Multivalve dysfunction and cardiogenic shock linked to scurvy: A case report

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Introduction

The cardiac manifestations of severe vitamin C deficiency, or scurvy, have been reported sporadically for centuries. The most common cardiopulmonary sequela of scurvy is pulmonary hypertension. We report a case of scurvy with multivalve dysfunction leading to cardiogenic shock.

Case Report

History of present illness

A 48-year-old female with generalized anxiety and interstitial cystitis presented with two weeks of rest and exertional dyspnea. She noted lower extremity edema, early satiety, and increased abdominal girth. Physical examination revealed anasarca, poor dentition, and new systolic and diastolic cardiac murmurs. She was recently admitted for liver injury secondary to polypharmacy. Laboratory analysis showed undetectable ascorbic acid level. The patient had been avoiding foods containing vitamin C to decrease her interstitial cystitis symptoms as per internet guidance.

Investigations

N-terminal pro B-type natriuretic peptide (NT-proBNP) was elevated but cardiac troponins were normal. Echocardiography revealed normal left ventricle (LV) systolic function, biatrial enlargement, moderate to severe mitral regurgitation, moderate aortic insufficiency, severe tricuspid regurgitation, decreased right ventricle (RV) function, and moderate to severe pulmonary hypertension. The estimated PASP was 60 mm Hg (Fig. 1-3). The microbubble study was negative for intracardiac shunting.

Further workup did not demonstrate other vitamin deficiencies, liver disease, infection, heavy metal toxicity, carcinoid syndrome, amyloidosis, sarcoidosis, or autoimmune diseases (Table 1). Pulmonary embolism and coronary artery disease were ruled out with CT angiography and invasive coronary angiography. Further history taking revealed no evidence of prior endocarditis, supplement, or drug use. Right heart catheterization demonstrated elevated left- and right-sided pressures, with an right atrium (RA) pressure of 20 mm Hg, mean pulmonary artery pressure of 35 mm Hg, mean pulmonary capillary wedge pressure of 16 mm Hg, and cardiac index of 2.1 L/min/m^2 using the Fick equation.

Management

The patient improved with diuretic therapy. Literature review suggested that pulmonary hypertension in the setting of scurvy

