

A Very Uncommon Case of Pulmonary Arterial Hypertension

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Abstract Pulmonary arterial hypertension (PAH) describes a rare, progressive disease of the pulmonary vasculature, involving a group of clinical conditions that result in precapillary pulmonary hypertension (PH). PAH is characterized by proliferative vasculopathy, and subsequent right heart failure. For the past several decades research has focused on identification of underlying molecular causes of this disease. Recently, there have been a number of reported cases of patients with scurvy developing pulmonary arterial hypertension. Thus, it has been hypothesized that vitamin C deficiency results in non-hypoxic activation of hypoxia inducible transcription factors (HIF) and low nitric oxide (NO) level in the pulmonary vasculature, leading to subsequent pulmonary vasculopathy and an exaggerated pulmonary vasoconstrictive response. Immediate supplementation of vitamin C is considered the definitive treatment, preventing an otherwise fatal outcome. In this paper, we describe a patient with a fatal case of scurvy related PAH, who was admitted with ecchymosis, oral ulceration, and dyspnea.

Keywords: *pulmonary arterial hypertension, scurvy, right side heart failure, hypoxia inducible transcription factors, nitric oxide*

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1. Introduction

Pulmonary hypertension (PH) is defined as an elevated mean arterial pressure ≥ 25 mmHg at rest. The World Health Organization (WHO) has classified PH into the five groups based upon etiology. The term PH is used when describing all five groups, while the term PAH specifically refers to group 1 PH with increased pulmonary vascular resistance (PVR). The prevalence of PAH is unknown in North America, while several European registries have reported rates of between 5 and 52 per million [1]. The French national registry [2] confirmed female predominance, with a mean age at diagnosis of 50 years. Moreover, the multicenter U.S. REVEAL registry, also confirmed onset of disease at an older age (53 years old) [3,4]. While in the past, it was postulated that PAH affected young women in their thirties, it is now considered a disease that affects men and women proportionately, most commonly presenting in midlife.

PAH, as a subgroup of PH, includes heritable (HPAH), idiopathic (IPAH), drug/toxin-mediated forms of PAH, as well as congenital heart disease with left-to-right shunts and connective tissue disease (CTD), in addition to HIV infection, portal hypertension, and schistosomiasis infection. Two other rare forms of PAH include pulmonary capillary

hemangiomatosis (PCH) and pulmonary veno-occlusive disease (PVOD). The pathogenesis of PAH is a proliferative vasculopathy, characterized by vasoconstriction, cell proliferation, fibrosis, and microthrombosis. Pathologic findings include hyperplasia and hypertrophy of all three layers of the vascular wall of the pulmonary arteries (intima, media, adventitia), as well as fibrosis, and in situ thrombosis of the small pulmonary arteries and arterioles (plexiform lesions).

While clinical scurvy is rare in the United States, vitamin C deficiency is not uncommon, and can affect up to 13% of the population, especially malnourished patients and those that suffer from alcohol abuse [5]. Vitamin C deficiency related PAH is thought to occur as a result of the loss of the vasodilatory effect of vitamin C, whereby vitamin C increases synthesis of endothelial NO in the pulmonary circulation [6]. Moreover, both iron and vitamin C are cofactors for prolyl hydroxylase enzymes, responsible for regulating the hypoxia inducible transcription factors [7], contributing to unregulated HIF-mediated pulmonary vasoconstriction, and subsequent PAH development. PAH related to ascorbic acid deficiency is a rapidly reversible; however, lack of reported cases in the literature contributes to delays in diagnosis of this rare and potentially fatal disease.

We report a 73-year-old female patient, 10 years post bariatric surgery, who presented to our hospital with shortness of breath hypoxia, and lower limbs spontaneous

ecchymosis. The patient was diagnosed with PAH with negative vasoreactivity test during right heart catheterization (RHC) and had negative work up for PAH. Additional history revealed that the patient's diet for the last few years was significantly lacking fresh fruits and vegetables. On account of ecchymosis, PAH, and dietary lack of vitamin C, scurvy was suspected, and an ascorbate level was ordered. Shortly after admission, the patient developed severe cardiogenic shock refractory to maximal supportive management. Laboratory data showed the patient's ascorbic acid level as zero; however, she died before supplementation with vitamin C.

2. Case Presentation

The patient in this case is a 73-years-old African American female with a past medical history of morbid obesity, treated 10 years prior with bariatric surgery resulting in a subsequent reported 80-kilogram weight loss. Her past medical history is also significant for osteoarthritis, right hip replacement, and 30-years pack history. The patient reportedly was not on any home medications other than occasional multivitamins. She presented to our hospital reporting two months of increasing shortness of breath, which progressed to dyspnea at rest on admission. She also reported oral ulceration and abdominal distension for the past 2 weeks. The patient additionally complained of bilateral lower limb swelling and spontaneous ecchymosis on her extremities, mainly her lower limbs.

