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Case Report

Congenital erythrocytosis – A condition behind recurrent thromboses: A case report and literature review

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Abstract. Congenital erythrocytosis (CE) is an extremely rare disease and an infrequent cause of heamoglobin and haematocrit elevation. Genetic testing of CE is not widely available. Patients in whom a cause of erythrocytosis is not identified are classified as idiopathic erythrocytosis (IE) patients. In some types of CE thrombotic events have been reported but there is little hard evidence to advise on management in asymptomatic patients. Similarly is true for patients with IE. We describe a young patient who suffered several thromboembolic complications before the diagnosis of CE type 4 was established.

Keywords: Congenital erythrocytosis, idiopathic erythrocytosis, thrombosis, DNA sequencing

1. Background

Congenital erythrocytosis (CE) is a rare disorder characterised by an increased number of red blood cells (RBC), elevated haemoglobin (Hb) and haematocrit (Hct). Etiologically, it can be caused by a molecular defect in the hematopoietic progenitor cells, usually in the erythropoietin (EPO) receptor (primary CE) or due to defects in oxygen sensing and transport (secondary CE). The letter group comprises mutations in Hb genes (*HBB, HBA2,HBA1*) and bisphosphoglycerate mutase (*BPGM)* gene resulting in high oxygen affinity and tissue hypoxia as well as mutations in the components of the oxygen sensing pathway due to mutations in genes *VHL, EGLN1, EPAS1* [1, 2]. Despite a high number of mutations associated with CE so far described, in the majority of patients with CE the causative molecular defect is not identified [3, 4]. Furthermore, due to rarity of the disease patients with CE can be easily unrecognized, remain classified as patients with "idiopathic" erythrocytosis (IE) with no recommended management [4]. As thrombotic events have been reported to occur in young individuals with some types of CE, low dose aspirin can be prescribed in prevention. Use of phlebotomy is controversial as, depending on the genetic defect, raised Hct could be physiological [5].

We describe a young patient with erythrocytosis of no familiar background who suffered several thromboembolic complications before a diagnosis of CE type 4 (ECYT 4) was established.

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2. Case report

A 21-year old female patient was referred to a haematologist in 2011 for persistent erythrocytosis, noticed since childhood (Hb 172–183 g/L). She reported no symptoms, no thromboembolic events and no family members with pathological blood counts. She was a smoker without regular therapy. Her blood results were as follows: Hb 197 g/L, Hct 0.588, RBC 6.35 10^{12}/L, MCV 9.6 fL, platelets and white blood cells as well as biochemistry were in the normal range. Pulse oximetry showed normal saturation, besides obesity (BMI 38 kg/m^2) clinical examination revealed no pathological signs. *JAK2 V617F* mutation was negative and no further diagnostics was performed. Half a year later she suffered pulmonary embolism which was attributed to a recent initiation of oral contraceptives and smoking. She started anticoagulation therapy but also had a phlebotomy of 500 mL due to high levels of Hb (183 g/L), Hct (0.532) and RBC (5.91 10^{12}/L). Bone marrow citology demonstrated reactive changes, *JAK2 exon 12* mutation was also negative. Hb electrophoresis demonstrated HbF of 0.7% which was considered clinically irrelevant. Oxygen pressure at 50 percent Hb saturation (p50) was not decreased. Anticoagulation was stopped after a year. In 2015 the patient suffered an extensive superficial thrombophlebitis of her left saphenous vein (at that time RBC 6.27 10^{12}/L, Hb 175 g/L, Hct 0.523), for which anticoagulation with fondaparinux was introduced for 6 weeks. In 2017 the patient became pregnant and a prophylactic low molecular weight heparin was commenced (dalteparin 7500 U/24h). At 8 weeks of pregnancy she suffered another pulmonary embolism and deep venous thrombosis of her left calf. Blood levels at that time were as follows: Hb 196 g/L, Hct 0.600, RBC 6.74 10^{12}/L. She had 3 phlebotomy sessions. Elevated serum EPO was determined (73.4 E/L; normal range 3.3–16.6). A CE was suspected but no genetic testing was available at that time. Anticoagulation was maintained the whole pregnancy and 6 weeks postpartum. The patient delivered a healthy boy at 38 weeks. In 2019 she was pregnant for the second time, this time a higher dose of dalteparin (10000 U/24 h) as well as phlebotomy was prescribed to avoid thromboembolic complications. The pregnancy terminated in the first trimester due to septic abortion. Due to another, this time highly elevated EPO value (400 E/L) ectopic secretion of EPO was suspected but CT of the chest and abdomen as well as ultrasound of the neck revealed no tumour. Instead, a thrombosis of v.cava inf. and right v.iliaca comm. was found. The patient was advised long-term anticoagulation. Echocardiography demonstrated moderate pulmonary hypertension. Finally, in 2019 the patient was included in a study using next generation sequencing (NGS) covering 24 erythrocytosis associated genes [6]. This revealed a mutation in the *EPAS1* gene (c.1609G > A, pGly537Arg), indicative for ECYT4. The variant was confirmed by Sanger sequencing. The management of this patient from then on includes maintenance of target Hct below 0.52, long-term anticoagulation, pulmonary hypertension monitoring and screening for neuroendocrine tumours. Testing of the patient's child and parents to find possible inheritance is in progress.

3. Discussion

Thromboembolic events are the major cause of morbidity and mortality in PV, but in IE the risk of thrombosis is low [5]. There are no studies evaluating the use of aspirin or venesection in IE. But also for CE, which is a very rare diagnosis of multiple causes there are no uniform guidelines for use of aspirin or venesection [5].

To our experience, patients with elevated Hct in whom myeloproliferative disease is excluded are rarely subject of further diagnostics. With J*AK2* mutation negative and EPO level elevated, thus excluding PV [2], our patient received no therapy to prevent thromboembolic events, as it is the case for IE. Genetic testing for CE was not available at that time. Normal p50 value in this patient only excluded

high-oxygen-affinity haemoglobinopathies, BPGM deficiency, methemoglobinemias and heavy smoking [7]. Similarly, haemoglobin electrophoresis has limited sensitivity for high-oxygen-affinity Hb variants, but cannot detect other forms of CE [8]. Because of elevated EPO ectopic secretion of EPO was suspected. Ectopic EPO secretion resulting in erythrocytosis can be a paraneoplastic manifestation of cerebellar hemangioblastomas, meningiomas, pheochromocytoma, uterine leiomyomas, parathyroid adenomas, hepatocellular carcinoma, and renal cell carcinoma, it has been reported also in association with renal cysts [8]; all these has been excluded in our patient by imaging techniques.

Genetic testing of erythrocytosis in our country became available through a research project in 2019 by introduction of NGS covering 24 erythrocytosis associated genes. At the same time an extended national diagnostic algorithm for erthrocytosis was developed [9], to encourage physicians to perform investigation beyond PV exclusion in erythrocytosis patients.

Our patient was finally diagnosed with a heterozygous mutation in *EPAS1* gene (*c.1609G>A*), which encodes the transcription factor HIF-2α, the primary transcription factor that induces EPO expression thus playing a critical role in the cell's ability to respond to hypoxia. Gain-of-function mutations in exon 12 of EPAS1 cause familiar erythrocytosis type 4 with autosomal-dominant inheritance [3]. So far over 55 patients with EPAS1 variants have been reported, majority of them were members of at least 12 families with history of erythrocytosis [10]. Serum EPO in these patients is usually elevated but can also be in the normal range [4, 11]. Clinical features described in ECYT4 are the following:

- Pulmonary hypertension due to possible up-regulation of HIF2α-regulated factors like endothelin-1 and less tolerance to hypoxia [12, 13]
- thrombembolic events even at young ages due to increased viscosity [3, 12]
- though usually asymptomatic patients can present with fuzziness or dizziness and awareness of increased redness of the face. Signs include a plethoric appearance, red suffused eyes and redness of the hands [3, 12]
- somatic mutations associated with paraganglioma (extra-adrenal pheochromocytoma) and erythrocytosis have been described. This can be explained by crucial role of hypoxia during tumorigenesis; but total and excessive activation of HIF-2α seems to be necessary for tumorigenesis [3, 12].

Due to rarity of the disease only sparse clinical information is available concerning management of patients with ECYT 4 or CE in general. Low-dose aspirin is of benefit in myeloproliferative neoplasms in the prevention of thromboembolic events [2] and, by extrapolation, may be of benefit in CE, provided there are no contraindications [5, 12]. Despite there is no evidence that reduction of the Hct is beneficial in reducing the incidence of thromboembolic events in patients with CE in general, as some increase in Hct may also be necessary for physiological functioning in these patients, phlebotomy is generally considered in patients with symptoms for which the raised Hct may be contributory or if a previous thrombotic episode has occurred, or in individuals who are asymptomatic but who have affected family members with a thrombotic episode. British recommendations for CE management propose a target Hct of 0,52 [5]. After recurrent thromboembolic complications our patient already ended on long-term anticoagulation. It should be mentioned though that this patient had other risk factors for thromboembolic complications besides viscosity, namely obesity, smoking and hormonal influences, which seemed to provoke thromboembolic events. Targeting all these factors could prevent further complications in this patient [14].

Additionally, in patients with ECYT4 screening for pulmonary hypertension and neuroendocrine tumours is recommended [5, 12]. Our patient already has moderate pulmonary hypertension that could be a consequence of previous pulmonary embolisms. Regular echocardiograms are planned in future and in case of worsening a pulmonologist will be consulted.

To conclude, CE is an extremely rare disorder which can easily get misdiagnosed among the more frequent and heterogenous types of erythrocytosis. A systematic diagnostic algorithm should be followed in patients with persistent erythrocytosis (Hct > 0,52 in men, Hct > 0,48 in women) [7] to identify the underlying aetiology of erythrocytosis before a diagnosis of IE is made. As some types of CE predispose patients to thrombosis, genetic testing of patients with IE is encouraged.

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Conflict of interest

The authors have no conflicts of interest to declare.

Informed consent

A written informed consent was obtained from the patient for publication of this case report.

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