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CASE REPORT
Cardiovascular imaging

Reversible severe pulmonary hypertension and right heart failure with cardiogenic shock due to scurvy: a case report

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Background The systemic complications of vitamin C deficiency, otherwise known as scurvy, have been well-documented in history. Few case reports have documented severe cardiopulmonary complications such as right heart failure (RHF) and pulmonary hypertension (PH).

Case summary A 25-year-old female presented to the hospital with two weeks of progressive fatigue, dyspnoea, myalgias, and arthralgias. She was admitted for symptomatic anaemia requiring transfusion. Her symptoms persisted and she developed severe PH and RHF, complicated by cardiogenic shock and multiple episodes of cardiac arrest. She was found to have severe vitamin C deficiency secondary to a severely self-restricted diet. After repletion of vitamin C, the patient had complete resolution of RHF and PH.

Discussion This case adds to the sparse literature documenting severe cardiopulmonary complications of vitamin C deficiency. We believe that this is the first adult case of scurvy causing RHF and PH leading to cardiogenic shock and episodes of cardiac arrest. There are multiple hypotheses on the pathogenesis of scurvy-associated PH and RHF, including overactivation of hypoxia-inducible transcription factors and deficiency of vitamin C's vasodilatory effect that acts through increased nitric oxide production in endothelial cells. When recognized, early vitamin C repletion may prevent severe cardiopulmonary complications of scurvy.

Keywords Pulmonary hypertension • Right heart failure • Scurvy • Vitamin C deficiency • Cardiogenic shock • Case report

ESC curriculum 2.2 Echocardiography • 6.4 Acute heart failure • 9.6 Pulmonary hypertension

Learning points

- To recognize the potential effects of restricted diets on changes in vitamin levels and their effect on cardiopulmonary function.
- To understand the physiologic role of vitamin C and the potentially fatal complications in its deficiency.

Introduction

Vitamin C deficiency results in a clinical disease known as scurvy, which most commonly presents in malnourished patients. Scurvy develops 1–3 months after the cessation of vitamin C intake, and its presentation ranges from lethargy to mucocutaneous and haematologic complications.[1,2] Case reports have documented vitamin C deficiency causing severe pulmonary hypertension (PH) and right heart failure (RHF).[3–9] Our case documents a rare occurrence of vitamin C deficiency that resulted in cardiogenic shock and multiple cardiac arrests. In this paper, we contribute to the growing documentation of severe PH and RHF caused by vitamin C deficiency.

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Summary figure

Time	Events
Five months prior to presentation	Shortness of breath and generalized weakness, found to have iron deficiency anaemia secondary to menorrhagia. Transthoracic echocardiogram (TTE) was unremarkable.
Initial presentation	Two weeks of progressive fatigue, shortness of breath, and generalized weakness. Admitted for symptomatic microcytic anaemia (HgB 7.1 g/dL, normal range 12.0–16.0) without bleeding and received 1 unit transfusion of packed red blood cells (pRBCs) with elevation of HgB to 10.6 g/dL. Five total units of pRBC were administered throughout hospitalization to maintain goal HgB of 7.0 g/dL. Sickle cell and beta thalassaemia were ruled out via haemoglobin electrophoresis.
Days 2 and 3 Upgrade to telemetry unit	Shortness of breath did not improve. Increasing tachycardia to 140 beats per minute (b.p.m.) and upgraded to telemetry unit for further work-up. Found to have urinary tract infection and treated with antibiotics.
Day 4 Cardiogenic shock and transfer to intensive care unit	Cardiogenic shock, with blood pressure of 77/56 mmHg, heart rate of 45 b.p.m., hypothermia to 95.7°F, and saturating 69% on room air. pro-BNP was 330 000 pg/mL, and mildly elevated troponin which lateralized later. Started on fluid resuscitation, oxygen supplementation, broad-spectrum antibiotics, and upgraded to intensive care unit. Computed tomography angiogram of the chest ruled out pulmonary embolism but revealed right ventricular (RV) strain. Transthoracic echocardiogram revealed normal left ventricular ejection fraction (LVEF), but severely dilated right atrium and right ventricle with pulmonary artery pressure of 70 mmHg.
Day 5	Two episodes of cardiac arrest with pulseless electrical activity. Return of spontaneous circulation achieved after 1–2 min in each arrest. She was intubated and connected to ventilator. Right heart catheter was inserted, and the readings were as follows: CVP (RAP) 21 [0–6 mmHg], PA 63/43/48 [25/10/12 mmHg], PCWP 13 [4–12 mmHg], CO 2.2 [4–8 L/min], CI 1.6 [2.5–4 L/min/m^2], PVR 16 [<2 WU]. SVR 1673 dynes-s/cm^5 [NL: 800–1200]. Extensive chart review and physical examination revealed that the patient has extremely restricted diet with gingivitis and petechial haemorrhage on her lower extremities. Started on vasopressors, inotropes, furosemide, and inhaled nitric oxide. Vitamin C level was sent, and she was empirically started on vitamin C intravenous supplementation.
Days 10–12	Patient's oxygen requirements improved, and she was extubated to high flow nasal cannula. Inotropes and vasopressors requirements decreased, and vitamin C dose was decreased. Inhaled nitric oxide was removed.
Day 14	Repeat Swan-Ganz on inhaled nitric oxide catheter revealed as follows: CVP (RAP) 12 mmHg, mPAP 39 mmHg, PCWP 19 mmHg, CO 4.6 L/min, CI 2.8 L/min/m^2, PVR 4.3 WU.
Day 15	Vitamin B1 and D level were within normal limits, but vitamin C level was reported undetectable. Dose of vitamin C was increased to 1000 mg oral daily.
Day 23	The patient's symptoms significantly improved, and vasopressors and inotropes were removed. Repeat TTE (17 days after vitamin C repletion) revealed LVEF of 55% and significant improvements with normal morphology and pressures of the right side. Repeat Swan-Ganz catheter revealed CVP of 7 mmHg, PAP of 36/9 mmHg, and PCWP of 9 mmHg.