On admission, she was afebrile, displaying moderate signs of respiratory distress, with a respiratory rate of 24 and desaturation of 84% on room air. Pulse oximetry increased to 94% with administration of 4 liters oxygen. She had mild tachycardia, and a hypotensive blood pressure of 77/56 mmHg. Her physical exam showed jugular non-pulsatile venous distension up to the base of the neck, and prolonged expiration with bilateral diminished air entry. Her cardiac exam showed right ventricular heave, regular heart sounds, loud P2, pan-systolic murmur, and S3 left to the xiphoid process. Tender hepatomegaly 5cm below the costal margin midclavicular line was evident, as well as positive shifting dullness, and bilateral symmetrical pitting lower limb edema to mid-tibial shaft, and scattered ecchymosis bilaterally. The rest of the patient's physical examination was unremarkable.

Laboratory data uncovered mild acute kidney injury with creatinine 1.26 (normal range 0.8 to 1.2 mg/dL), BUN 25 (normal range 7 to 20 mg/dL), and normal electrolyte levels. There was mild elevation in total bilirubin (1.4) and direct bilirubin (0.7). Liver enzymes and a coagulation panel were unremarkable. There was evidence of cardiomegaly on the patient's chest x-ray (CXR). Electrocardiogram (ECG), showed normal sinus rhythm, mild tachycardia at 102 beats per minute, right axis deviation, poor R-wave progression, right ventricular hypertrophy, and right bundle branch block. Furthermore, there were signs of right ventricular strain, including ST depression and T-wave inversion in V2-5, as well as right atrial dilatation, manifested by high amplitude P wave (P pulmonale) in limb lead 2 (Figure 1). Echocardiography

(ECHO) showed significant signs of left ventricular concentric hypertrophy, with normal global systolic function, and an ejection fraction (EF) of 75% with normal diastolic function. There was evidence of increased right ventricular wall thickness, as well as severe right ventricular dilatation, accompanied by moderately reduced function (Figure 2), flattening of the interventricular. Furthermore, the ECHO showed moderate dilatation of the right atrium (Figure 4), severe tricuspid regurgitation (TR) with an estimated TR jet velocity of 5.14 m/sec. The pressure gradient between the right ventricle and right atrium was calculated to be 105.53 mmHg, whereas estimated right ventricular systolic pressure (RVSP) was measured at 112 mmHg (Figure 3), corresponding to pulmonary artery systolic pressure (PASP). Pulmonary function tests (PFTS) showed a mild decline in diffusing capacity for carbon dioxide (DLCO).

Given the patient's presentation, findings in her physical exam, ECG, and ECHO, she was diagnosed with pulmonary hypertension. Moreover, on account of that fact that the patient presented with normal systolic and diastolic function of the left ventricle, PFT ruled out significant lung disease, had no obstructive sleep apnea syndrome as documented by polysomnography few months prior to her admission, and chronic thromboembolic pulmonary HT was excluded by means of a ventilation perfusion scan (V/Q). Thus, PAH (pre-capillary PH) was suspected. The diagnosis of PAH was confirmed during right heart catheterization (RHC), with a mean PAP of 50 mmHg. While pulmonary artery wedge pressure (PCWP) was within normal range, 9 mmHg, the patient displayed high pulmonary vascular resistance (6.7 Wood units), and a cardiac index of 2.76 L/min/m². Vasoreactivity test with adenosine infusion was negative, as there was a decrease of mean pulmonary arterial pressure to 46 mmHg. The patient was started on diuretics (furosemide and spironolactone), oxygen at 4 liters per minute (L/Min), which was later increased to 6 L/Min. Sildenafil 20 mg was administered three times a day (TID), with no hemodynamic improvement. Subsequently systemic prostacyclin agonists were considered. The patient's systemic blood pressure dropped to 70/50 mmHg, at which time a central venous catheter was inserted, and inotropic therapy was initiated with no significant clinical improvement. A series of tests including HIV, hepatitis panel, antinuclear antibodies (ANA), anti-Scl-70, anti-ribonucleoprotein (anti-RNP), anti-centromere, anti-double stranded DNA, anti-RO, and anti-LA antibodies returned no positive results. Furthermore, laboratory tests indicated a normal rheumatoid factor (RF), C3, and C4. There was no recorded history of drug administration or family history of PAH, and abdominal ultrasounds excluded cirrhosis or signs of portal hypertension, although mild ascites was confirmed. As previously eluded to, ECHO ruled out congenital heart disease. A reviewed history revealed that her diet was significantly unbalanced, lacking fruits and vegetables for the last two years, and that the patient had poor compliance to vitamins and supplements prescribed after her bariatric surgery. Given the patient's history of poor diet, ecchymosis, oral ulceration, and current PAH presentation,

vitamin C deficiency was suspected, and levels were ordered. The patient's general condition deteriorated rapidly, and severe cardiogenic shock developed. The patient was non-responsive to maximal medical supportive

therapy and died few days after her admission. Ascorbic acid level returned zero, subsequent to her death, and she was therefore not administered supplementary doses of Vitamin C.

