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HEART FAILURE

CASE REPORT: CLINICAL CASE

An Unusual Etiology of Severe Right Heart Failure Deserving of Wider Recognition

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ABSTRACT

A previously healthy 31-year-old man presented with worsening shortness of breath and a petechial rash. Echocardiography showed severe right-sided heart failure with midsystolic notching of the antegrade right ventricular outflow Doppler envelope suggesting pulmonary hypertension. An extensive work-up revealed scurvy, with a dramatic resolution of symptoms shortly after vitamin C supplementation. (J Am Coll Cardiol Case Rep 2024;29:102222) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 30-year-old man without any known past medical history was evaluated at the hospital after exertional dyspnea for the previous few weeks and 2 episodes of positional syncope. He noticed petechial rashes in his extremities and reported generalized malaise and weakness with decreased appetite for the previous 3 to 4 weeks. On the day of admission, he attempted to walk out of his apartment but felt extreme shortness of breath after a few steps, followed by a brief syncopal episode on attempting to stand up, before emergency medical services were called.

He used to be physically active and represented his swim team in college; however, now he was barely able to take a few steps without shortness of breath. He denied chest pain, leg swelling, orthopnea, paroxysmal nocturnal dyspnea, or bleeding issues. He appeared jaundiced and pale, and nontender petechiae covered his back and extremities. On examination, he had no murmur, and his lungs were clear to auscultation bilaterally. Mild hepatomegaly but no splenomegaly was palpable. Peripheral pulses were normal. He admitted to drinking 60 ounces of beer daily for the last 3 years, smoking tobacco 3 pack-years for the last 6 years, and using cannabis daily. He had not changed the cannabis vendor, nor had he

LEARNING OBJECTIVES

- To be able to work up and develop an appropriate differential diagnosis in a young, previously healthy patient presenting with new onset RV failure and PH.
- To understand the importance of in-depth history taking and recognize high-risk groups with nutrition deficiency in the current era.

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ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

G6PD = glucose-6-phosphate dehydrogenase

HIF = hypoxia-inducible factor

NO = nitric oxide

PE = pulmonary embolism

PH = pulmonary hypertension

PNH = paroxysmal nocturnal hemoglobinuria

PVR = pulmonary vascular resistance

ROS = reactive oxygen species

RV = right ventricular

TTP = thrombotic thrombocytopenic purpura

been sexually active. Initial laboratory test results were significant for the following: hemoglobin, 7.6 g/dL; mean corpuscular volume, 100.9 fL; platelets, 224,000; sodium, 128 mEq/L; anion, 18.5 mEq/L; and creatinine, 1.38 mg/dL. Urinalysis showed 2+ ketone, 2+ bilirubin, positive nitrite without white blood cells, and trace blood. The patient's fractional sodium excretion was 0%, a finding supporting a prerenal cause of acute kidney injury. The rest of the metabolic panel showed the following: total bilirubin, 3.65 mg/dL; direct bilirubin, 0.84 mg/dL; total protein, 4.6 g/dL; and albumin, 2.5 g/dL. Troponin values were negative.

PAST MEDICAL HISTORY

The patient had no previous medical history.

DIFFERENTIAL DIAGNOSIS

Our list of initial differential diagnoses included arrhythmogenic right ventricular cardiomyopathy (ARVC), pulmonary hypertension (PH) with or without pulmonary embolism (PE), thrombotic thrombocytopenic purpura (TTP), glucose-6-phosphate dehydrogenase (G6PD) activity deficiency, and paroxysmal nocturnal hemoglobinuria (PNH), considering his right ventricular (RV) failure, anemia, and petechial rash (Figure 1).

