



Case Report

Autoimmune Hemolytic Anemia Causing Group 5 Pulmonary Hypertension: A Rare Case

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ABSTRACT

Background : Pulmonary hypertension (PH) related to autoimmune hemolytic anemia (AIHA) is still rarely discussed, and there is a paucity of literature regarding its precise pathophysiology and treatment.

Objective : We aimed to describe a case of PH associated with AIHA.

Case : A 34-year-old woman came to our emergency department with a chief complaint of dyspnea on exertion. She was previously diagnosed with AIHA with a positive direct Coomb's test. Group 5 pulmonary hypertension was established after findings from physical examination, chest X-ray, and echocardiography were consistent with pulmonary hypertension. Although it was rare, it was believed that the association between chronic hemolytic anemia and PH is occurred through several mechanisms involving nitric oxide inactivation, direct injury of the endothelium, oxidative damage, thromboembolic formation, and left ventricular dysfunction. The treatment of underlying hemolytic disorder and PH-specific therapies were done as the management of PH in hemolytic disorders. For PH-specific therapy, to date, no treatment has been comprehensively studied for these specific patient populations. Our patient was given bisoprolol, furosemide, amlodipine, spironolactone, candesartan, beraprost sodium, and sildenafil. On a two-month follow-up, her functional status was improved.

Conclusion : In summary, PH in AIHA could be detected with meticulous history taking, physical examination, chest X-ray and echocardiography, and treatment with vasodilating agents were shown to improve the PH.

1. Introduction

Resting mean pulmonary artery pressure (mPAP) sustained above 25 mmHg is defined as Pulmonary hypertension (PH). It can be caused by a primary elevation of pressure in the pulmonary artery or secondary to pressure elevation in the pulmonary venous and capillary systems.¹ The incidence was reported around 10-52 cases per million.² This disease is rare but can be progressive and fatal, especially if it is undetected and untreated. The one-year mortality rate after diagnosis ranges from 2,8-21,2%, varying among different etiologies of PH.³

PH has been described to associate with hemolytic anemia, including group 5 PH. The prevalence of PH in patient with hemolytic anemia was estimated to be as high as 10-40%, and several reports presented poor prognosis of PH in this subset of patients. One of the common forms of hemolytic anemia is autoimmune hemolytic anemia (AIHA). However, PH associated with AIHA is rarely discussed, and there is a paucity of literature in its precise pathophysiology and treatment. Here we described a case of PH associated with AIHA.

2. Case Presentation

A 34-year-old woman came to our hospital with chief complaint of dyspnea on exertion (WHO functional class III) and abdominal bloating. She was previously diagnosed AIHA with positive direct Coomb's test. Vital signs examination revealed normal result; the blood pressure was 130/80 mmHg, heart rate was 80 bpm, and respiratory rate was 18x/mins. On physical examination, we found a raised JVP, loud S2 with accentuation of pulmonary component, and holosystolic murmur on the tricuspid area. The peripheral saturation was 98% on room air. 12-lead ECG revealed sinus rhythm with incomplete RBBB and fragmented QRS in inferior leads.

Chest X-ray showed an inverted comma sign, pruning of peripheral pulmonary vessel, and prominent pulmonary outflow tract. Echocardiography showed dilated RA and RV, normal left ventricular function with LVEF 67.7% (Teich), normal LV diastolic function (E/A value 1.13), and normal right ventricular function with TAPSE 3.17 cm. We also found severe tricuspid regurgitation with TR Vmax 4.69 m/s

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and pressure gradient 87.9 mmHg (figure 1) and decreased PVACCT (99 msec), consistent with pulmonary hypertension. The LV was also D-shaped, indicating that right ventricular pressure exceeded the left ventricular pressure. No other cardiac structural abnormality was found on echocardiography. The diagnosis of group 5 PH was established (due to chronic hemolytic anemia). She was then given bisoprolol 2.5 mg od,

furosemide 40 mg od, amlodipine 5 mg od, spironolactone 25 mg od, candesartan 8 mg od, dorner (beraprost sodium) 10 mcg bid, and sildenafil 12.5 mg bid. On two-months follow up, her functional status was improved. She was able to perform ordinary physical activity without any symptoms (WHO functional class I-II).