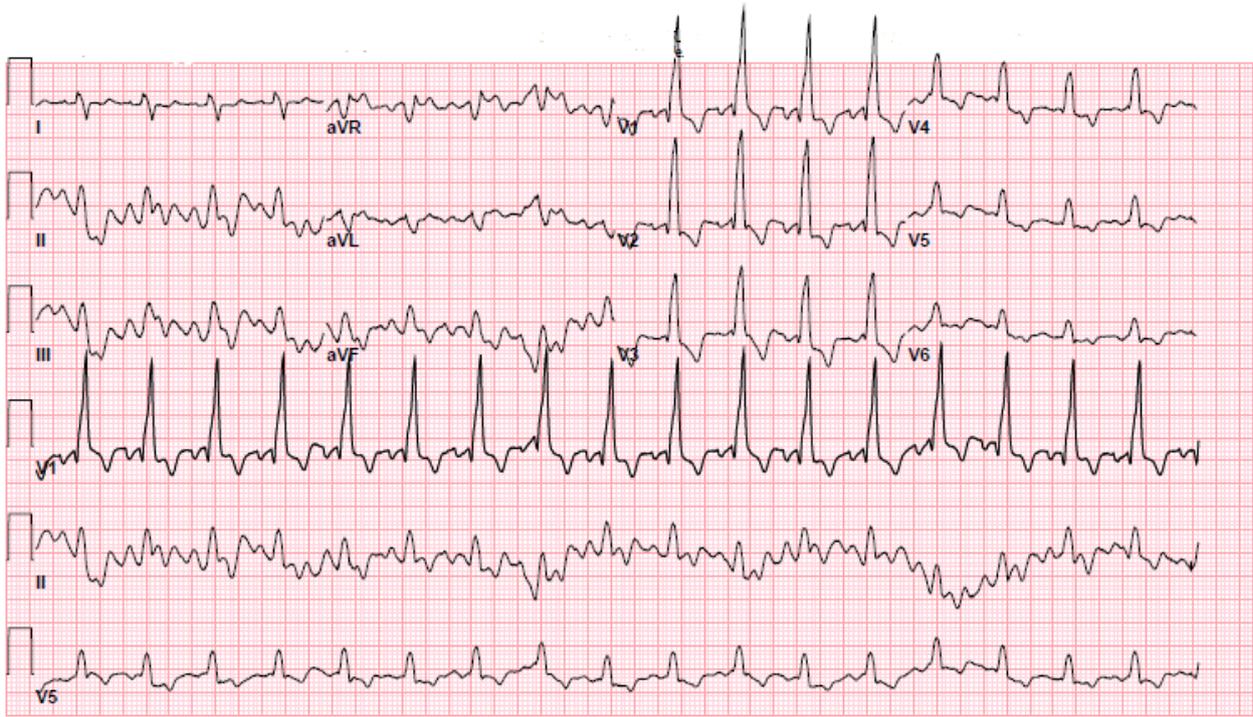


Figure 1. ECG: normal sinus rhythm, mild tachycardia at 102 beats per minute, right axis deviation, poor R-wave progression, right ventricular hypertrophy, and right bundle branch block. Signs of right ventricular strain, including ST depression and T-wave inversion in V2-5



Figure 2. Echocardiography, 4 Chambers view showing severe RT ventricular dilatation, basal diameter is 5.6 cm (normal 3.29 ± 0.47 cm), right atrial dilatation and flattening of the interventricular septum