FIGURE 1 Ecchymosis and Petechial Hemorrhaging on the Lower Extremities

INVESTIGATIONS

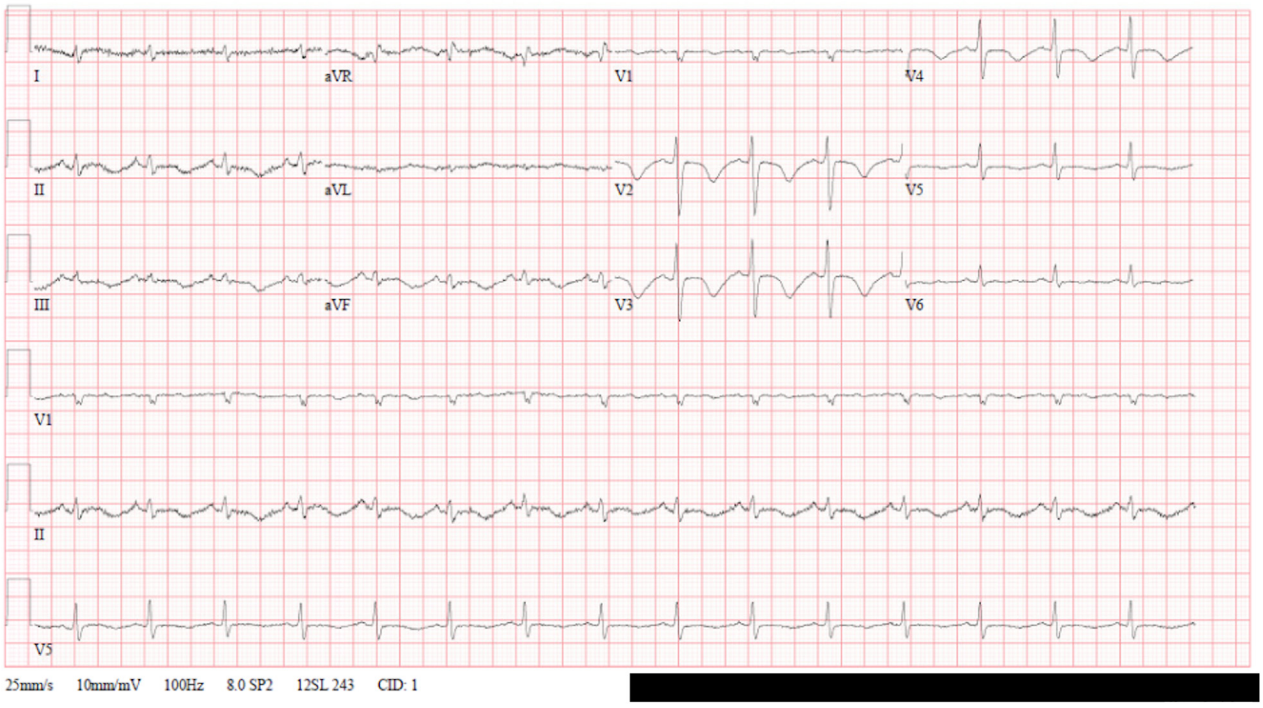
Given the generalized petechiae, moderate anemia, and elevated indirect bilirubin, hematology was consulted. The patient was found to have an increased reticulocyte count (5.4%), low haptoglobin (<30 mg/dL); high lactate dehydrogenase (362 U/L), normal prothrombin time (12.4 seconds) and partial thromboplastin time (23.9 seconds), but an elevated international normalized ratio (1.17) and D-dimer (9.41 mg/L). Protein C and S levels were low at 56% and 47 U/dL, respectively. A peripheral blood smear revealed many burr cells and very few schistocytes. The direct antiglobulin test was used to distinguish between immune and nonimmune hemolysis, and the result was negative for immunoglobulin G and complement. Findings on a liver ultrasound examination were unremarkable. Thus far, the patient's laboratory findings were consistent with Coombs-negative hemolytic anemia. Results of HIV and hepatitis viral panels were negative.

The patient's B-type natriuretic peptide was elevated on admission (615 ng/L), and he exhibited bilateral grade +2 leg swelling , prompting initiation of oral furosemide at a dose of 20 mg daily. The patient's family history revealed that a paternal aunt had a C677T sequence variant (alteration of the methylenetetrahydrofolate reductase gene).

Cardiology was consulted for T-wave inversion in electrocardiographic leads V_1 to V_4 with right bundle branch block (Figure 2), prompting initial concern for ARVC. However, cardiac magnetic resonance revealed no focal RV abnormalities, but instead detected nonspecific mild biventricular fibrosis and a moderately enlarged main pulmonary artery and branches suggesting PH (Figure 3). Findings on a computed tomography PE test were negative for PE.

