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Case Report

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Fanconi anemia and paroxysmal nocturnal hemoglobinuria, case report

Abstract

Introduction: Fanconi Anemia is a congenital disease associated with defects in the mechanisms of repair of the genetic material that allow to maintain the stability of the human genoma. Paroxysmal Nocturnal Hemoglobinuria is a clonal and acquired disease caused by a somatic mutation in the gene PIG-A.

Objective: to present the characteristics of a child with diagnosis of Fanconi Anemia with a Paroxysmal Nocturnal Hemoglobinuria clone.

Development: An 8 year-old female infant who come to the consultation for mucosal-skin paleness and purpuric manifestations. After several studies the diagnosis of Fanconi Anemia with Paroxysmal Nocturnal Hemoglobinuria clone was made.

Conclusions: patient with a medullary failure congenital and acquired, that given their characteristics require of the bone marrow transplantation like only curative therapy.

Keywords: fanconi anemia, paroxysmal nocturnal hemoglobinuria

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Ariel Raúl Aragón Abrantes,[1] Danelis Hernández Aguiar,[2] Alberto Raúl Medina Martín[3]

[1]Department of Hematology, University of Medical Sciences of Sancti Spíritus, Cuba
[2]Department of Neonatology, University of Medical Sciences of Sancti Spíritus, Cuba
[3]Department of Pediatric, University of Medical Sciences of Sancti Spíritus, Cuba

Correspondence: Ariel Raúl Aragón Abrantes, Deaprtment of Hematology, University Pedaitric Hospital Jose Martí, Cuba, Email ariel.rau89@gmail.com

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Introduction

Fanconi Anemia (FA) is a rare hereditary disease, associated with defects in the repair mechanisms of genetic material that allow the stability of the human genome to be maintained.[1] Clinically it is characterized by a variety of congenital anomalies, progressive bone marrow failure, and a greater tendency to develop leukemia and other types of cancer.[2] Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal and acquired disease caused by a somatic mutation in the PIG-A (Phosphatidyl inositol glycan-A) gene, which is located on the X chromosome and encodes a protein involved in the synthesis of glycosylphosphatidylinositol (GPI), which serves as an anchor to many cell membrane proteins, producing greater sensitivity to complement.[3] It is manifested by intravascular hemolytic anemia, frequently presents neutropenia and thrombocytopenia, causing thrombosis, end-organ damage, and bone marrow failure. It can be associated with other hematological diseases, especially marrow failure syndromes such as aplastic anemia and myelodysplastic syndromes.[4,5] A clinical case of an 8-year-old female schoolchild diagnosed with FA with an emerging PNH clone is presented. The objective of the case presentation is to describe the characteristics of this patient in whom these two diseases are co-occurring.

Case presentation

An 8-year-old female patient who attended the hematology clinic presenting bruises on one leg, petechiae from exertion in the peri-orbital area, and mucosal skin pallor. No other abnormalities were found on physical examination. Complementary tests revealed severe anemia (Hb: 60 g/L and Hct: 0.19), peripheral lamina: macrocytosis, polychromatophilia and basophilic dotting, normal leukocytes with a predominance of lymphocytes, moderate thrombocytopenia (platelet count: $75x10^9$/L). Reticulocyte count: 29 x 10^{-3}/L. Chest X-Rays, abdominal and soft tissue ultrasound without alterations, and negative direct Coobms test. A medulogram was performed, showing a depressed megakaryopoietic system, an intact granulopoietic system without alterations, and a slightly hyperplastic erythropoietic system, with morphological alterations (cytoplasmic mamelons, binuclearity, karyorrhexis, normoblast niches). Due to this, it was decided to perform a bone marrow biopsy and immunophenotyping by flow cytometry.

The bone marrow biopsy was conclusive with marrow failure syndrome (bone marrow cast with more than 6 identifiable marrow spaces with less than 10% cellularity), while the immunophenotype reported aberrations in two cell lines (erythrocyte and granulocytic) with loss of antigen expression that may correspond to a myelodysplastic syndrome.

Due to these results, studies of chromosomal ruptures were carried out, which reported that the patient presented 4-5 times more spontaneous ruptures with respect to the control. No significant differences when comparing the percentage of cells with aberrations between treated cells (300 nm of Mitomycin) of the patient and the control. Although the rate of rupture per cell was higher in the patient at the concentration of 300NM MMC, most of the cells behaved similarly to the control. However, 3 typical Fanconi Anemia cells (6%) are observed with 10 or more ruptures per cell; results suggesting a somatic mosaicism in the patient's lymphocytes. In addition, studies of paroxysmal nocturnal hemoglobinuria were indicated where cell clones deficient in the expression of proteins related to the disease in the granulocyte and monocyte populations were observed, for which it was concluded as a positive study. The results were discussed collectively, concluding the case as Fanconi Anemia with a clone of emerging Paroxysmal Nocturnal Hemoglobinuria.

