ejpmr, 2021,8(4), 220-222

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Case Report

ISSN 2394-3211

EJPMR

ACUTE TRANSFORMATION FROM FANCONI ANEMIA (FA) TO ACUTE MYELOID LEUKEMIA (AML) IN CHILD: CASE REPORT

S. Hasnane[1*], A. Jarmoumi[1], S. Laajouri[2], H. Bencharef[1], A. Quessar[2] and B. Oukkache[1,2]

[1]Hematology Laboratory, Ibn Roch Hospital University-Casablanca.
[2]Department of Pediatric Hematology and Oncology, Hospital 20 August Ibn Roch Hospital University-Casablanca.

***Corresponding Author: S. Hasnane**
Hematology Laboratory, Ibn Roch Hospital University-Casablanca.

Article Received on 10/02/2021 **Article Revised on 01/03/2021** **Article Accepted on 21/03/2021**

ABSTRACT

Fanconi Anemia (FA) is a rare autosomal recessive disease that is part of the chromosomal instability syndromes. In addition to their risk of hematologic malignancies, people with FA have a too high risk of developing a solid tumor. In this article, we report the case of a young patient with fanconi anemia who developed a malignant transformation into acute myeloid leukemia after one year from his diagnosis of fanconi anemia and during his allograft programming.

KEYWORDS: Fanconi anemia, child, AML, transformation.

INTRODUCTION

Fanconi Anemia (FA) is a rare genetic disease with heterogeneous phenotypes, its mode of transmission is autosomal recessive due to mutations in more than 16 genes, whose gene products collaborate in a DNA repair pathway.[1] It is one of the rare inherited bone marrow failure syndromes (IBMFS), characterized by various congenital malformations, defective hematopoiesis with a predisposition to hematological changes leading to one or more cytopenias, as well as a very high risk of acute transformation into leukemia, in particular Acute Myeloid Leukemia (AML) and solid tumors,[1],[2]

The recent determination of the frequency of heterozygotes gives an estimate of more than 1/300 with an expected birth prevalence of 1/160,000. In some populations, the frequency may be higher due to founder variants, with increased carrier frequencies (<1:100), including Ashkenazi Jews (FANCC, BRCA2), Northern Europeans (FANCC), Afrikaners (FANCA), Sub-Saharan blacks (FANCG), Spanish Gypsies (FANCA) "parinda".

FA occurs in 1 in 160,000 people worldwide,[3] with an estimated frequency of heterozygosity of 1/300 in the general population.[7] It is observed in all ethnic groups, with a higher frequency among people of Ashkenazi Jewish origin, and in South Africa.[3] These populations are characterized by a high rate of consanguinity, in our observation, the patient is also from a consanguineous marriage. Always in Morocco, according to a study carried out at the University Hospital of Fez between 2010 and 2013, 6 cases were recorded during this period.[7]

Always in Morocco, very few studies have been conducted on patients with FA, given its rarity and severity related to the increased risk of transformation into acute leukemia, hence the interest to report this case.

In the present work, we report the case of a young patient followed for FA who made an acute transformation into AML.

Clinical case

This is a male patient, 16 years old, followed for a fanconi type medullary aplasia and scheduled for an allograft. The patient had a family history of 2nd degree consanguinity. He was admitted to the Hematology-Oncology Department for a hemorrhagic syndrome consisting of epistaxis, gingivorrhages and macroscopic hematuria. The clinical examination on admission revealed a weight of 30 kg, a staturo-ponderal retardation, dysmorphic triangular facies, normocolored conjunctiva, poor oral condition with adenopathies under the left mandibular 2 cm and right axillary 1 cm. No hepatomegaly or splenomegaly.

