1] Second, vitamin C and iron are essential

Table 1—*Findings From Right-Sided Heart Catheterization and Echocardiography at Diagnosis of Pulmonary Hypertension and After Starting Supplementation With Vitamin C*

Measurement	Weeks After Starting Vitamin C		
	0	1	8
Catheterization, the patient breathing room air			
Pulmonary artery pressure, mm Hg (mean)	74/36 (48)	…	26/9 (15)
Mean pulmonary wedge pressure, mm Hg	3	…	6
Mean right atrial pressure, mm Hg	13	…	1
Femoral artery oxygen saturation, %	67	…	96
Pulmonary artery oxygen saturation, %	30	…	78
Systemic flow, L/min	2.7	…	6.7
Pulmonary flow, L/min	1.5	…	6.7
Right-to-left shunt, L/min	1.2	…	0
Pulmonary vascular resistance, dyn/s/cm^5	2,400	…	107
Echocardiography			
RV + RA, cm^2	52	38	28
VCI, mm	27	18	5
Left ventricular eccentricity index[a]	2.5	1.0	1.0
TAPSE, mm	7	20	23

RV + RA = right ventricular + right atrial maximal cavity area in four-chamber view (reference for adults in our laboratory, < 35 cm^2); TAPSE = tricuspidal annular plane systolic excursion (reference > 17 mm); VCI = vena cava inferior maximal diameter.

[a]The diastolic ratio of two perpendicular midleft ventricular short-axis dimensions, one of which bisects the septum (Fig 1).

cofactors for the prolyl hydroxylase domain enzymes that act as oxygen sensors regulating the activity of the hypoxia-inducible family (HIF) of transcription factors.[2] The HIF transcription factors coordinate the cellular responses to hypoxia, including the development of pulmonary vasoconstriction.[2] Importantly, genetic, nonhypoxic activation of HIF results in elevated pulmonary artery pressure with exaggerated vasoconstrictive responses to hypoxia and even frank pulmonary artery hypertension.[2] A combined deficiency of vitamin C and iron, as in the patient in this report, could inactivate the prolyl hydroxylase domain enzymes and lead to uncoupling of HIF from oxygen control with activation of pulmonary hypertensive mechanisms. Of note, the bleeding diathesis and other clinical manifestations of scurvy are due to inactivation of prolyl (and lysyl) hydroxylases critical for collagen synthesis.[3] Although oxygen sensing is maintained in vitamin-C-deprived knockout mice,[4] this model is not relevant to human scurvy because the animals do not show defective collagen synthesis either.[5]

Clinical scurvy is rare in Western societies but vitamin C deficiency, defined as abnormally low plasma ascorbate, is not.[6,7] Recent studies have shown that iron deficiency is common in idiopathic pulmonary arterial hypertension and that iron status may influence symptoms, exercise capacity, and prognosis.[8-10] Clinical trials are underway to explore the effect of iron repletion in these patients.[8] Our case suggests that it may also be worthwhile to explore the role of vitamin C in the different forms of pulmonary hypertension in humans.

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Additional information: The Videos can be found in the "Supplemental Materials" area of the online article.

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