Case presentation

A 25-year-old female presented with progressive fatigue, dyspnoea, myalgias, and arthralgias. She had a history of iron deficiency anaemia secondary to menorrhagia, for which she follows in a haematology clinic. Sickle cell anaemia and beta thalassemia were previously ruled out via haemoglobin electrophoresis, and her baseline haemoglobin ranged between 9.0 and 11.0 g/dL (normal range 12.0–16.0 g/dL).

On admission, she was afebrile with a blood pressure of 131/93 mmHg, a heart rate of 123 b.p.m., and an O_2 saturation of 100% on room air. Labs on admission revealed non-haemolytic anaemia with a haemoglobin level of 7.1 g/dL (normal range of 80.0–99.0 fL), which increased to 10.6 g/dL following transfusions of packed red blood cells (pRBCs). A total of 5 U of pRBCs were administered throughout her hospitalization to maintain a goal HgB of 7.0 g/dL. Her kidney and liver function tests were normal. The faecal occult blood test was positive in the emergency department (ED); however, since there were no signs of overt bleeding, clinical suspicion for gastrointestinal bleed was low. The electrocardiogram (ECG) revealed sinus tachycardia with right axis deviation (*Figure 1*). She was admitted to the hospital for anaemia requiring a transfusion. A computed tomography angiogram of the chest ruled out pulmonary embolism; however, it revealed significant right heart strain. Transthoracic echocardiogram (TTE) revealed an ejection fraction of 55%, severe PH (70 mmHg), and dilated right ventricle and atrium (*Figures 2* and *3*).

On Day 4, the patient decompensated into cardiogenic shock due to RHF. Norepinephrine was initiated at a rate of 5 µg/min, and she was transferred to the medical intensive care unit. Shortly afterward, the patient experienced two episodes of cardiac arrest with pulseless electrical activity but return of spontaneous circulation was achieved on both occasions. Swan-Ganz catheter measurement on Day 5 confirmed pulmonary capillary wedge pressure (PCWP) of 13 mmHg, pulmonary arterial pressure (PAP) of 63/43/48 mmHg, central venous pressure (CVP) of 21 mmHg, cardiac output (CO) of 2.2 L/min, cardiac index (CI) of 1.6 L/min/m^2, and systemic vascular resistance was 1673 dynes-s/cm^5. These readings are consistent with PH and RHF, which resulted in reduced preload to left ventricle, leading to low CO and cardiogenic shock. On that same day, the blood lactate level was elevated to 8.6 mmol/L (normal range 0.6–1.4 mmol/L), creatinine was elevated to 1.7 mg/dL (normal range 0.50–0.90 mg/dL) from a normal baseline, and liver function tests revealed elevated AST of 136 U/L (normal range 11–39 U/L) and ALT of 71 U/L (normal range 11–35 U/L) from a normal baseline. The cortisol level was checked and did not indicate adrenal insufficiency. Notably, a TTE completed four months prior to this admission was normal (*Figure 4*). Cardiac inotropes were initiated, with dobutamine up to

