CASE REPORT

Adding insult to injury: autoimmune haemolytic anaemia complicated by pulmonary embolism

Kevin Andrew Woodson,¹ Yungah Lee,² Kavitha Gopalratnam,¹ Stephanie Halene³¹Department of Internal Medicine, Bridgeport Hospital—Yale New Haven Health, Bridgeport, Connecticut, USA²Department of Internal Medicine, Yale New Haven Hospital, New Haven, Connecticut, USA³Department of Hematology, Yale School of Medicine, New Haven, Connecticut, USA**Correspondence to**

Dr Kevin Andrew Woodson, kevinwoodson@gmail.com

Accepted 18 December 2015

SUMMARY

Autoimmune haemolytic anaemia (AIHA) is a disease characterised by the production of pathological antibodies that attach to the surface of a patient's own red blood cells, resulting in haemolysis. It can present in either an acute or a chronic manner. In addition to the obvious consequence of anaemia, there are other potentially deadly complications that can arise from AIHA, such as venous thromboembolism (VTE) and pulmonary hypertension. We report a case of a 52-year-old woman who developed a pulmonary embolism (PE) soon after being diagnosed with AIHA. Despite having a very small pulmonary venous clot burden, she developed profound haemodynamic compromise with severe right ventricular dysfunction, which quickly reversed with inhaled nitric oxide treatment. This case makes an interesting observation of cell-free haemoglobin-associated nitric oxide scavenging as a mechanism of pulmonary hypertension and highlights the possible benefit of nitric oxide in treatment.

BACKGROUND

Autoimmune haemolytic anaemia (AIHA) is a rare disease, and is typically subcategorised as either warm (IgG), cold (IgM) or mixed. The overall incidence of AIHA is 1–3 people per 100 000 per year. Warm AIHA is substantially more common than cold AIHA or mixed AIHA.¹ The disorder can lead to a number of potential complications. Among these is the possibility of developing a pulmonary embolism (PE). In this case, we describe the development of a PE in a patient recently diagnosed with AIHA.

CASE PRESENTATION

A 52-year-old African-American woman was admitted to a medical intensive care unit (MICU), with severe acute warm AIHA and hypoxaemia due to PE. She was in her usual state of health until 3 days prior to admission, when she developed severe generalised weakness, dysuria and dark coloured urine. Her primary care provider prescribed her empiric ciprofloxacin and pyridium for a presumed urinary tract infection. Two days prior to admission, she was found to have a new anaemia with haemoglobin (Hgb) 7.3 g/dL at a local emergency room. She was discharged with a plan for outpatient work up of the anaemia. However, she had progressive fatigue, weakness and palpitations. She was admitted to an outside hospital, with worsening anaemia of Hgb 5.2 g/dL, and subsequently transferred to our institution. Her medical history was notable for well-controlled asthma, non-toxic thyroid nodules

and chronic abdominal pain associated with pancreatic intraepithelial neoplasm for which she had undergone pylorus-sparing Whipple procedure 3 months prior to presentation. She had no known history of acute anaemia, autoimmune disease or respiratory failure.

The patient's initial vital signs included temperature 97.1°F, pulse rate 128 bpm, blood pressure 96/77 mm Hg, respiratory rate 36/min and oxygen saturation 96% on 2 L of supplemental oxygen. Within 12 h of admission, she developed progressive hypoxaemia with impending hypoxaemic respiratory failure requiring intubation. Physical examination was notable for visible respiratory distress, scleral icterus, conjunctival pallor, prominent jugular venous distension, tachycardia and loudly split S2 best heard at the left upper sternal border. She had no lower extremity oedema, no erythema and no palpable cords.

The patient had strong laboratory evidence for AIHA including a reticulocyte count of 18.3% with absolute reticulocyte count of 385 000/μL, total bilirubin 3.89 mg/dL, direct bilirubin 1.65 mg/dL, lactate dehydrogenase 1740 U/L and undetectable serum haptoglobin. An alloantibody to the Lutheran A (Lua) red blood cell (RBC) antigen was identified by the indirect antiglobulin test (antibody panel). In addition, the patient's direct antiglobulin test was strongly (3+) reactive for IgG and was negative for complement. A panagglutinin was identified in an eluate prepared from the patient's RBCs. Review of a peripheral blood smear revealed

Figure 1 CTOF of the chest and angiogram revealed small bilateral subsegmental pulmonary emboli.

CrossMark

To cite: Woodson KA, Lee Y, Gopalratnam K, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213575

normocytic, normochromic RBCs with frequent microspherocytes. Her laboratory findings were also significant for anion-gap metabolic acidosis with elevated lactate and cardiac enzymes.