A transthoracic echocardiogram showed the following: a normal left ventricular ejection fraction of 55% to 60% but a severely dilated and hypokinetic RV, as well as a flattened septum during both systole and diastole, findings indicating RV pressure overload and elevated RV end-diastolic pressure (Videos 1 and 2); mild tricuspid regurgitation with RV systolic pressure of 50.0 mm Hg; and midsystolic Doppler notching of the antegrade RV outflow flow (Figure 4), consistent with PH and elevation of pulmonary vascular resistance (PVR) (Figure 5). The bubble study

FIGURE 2 Electrocardiogram on Admission: T-Wave Inversion in Leads V_1 to V_4 With a Right Bundle Branch Block Pattern



did not reveal intracardiac or intrapulmonary shunting.

The origin of hemolysis was evaluated further with G6PD, coagulation function studies, ADAMTS13 activity, and clone size assay of PNH granulocytes by flow cytometry. Rare schistocytes on the peripheral blood smear and ADAMTS13 activity of 31% made TTP unlikely to be the cause. G6PD deficiency and PNH were also ruled out.

At this point, a more in-depth social history was obtained. The patient reported a habit of skipping breakfast and lunch and consuming 60 ounces of beer with minimal snacks as his evening meal. This raised concerns of micronutrient deficiency, along with low total protein and albumin levels. His vitamin B_{12} level was normal, and folic acid level was slightly low at 5.4 nmol/L. On admission day 4, a vitamin C level was ordered, and a 6-minute walk test was conducted. The patient experienced a near-syncopal episode after 5 steps with drastic oxygen desaturation to 84%. Right-sided heart catheterization revealed the following: PVR, 3.0 WU; mean pulmonary artery pressure, 32 mm Hg; mean right atrial pressure, 11.0 mm Hg; and pulmonary capillary wedge pressure, 15 mm Hg. These findings were consistent with borderline mild PH.

One week after the vitamin C level was drawn, the result returned as undetectable.

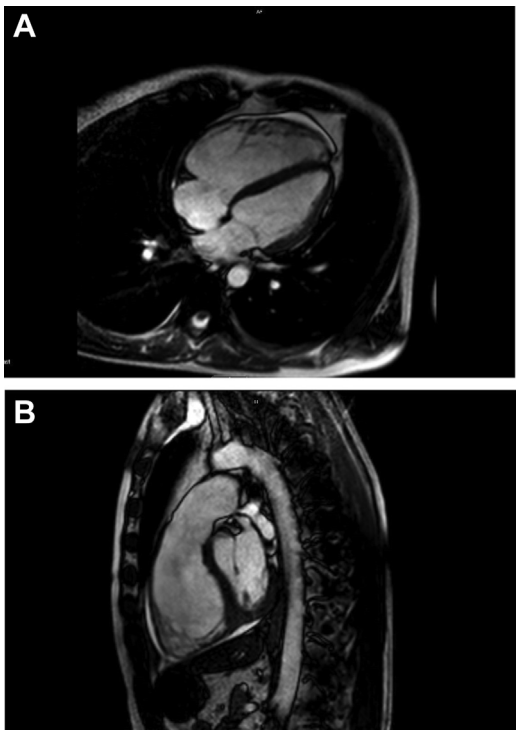
MANAGEMENT

In addition to diuretic therapy for volume overload associated with heart failure, multivitamins were added to his medication regimen on admission day 2 to correct the potential nutritional deficiency while awaiting the results of the micronutrient laboratory test results (**Figure 6**). Education on lifestyle modification, including a healthier diet, regular exercise, and sleep hygiene, was conducted.

DISCUSSION

The underlying cause of RV failure and PH in our patient was attributed to a severe vitamin C deficiency, scurvy. Pulmonary vasculature remodeling and the emergence of endothelial dysfunction are 2 commonly proposed pathologic consequences of scurvy. Vitamin C acts as a metal ion reducer, thus making it a catalytic driver for enzymes that preserve tissue and vascular integrity by using reduced irons as drivers for further reactions.[1] Hypoxia-inducible factor (HIF) transcription factor is one such

