CASE REPORT

Congenital Familial Erythrocytosis: A Case Report with Literature Review

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ABSTRACT

Familial erythrocytosis is a heterogeneous group of hereditary conditions with an increased total red blood cell volume. The disease occurs in a familial pattern and follows a relatively benign course. The absence of leukocytosis and thrombocytosis differentiates it from polycythemia vera. The best characterized primary erythrocytosis is the autosomal dominant primary familial and congenital polycythemia. In most families, erythrocytosis is due to abnormal hemoglobin with increased oxygen affinity. In other families, erythrocytosis is caused by an autonomous production of erythropoietin (EPO). EPO receptor gene mutations are also responsible for erythrocytosis when no secondary causes are apparent. Presented herein is a family with familial erythrocytosis possibly due to high autonomous production of EPO, which as per the literature is the first of its kind in the Indian context.

Key words: Abnormal haemoglobin, congenital polycythemia, erythrocytosis, erythropoietin, erythropoietin receptor, gene mutation

ملخص البحث:

يعرض الباحثون حالة لأسرة مصابة بكثرة كريات الدم الحمراء الوراثية والذي قد يكون ناتجًا من ارتفاع في الإنتاج الذاتي لمادة الارثروبويتين. تعتبر هذه الحالة الأولى من نوعها لهذا المرض في الهند. تمثل كثرة الكريات الحمراء مجموعة متغايرة المنشأ من الحالات الوراثية التي يكثر فيها حجم الكريات الحمراء. غياب زيادة عدد الكريات البيضاء وكثرة الصفيحات يفرق هذه الحالة من مرض بوليثايثميا فيرا. في أغلب العائلات تكون كثرة الكريات الحمراء بسبب الهيموقلوبين غير الطبيعي وازدياد الانجذاب للأوكسجين.

INTRODUCTION

Absolute erythrocytosis is a condition with increased red cell mass.[1] It may be due to a myeloproliferative disease (primary proliferative polycythemia) as polycythemia vera or secondary to hypoxia, renal lesions or one of the several conditions occasionally associated with increased erythropoiesis.[2] Familial erythrocytosis or benign familial polycythemia is characterized by an increase in the haemoglobin (Hb) concentration and red blood cell (RBC) count leading to an increase in the total circulating red cell mass and the absence of leukocytosis and thrombocytosis.[3] Common causes include abnormal haemoglobins, disturbances in 2,3 diphosphoglycerate (DPG) metabolism and increased erythropoietin (EPO). Some recessively and dominantly inherited cases and some sporadic cases have no known cause.[4] Familial erythrocytosis patients can be asymptomatic or associated with minor manifestations of headache, dizziness, lethargy and easy fatigability. In the treatment of these patients, it is essential to control the packed cell volume (PCV) to minimize the risk of vascular occlusive events. Hence, only venesection should be used and chemotherapy has no role in this disease.[5]

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CASE REPORT

We present herein a case of 25-year-old unmarried male patient, milkman by profession, non-smoker who was born of a consanguineous marriage. He presented with a 1-year history of epigastric discomfort, pain in the left