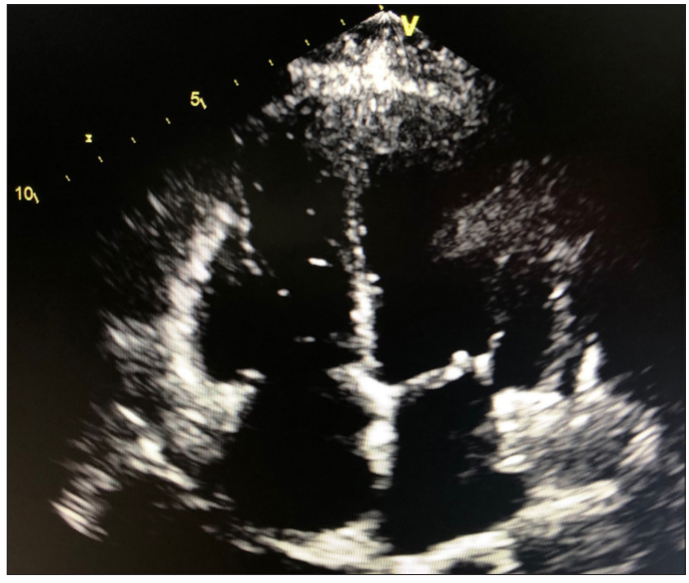

Figure 1. Apical four-chamber view. Pre-surgical right-sided chamber dilation

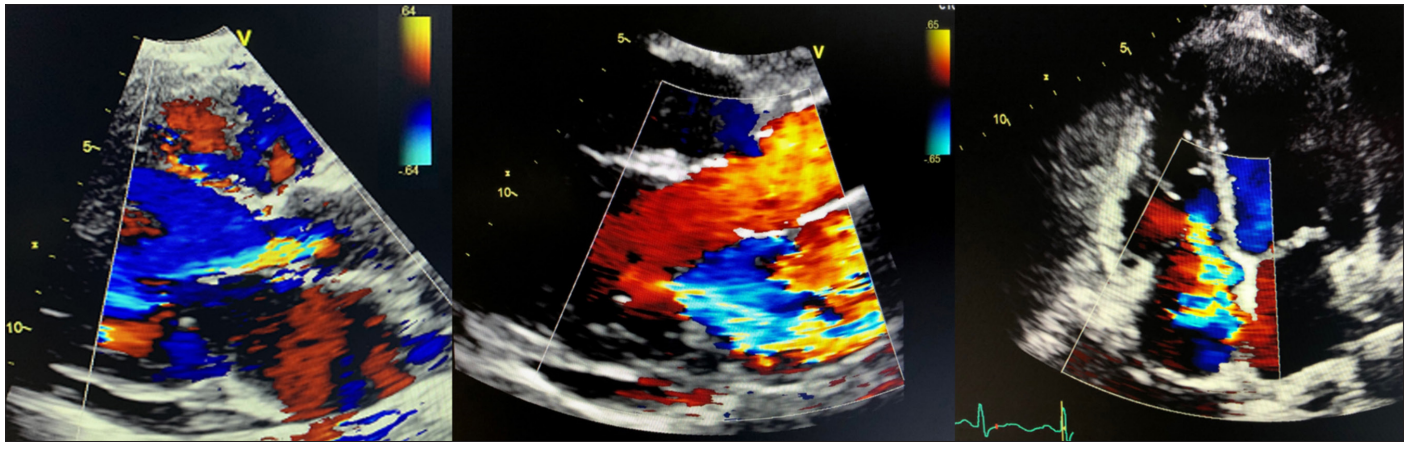

Figure 2. Valvular regurgitation. Color doppler demonstrating significant multivalve regurgitant disease

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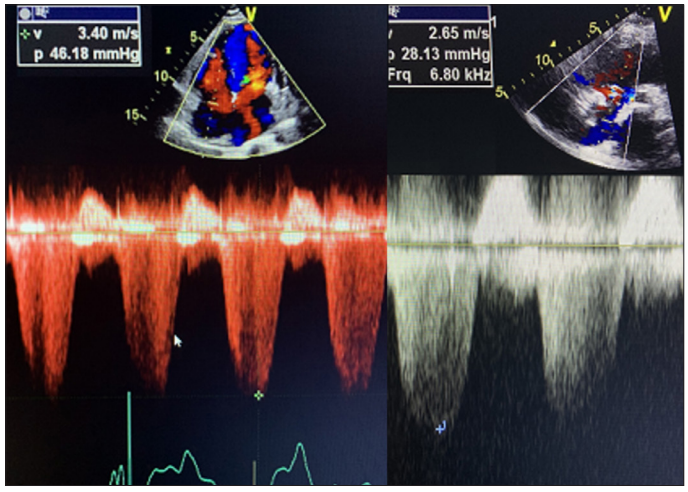

Figure 3. Assessment of pulmonary systolic pressure. Continuous-wave doppler through the tricuspid valve. Pre-surgery PASP of 61 mm Hg, assuming RA pressure of 15 mm Hg. Post-surgery PASP of 36 mm Hg, assuming RA pressure of 8 mm Hg

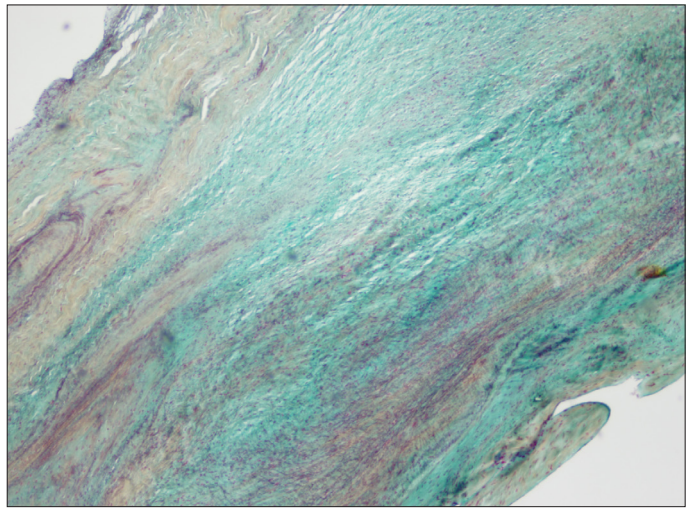

Figure 4. Tissue analysis of explanted mitral valve. Movat's pentachrome stain of the explanted mitral valve reveals collagen fiber loss (yellow stain) in the areas of myxoid degeneration (teal).

is often reversible with adequate replenishment. Given this and the patient's response to diuretics, conservative management was pursued with vitamin C repletion and close follow-up.