FIGURE 3 Cardiac Magnetic Resonance



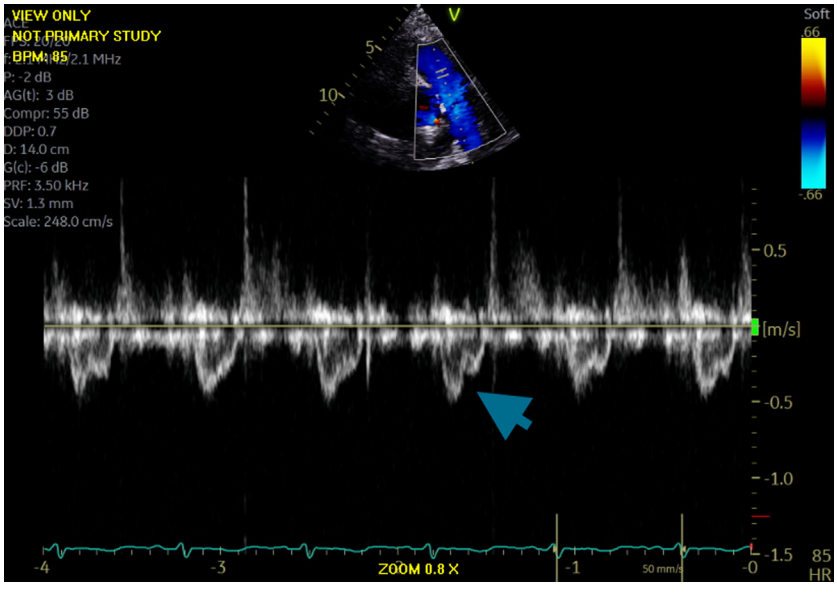
(A and B) Prominently dilated pulmonary artery and right ventricle without regional wall motion.

enzymatic target, and these are well-documented propulmonary vasoconstrictive mediators transcribed under hypoxic conditions. A chronically elevated HIF level is associated with manifesting PH through the modulation of arterial smooth muscle. In patients with low vitamin C levels, HIF transcription factors continue to permeate and propagate PH.

Vasodilation of the pulmonary artery by nitric oxide (NO), an endogenously produced smooth muscle dilator, is a vital mediator in PH prevention.[2] Oxidative stress from elevated concentrations of naturally occurring reactive oxygen species (ROS) can reduce NO bioavailability, and this affects vascular integrity through primary damage of endothelium that causes reduced arterial compliance and consequently a transient pressure elevation.[3] In vitro investigations suggest that vitamin C functions to neutralize ROS and reduce their generation.[3] Through these pathways, scurvy can induce pulmonary arterial wall dysfunction while preventing endogenous mediators that would otherwise antagonize such changes, thereby ultimately precipitating PH. This is an illustrative instance wherein systemic and metabolic disorders contributed to group 5 PH through multifactorial mechanisms.

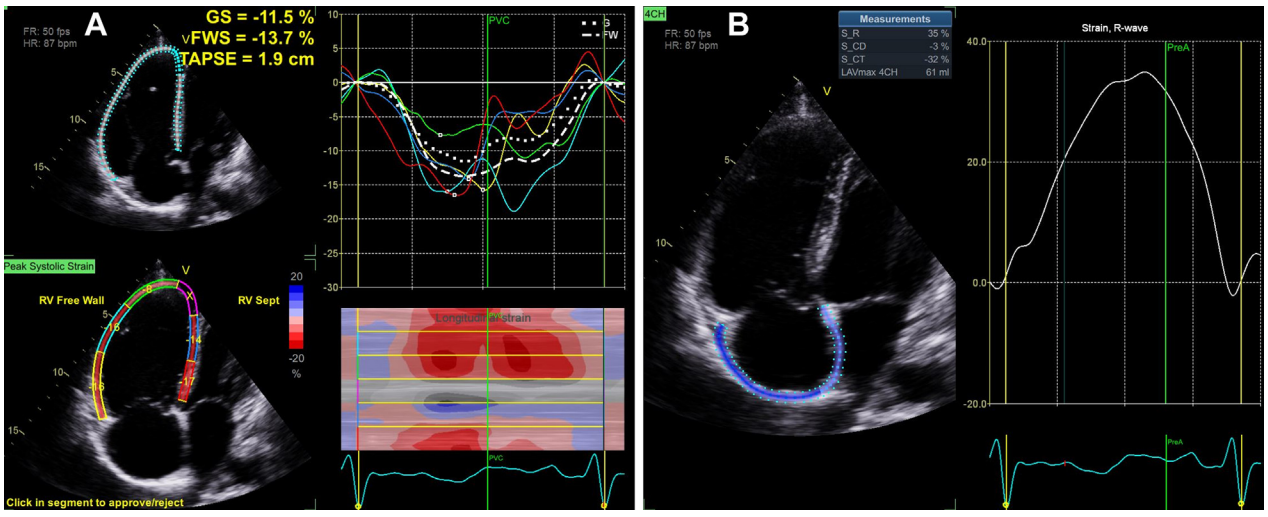
Vitamin C deficiency in the United States is uncommon relative to the global prevalence, which is estimated at 7.1%. Nonetheless, a single-cohort study of populations randomly selected to determine their