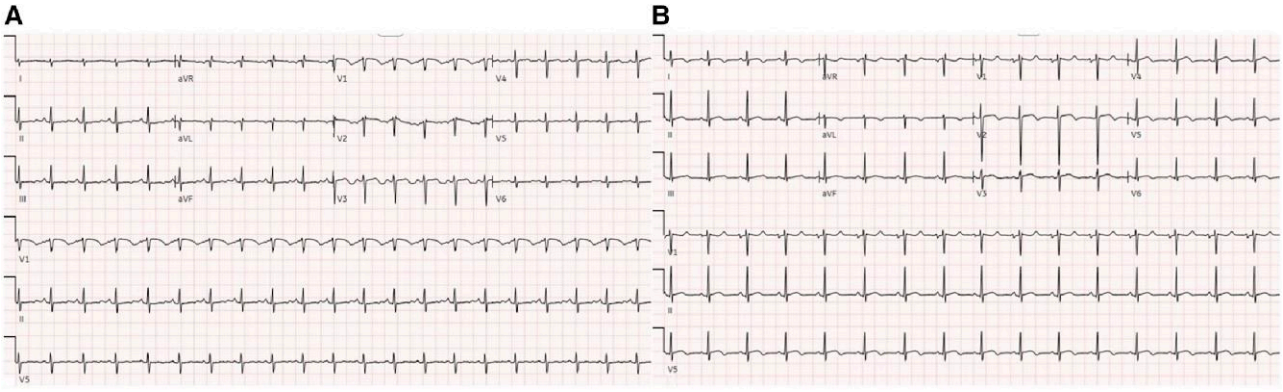

Figure 1 Electrocardiogram (ECG) before and after vitamin C repletion: (*A*) ECG on admission revealed sinus tachycardia with right axis deviation. (*B*) Repeat ECG post-vitamin C repletion showed normal sinus rhythm with resolution of right axis deviation. ECG, electrocardiogram.

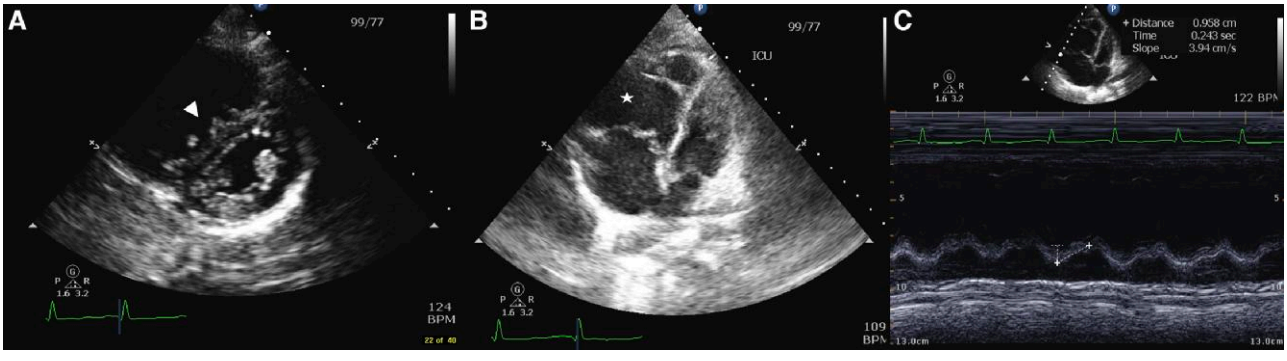

Figure 2 Admission transthoracic echocardiogram (TTE): (*A*) parasternal short axis view with D shaped (arrowhead) left ventricle. (*B*) Apical four chamber view with an enlarged right ventricle (star). (*C*) Tricuspid annulus planar systolic excursion (TAPSE) severely reduced to 0.95 cm. TTE, transthoracic echocardiogram; TAPSE, tricuspid annulus planar systolic excursion.