She returned one month later with hypervolemia and end-organ dysfunction. Repeat right heart catheterization demonstrated a cardiac index of 1.5 L/min/m^2 using the Fick equation. Vitamin C levels were at the lower normal limit. The patient was started on milrinone and referred for valve surgery. She underwent aortic and mitral valve replacement and tricuspid valve annuloplasty while continuing vitamin C supplementation.

Discussion

The relationship between scurvy, right-sided valvular disease, and pulmonary hypertension has been previously described. This case is the first report of left-sided valvular involvement. The classic manifestations of scurvy involve mucocutaneous and follicular degeneration. Right-sided pathology has been described for centuries, with early reports describing exaggerated dyspnea and tachycardia (1). Historically, clinicians hypothesized that these presentations were related to weakened pulmonary vasculature failing to accommodate right-sided blood flow (2). More recent literature supports these findings, suggesting that pulmonary hypertension may be the universal cardiopulmonary finding in patients with scurvy (Table 2) (1-6). The historical absence of echocardiography to fully assess cardiac complications coupled with decreased prevalence of scurvy made it possible that evidence of left-sided involvement was previously missed. Our review of the literature provides provides three possible mechanisms for our patient's development of pulmonary hypertension and bilateral valvular degeneration: loss of pulmonary vasodilatory effects, oxygen free radial damage, and ineffective collagen synthesis and maintenance (7).

The first mechanism where vitamin C deficiency may lead to pulmonary hypertension is through hypoxia-inducible family of transcription factors. Without vitamin C, these factors trigger a complex cascade that ultimately ends in pulmonary vasoconstriction (1, 3, 4). Vitamin C is also thought to have indirect vasodilatory properties by buffering oxygen free radicals that normally inhibit nitric oxide, a potent endogenous vasodilator. Taddei et al. (7) demonstrated that vitamin C augments nitric oxide's ability to modulate systemic vascular tone, and its deficiency results in nitric oxide degradation and vasoconstriction. These studies support that vitamin C can help prevent inappropriate pulmonary vasoconstriction through its antioxidant affects in the pulmonary vasculature (7).

Valvular integrity is also an important consideration in disease development. Cardiac valves are largely made of elastin, proteoglycan, and collagen. Vitamin C is involved with the synthesis and maintenance of the collagenous components that give the valves their tensile strength. Aikawa et al. (8) examined the cardiac valve remodeling and described that while collagen content does not substantially change after childhood. There are structural changes in adult valves which result in thickened collagen when reinforced with elastin (8). Vitamin C deficiency could cause the inability to perform effective maintenance on the valvular collagen matrix, leading to degeneration. It is critical to note that numerous cases endorse the reversal of these manifestations with the replenishment of vitamin C. Our patient was expected to complete the vitamin C replenishment; however, her progression to cardiogenic shock necessitated urgent valve surgery. Multivalve dysfunction may symbolize chronic deficiency and increased risk for clinical deterioration. Another consideration is that pulmonary hypertension may not be reversible in patients who have developed left-sided valve disease due to the continued effects of elevated left ventricular end-diastolic pressure. Patients with scurvy and left-sided involvement should prompt close observation, as they may be less likely to recover with supplementation and at higher risk for decompensation.