The biological assessment: A blood count (CBC): Hb = 3.0 g/dl, GMV = 91.2 fl, Reticulocytes = 15800/mm3, Leukocytes = 2730/mm3 with PNN=760/mm3 and

Platelets = 6000/mm3. With the presence of anisopoikilocytosis on the blood smear;
- Biochemical and hemostasis tests were normal.
-The osteo-medullary biopsy (BOM) found a medullary aplasia;
Constitutional cytogenetic analysis revealed: 20 mitoses showing a diploid 46, XY male karyotype, compatible with a chromosomal instability syndrome after culture with *mitomycin C* compared to a normal control;
-The rest of the malformative assessment: renal ultrasound, abdominal-pelvic ultrasound and hand radiography were free of abnormalities;

The patient was programmed for allograft, hence the HLA typing which came back compatible with his brother:
HLA typing of the patient Locus A A*01 A* 30
Location B B*44 B*49 Locus DRB1*13 DRB1*--

HLA Typing of Brother Locus A A*01 A* 30
Location B B*44 B*49 Locus DRB1*13 DRB1*--

As part of the pre-graft assessment, a CBC was performed after one year of hospitalization and the beginning of the symptomatology, which revealed an Hb level of 5.5 g/dl, leukocytes at 3270/mm3 with the presence of 60% blasts. Following this result, a myelogram was performed, showing a hemodiluted puncture of 30 to 35% of large blast cells, with a nucleolated, cross-linked chromatin nucleus, granular cytoplasm with positive myeloperoxidase, result in favor of AML, in order to confirm the diagnosis of AML and its classification, an immunophenotyping was performed showing the presence of a low (40.3%) CD45 blast population expressing the following markers: MPOcyt (64.1%), CD33 (70.1%), CD117 (CD64.7%), CD13 (62.2%), CD64 (33.3%) and HLADR (86.4%). Lymphoid markers are negative. Immunophenotypic profile in favor of acute myeloblastic leukemia with granular maturation The bone marrow karyotype was not performed because the patient abandoned all treatment, refused to take chemotherapy and left the service against medical advice under the will of his family, 6 months after his departure, he died.

DISCUSSION

FA is a rare autosomal recessive disease that is part of the chromosomal instability syndromes. In addition to their risk of hematological malignancies, people with FA have a too high risk of developing a solid tumor. Compared to the general population, the risk is about 50 times higher for all solid tumors combined, including cancers of the head and neck, esophagus, liver, vulva and cervix.[1]

Swiss pediatrician Dr. Guido Fanconi first described the disease in 1927 when he published a report on siblings with severe aplastic anemia associated with several congenital malformations.[6] The main clinical manifestation of FA is the development of aplastic anemia with a peak of discovery around the age of 7 years, however, diagnosis may not occur until adulthood.[1] The majority of known patients present with a variety of physical abnormalities, including short stature, latte stains associated with hyper/hypo-pigmentation, thumb abnormalities, microcephaly, microphthalmia, reduced fertility, and structural renal abnormalities.[7]

19 human genes were involved in FA. These genes code for a group of proteins called "FANC", which function cooperatively in a pathway of recognition and repair of DNA damage.[3] The set of FANC proteins defines a pathway called FANC/BRCA that is involved in several crucial mechanisms: DNA repair and resolution of the blockade of the replication forks that occurs through covalent binding of DNA strands, control of the activity of the pro-inflammatory and cytotoxic cytokine TNF-α, maintenance of cell cycle homeostasis through control of the oxidative metabolism of the cell, hematopoiesis and gametogenesis.[2],[5]

The identified FANC genes are located on different chromosomal regions. They consist of 1 to 44 exons and code for proteins of different sizes with very few homologies between them. The FANC proteins identified to date are found in all tissues, with higher expression in the Thymus and testicles. The A, C, G and F proteins are present in both the cytoplasm and the nucleus, while the other FANC proteins are exclusively nuclear.[5]

Patients with bialyl mutations in FANCD1 /BRCA2 are a special subset with unique genotypic and phenotypic associations. Their characteristic abnormalities are included in the acronym VATER association (Vertebrae, Anus, Trachea, Esophagus and Kidney).[1]