FIGURE 4 Transthoracic Echocardiogram



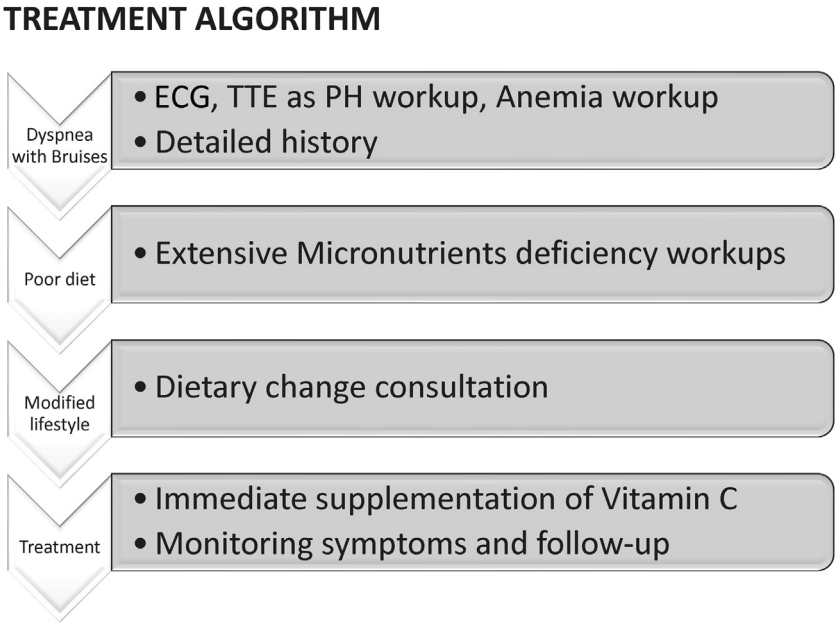
A pulsed-wave Doppler signal from the right ventricular outflow tract shows midsystolic notching (arrow), suggesting pulmonary hypertension.

FIGURE 5 Strain Imaging of the Right Ventricle and Right Atrium in Echocardiography



(A) Decreased right ventricular (RV) global strain (GS) at −11.5% and right ventricular free wall strain (FWS) at −13.7% suggesting right ventricular dysfunction, with normal tricuspid annular plane systolic excursion (TAPSE) of 19 mm. (B) Right atrial (RA) strain reservoir component is significantly impaired, which predicts outcomes in pulmonary hypertension. FR = frame rate; FW = free wall; HR = heart rate; S_CD = strain conduit; S_CT = strain contractile; S_R = strain reservoir; Sept = septum; 4CH = 4-chamber.

FIGURE 6 Treatment Algorithm for Scurvy-Related PH



ECG = electrocardiogram; PH = pulmonary hypertension; TTE = transthoracic echocardiogram.