CT angiogram revealed small pulmonary emboli in bilateral subsegmental arteries supplying the left and right upper lobes; no large central or saddle pulmonary emboli were observed and blood flow was largely intact to all peripheral lung fields (figure 1). Echocardiogram showed normal left ventricular function with severely increased right ventricle (RV) size, moderately decreased RV systolic function and septal flattening with RV systolic pressure of 65 mm Hg consistent with acute RV pressure overload (figure 2 and video 1). Work up for inherited thrombophilia including antiphospholipid syndrome was negative. Also of note, the patient was found to be negative for sickle cell disease, thalassaemia and paroxysmal nocturnal haemoglobinuria.

TREATMENT

Owing to the underlying warm autoantibody, it was not possible to identify crossmatch-compatible RBCs for transfusion. Owing to her symptomatic anaemia, the patient was transfused with 1 unit of weakly crossmatch-incompatible RBCs and was started on intravenous corticosteroids. She was intubated and received mechanical ventilation for the hypoxaemic respiratory failure thought to be caused by the PE. Therapeutic heparin infusion was initiated. On hospital day 7, she was transfused with a second unit of weakly crossmatch-incompatible RBCs. Thrombolytic therapy was entertained but not performed given the small, peripheral pulmonary clot burden as well as initial concern for pulmonary infarction based on the chest CT and history of bleeding from uterine fibroids. The patient was started on inhaled nitric oxide to decrease RV afterload evidence of heart strain and severe hypoxia.

OUTCOME AND FOLLOW-UP

After initiation of inhaled nitric oxide, there was rapid, significant reduction in vasopressor requirements and improvement in FiO_2 requirements. The patient made a remarkable recovery within 3 days of starting nitric oxide, and was weaned off nor-epinephrine and extubated. Follow-up echocardiogram 7 days after the initial echocardiogram revealed resolution of the RV dysfunction.

The patient was transferred from the MICU to a general medicine floor. In addition to steroids, she received 2 g/kg of intravenous immunoglobulin (IVIG) for on-going haemolytic

Figure 3 Short-axis view of the patient's echocardiogram after nitric oxide treatment demonstrating resolution of the septal wall flattening. Image was captured during diastole.

anaemia. She was discharged home on room air with slow corticosteroid taper and oral anticoagulation with rivaroxaban, and a plan for pulmonary and haematology follow-up. Follow-up echocardiogram performed 3 months after hospital discharge revealed normal RV size and function (figure 3 and video 2). Echocardiogram also showed residual pulmonary hypertension with RV systolic pressure of 50 mm Hg. Ventilation-perfusion (VQ) scan at this time revealed low probability of PE. The patient's haemolytic anaemia responded, allowing the tapering of her prednisone. Her anaemia essentially resolved within 2 months of presentation.

DISCUSSION

This case describes a 52-year-old woman with an acute severe idiopathic AIHA complicated by haemodynamically unstable PE. In this case, the severity of pulmonary hypertension and RV dysfunction was out of proportion to the small clot burden detected on the pulmonary angiogram. This finding is paradoxical, as the clot burden, predicted by CT angiographic pulmonary artery obstruction scores, is thought to correlate with RV dysfunction in acute PE. Pulmonary artery obstruction scores have not, however, been found to correlate with clinical outcome, which limits its usefulness in clinical practice.^{2 3}

Figure 2 Short-axis view of the patient's echocardiogram on presentation demonstrating septal wall flattening causing 'D'-shaped left ventricle. This finding is consistent with right ventricle pressure overload. Image was captured during diastole.

Video 1 Short-axis view of the patient's echocardiogram on presentation demonstrating septal wall flattening causing 'D'-shaped left ventricle. This finding is consistent with right ventricle pressure overload. Image was captured during diastole.

Video 2 Short-axis view of the patient's echocardiogram after nitric oxide treatment demonstrating resolution of the septal wall flattening. Image was captured during diastole.

The higher risk for thromboembolism in AIHA was recognised as early as the 1960s, when a review of 47 patients found the most common cause of death to be PE.⁴ Hypercoagulability is also well described in multiple intravascular haemolytic conditions such as sickle cell anaemia, thalassaemia and paroxysmal nocturnal haemoglobinuria, despite their varied mechanisms of haemolysis.^{5–7} Although poorly understood, multiple mechanisms have been proposed to explain the increased tendency for thrombosis in haemolytic conditions.