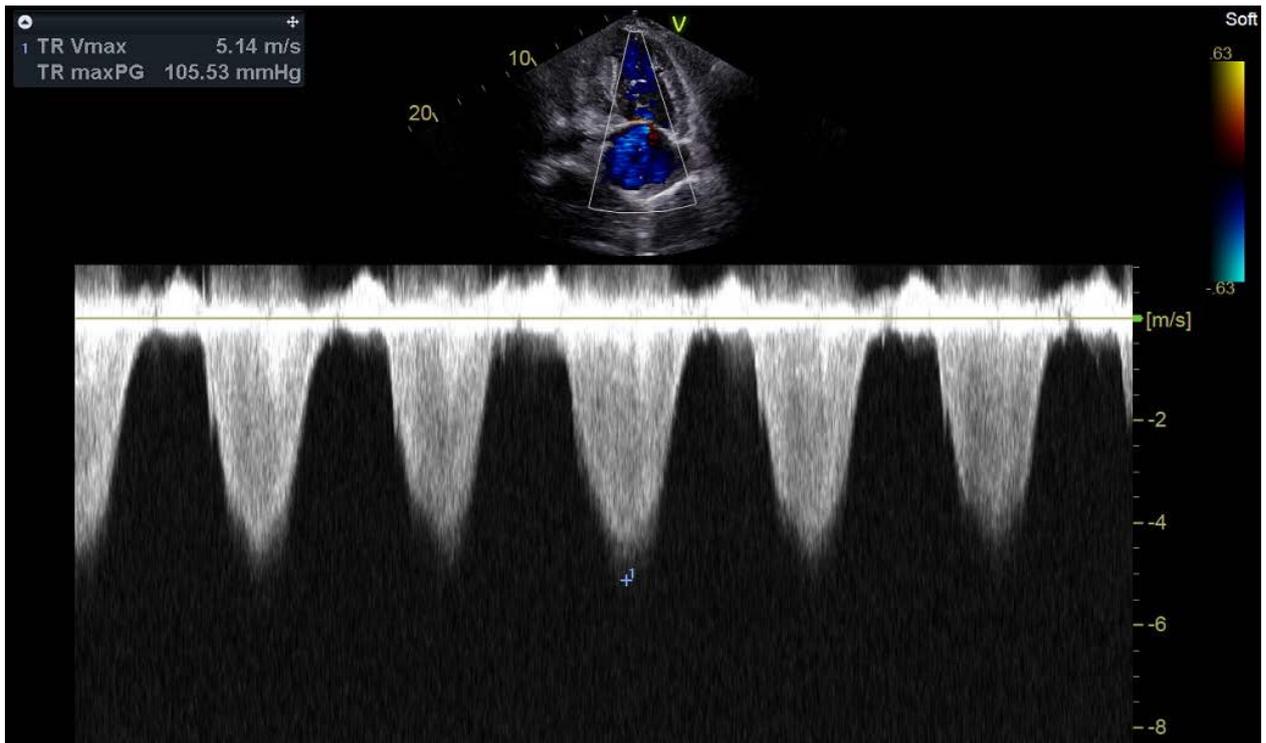


Figure 3. Apical four chamber view with continuous wave Doppler interrogation across the tricuspid valve. The Peak Velocity is 5.14m/s. The estimated pressure gradient between the RT atrium and RT ventricle is 105.53 mmHg. Adding to this the right atrial pressure will give the estimated pulmonary artery systolic pressure