TABLE 1 Reported Cases of RV Failure/PH Induced by Vitamin C Deficiency

First Author	Patient Description	Diet	Presenting Symptoms	Chest and Cardiac Imaging
Kupari et al	40-year-old woman	Diet deficient of fruit and vegetables for several years	Tender red-bluish nodules, ecchymoses, palpable purpura, and anemia	TTE: Dilated and hypocontractile right ventricle, eccentrically deformed left ventricle, pericardial effusion, peak tricuspid jet velocity of 3.5 m/s Pulmonary CT angiography: Dilatation of PA with no PE RHC: Severe precapillary PH with RV failure and large right-to-left shunt
Duvall et al	9-year-old boy with autism	Consisted mainly of white foods (chicken nuggets, crackers, cookies, and water) for the last 3-years; refusal to eat milk, juice, and vegetables	Limp for the last 4 months	Chest radiograph: Diffuse, nodular, and ill-defined airspace opacities; increased volume in right lung; small right pleural effusion with enlarged main PA TTE: Severely dilated right ventricle with mild to moderately depressed systolic function; dilated right atrium and PA
Abbas et al	50-year-old woman	Cereal, eggs, and milk only	3 months of progressive shortness of breath with extreme tiredness, anorexia, weight loss, jaundice, LE rash, and heavy menstrual bleeding; presence of ecchymosis on thighs and buttocks	TTE: Enlarged right atrium and ventricle with moderate RV hypokinesis; mild to moderate TR
Ghulam Ali et al	66-year-old man with celiac disease and lactose intolerance	Mostly rice and chicken for the previous 8 months with no fresh fruits or vegetables	Dyspnea with large, spontaneous ecchymosis on left thigh and diffuse purpura over upper extremity and LE	Chest radiograph: No abnormal findings TTE: Severe RV pressure overload
Dean et al	6-year-old boy	—	3-month history of bilateral LE pain with refusal to bear weight;. was sedated for bone marrow aspiration and bone biopsy, resulted in PEA	TTE: Post arrest showing abnormal right ventricle-to-left ventricle ratio of 2.8; Repeat study 5 days later showed RV dysfunction with RA and RV dilation and prominent septal bowing RHC: Performed on day 9 showed mild PH
Gayen et al	60-year-old man	Candy and sports drinks main parts of diet	Dyspnea, hypertensive emergency, LE swelling, petechial LE rash bilaterally, hair loss in extremities, joint pain in hips, knees, and feet for 4 months	TTE: Mildly dilated right ventricle
Tan et al	7-year-old man with autism	Daily fish and soup	Dyspnea, bilateral ankle, edema, hepatomegaly	TTE: Hypertrophied right ventricle with septal shift to the left; moderate TR with peak gradient of 75 mm Hg
Ferreira et al	51-year-old man	—	Dyspnea on minimal exertion, LE edema, and painful bruises on LEs	TTE: Showed enlarged right chamber with RV systolic dysfunction.
Shah et al	40-year-old woman with beta-thalassemia trait, severe allergies to variety of fruits and vegetables	—	Several months of LE swelling, syncope, bleeding gums, multiple bruises, and noticeable JVD	TTE: LVEF of 59%
Sakamornchai et al (Case #1)	6-year-old boy with autism spectrum disorder	Mostly rice porridge and boiled egg	Dyspnea, bilateral knee swelling, left leg pain swelling, refusal to walk for 2 months	TTE: TR with PG at 80 mm Hg
Sakamornchai et a. (Case #2)	5-year-old boy with autism spectrum disorder, allergic rhinitis with snoring	Rice porridge without any meat for 1 year	Progressive dyspnea; refusal to walk for 2 weeks; gingival bleeding	Chest radiograph: Cardiomegaly with no pulmonary congestion TTE: Moderate to severe TR with PG of 80 mm Hg; RA and RV enlargement; impaired RV function; flattened interventricular septum
Quinn et al	6-year-old boy with developmental delay with concern for autism	Nutritionally complete supplemental beverage; 6 months earlier, narrowed to peanut butter cups and water	Inability to bear weight on left leg	Leg radiograph: Showing demineralization diffusely in the legs without any fractures TTE: Done post cardiac arrest showed elevated TR peak velocity; diminished RV function; significant RV hypertrophy CT angiography: PE not detected
Niari et al	2-year-old girl	—	Weight loss, with muscle weakness, difficult walking, and gingival bleeding for 2 months	TTE: Dilation of right atrium and ventricle; mild TR with peak gradient of 75 mm Hg

CT = computed tomography; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; JVD = jugular venous distention; LAD = left anterior descending; LE = lower extremity; LV = left ventricular; LVEF = left ventricular ejection fraction; NO = nitric oxide; PA = pulmonary artery; PASP = pulmonary artery systolic pressure; PE = pulmonary embolism; PEA = pulseless electrical activity; PG = pressure gradient; PH = pulmonary hypertension; RA = right atrial; RBBB = right bundle branch block; RHC = right-sided heart catheterization; RV = right ventricular; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation; TTE = transthoracic echocardiogram.