Discussion

Fanconi Anemia (FA) is a genotypically and phenotypically heterogeneous disorder first described by the Swiss pediatrician Guido Fanconi in 1927, characterized by a variety of congenital anomalies (short stature, microphthalmia, skin hyperpigmentation, cardiac, renal, and genitourinary malformations, among others), progressive bone marrow failure, and a greater tendency to develop leukemia and other types of cancer.[2,6] The cells of this patients have a high susceptibility to clastogenic agents, which constitutes the clinical basis of diagnostic tests for the disease.[3] Its prevalence is estimated at 10 cases per million individuals with a mean age of diagnosis of

7 years and it is considered the most common hereditary cause of bone marrow failure syndromes. And up to a third of patients will not clinically have any physical abnormalities.[1,3] No clinical abnormalities were found in this patient, who manifested as progressive spinal cord failure, being detected at 8 years of age. They frequently develop malignant diseases, the most frequent being acute myeloid leukemia and myelodysplastic syndrome, as well as squamous cell carcinoma of the head and neck and of the genital region.[1] In this patient, a myelodysplastic syndrome was detected. Twenty-one genes have been found to be involved in the molecular pathogenesis of this disease, and it is suggested that it presents autosomal recessive inheritance in all subtypes except FANCB (FA complementation group B), linked to the X chromosome, and FANCR (AF complementation group R), whose mutation causes an autosomal dominant form of the disease.[7,8]

Cells derived from patients with FA must unequivocally display hypersensitivity to chromosome breaks induced by DNA crosslinking agents, such as mitomycin C (MMC), diepoxybutane (DEB), or cisplatin, which is a distinctive diagnostic feature in these patients.[6] Therefore, the most widely used diagnostic test is hypersensitivity to the clastogenic effect (chromosomal break and radial forms) of diepoxybutane (DEB) or mitomycin C (MMC). The diagnosis is made when an increase between 3 and 10 times in the number of chromosomal breaks with respect to normal controls is demonstrated.[3] Chromosomal break studies were performed on the patient where 3 typical FA cells (6%) were observed with 10 or more breaks per cell; Therefore, the diagnosis of the disease is reached. The presence of a clone of paroxysmal nocturnal hemoglobinuria (PNH) was also detected in the girl, due to the presence of cell clones deficient in the expression of proteins related to the disease in the granulocyte and monocyte populations. PNH is an acquired clonal disease caused by a somatic mutation in the PIG-A gene (phosphatidylinositolglycan-class A) located on the short arm of the X chromosome (Xp22.1). The mutation occurs at the level of the hematopoietic precursor cell, and the affected gene codes for a protein involved in the synthesis of glycosylphosphatidylinositol (GPI). The result of this mutation is a partial or total deficiency in the expression of proteins normally anchored to the surface of the cell membrane.[9]

It has four clinical forms

In patients with intravascular haemolysis:

- Classic PNH: no history or current evidence of another myelopathy causing marrow failure.
- PNH in the context of another spinal cord disease: with a history or current evidence of spinal cord failure.

In patients without intravascular haemolysis:

- PNH in the context of another spinal cord disease: patients with spinal cord failure and a PNH clone >10%.
- Subclinical PNH: Patients with aplasia, myelodysplasia, or myelofibrosis, in whom a small population of GPI-negative hemopoietic cells is detected by flow cytometry.[3,10] According to the authors, in the investigation carried out we did not find the presence of intravascular hemolysis, only a slight reticulocytosis in the non-hemolytic range, so it could be PNH in the context of another medullary disease. The clinical expression depends on the type of membrane protein. It is characterized by the triad: intravascular hemolysis, thrombosis and cytopenias and bone marrow failure that can range from the subclinical form to severe aplastic anemia.[4] The technique of choice for the diagnosis of PNH is multiparametric flow cytometry, where it is necessary to demonstrate the expression deficit of 2 or more GPI-associated proteins in 2 or more different hematopoietic cell lines.[3,5] In the flow cytometry study performed on the patient's peripheral blood, cell clones deficient in protein expression were observed in the granulocyte and monocyte populations, which is why it was concluded as a positive study. In both cases, (FA and in PNH), one of the therapeutic options is hematopoietic progenitor cell transplantation (HSCT). In FA, HSCT is considered the only curative treatment for spinal cord failure.[3,5]

Conclusion

This patient presents FA, which is the most frequent cause of congenital bone marrow failure, as well as a PNH clone, which is one of the causes of acquired bone marrow failure, and MDS that can present as a complication or associated with both processes, for which reason HSCT is required as the only curative treatment option in this case.

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Conflicts of interest

The author declares that there is no conflict of interest.

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