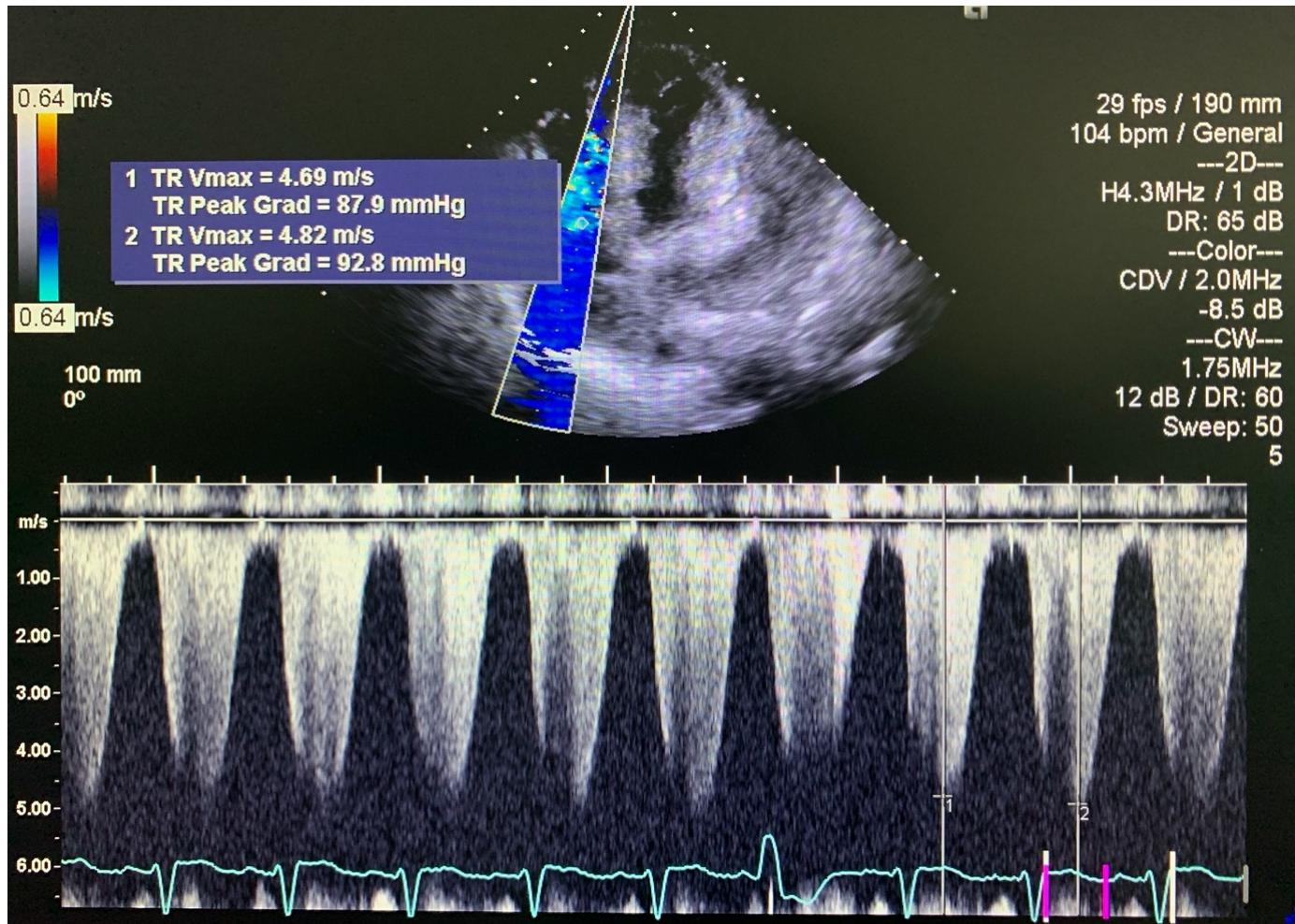


Figure 1. Echocardiography of the patient showing severe TR, with TR Vmax of 4.69 m/s and peak gradient of 87.9 mmHg.

3. Discussion

Pulmonary hypertension (PH) is an increase in mPAP of 25 mmHg or higher at rest, confirmed by right heart catheterization (RHC). In clinical practice, it is usually diagnosed by echocardiography, using the velocity of tricuspid regurgitation jet to estimate the pressure of the pulmonary artery although the gold standard of PH diagnosis is by RHC. WHO classifies PH into five groups. Group 1 PH (pulmonary arterial hypertension) most commonly has an idiopathic causes. It may be also caused by drug, human immunodeficiency virus, or congenital heart defect. Group 2 PH is caused by left-sided heart disease, such as mitral or aortic valve disease, or left ventricular dysfunction. Group 3 PH is caused by chronic respiratory disorders such as chronic obstructive pulmonary disorder (COPD) or interstitial pulmonary fibrosis. Group 4 PH is caused by chronic thromboembolism. Group 5 PH comprises PH with unclear or multifactorial causes, such as in hematologic disorder as found in our patient.^{4,5}

Evaluation of PH may be conducted through several modalities, including history taking, physical examination, echocardiography, and RHC for the gold standard. From history and physical examination,

PH can be asymptomatic, but it is often associated with exertional dyspnea or fatigue. Hemoptysis, angina, presyncope, and syncope suggest severe disease. Physical examination may reveal a parasternal lift, tricuspid regurgitation murmur, widely split S2 in the absence of RBBB/ASD, and pulmonary ejection sound.⁶ Loud pulmonary component of the second heart sound, as found in our patient, reflects an increase in pulmonary artery pressure.