Continued on the next page

TABLE 1 Continued

ECG	PASP/ RVSP, mm Hg	Vitamin C Level	Medication Intervention	Outcome and Follow-Up?
Flattening of T waves in right precordial leads	52	Undetectable (<10 μmol/L)	Inpatient supplementation of 1 g/d vitamin C, sildenafil 20 mg 3 times/d	Discharged; 8-week follow- up showed improved vitamin C levels and PA pressures on catheterization evaluation
LAD artery, and right-sided heart strain pattern with incomplete RBBB and nonspecific ST-segment and T-wave changes	45	Undetectable	Days 2-5: diuresis; Day 6-14: intravenous vitamin C, thiamin, ergocalciferol. and vitamin B_{12} injection	Improved RV pressures during serial imaging; was able to ambulate at the time of discharge; 18-month follow-up showed normalized vitamin C levels.
Low voltage in anteroinferior leads	–	0.1 mg/dL	Folic acid, thiamin, and vitamin C supplementation	No stated when discharged, but 4-week echocardiogram showed evidence of normal PA pressure
Mild ST-segment depression with inverted T waves in leads V_1-V_4	80	Undetectable	Oral vitamin C and improvement in relief of dyspnea seen; bosentan for suspected PH	Discharged with TTE showing mild RV dilation but normalization of PASP; on 1-year follow-up, normalization of vitamin C levels
–	–	Undetectable	Needed immediate intubation and dopamine, epinephrine, and phenylephrine bolus for 1 day; on hospital day 5 started on milrinone infusion (0.5 μg/kg/min and inhaled NO, 20 ppm)	Transferred to inpatient rehabilitation and then discharged on sildenafil and vitamin C; 6-month follow-up with echocardiogram showed no evidence of PH
–	41 (mean)	<0.1 mg/dL	–	Discharged on supplemental vitamin C and 1,000 U vitamin D_3; 5-month follow-up showed level to be 1.5 mg/dL with recovery on echocardiogram
Sinus tachycardia	75	Undetectable (<5 μmol/L)	Inhaled NO, phosphodiesterase 5 inhibitor, endothelin-receptor antagonist	Discharged. and 3-month follow-up showed return of strength with RHC showing PA pressure of 14 mm Hg
ST-segment elevation in leads II, III, aVF, with inverted T waves in leads V_1-V_4	61	0.05 mg/dL	Parenteral vitamin C (1,000 mg/d).	Discharged, but readmitted 16 months later for weakness and severe anemia; echocardiogram at this time showed normal RV function with a normal range serum ascorbic acid level
–	69	<0.1 mg/dL	Intravenous followed by oral vitamin C levels	Discharged and follow-up repeat echocardiogram showed complete recovery of function
–	–	Undetectable	Placed on respiratory support with inotropic drug and pulmonary vasodilator; also given 300 mg/d of vitamin C	Discharged with vitamin C and vasodilator and followed up 1 month later with recovery of bilateral extremity pain and no dyspnea; 2-month follow-up echocardiogram showed normal pressures
Right-axis deviation with low QRS interval voltage	–	Undetectable	Noninvasive ventilatory support with inpatient pulmonary vasodilation; 100 mg of thiamin and 300 mg of vitamin C	Discharged on multivitamins, iron, and folate supplementation; 3-month follow-up showed improvement in physical capacity
During endoscopy, multiple episodes of PEA recorded	–	–	Started on vitamin C, thiamine, and multivitamin 1 d; inhaled NO	Decannulated from ECMO on day 4 with improvement of TR on echocardiogram; on day 13, gastric-tube placed and patient found to have extensive thalamic and cerebral hemorrhagic and ischemic strokes; discharged 6 weeks later, and predischarge echocardiogram showed normalized TR and only persistent RV hypertrophy; given sildenafil alongside multivitamin
–	–	–	Placed on high-flow nasal cannula; supplemented with thiamine (200 mg/d) and vitamin C (100 mg/kg/d)	Able to walk by day 35; discharged with echocardiogram revealing normalization of TR PG and normal ambulation; 10 weeks later, vitamin C supplementation discontinued

vitamin C levels revealed a deficiency as high as 32%.[4] Individuals from low-income groups are at the highest risk.[5]

FOLLOW-UP

Dramatic, complete resolution of symptoms occurred after 1 week of vitamin C supplementation.

CONCLUSIONS

Multiple socioeconomic antecedents have a high propensity for causing vitamin C deficiency, thus making a social and diet history imperative. There are numerous, highly dense regions of the United States with socioeconomic disparities. Therefore, clinicians in these regions must be aware of the potential of this micronutrient deficiency in patients with right-sided heart failure and PH and should consider checking vitamin C levels as a part of the work-up.

A tabulated literature review of reported cases of RV failure/PH induced by vitamin C deficiency is provided in **Table 1**.

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KEY WORDS pulmonary hypertension, right-sided heart failure, scurvy, vitamin C deficiency

APPENDIX For supplemental videos, please see the online version of this paper.

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