Hereditary Xerocytosis, a misleading anemia.

Del Orbe Barreto, R[1]; Arrizabalaga, B[1,2]; De la Hoz R, AB[1]; García-Orad, A[1,3]; Gonzalez Vallejo, I[4] ;Bento, C[5]; Ródenas de la Rocha, S[6]; García-Ruiz, JC[1,2].

1. Instituto de Investigación Sanitaria BioCruces, Barakaldo, España
2. Servicio de Hematología, Hospital Universitario Cruces. Barakaldo, España
3. Departamento de genética, antropología física y fisiología animal. Facultad de Medicina y Odontología. Universidad del País Vasco (UPV/EHU), España
4. Servicio de Hematología, Hospital Universitario de Araba. Vitoria-Gasteiz, España
5. Serviço de Hematologia Clínica, Centro Hospitalar e Universitário de Coimbra, Portugal
6. Sección departamental de Química analítica. Facultad de Farmacia. Universidad Complutense de Madrid. Madrid, España

Hereditary Xerocytosis (HX), formally known as hereditary dehydrated stomatocytosis, is an autosomal dominant congenital hemolytic anemia associated with a leak of intracellular potassium usually accompanied by increased mean corpuscular hemoglobin (Hb) concentration [1]. Gain-of-function mutations in *PIEZO1*, encoding a mechanosensitive cation channel, and deleterious mutations of *KCNN4*, encoding the Gardos channel have been implicated in its pathogenicity [2].

Clinical manifestations may be slight and includes well compensated hemolysis and iron overload [3]. In fact, HX can be detected from different syndromes as familial hyperkalaemic hypertension [4], hepatosiderosis [5], or MDS [6].

Here we report a case of a young woman misdiagnosed with unclassifiable congenital dyseritropoietic anemia, in which we identified a missense mutation in *PIEZO1* gene causing HX. A 35-year-old woman of spanish origin initially presented at the age of 16 years with mild macrocytic anemia (Hb 125g/l and MCV 125fl) with reticulocytosis (89,000/µl) and unconjugated hyperbilirrubinemia (1.9 mg/dL). Abdominal echography demonstrated asymptomatic cholelitiasis. Further studies revealed hyperferrtinemia (ferritin 332ng/ml) with normal iron liver concentration measured by magnetic nuclear resonance. The blood film showed anysocytosis, macrocytosis, hyperreticulocytosis and isolated stippling. A bone marrow aspirate showed a hypercellular marrow with dyserythropoietic and megaloblastic traits. Cytogenetics revealed a normal karyotype (46, XX).

Targeted sequencing focused on congenital hemolytic anemia revealed a missense mutation in *PIEZO1* in heterozygous state (c.7505A>G; p.Lys2502Arg. dbSNP: rs34830861). The founded variation was analysed in silico by the pathogenicity prediction programs: Mutation Taster, PolyPhen-2 and SIFT to help assess the damaging effect, predicting to be disease causing. To confirm the pathogenicity of this mutation the intracellular concentration of potassium and sodium was measured (table 1). Additionally, osmotic gradient ektacytometry was performed showing an abnormal curve shifted to the left, indicating an increase in osmotic resistance. These findings supported the diagnosis of HX.

Our case demonstrates the genotype/phenotype relationship of the mutation p.Lys2502Arg in *PIEZO1* as causative of HX and reflects the importance of keeping in mind this emulator pathology.

Acknowledgments: The author was supported by a grant from BBK – BioCruces (BBK-BC/POST-MIR/2015/001).

Table 1. Cation levels and transmembrane flux in red blood cells (RBC).

	Patient	Normal control
RBC potassium	77.4 mmol/L	100.0 mmol/L
RBC sodium	12.5 mmol/L	10.8 mmol/L
Intracellular water	72%	77%
Passive net flux	-1.00 mmol/L RBC/hour *	0.90 mmol/L RBC/hour
Active net flux	-0.92 mmol/L RBC/hour *	0.08 mmol/L RBC/hour
Na^{++}/K^{+} pump activity	1.38	1.62

*negative values

Reference:

[1] Andolfo I, Alper SL, De Franceschi L, Auriemma C, Russo R, De Falco L, Vallefuoco F, Esposito MR, Vandorpe DH, Shmukler BE, Narayan R, Montanaro D, D'Armiento M, Vetro A, Limongelli I, Zuffardi O, Glader BE, Schrier SL, Brugnara C, Stewart GW, Delaunay J, Iolascon A. Multiple clinical forms of dehydrated hereditary stomatocytosis arise from mutations in PIEZO1. Blood. 2013 May 9;121(19):3925-35, S1-12.

[2] Layton DM, Bain BJ. Dehydrated hereditary stomatocytosis. Am J Hematol. 2016 Feb;91(2):266.

[3] Delaunay J. The hereditary stomatocytoses: genetic disorders of the red cell membrane permeability to monovalent cations. Semin Hematol. 2004 Apr;41(2):165-72.

[4] Beaurain G, Mathieu F, Grootenboer S, Fiquet B, Cynober T, Tchernia G, Delaunay J, Jeunemaitre X. Dehydrated hereditary stomatocytosis mimicking familial hyperkalaemic hypertension: clinical and genetic investigation. Eur J Haematol. 2007 Mar;78(3):253-9.

[5] Syfuss PY, Ciupea A, Brahimi S, Cynober T, Stewart GW, Grandchamp B, Beaumont C, Tchernia G, Delaunay J, Wagner JC. Mild dehydrated hereditary stomatocytosis revealed by marked hepatosiderosis. Clin Lab Haematol. 2006 Aug;28(4):270-4.

[6] Paessler M, Hartung H. Dehydrated hereditary stomatocytosis masquerading as MDS. Blood. 2015 Mar 12;125(11):1841.