The patient's dramatic positive response to inhaled nitric oxide (NO) in the absence of notable pulmonary artery obstruction highlights the role that intravascular nitric oxide depletion plays as a mechanism of disease. Severe haemolysis results in the release of an overwhelming amount of cell-free haemoglobin, which saturates the physiological haemoglobin clearance mechanisms. The excess cell-free haemoglobin efficiently and irreversibly scavenges NO. Erythrocyte arginase also further reduces NO availability. NO plays a major role in vascular homeostasis, and its deficiency may result in vascular constriction, especially in the distal small vessels not easily visualised on CT angiogram. This can lead to significant pulmonary hypertension and right heart dysfunction. Given that pulmonary hypertension is a major complication in many haemolytic conditions, administration of inhaled NO in acute haemolytic conditions may be beneficial. However, NO-based therapies may be limited in their efficacy, as exemplified by recent early termination of a large multicentre trial where sickle cell patients with pulmonary hypertension receiving PDE5 inhibitor had more severe pain crises leading to an increase in hospitalisations.^{8–9} It has not been demonstrated whether there is benefit to the use of inhaled NO for patients with pulmonary artery hypertension in the setting of AIHA.

One of the major dilemmas in the management of this case was whether to administer thrombolytics. While thrombolytics have an established role in acute ST-elevation myocardial infarction or acute thromboembolic stroke, their role in the treatment of massive PE is controversial. Recent studies suggest that the use of thrombolytics for treatment of PE may improve haemodynamic outcomes, lower rates of all-cause mortality and reduce the risk of recurrent PE. This, however, is at the expense of an increased risk of major bleeding.^{10–12} However, the role of thrombolytics for PE in the setting of AIHA remains undefined. In this case, the patient was acutely heparinised and transitioned

to long-term rivaroxaban therapy at the time of discharge to prevent recurrent venous thromboembolism (VTE); thrombolytics were deferred due to the small VTE burden and concern for increased risk of major bleeding in a severely anaemic patient. While no clear guideline for primary or secondary prophylaxis for VTE in AIHA exists,¹³ more research into the possible prophylactic use of anticoagulants and/or antiplatelet agents in haemolytic anaemias is warranted.

Learning points

- ▶ In addition to the obvious consequence of anaemia, there are other potentially deadly complications that can arise from autoimmune haemolytic anaemia (AIHA), such as venous thromboembolism (VTE) and pulmonary hypertension.
- ▶ Cell-free haemoglobin as a result of severe haemolysis may play a role in the development of pulmonary artery hypertension.
- ▶ Inhaled NO is a potential therapeutic measure for patients with pulmonary artery hypertension in the setting of AIHA.
- ▶ There are no clear guidelines that delineate when a patient with AIHA might benefit from anticoagulation as prophylaxis against VTE.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Bottiger LE, Westerholm B. Acquired haemolytic anaemia. I. Incidence and aetiology. *Acta Med Scand* 1973;193:223–6.
- 2 Apfaltrer P, Henzler T, Meyer M, et al. Correlation of CT angiographic pulmonary artery obstruction scores with right ventricular dysfunction and clinical outcome in patients with acute pulmonary embolism. *Eur J Radiol* 2012;81:2867–71.
- 3 Rodrigues B, Correia H, Figueiredo A, et al. [Clot burden score in the evaluation of right ventricular dysfunction in acute pulmonary embolism: quantifying the cause and clarifying the consequences]. *Rev Port Cardiol* 2012;31:687–95.
- 4 Allgood JW, Chaplin H Jr. Idiopathic acquired autoimmune hemolytic anemia. A review of forty-seven cases treated from 1955 through 1965. *Am J Med* 1967;43:254–73.
- 5 Ataga KI. Hypercoagulability and thrombotic complications in hemolytic anemias. *Haematologica* 2009;94:1481–4.
- 6 Cappellini MD. Coagulation in the pathophysiology of hemolytic anemias. *Hematol Am Soc Hematol Educ Program* 2007;74–8.
- 7 Rother RP, Bell L, Hillmen P, et al. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA* 2005;293:1653–62.
- 8 National Heart L, and Blood Institute. Sildenafil Therapy for Pulmonary Hypertension and Sickle Cell Disease. ClinicalTrials.gov, Last verified: June 2011.
- 9 Wahl S, Vichinsky E. Pulmonary hypertension in hemolytic anemias. *F1000 Med Rep* 2010;2:pii:10.
- 10 Meyer G, Vicaute E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370:1402–11.
- 11 Morton MJ, Omron R. Are thrombolytics indicated for pulmonary embolism? *Ann Emerg Med* 2013;61:455–7.
- 12 Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA* 2014;311:2414–21.
- 13 Pullarkat V, Ngo M, Iqbal S, et al. Detection of lupus anticoagulant identifies patients with autoimmune haemolytic anaemia at increased risk for venous thromboembolism. *Br J Haematol* 2002;118:1166–9.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow