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CASE REPORT Open Access

Erythrocytosis and iron status in Eisenmenger syndrome: an illustrative case study

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Abstract

Background: Patients with Eisenmenger syndrome are chronically hypoxaemic and should therefore mount a secondary erythrocytosis. This response can be attenuated by iron deficiency. Historically, patients with Eisenmenger-associated erythrocytosis often underwent venesection but recent data have challenged this practice.

Case presentation: An illustrative case of a 30-year-old female with Eisenmenger syndrome secondary to a ventricular septal defect is discussed. Her resting saturations on room air were 84%. She was receiving pulmonary arterial hypertension targeted therapy with sildenafil 25 mg three times a day and bosentan 125 mg twice daily. Her local haematologist was planning on therapeutic venesection as her haematocrit was elevated at 0.57. Her haemoglobin was 16.7 g/dl, ferritin levels were 15 μg/L and transferrin saturations were 10.5%. What are the indications for venesection? Should she receive iron supplementation instead? Data to help guide decision-making are reviewed and a clinical approach is suggested.

Conclusions: Iron status should be regularly checked in Eisenmenger syndrome patients and replaced appropriately. There is no role for routine venesection in patients with Eisenmenger syndrome; this should be reserved for the small proportion of patients with symptoms of hyperviscosity in the absence of dehydration.

Keywords: Erythrocytosis, Polycythaemia, Eisenmenger syndrome, Iron, Pulmonary hypertension

Background

Patients with Eisenmenger syndrome (ES) are chronically hypoxaemic and should therefore mount a secondary erythrocytosis. This response can be attenuated by iron deficiency. Historically, patients with Eisenmenger-associated erythrocytosis often underwent venesection, but recent data have challenged this practice. In this paper, a case of a patient with ES secondary to a ventricular septal defect (VSD) is presented. The clinical details described in this illustrative case are based on experience gained from multiple patients. Data to help guide decision-making are reviewed and a clinical approach is suggested.

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Case presentation

This is the case of a 30-year-old female who had moved to the UK from the Indian sub-continent at the age of 18. A VSD was identified during childhood but closure was not performed. She was subsequently diagnosed with ES and commenced pulmonary arterial hypertension targeted therapy in 2007 in the form of bosentan 125 mg twice daily (bd), with symptomatic and functional benefit. In 2012, sildenafil 25 mg three times daily (tds) was added due to symptomatic worsening, again with benefit. Over the last year she had complained of some worsening of breathlessness but denied any headaches or overt lethargy. She had regular periods, which were not particularly heavy, and had no other history of bleeding. Her only other medication was desogestrel of which she took 2 tablets daily in view of the potential interaction with bosentan.

On examination, her resting saturations (SaO_2) on room air were 84%. Her heart rate was 72 beats per minute and blood pressure 135/70 mmHg. She was clubbed. She had no peripheral oedema and her jugular venous pressure was not elevated. She had a systolic murmur at the left lower sternal edge and had a loud P2. Her chest was clear.

Electrocardiogram demonstrated sinus rhythm with right axis deviation and inferior and anterior T wave inversion. Chest X-Ray demonstrated cardiomegaly with enlarged central pulmonary arteries. Echocardiography demonstrated mild right atrial dilatation, a hypertrophied and mildly dilated right ventricle with preserved systolic function, normal-sized left atrium and ventricle with preserved left ventricular systolic function. A large VSD was noted with a predominant right-to-left shunt. Moderated tricuspid regurgitation was present with a maximum regurgitant velocity of 4.8 m/s giving an estimated systolic pulmonary arterial pressure of 92 mmHg plus right atrial pressure. She walked 375 m on the incremental shuttle walk test with SaO_2 falling to 70%.

She had previously been found to have an erythrocytosis and, in view of her worsening symptoms, her local haematologist was planning on performing therapeutic venesection. Haemoglobin concentration was 16.7 g/dL, with a haematocrit of 0.57 and a mean corpuscular volume (MCV) of 86 fL. Platelets were reduced at 115,000/mL and she had a normal white cell count. Ferritin levels were 15 microgram/L and transferrin saturations were also low at 10.5%. Serum folate and vitamin B12 levels were normal.

Her haematologist was advised to cancel the venesection and instead she was commenced on iron supplementation in the form of ferrous sulphate 200 mg tds. After 3 months her haemoglobin level had increased to 18.9 g/dL and haematocrit had increased to 0.6. Her ferritin level had also increased to 95 μg/L and transferrin saturations were now within normal limits at 21%. Her incremental shuttle walking distance had increased to 410 m and she reported improvement in her breathlessness on exertion.

Discussion

ES is characterised by elevated pulmonary vascular resistance resulting in chronic hypoxaemia due to right-to-left shunt through an intracardiac defect or persistent ductus arteriosus. Oxygen delivery (DO_2) can be described by the equation:

$$DO_2 = CO \text{ x } CaO_2$$

Where CO is cardiac output and CaO_2 is systemic arterial oxygen content. CaO_2 is described as:

$$CaO_2 = \text{oxygen saturation x haemoglobin (g/dL) x } 0.0134$$

In an effort to maintain systemic oxygen content and hence physiological homeostasis, ES patients should therefore develop a compensatory secondary erythrocytosis. This results in a raised haematocrit with an associated increase in whole blood viscosity (WBV) [1], which may promote hyperviscosity symptoms and increase right ventricular (RV) afterload [2, 3]. Furthermore, it has been feared that the erythrocytosis may promote thrombotic events, similar to patients with polycythaemia due to myeloproliferative disease [4]. Consequently, historical standard practice was to venesect patients with ES to reduce the risk of thrombotic events, especially stroke. Several studies have, however, challenged this practice. In an observational study of 162 patients with ES, Ammash et al observed that the risk of stroke was actually increased in patients with low MCV and previous venesection [5]. Van De Bruaene et al subsequently studied 68 ES patients and observed worse outcomes in patients with iron deficiency [6]. They also found that iron deficiency was more common in patients who had undergone venesection or were receiving anticoagulation therapy. Tay et al. studied 25 patients with cyanotic congenital heart disease and demonstrated improved exercise capacity and quality of life following iron replacement [7]. As such, current guidelines advise against routine venesection in patients with ES [8].

Certain patients with symptoms of hyperviscosity (such as headache, dizziness and lethargy) in the absence of dehydration may benefit from venesection; typically these patients will have a haematocrit > 0.65 [9]. Similar symptoms can, however, develop in patients with iron deficiency and venesection should not be performed in the context of iron depletion [1]. Selection of symptomatic patients for venesection is, therefore, not straightforward and should only be repeated if associated with definite symptomatic improvement. When performed, crystalloid should be infused to match the volume of blood removed: "isovolumic venesection" [10]. An additional rare indication for venesection is to augment platelet numbers pre-operatively.

Instead of venesection, the more common treatment decision in patients with ES is commencing iron supplementation. Diller et al studied 171 ES patients and observed a positive correlation between resting peripheral oxygen saturations and haemoglobin levels in iron replete patients, which was not present in iron deficient patients [11]. Broberg et al subsequently studied 65 ES patients and derived a predictive equation for haemoglobin concentration in the presence of normal iron studies and vitamin B12 and folic acid levels:

$$\text{Predicted haemoglobin (g/dL)} = 61 - (SaO_2/2)$$

Our patient with resting SaO_2 of 84%, therefore, had an expected haemoglobin concentration of 19 g/dL and was appropriately commenced on iron supplementation.

Although there is a concern of an over-exuberant response to iron supplementation, resulting in a "rebound erythrocytosis" and development of hyperviscosity symptoms, Tay et al observed no symptoms attributed to hyperviscosity in 23 patients following 3 months of oral iron supplementation with ferrous fumarate 200 mg tds [7]. Some patients tolerate even low-dose oral iron supplementation poorly and intravenous iron replacement may be required. Blanche et al recently reported on the safety of intravenous iron supplementation (in the form of iron carboxymaltose in their case – other forms of intravenous replacement are available) in cyanotic patients with pulmonary hypertension and/or congenital heart disease [12].

Conclusion

The normal response to chronic hypoxaemia in ES is a secondary erythrocytosis, but this response may be blunted in the presence of iron deficiency. Iron status should, therefore, be regularly checked in ES patients and replaced appropriately. There is no role for routine venesection in patients with ES; this should be reserved for the small proportion of patients with symptoms of hyperviscosity, in the absence of other causes.

Abbreviations

CaO_2: Oxygen concentration; CO: Cardiac output; DO_2: Oxygen delivery; ES: Eisenmenger syndrome; MCV: Mean corpuscular volume; RV: Right ventricle; SaO_2: Systemic oxygen saturation; VSD: Ventricular septal defect; WBV: Whole blood viscosity

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Consent for publication

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Competing interests

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