hypochondrium, easy fatigability, intermittent headache and dizziness. Examination revealed a conscious, cooperative, well-built man with a plethoric look, ruddy complexion, mild icterus, mild conjunctival injection, macroglossia with a deep median fissure, tongue tie, an accessory thumb on the left hand, a pulse rate of 52/minute regular, normal peripheral pulses and blood pressure of 110/70 mmHg. No digital infarcts, ulcers or gangrene was seen. Chest, cardiovascular system and central nervous system examinations including fundus examination were normal. Abdominal examination revealed a palpable firm liver 2 cm below the right costal margin and a palpable firm spleen 8 cm below the left costal margin. Investigations revealed a RBC count of more than $6.50 \times 10^6/\mu L$ on several occasions with normal Hb and normal leukocyte and platelet counts. Hematocrit (PCV) was more than 55% repeatedly. Peripheral blood film was hypochromic with no abnormal cells. Renal profile (kidney function tests), blood sugar, electrolytes, serum iron, serum uric acid and lipid profile were normal. Liver function tests showed a mild increase in serum bilirubin with normal enzymes. Hepatitis serology was negative. Leucocyte alkaline phosphatase and serum vitamin B-12 levels were normal. Urine exam and chest X-ray were normal. Electrocardiogram revealed sinus bradycardia. Echocardiography was normal. Abdominal ultrasound showed a normal liver and kidneys with a portal vein size of 15 mm and splenic vein of 10 mm with moderate splenomegaly. Upper gastrointestinal endoscopy showed grade 1 esophageal varices. Bone marrow (trephine biopsy from left posterior superior iliac spine) revealed hypercellular marrow with reversed Myeloid: Erythroid (M/E) ratio (1:2), active myelopoiesis, normoblastic erythropoiesis and normal maturation. Pulmonary function tests were normal. Arterial blood gas revealed an oxygen saturation of 99%. Hb electrophoresis did not reveal any abnormal Hb type. JAK-2 mutation was negative. Carcinoembryonic antigen was normal at 0.34 ng/ml (normal up to 3 ng/ml). Alpha-fetoprotein level was normal at 0.7 IU/ml (normal < 10 IU/ml). 2,3 DPG levels were normal. EPO levels checked three times were found to be elevated at 37.3, 39.7 and 63.7 mu/ml (normal 10-25 mu/ml). No erythropoietin receptor (EPOR) studies for mutations were possible. Chromosomal analysis revealed a normal male karyotype. Computed tomography scan of the abdomen (with contrast) did not reveal any evidence of malignancy in the abdomen or pelvis. Magnetic resonance angiography of the brain was normal. Of the 25 members in two generations, four of the family members excluding the index case were found to be polycythemic. Family screening [Figure 1] revealed a Hb of 18.8 g%, RBC count of $7.21 \times 10^6/\mu L$, PCV of 56% and EPO level of 57.2 mu/ml in the sister of the index case, but she did not have any symptoms or clinical signs. Her three children (two boys, one girl) had Hb of 18.8, 22.1 and 19.2 g%; RBC count of 6.7, 7.62 and 7.93 $\times 10^6/\mu L$; PCV of 56.6, 64.8 and 61.1%; and EPO levels of 13.5, 25.2 and 13.5 mu/ml, respectively. One of the three siblings with the very high PCV was symptomatic with headache and had splenomegaly. The index case as well as the symptomatic child is being managed with periodic venesections, Aspirin and antihistaminics. Informed consent was obtained from the patient.

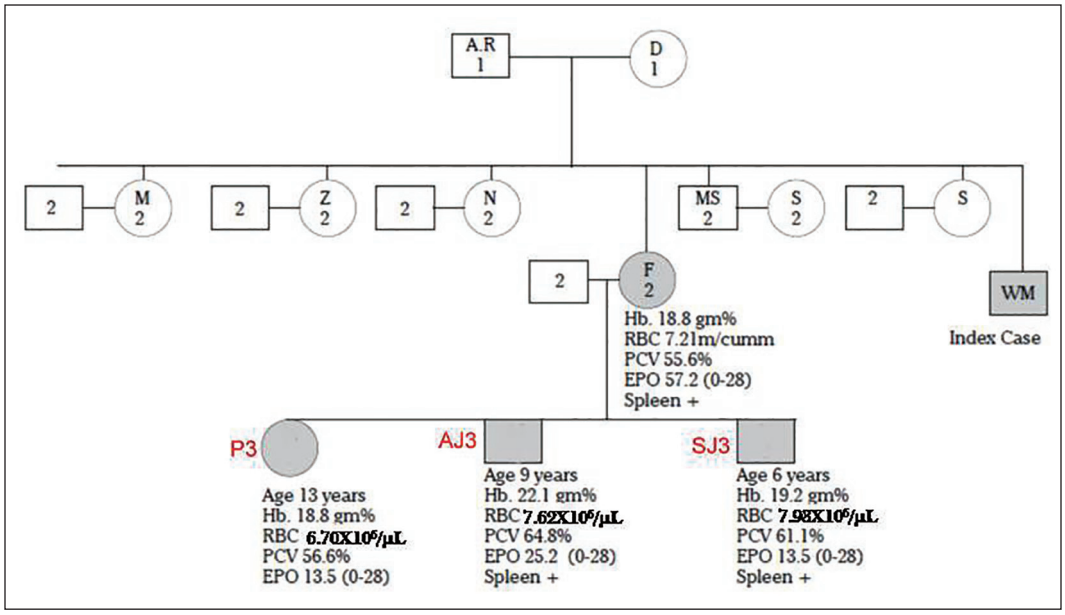

Figure 1: Family tree of the index case with siblings and affected children.

DISCUSSION

Absolute erythrocytosis can be due to hypoxia with alteration of the normal erythropoietic mechanism, inappropriate secretion of EPO, neonatal erythrocytosis, androgen therapy, Cushing's disease, truncation of EPOR and hypertransfusion, in addition to the familial erythrocytosis and idiopathic erythrocytosis.[6] Familial erythrocytosis was first recognized as an entity by Spodaro and Forkner[6] in 1933. Various designations have been used to describe the clinical syndromes of erythrocytosis or polycythemia in families, such as benign familial erythrocytosis or polycythemia vera of childhood, names that stressed the non-progressive course of the disease, its familial occurrence and the fact that secondary causes of erythrocytosis were not evident.[7] Subsequent studies of these syndromes revealed variant Hbs: Chesapeake, J (Capetown), Yakima, Kempsey, and Rainier, with an autosomal dominant inheritance.[8] Davey *et al.*[9] found erythrocytosis in a brother and sister, off-spring of a second cousin marriage and raised the question of recessive inheritance. A mutation in the regulation of 2,3 DPG can result in one form of dominant erythrocytosis.[10] Erythrocytosis due to autonomous EPO production was discussed by Distelhorst *et al.*,[11] Dainiak *et al,*[12] and Yonemitsu *et al.*[13]

In the family studied in the current report, extensive investigations revealed an abnormally high EPO in members of the family with elevated Hb and hematocrit with no other secondary cause for the same, suggestive of an erythrocytosis due to an autonomous EPO production.

A leading difficulty in defining the mechanism in familial erythrocytosis is lack of a suitably sensitive assay for EPO. It is likely that multiple mechanisms for familial erythrocytosis will eventually be recognized, each related to one of the steps in the regulation of erythropoiesis.

De La Chapelle *et al.*[14] found a mutation in the EPOR gene as the most probable cause of erythrocytosis in a family consisting of at least 33 affected living members descended from a couple five generations back. Emanuel *et al.*[15] reported studies of two extensively affected families with familial and congenital erythrocytosis with 15 affected individuals and another isolated case. In all three families, secondary causes were ruled out, EPO levels were normal or low and no evidence of rearrangement or amplification of the EPOR gene could be demonstrated. He concluded that the erythrocytosis in these families that did not involve the EPOR may have resulted from alterations in the post receptor response.

Kralovics and Prchal[1] studied 53 unrelated subjects with primary familial and congenital erythrocytosis to estimate the role of EPOR gene mutations. Only five EPOR mutations (10%), each unique for an individual family, were found in these patients. It was suggested that in approximately 90% of the families, genes other than the EPOR must be mutated, which may be a defect at the level of the EPOR signaling pathway. In a form of congenital erythrocytosis endemic in the Chuvash population of the Russian Federation, erythrocytosis patients have been found to have high serum EPO concentrations associated with early mortality because of vascular and hemorrhagic complications. Absence of linkage of the polycythemic phenotype to either EPO or the EPOR gene was also demonstrated. It was suggested that Chuvash polycythemia represents a secondary form of familial and congenital erythrocytosis of as yet unknown etiology. However, a recent unreported study of a single Chuvash boy has raised the possibility that the causative mechanism could be an abnormality in the oxygen sensing pathway.[16]

In the family under study, elevated hematocrit, elevated Hb concentration and elevated red cell mass were the prominent features with absence of thrombocytosis or leukocytosis. The pattern of inheritance in the family was autosomal dominant. The serum EPO levels were elevated and the karyotype was normal. All apparent secondary causes for the erythrocytosis were ruled out. EPOR studies were not possible. It was postulated that the erythrocytosis in this family was possibly because of an autonomous high EPO production and the same has been reported by Distelhorst *et al.*, Dainiak *et al.* and Yonemitsu *et al.* in their respective studies.[11-13]

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