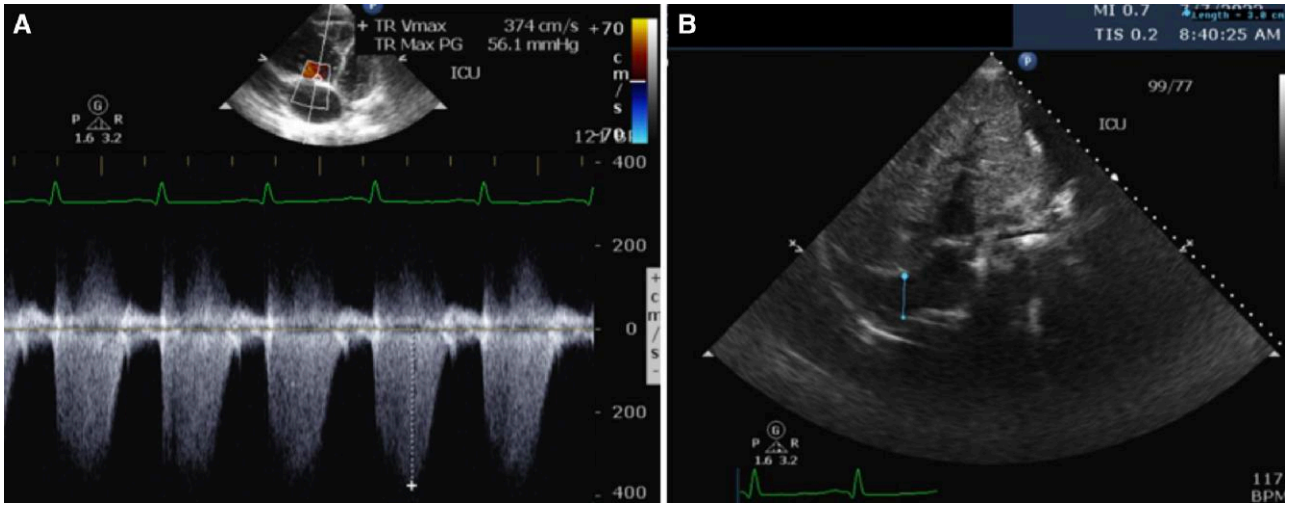

Figure 3 Admission transthoracic echocardiogram (TTE): severely elevated pulmonary artery systolic pressure. (*A*) Apical view with tricuspid regurgitation pressure gradient of 56.1 mmHg. (*B*) Non-collapsible inferior vena cava dilated to 3.0 cm (patient not intubated). RA pressure is 15 mmHg. Calculated PASP is 71.1 mmHg. PASP, pulmonary artery systolic pressure; RA, right atrium; TTE, transthoracic echocardiogram.

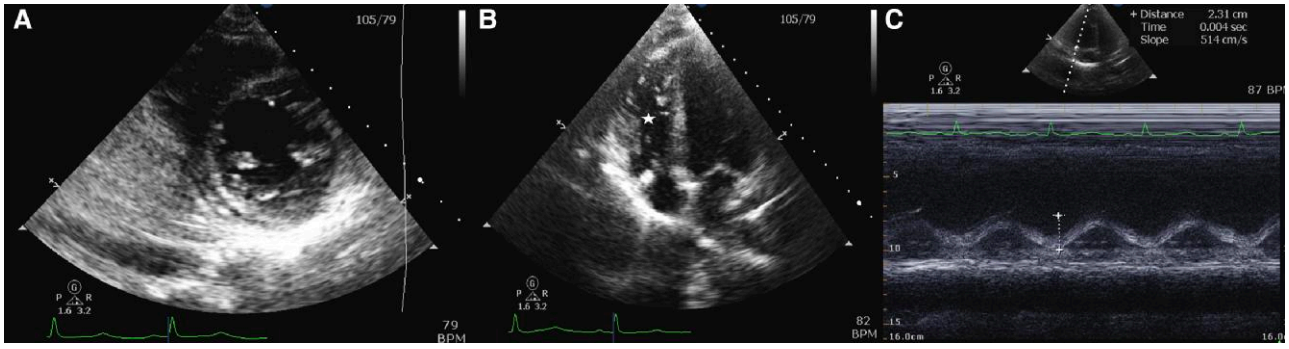

Figure 4 Transthoracic echocardiogram (TTE) 4 months prior to admission: (*A*) Parasternal short axis view showing normal ventricles and papillae. (*B*) Apical four chamber view with normal size right ventricular (star). (*C*) Normal tricuspid annulus planar systolic excursion (TAPSE) of 2.3 cm. TTE, transthoracic echocardiogram; TAPSE, tricuspid annulus planar systolic excursion.

5 μg/kg/min and milrinone at 0.125 μg/kg/min. Upon further investigation into the patient's medical history, she previously presented to the ED with gingival swelling, bleeding, and a petechial rash. Further questioning revealed that she followed a severely restricted diet lacking fruits and vegetables. This realization led to the discovery of severe vitamin C deficiency of <0.1 mg/dL (normal range 0.4–2.0 mg/dL).