In PH, echocardiography evaluation would demonstrate elevated tricuspid regurgitation peak velocity that suggests elevated right ventricular systolic pressure.⁷ From echocardiography of our patient, no right ventricular hypertrophy was found. Although, the size of the right atrium and the right ventricle were increased. Our patient had TAPSE of 3.17 cm, indicating normal RV function. However, the LV was found to be D-shaped, suggesting that the RV pressure exceeded LV pressure. Severe TR and decreased PVACCT were found in our patient, indicating elevated pulmonary pressure.

PH has been associated with hemolytic anemia, including group 5 PH. One of the common forms of hemolytic anemia is AIHA. In AIHA, it was known that antibodies against self-antigens on red blood

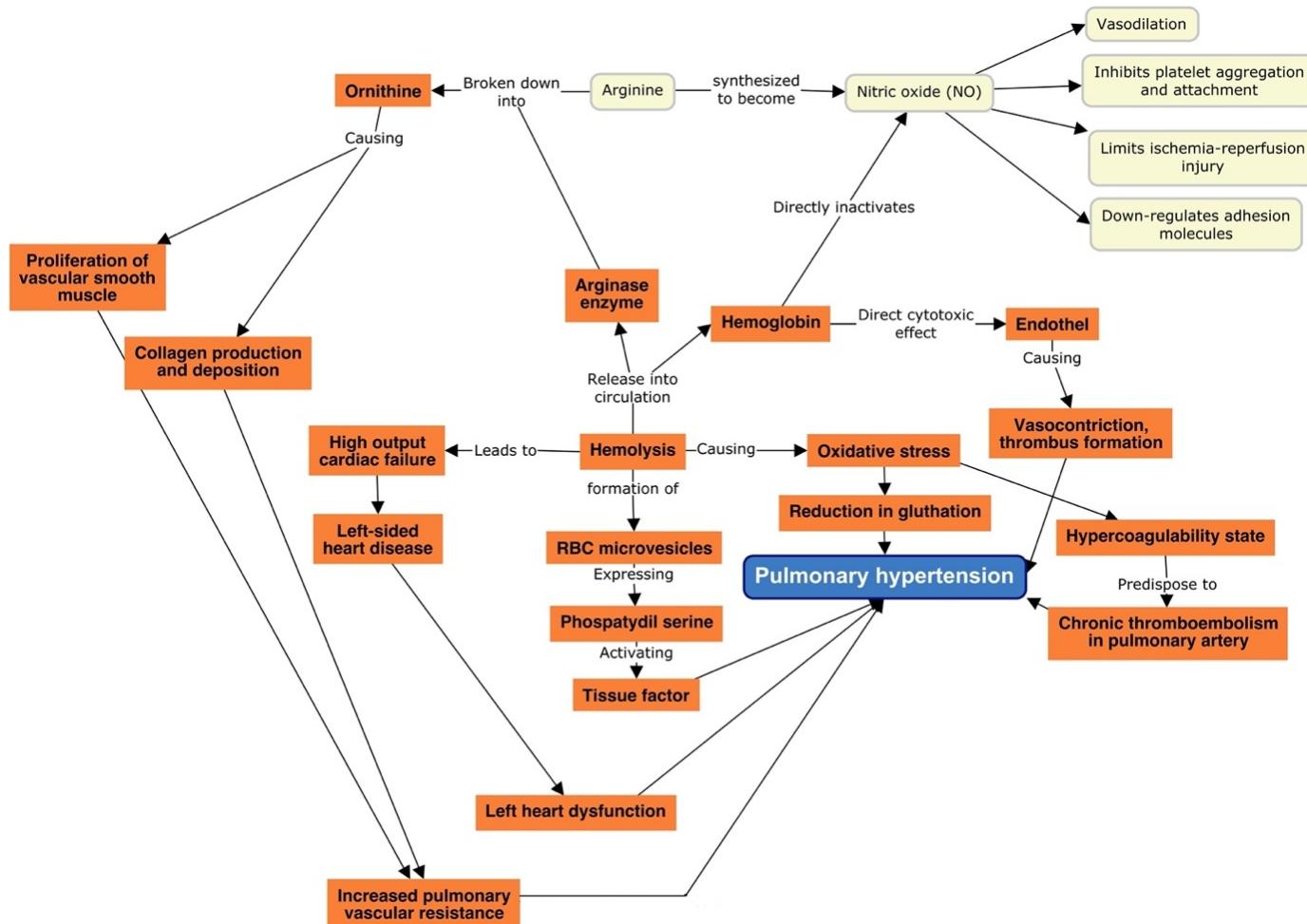


Figure 2. Mechanism of pulmonary hypertension in hemolytic anemia. The association between chronic hemolytic anemia and PH is evident, through several mechanisms involving nitric oxide inactivation, proliferation of vascular smooth muscle, collagen deposition, direct injury of the