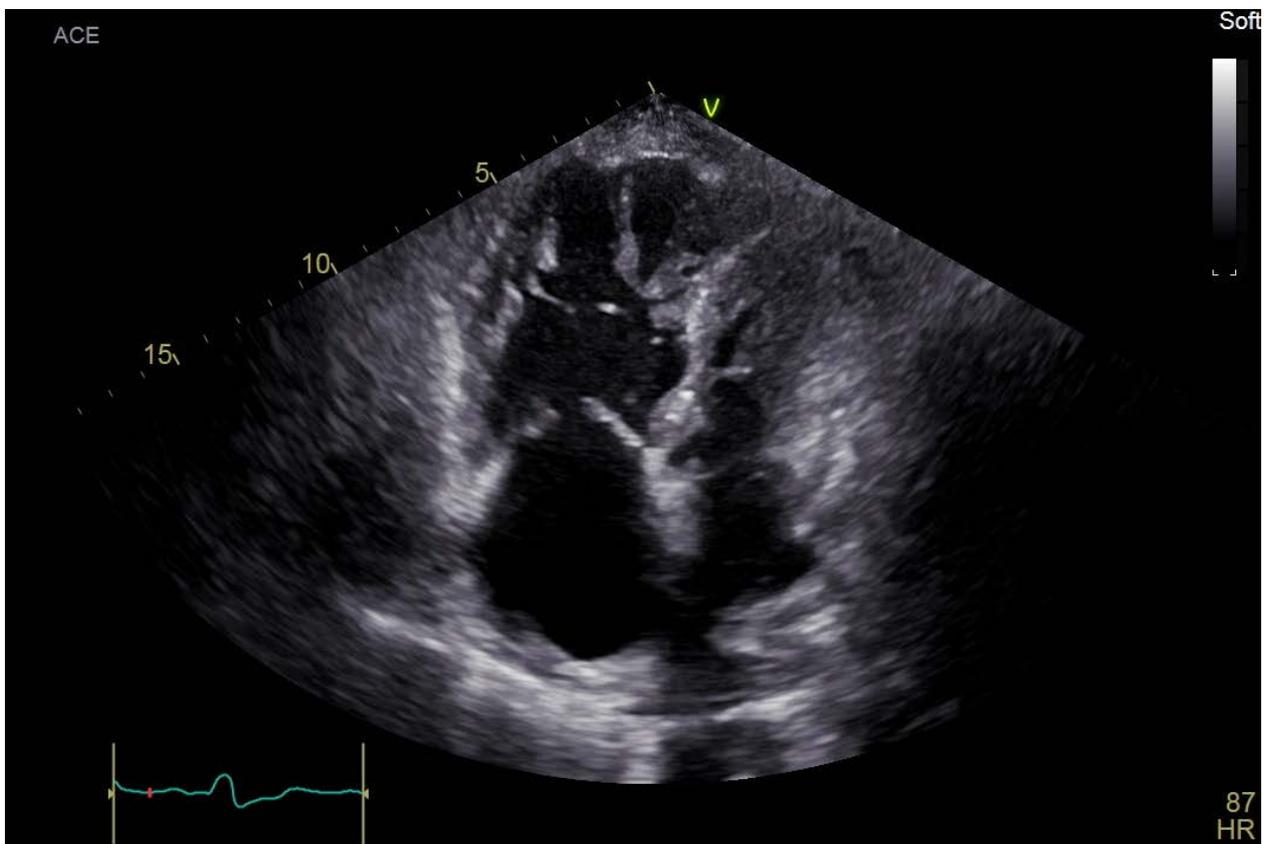


Figure 4. 4 chambers view showing right atrial dilatation and right ventricular dilatation. Flat interventricular septum

3. Discussion

Pulmonary hypertension (PH) is characterized by a mean pulmonary arterial pressure ≥ 25 mmHg, and may be related to elevations in left atrial pressure, pulmonary vascular resistance, cardiac output, or a combination of the above. When the mechanism of PH is caused by an elevation in vascular resistance, the term pulmonary arterial hypertension (PAH) is used. PAH is defined by a mean pulmonary artery pressure (mPAP) of greater than 25 mmHg at rest, in the setting of a normal pulmonary arterial wedge pressure of 15 mmHg or less, and pulmonary vascular resistance (PVR) measured at greater than 3 Wood units. Vascular smooth muscle (SMCs) and endothelial cells (ECs) participate in the regulation of blood flow in the pulmonary vasculature. Patients with PAH have normal lung parenchyma, yet present with pulmonary vascular remodeling and proliferation involving all three components of the vessel wall. Intimal and medial thickening of the wall as well as intraluminal findings of cellular proliferation are common, and often accompanied by the presence of thrombotic material and pulmonary vasoconstriction.

Nitric oxide is a powerful vasodilator produced from the metabolism of L-arginine by the enzyme nitric oxide synthase (NOS). In the pulmonary vasculature, NOS (eNOS) is the predominant isoform of NO, and promotes the conversion of L-arginine to L-citrulline, whereby causing increased NO levels in the endothelial cells of pulmonary vasculature. Nitric oxide acts by increasing cyclic guanosine monophosphate (cGMP) within the pulmonary artery SMCs, causing relaxation by activation of cGMP-dependent protein kinase (PKG). Lung specimens from subjects with PAH show reduced or absent eNOS expression and higher levels of asymmetric dimethyl L-arginine (ADMA), an eNOS inhibitor [8]. The presence of low endothelial NO level has been associated with the development of PAH. Conversely, vitamin C has been shown to increase NO production within the ECs by means of eNOS inhibitor (ADMA) degradation. Moreover, ascorbic acid stabilizes and increases eNOS cofactor (i.e. Tetrahydrobiopterin), while concurrently inhibiting the arginase pathway that competes for arginine. Thus, vitamin C deficiency decreases NO level with subsequent pulmonary vasoconstriction and proliferative vasculopathy. Another important mechanism involved in the pathogenesis of vitamin C related PAH is the non-hypoxic activation of hypoxia-inducible transcription factors (HIF). This leads to the unregulated function of HIF, followed by an exaggerated pulmonary vasoconstrictive response, as ascorbic acid is an essential cofactor for prolyl-hydroxylase enzyme and regulation of HIF activity [9].

PH commonly presents with non-specific symptoms, including dyspnea, particularly on exertion, fatigue, chest pain, edema, pre-syncope or even syncope, and palpitations, thus necessitating the clinician to maintain a high index of suspicion in order to minimize diagnostic delay. This is particularly important when the history and results of ancillary testing do not suggest an alternative reasonable explanation for cardiopulmonary symptoms. Physical examination often shows jugular venous distension (JVD), congested hepatomegaly, ascites and lower limb edema, as well as prominent pulmonary components of

the second heart sound (P2), and tricuspid valve insufficiency. RV heave and right-sided S4 are often indicative of RV hypertrophy. The presence of right sided S3 denotes RV systolic dysfunction and is correlated by reduced cardiac output.