The patient was initiated on intravenous vitamin C repletion with 2 g daily and gradually showed improvement, leading to the removal of vasopressors and inotropes. On Day 14 during treatment with inhaled nitric oxide, Swan-Ganz catheter readings revealed a CVP of 12 mmHg, mean PAP of 39 mmHg, PCWP of 19 mmHg, CO of 4.6 L/min, CI of 2.8 L/min/m^2, and PVR of 4.3 WU. A repeat TTE conducted on Day 23 revealed the resolution of right ventricular dilation with complete resolution of RHF and PH (*Figure 5*). Additionally, a repeat Swan-Ganz measurement on Day 23 showed a PCWP of 9 mmHg, PAP of 36/9 mmHg, and CVP of 7 mmHg. A repeat ECG demonstrated the resolution of right axis deviation (*Figure 1*, panel *B*). The patient was stabilized and safely discharged with plans for outpatient cardiology follow-up. She was discharged on oral vitamin C 1000 mg daily.

Discussion

The classic mucocutaneous complications of vitamin C deficiency, or scurvy, have been well-documented.[1] Here, our focus is on the role of vitamin C in the cardiopulmonary system.

Humans are only able to meet their physiological requirements for vitamin C through exogenous sources. Despite the wide availability, a large study conducted in England found a 1.4% overall prevalence of vitamin C deficiency with a greater prevalence in males vs. females (2.2% vs. 0.8%).[2] Scurvy symptoms typically manifest 1–3 months after cessation of vitamin C intake. The clinical presentation can vary, ranging