cells (RBC) membrane causing a shortened RBC lifespan. RBC will be coated by antibodies; then, a macrophage will bind to them via their Fc receptor, digesting them with proteolytic enzyme, and causing the RBC to be spherical and more susceptible to osmotic lysis. This lysis may occur both in intravascular and extravascular. Furthermore, attachment of other antibodies such as IgG1, IgG3, IgM, and IgA can fix the complement, causing intravascular hemolysis.⁸

The pathways that lead hemolytic anemia to PH are multifactorial, involving a reduction in nitric oxide (NO), dysregulation of arginine metabolism, endothelial injury, hypercoagulability, thromboembolic formation, and left ventricular dysfunction (figure 2).

In hemolysis, the breakdown of erythrocyte will release hemoglobin and arginase enzyme into circulation. Cell-free hemoglobin can inactivate NO. NO is a substance that maintains vasodilation by activating cGMP-dependent protein kinases, inhibiting platelet aggregation and attachment, and reducing adhesion molecules such as vascular cell adhesion molecule and the potent vasoconstrictor endothelin-1. In addition, arginase enzyme, released from erythrocyte, can convert arginine to ornithine, while arginine is the substrate for NO synthesis, thereby decreasing the substrate for NO production. The conversion of arginine to ornithine also produces proline and polyamines, which can increase vascular smooth muscle proliferation and cause production and deposition of collagen. All these changes would result in pulmonary vascular endothelium remodeling and vasoconstriction.⁹ Hemoglobin can also impair endothelial function via direct cytotoxic and pro-oxidant effects.¹⁰

The hypercoagulable state associated with an inflammatory state in hemolytic anemia has also been shown to contribute to the development of PH through endothelial dysfunction and thromboembolic formation.⁹ Hemolysis may also cause activation of tissue factor by formation of RBC microvesicles expressing phosphatidylserine, which increase the risk of thrombosis.

Hemolysis is also associated with decreased systemic resistance (due to a decrease in viscosity), causing high output cardiac failure. This condition will cause activation of the neurohormonal system leading to cardiac remodeling in heart failure. This cardiac remodeling will cause left heart disease, causing increased end-diastolic pressure, congestion of pulmonary vein, and PH.¹¹ However, in our patient, the LV diastolic function was still normal, suggesting that cardiac remodeling might not have occurred.

The treatment of underlying hemolytic disorder and PH-specific therapies were done as part of pH management in hemolytic disorders. Corticosteroids are the first-line treatment for AIHA by reducing the autoimmune activity.¹⁰ For the PH-specific therapy (such as prostacyclin antagonist, soluble guanylate cyclase stimulators, and phosphodiesterase-5 inhibitors, and endothelin receptor antagonist,), no treatment was studied and approved by FDA for these specific populations.¹²

Our patient was treated with bisoprolol (to prevent right heart failure), furosemide (to relieve congestion), amlodipine (to manage the BP), spironolactone, candesartan (to manage BP and prevent myocardial remodeling), beraprost sodium (vasodilator), and

sildenafil (vasodilator).¹³ These treatments were shown to improve the functional status of the patient. As explained before, in a patient with AIHA, reduction in NO, the free hemoglobin, and other oxidative damage may cause endothelial dysfunction and vasoconstriction, therefore vasodilating agents may cause improvement as found in our patient.

4. Conclusion

PH associated AIHA develop via multifactorial and complex mechanisms, and the data regarding the pathophysiology and management are limited. In our case, we inferred that PH in AIHA could be detected with meticulous history taking, physical examination, chest X-ray and echocardiography, and treatment with vasodilating agents such as beraprost and sildenafil were shown to improve the PH.

5. Declarations

5.1. Ethics Approval and Consent to participate

Patient has provided informed consent prior to involve in the study.

5.2. Consent for publication

Not applicable.

5.3. Availability of data and materials

Data used in our study were presented in the main text.

5.4. Competing interests

Not applicable.

5.5. Funding source

Not applicable.

5.6. Authors contributions

Idea/concept: MDHQ. Design: MDHQ. Control/supervision: MHDQ. Data collection/processing: MDHQ, HA. Extraction/Analysis/interpretation: MDHQ, HA. Literature review: HA. Writing the article: MDHQ, HA. Critical review: MDHQ, HA. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

5.7. Acknowledgements

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