Serologic tests can provide useful information in establishing potential etiologies of PH as well as help guide therapy. These tests play a central role in confirming chronic viral hepatitis or HIV infection. Moreover, the presence of certain autoantibodies may suggest the existence of an underlying connective tissue disease when considered in the context of appropriate clinical features. In cases of suspected scleroderma, anticentromere antibodies are usually associated with limited scleroderma, and anti-Scl-70 antibodies with diffuse disease. Anti ribonucleoprotein antibodies (anti RNP) are seen in patients with mixed connective tissue disease. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti CCP) antibodies are tested for in cases of suspected rheumatoid arthritis. Antinuclear antibodies (ANA), anti-double stranded DNA antibodies, anti-Ro and anti-La antibodies are tested for in patients with suspected systemic lupus erythematosus (SLE). BNP and NT-proBNP are proteins released from myocardial tissue in the setting of increased pressure or volume overload. Serum levels of BNP may be elevated in patients with PAH and RV dysfunction; however, lower levels of these peptides have been associated with better outcomes. Other laboratory tests frequently obtained are complete blood count and general chemistries including indices of renal and hepatic function.

Initial radiologic evaluation for patients with PAH must include a chest x-ray. Typical findings of PH include enlarged main pulmonary arteries and right-sided cardiac chamber enlargement. Rapid tapering of the pulmonary arteries is observed in patient with PAH, in contrast to increased vascular markings and Kerley B lines, which would be present in cases of pulmonary venous hypertension and PVOD. Chest CT findings, which may also be observed in patients with pulmonary hypertension, include an enlarged pulmonary artery (>29 mm in diameter or pulmonary artery/aorta diameter ratio >1) and enlarged right cardiac chambers with or without septal shift. Pericardial effusion and reflux of contrast into the IVC and hepatic veins may be evident in the setting of elevated right atrial pressure. The use of MRI in the management of patients with PH is evolving and phase contrast MRI is useful in calculating pulmonary vascular index and acceleration time. However, its use is somewhat limited in the setting of PH [10].

Findings on an ECG of a patient with PH may include right axis deviation, right ventricular (RV) hypertrophy, RV strain, and right atrial enlargement. The transthoracic echocardiogram (TTE) remains the most common screening tool used to assess patients suspected of having PH. It is used to estimate pulmonary arterial systolic pressure according to the modified Bernoulli principle [11]. Echocardiogram is helpful when evaluating right ventricular size, function, and septal position. The presence of a mid or late-systolic notch within the right ventricular outflow tract (RVOT) and Doppler flow velocity strongly predict the presence of a PVR >3 Wood units, suggesting PAH [12]. A reduced tricuspid annular plane systolic excursion (TAPSE) is an easily obtainable

reflection of compromised RV longitudinal shortening and cardiac output, and has prognostic value in PAH [13]. Moreover, serial assessment of the right heart is essential when monitoring response to therapy in PH related to pulmonary vascular disease.

Pulmonary Function Tests (PFTs) are important in order to exclude the presence of airway or parenchymal lung processes. On the other hand, assessment of diffusing lung capacity of carbon monoxide (DLCO) may be a more specific marker of pulmonary vascular disease, particularly when capacity is reduced in proportion to reductions in lung volumes, as seen in our case. Ventilation/perfusion scan (V/Q) scan is an integral component of the workup of patients with suspected PH, mainly to exclude the presence of chronic thromboembolic disease. Perfusion images will show one, or multiple, segmental mismatched defects in cases with chronic thromboembolic pulmonary hypertension (CTEPH).

Right heart catheterization (RHC) remains the gold standard for the diagnosis and characterization of PH. RHC is essential when establishing a diagnosis of PH and helps distinguish between pre- and postcapillary causes; a transpulmonary gradient (TPG) value of 12 mmHg suggests intrinsic pulmonary vascular disease. However, research suggests that a diastolic pressure gradient (DPG) between PAP and pulmonary arterial wedge pressure (PCWP) is a more accurate indicator for PAH [14]. Criteria for a confirmed diagnosis of PAH, by way of RHC, includes:

- Mean pulmonary artery pressure (mPAP) of greater than 25mmHg at rest, in the setting of a normal pulmonary arterial wedge pressure (PCWP) of 15 mmHg or less.
- Pulmonary vascular resistance (PVR) of greater than 3 Wood units [15].

RHC is also used to estimate the CO using either Fick or thermodilution techniques and should be corrected for the patient's body surface area and expressed as cardiac index (CI).

Endothelin level, decreased nitric oxide, and prostacyclin levels are the main modifiable factors that activate or perpetuate the disease. Thus, treatment of PAH is based mainly on medications that augment prostanoid-mediated pathways, block endothelin receptors, or enhance NO signaling pathways.

Soichiro et al. [16], reported a female patient with history of progressive dyspnea, and a clinical presentation suggesting scurvy (ecchymosis, gingivitis, and dental caries). In this case the patient had a normal V/Q scan, PFTS showed significantly low DLCO, severe pulmonary HT, and severe TR on ECHO. PAH was confirmed through RHC with reported mean PAP 48 in the setting of normal PCWP and low CI. Vasoreactivity test for adenosine infusion was positive after the patient's mean PAP dropped to 30 mmHg. A detailed history revealed that the patient was sensitive to many foods, raising suspicion of scurvy related PAH. Subsequent vitamin C level was undetectable, confirming deficiency. The patient was started on vitamin C and Nifedipine, and the patient reported complete recovery at the 3-month follow-up, with a normal RVSP on ECHO.