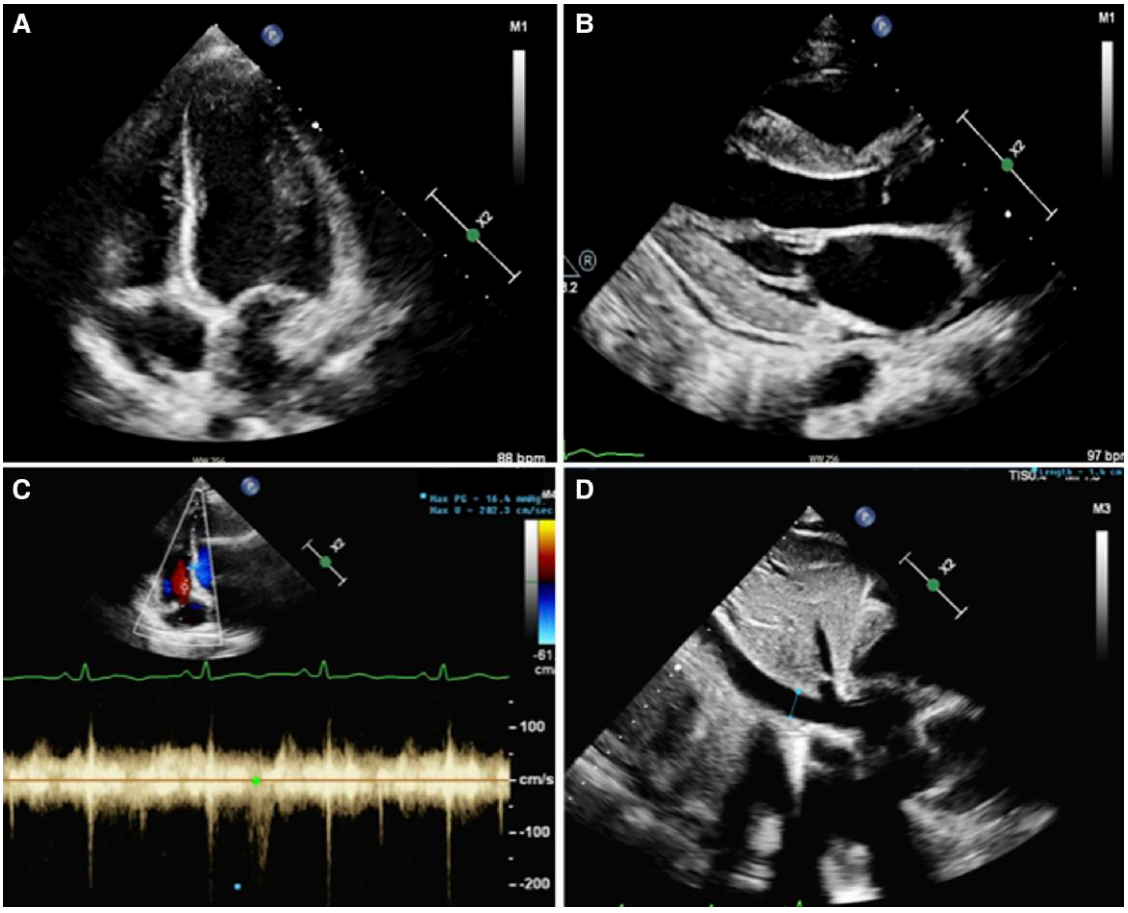

Figure 5 Repeat transthoracic echocardiogram (TTE) 3 weeks post-vitamin C repletion: (*A*) Apical four chamber view with normal RV size. (*B*) Parasternal long axis view with normal LV and RV size. (*C*) Parasternal long axis view with normal tricuspid jet velocity and tricuspid regurgitation pressure gradient of 16 mmHg. (*D*) Collapsible inferior vena cava measuring 1.4 cm. LV, left ventricle; RV, right ventricle; TTE, transthoracic echocardiogram.

from malaise and lethargy to mucocutaneous and haematologic complications.[1,3] To the best of our knowledge, there have been only 12 reported cases of vitamin C-induced PH in adults.[4–10]

There are multiple hypotheses regarding the pathogenesis of scurvy-associated PH and RHF. One proposed mechanism involves the overactivation of Hypoxia-Inducible Family transcription factors (HIF TF), which mediate cellular response to low-oxygen conditions and are dependent on vitamin C and iron.[4] Deficiencies in vitamin C or iron can disrupt the regulation of these factors, leading to widespread pulmonary vasoconstriction.[4,5] Vitamin C is also essential for iron absorption in the duodenum and jejunum. It facilitates the conversion of ferric iron (non-absorbable state) to ferrous iron (absorbable state). Moreover, vitamin C chelates with ferric iron in the stomach, maintaining its solubility in the alkaline pH of the duodenum.[11] As a result, vitamin C deficiency can directly affect the function of HIF-TFs and indirectly impact them through associated iron deficiency.[5,11,12]

Vitamin C also exerts a vasodilatory effect by increasing nitric oxide production and availability in endothelial cells.[5,13] The resolution of vitamin C-induced PH in the reported cases following repletion further emphasizes this function.[12] Additionally, vitamin C has been shown to improve left ventricular function. A meta-analysis of six trials assessing vitamin C's effects on left ventricular systolic function demonstrated that supplementation with this nutrient increased left ventricular ejection fraction by an average of 12.0%.[14] Our patient's clinical course and response to vitamin C repletion are consistent with prior cases demonstrating the effect of intravenous repletion of vitamin C on scurvy-associated RHF and PH.[3–7] While the incidence of scurvy-associated PH and RHF is very rare, their systemic consequences are severe and impose an additional burden on patients, leading to adverse outcomes. These findings underscore the importance of conducting a thorough dietary history and initiating early vitamin C repletion in patients with scurvy to prevent life-threatening cardiopulmonary complications.

Our literature review revealed a lack of clinical trials or cohort studies investigating the role of vitamin C supplementation as a prophylaxis for preventing PH in humans. However, experimental animal models, specifically broilers, have demonstrated the effectiveness of vitamin C in preventing PH.[15] Nevertheless, these findings have not been extensively studied in humans. Additionally, there are currently no guidelines recommending testing of vitamin C deficiency as a potential factor contributing to PH.[16]

Conclusion

Vitamin C deficiency has been widely documented to cause systemic complications, including fatigue, arthralgias, bleeding gums, poor wound healing, and cardiopulmonary symptoms such as PH and RHF. As demonstrated in our patient, vitamin C repletion can reverse

scurvy-associated RHF and PH. However, as observed in our case, rare but potentially fatal complications like cardiogenic shock and cardiac arrest may occur. Therefore, it is crucial to obtain a comprehensive dietary history in patients presenting with symptoms of RHF and PH, particularly if they exhibit characteristic symptoms of vitamin C deficiency such as abnormal bleeding. Furthermore, measuring serum vitamin C and iron levels and initiating early repletion can prevent life-threatening complications.

Lead author biography

Adam Kurnick received his bachelor's degree in biology from Yeshiva University, and MD degree from Sackler School of Medicine at Tel Aviv University. He is currently an internal medicine resident at SUNY Downstate Health Sciences University in Brooklyn, New York.

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Conflict of interest: None declared.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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