Table 1. Laboratory data

	Patient's values	Hospital reference ranges
Vitamin deficiencies		
Folate (ng/mL)	6.34	4.6-34.8
Vitamin B1 (Thiamine) (nmol/L)	142.5	66.5-200.0
Vitamin B6 (Pyridoxine) (mcg/L)	3.6	2.0-32.8
Vitamin B12 (Cyanocobalamin) (pg/mL)	2512	232-1245
Vitamin C (Ascorbate) (mg/dL)	0.0	0.2-2.0
25-hydroxy vitamin D (ng/mL)	24.7	29-100
Vitamin E (alpha-tocopherol) (mg/L)	7.5	4.6-17.8
Selenium (mcg/L)	96	79-326
Zinc, urine, 24-hour excretion (mcg/24 hours)	4234	150-1200
Deposition diseases		
Kappa/Lambda light chains ratio (mg/L)	1.23	0.26-1.65
Serum protein electrophoresis with Immunofixation	No monoclonal spike	No monoclonal spike
Urine protein electrophoresis with Immunofixation	No monoclonal spike	No monoclonal spike
5-hydroxtindoleacetate (ng/mL)*	56	0-22
Urine 5-hydroxyindoleacetate/creatinine ratio (mg/g)*	8.7	0.0-6.9
Chromogranin A (nmol/L)*	12	0-5
Ferritin, serum (ng/mL)	558	13-150
Ceruloplasmin, serum (mg/dL)	57.3	16-45
Autoimmune diseases		
Anti-nuclear antibody	Negative	Negative
Anti-smooth muscle antibody (Units)	9	0-19
Anti-mitochondrial antibody (Units)	9.1	0.0-20.0
Anti-liver-kidney microsomal antibody (Units)	2.1	0.0-20.0
Endocrinopathies		
Thyroid stimulating hormone (mcIU/mL)	2.95	0.27-4.2
Infectious diseases		
HIV screen	Negative	-
Aerobic, anaerobic blood cultures	No growth for 5 days	-
Borrelia burgdorferi antibody	Negative	Negative
Treponema pallidum antibody	Negative	Negative
Chronic hepatitis panel	Negative	Negative
Heavy metal toxicities		
Urinary arsenic (mcg/L)	11	0-50
Urinary lead (mcg/L)	Negative	0-49
Urinary mercury (mcg/L)	Negative	0-19
Substances use		
Drug abuse screening	Negative	Negative

*Gastroenterology determined labs regarding carcinoid syndrome were not significant given other negative imaging studies

It is also important to recognize which contemporary populations may develop scurvy. In a recent review by Ferreira et al. (3), 44% of scurvy patients carried a comorbid psychiatric diagnosis (3). This was also true in our patient, which possibly plays a role in her avoidance of vitamin C.

Follow-up

The patient did well post-operatively, with resolution of her pulmonary hypertension and heart failure symptoms (Fig. 3). The pathology of the explanted native valves showed collagen fiber loss and myxoid degeneration (Fig. 4).

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Table 2. Summary of reported cardiopulmonary manifestations of scurvy

Lead study author	Year reported	Age	Vitamin C level (mg/dL)	Other reported deficiencies	Deficiency etiology	Echocardiogram findings	Echocardiographic PASP* (mm Hg)	Invasive PASP (mm Hg)	Time to documented resolution
Penn et al. (1)	2019	48	Undetectable	None	Dietary restriction	RV dysfunction	84	57	6 weeks
Abbas et al. (2)	2016	50	0.1	Iron	Dietary restriction	RV[†] dilation and dysfunction	NR[‡]	NR	4 weeks
Ferreira et al. (3)	2020	51	0.05	Iron, Folic acid, Vitamin B12	Dietary restriction	RV dilation and dysfunction, mild TR[§]	61	NR	16 months
Kupari et al. (4)	2012	40	<0.2	None	Dietary restriction	RV dilation and dysfunction, eccentrically deformed LV[?], pericardial effusion	49	74	8 weeks
Dean et al. (5)	2019	6	<0.088	Vitamins A, B6	Dietary restriction	RV dilation and dysfunction, eccentric LV deformation, septal bowing	68	21	6 months
Frank et al. (6)	2019	17	Undetectable	Iron, Vitamin D	Dietary restriction	Structurally normal	70	NR	6 months
Ghulam et al. (9)	2018	66	Undetectable	None	Dietary restriction	RV dilation and dysfunction	97	NR	2 weeks[#]
Present case	2020	48	Undetectable	None	Dietary restriction	RV dysfunction	60	50	8 weeks

Table modified from "Reversible Pulmonary Hypertension Secondary to Scurvy in a Patient with a Psychiatric Disorder: A Case Report and Literature Review" by Ferreira et al., Eur J Case Rep Int Med 2020;4. Adapted with permission.
Footnotes: [#]Echocardiogram at two weeks showed normalization of PASP (31 mm Hg) but persistent RV dilation. LV[?]: left ventricle, NR[‡]: not reported, NT-proBNP: N-terminal pro B-type natriuretic peptide, PASP*: pulmonary artery systolic pressure, RV[†]: right ventricle, TR[§]: tricuspid regurgitation

Conclusions

Although uncommon, severe vitamin C deficiency can have significant cardiopulmonary manifestations. The most prevalent is pulmonary hypertension which can be reversible with vitamin replenishment. Nutritional evaluation should be considered in patients presenting with pulmonary hypertension of unknown etiology. Patients with scurvy and left- and right-sided valvular degeneration may be at higher risk for decompensation and warrant close observation.

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