Kupari et al. [17], described a 40 years old female who was admitted with dyspnea, palpable purpura, and

ecchymosis. The patient had no pulmonary embolism in CT angiography, but did have signs of dilated pulmonary artery with a negative V/Q scan. The patient was diagnosed with pulmonary HTN (RVSP 52mmHg). PAH was confirmed through RHC with a mean PAP of 48mmHg, and PVR of 13.6 Wood units in the setting of normal PCWP. In this case, Epoprostenol infusion failed to significantly reduce the mean PAP. Further history showed that the patient's diet was lacking fruits and vegetables and vitamin C level was undetectable. on the patient was started on vitamin C intravenous supplementation (IV) (1 gram/day), as well as Sildenafil 20 mg TID. Oxygen pulse oximetry returned to normal within 48 hours with significant clinical improvement. One week later the patient's ECHO was reported as normal. Sildenafil was stopped 3 weeks later. Follow up visit at 8 weeks showed a full recovery with normal ECHO and RHC.

Furthermore, Ghulam et al. [18], reported a 66-year-old male patient with celiac disease presenting with progressive dyspnea and ecchymosis. This patient was diagnosed with pulmonary HTN in the setting of normal CT angiography and VQ scan. Initially, he improved on diuretics and anticoagulation with a drop of RVSP from 97 to 30 mmHg, but was admitted a few months later with severe dyspnea and ecchymosis. Repeat ECHO showed RVSP 80 mmHg, with no clinical improvement despite treatment with Bosentan. During reassessment, the patient reported that his diet was lacking fruits and vegetables for the past 8 months. Vitamin C level was undetectable, and he was started on ascorbate supplement with subsequent dramatic improvement leading to a full recovery within one week, confirmed by a normal ECHO and RVSP of 31mmHg.

Abbas et al. [5], described a case of a 50-year-old female presenting with dyspnea, ecchymosis, heavy menses, and jaundice. After detailed evaluation she was diagnosed with pulmonary HT. Her diet was restricted to eggs, cereal, and milk. Vitamin C level was found to be 0.1 mg/dl (normal reference ranges 0.4-1.7 mg/dl). Thus, the patient was started on vitamin C supplementation with rapid clinical recovery, and her ECHO was reported as normal at her subsequent 4-week follow up visit.

Singh et al. [19], described a 48-year-old female with dyspnea, pericarditis, ecchymosis, and oral ulceration, who had a normal ECHO 6 months prior to her admission. After excluding pulmonary embolism by CT angiography, she underwent an ECHO that showed pulmonary HTN. PAH was diagnosed per RHC with a reported mean PAP 41mmHg, PVR of 13.12 Wood Units, and normal PCWP. Cardiac output (CO) was 2.7 L/M. The patient had a positive vasoreactivity test in response to inhaled NO, with a drop in mean PAP down to 34mmHg, and an increase in CO to 5.1 L/M. The patient's condition deteriorated and progressed to severe cardiogenic shock after she was started on IV treprostinil. Additional history revealed that lettuce was the main component of her diet for the past year, leading to a differential diagnosis of scurvy, that was confirmed by the patient's undetectable vitamin C level. Ascorbate acid IV supplementation was started with rapid clinical improvement after 36 hours. A repeat ECHO that was done at a follow up visit 1 month later was normal, and PAP decreased to 28mmHg.

Table 1. Reported Cases with PAH Related to Vitamin C Deficiency.

Report	A/G	presentation	mPAP	PVR	PAWP	CO/ CI	V	RVSP	Treatment	outcome
Soichiro et al.[16]	73/F	dyspnea, scurvy	48		NL	_/1.2	+	35	Ascorbate Nifedipine	Full recovery
Kupari et al.[17]	40/F	dyspnea, scurvy	48	14	3	_/2.7		52	Ascorbate sildenafil	Full recovery
Ghulam et al.[18]	66/M	dyspnea, scurvy						97	Ascorbate Bosentan	Full recovery
Farrukh Abbas et al.[5]	50/F	dyspnea, scurvy							Ascorbate	Full recovery
Singh et al. [19]	48/F	dyspnea, scurvy	41	13	5	2.7/-	+	84	Ascorbate, inhaled Epoprostenol	Full recovery
Petersen et al.[20]	5/ M	autism, dypnea ecchymosis, gingival bleeding						High PAP	Ascorbate Thiamin	Full recovery
Terry et al.[21]	6/M	painful multifocal bone lesions, dyspnea						78	Inhaled NO, Milrinone, Ascorbate, sildenafil	Full recovery
Our case	73/ F	dyspnea , oral ulceration ecchymosis	50	6.7	9	6/2.76	-	129	Sildenafil	Death

A: age, G: gender, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary artery wedge pressure, NL: normal, CO: cardiac output, CI: cardiac index, V: Vasoreactivity test, + : positive, - : negative RVSP: right ventricular systolic pressure.

