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

Lisa Conte*, Joseph Louden**, Lauren Ann Weber**
Departments of *Internal Medicine, and **Cardiology, Walter Reed National Military Medical Center, Bethesda-United States

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/m² 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
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/m² 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 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.
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).

Table 1. Laboratory data

| Vitamin deficiencies | Patient's values | Hospital reference ranges |
|----------------------|------------------|--------------------------|
| 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-hydroxyindoleacetaetate (ng/mL)* | 56 | 0-22 |
| Urine 5-hydroxyindoleacetaetate/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 (mclU/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
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.

Disclosures: The identification of specific products or scientific instrumentation does not constitute endorsement or implied endorsement on the part of the author, DoD, or any component agency. The views expressed in this presentation are those of the author and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government.

Acknowledgements: Special thanks to Dr. Michael Goold, MD and Dr. Alana Dasgupta, MD from the WRNMMC Pathology Department for their contributions to this manuscript in providing the summary for the pathologic specimen.

Informed consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

References

1. Penn EH, Olenchock BA, Marston NA. A Shocking Deficiency. Circulation 2019; 140: 613-7. [Crossref]
2. Abbas F, Ha LD, Sterns R, von Dohnhoff L. Reversible Right Heart Failure in Scurvy Rediscovery of an Old Observation. Circ Heart Fail 2016; 9: e003497. [Crossref]
3. Ferreira CCG, de Sá Pereira Belfort D, Neto PMC, Gouveia PADC. Reversible Pulmonary Hypertension Secondary to Scurvy in a Patient with a Psychiatric Disorder: a Case Report and Literature Review. Eur J Case Rep Intern Med 2020; 7: 001404.
4. Kupari M, Rapola J. Reversible pulmonary hypertension associated with vitamin C deficiency. Chest 2012; 142: 225-7. [Crossref]
5. Dean T, Kaushik N, Williams S, Zinter M, Kim P. Cardiac Arrest and Pulmonary Hypertension in Scurvy: a case report. Pulm Circ 2019; 9: 2045894018812052. [Crossref]
6. Frank BS, Runciman M, Manning WA, Ivy DD, Abman SH, Howley L. Pulmonary Hypertension Secondary to Scurvy in a Developmentally Typical Child. J Pediatr 2019; 208: 291. [Crossref]

7. Taddei S, Virdis A, Ghiadoni L, Magagna A, Salvetti A. Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. Circulation 1998; 97: 2222-9. [Crossref]

8. Aikawa E, Whittaker P, Farber M, Mendelson K, Padera RF, Aikawa M, et al. Human semilunar cardiac valve remodeling by activated cells from fetus to adult: implications for postnatal adaptation, pathology, and tissue engineering. Circulation 2006; 113: 1344-52. [Crossref]

9. Ghulam Ali S, Pepi M. A Very Uncommon Case of Pulmonary Hypertension. CASE (Phila) 2018; 2: 279-81. [Crossref]