Furthermore, there have been two reported cases in the pediatric age group. Petersen et al. [20], reported a 5-year-old male child with a history of autism who was admitted as a result of fatigue, gingival bleeding, ecchymosis, and failure to thrive. The patient's ECHO showed severe right ventricular dysfunction and dilatation, and a high PAP. Vitamin C was significantly low in this child on account of his restricted diet of pasta, peanut butter, and bread. The patient received Vitamin C and thiamin with immediate clinical improvement and resolution of pulmonary HT. RT ventricular size and function improved, as evident by ECHO 1 week after Ascorbate supplementation. Finally, Terry et al. [21] described a 6-year-old male child with a 3-month history of painful multifocal bone lesions who developed cardiac arrest during bone marrow aspiration. The patient recovered after CPR, and then developed persistent tachycardia. ECHO showed pulmonary HT with a TR max gradient of 68mmHg. Given the bone lesion and PHT, vitamin C deficiency was suspected, and the patient's level were undetectable. Initially, he was given inhaled NO and Milrinone, and then switched to Ascorbate and sildenafil. The patient improved to a full recovery with a normal ECHO at 4 weeks. It was hypothesized that pulmonary HT was related to cardiac arrest.

Our patient presented with a three-month history of progressive dyspnea on exertion. Oxygen saturation, as measured by pulse oximetry, was 84% on room air. Oxygen saturation increased to 94% upon the administration of oxygen at 4 L/min. On physical exam, the patient displayed JVD, right ventricular heave, severe TR, loud S2, and S3 left of the xiphoid process. Furthermore, there was tender hepatomegaly 5 cm below the costal margin midclavicular line, ascites, and symmetrical bilateral lower limb edema reaching the height of the mid-tibial shaft.

The initial diagnostic workup included routine investigations, BNP, troponin, complete blood count and general chemistries including indices of renal and hepatic function. Further laboratory testing included serology for viral hepatitis and HIV, beside autoantibodies panel for connective tissue disease. Right axis deviation was evident on the ECG, as well as right ventricular hypertrophy, right bundle branch block, and right ventricular strain.

Furthermore, ST depression and T-wave inversion in V2-5 was apparent (Figure 1). The patient's ECHO showed left ventricular normal global systolic function, an ejection fraction (EF) of 75%, and normal diastolic function. However, severely dilated right ventricle with moderate reduced function was evident. There was evidence of severe TR with estimated TR jet velocity of 5.14 m/sec, a pressure gradient between the right ventricle and right atrium of 105.53 mmHg, and an estimated RVSP 112, representing the PASP (Figure 2, Figure 3, Figure 4). There was no observed mismatch in the V/Q scan. RHC in our reported case confirmed the diagnosis of PAH with a mPAP of 50 mmHg, normal PCWP 9 mmHg, PVR reported as 6.7 Wood units, cardiac index 2.76 L/min/m², and a negative vasoreactivity test.

In our reported case, we came to the conclusion of PAH related vitamin C deficiency based on the patient's history of an unbalanced diet, and exclusion of other possible causes which might explain her presenting symptoms. Furthermore, the patient's clinical presentation suggested scurvy on account of her clinical picture, i.e. oral ulceration, ecchymosis, and PAH. Initial treatment involved supportive therapy with inotropic medications and sildenafil. The treatment plan included systemic prostacyclin and IV vitamin C; however, shortly after her admission the patient deteriorated to severe cardiogenic shock that was unresponsive to maximal supportive management, resulting in death 5 days after admission. The patient did not receive supplemental vitamin C, which might have potentially prevented this fatal outcome. We report this case in order to raise awareness about a modern presentation of scurvy, and the role it plays in the development of life threatening PAH. We recommend clinicians consider the possibility of vitamin C deficiency in high risk patients with a clinical presentation suggesting ascorbic acid deficiency and a confirmed diagnosis of PAH.

4. Conclusion

PAH related to ascorbic acid deficiency can occur due to non-hypoxic activation of hypoxia inducible transcription factors (HIF) and low Nitric oxide (NO)

level in the pulmonary vasculature. This has been shown to lead to pulmonary vasculopathy and an exaggerated pulmonary vasoconstrictive response.

Clinicians must maintain a high index of suspicion in order to minimize diagnostic delay, and should consider this diagnosis in high risk patients presenting with a clinical picture that might suggest nutritional deficiencies.

PAH related to Vitamin C deficiency is a reversible disease with the definitive treatment of immediate supplementation of vitamin C, preventing a fatal outcome.

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