The eight FA-associated proteins: FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL and FANCM are activated and combine to form a complex known as the central FA complex. This complex is necessary for the ubiquitination of the two proteins FANCD2 and FANCI which form the ID complex. Activation of the ID complex leads to the production of other DNA repair proteins by activating other genes: FANCJ / BRIP1, FANCD1 / BRCA2, FANCN / PALB2, RAD51, FANCP / SLX4 and FANCQ / ERCC4. The proteins produced are brought into the ICL zone so that cross-linking can be suppressed and DNA replication continues.[3],[4]

Based on the above data, the main causative factor of FA thus involves chromosomal instability in haematopoietic stem cells as a result of defective DNA repair, due to a somatic mutation in both alleles of the specific FANC

gene, a notable exception is FANCB in which the mutation occurs on the X chromosome.[1],[8]

Hematologic damage in patients with FA occurs progressively, beginning with macrocytic anemia followed by thrombocytopenia and neutropenia. The onset of pancytopenia peaks at about 7 years of age.[1]

A high risk of carcinogenesis, particularly in hematopoietic cells, is another characteristic phenotype in these patients, due to the loss of FANC protein function.[8] Statistical analysis of 1,300 identified FA cases revealed the highest incidence of leukemia (9%), followed by myelodysplastic syndrome (MDS) (7%), and solid tumors (5%).[4],[8] The same results were reported in a study conducted in 2015 in the United States which reported that more than 400 of the 2000 cases of FA patients had a malignant tumor type with 188 leukemias and 286 solid tumors, 84% of the leukemias were AML,[1] a typical adult and pediatric blood disorder, exceptionally affects FA patients even at an early age, because of the intrinsic chromosomal instability, favoring the clonal evolution and frequent emergence in adolescents or young adults of AML or myelodysplastic syndrome, which was the case in our patient who developedAML at the age of 16 years.

Monoallelic germline mutations or hypermethylations in the FA pathway genes are increasingly implicated in the increased risk of multiple cancers.[4] The most higher risk of developing breast and ovarian cancer is the inheritance of mutations in one of the breast cancer susceptibility genes, BRCA1 and BRCA2, leading to a clinically autosomal dominant hereditary breast and ovarian cancer (HBOC) syndrome.[9] HBOC also increases the risk of pancreatic, stomach and prostate cancers. In high-grade ovarian carcinoma, BRCA1 and BRCA2 function as classical tumor suppressors, and cancer development is usually associated with a loss of heterozygosity (LOH) of the other allele.[4]

CONCLUSION

The FA pathway preserves genomic instability as well as being largely connected to other DNA repair pathways. Although it is a rare disease, FA is important to study for two reasons. First, a better understanding of the molecular pathogenesis of FA may improve the treatment of bone marrow aplasia and associated malignancies. Second, somatic mutations in FA genes can have profound effects on cancer progression and treatment and may affect patient survival.

The management of patients with FA must be multidisciplinary. Hematopoietic stem cell transplantation (HSC) is the only curative treatment for bone marrow aplasia. It is indicated when the need for transfusion becomes regular, reflecting the progressive evolution towards insufficiency and then bone marrow aplasia. In our case, the patient had to receive anadequate chemotherapy protocol to treat his leukemia before performing the transplant, but he abandoned the treatment following a family decision.

Conflit of interest

The authors declare that they haven't known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding Sources

The research has not been externally funded **Ethics approval and consent to participate** Not applicable

REFERENCES

1. B. P. Alter, « Fanconi anemia and the development of leukemia », *Best Pract. Res. Clin. Haematol.*, 2014; 27(0): 214‑221.
2. G. Macé, D. Briot, J.-H. Guervilly, et F. Rosselli, « L'anémie de Fanconi : aspects cellulaires et moléculaires », Pathologie Biologie, 2007; 55(1): 19-28.
3. G. H. Reference, « Fanconi anemia », *Genetics Home Reference*. https://ghr.nlm.nih.gov/condition/fanconi-anemia consulté le févr. 2020.
4. J. Niraj, A. Färkkilä, et A. D. D'Andrea, « The Fanconi Anemia Pathway in Cancer », *Annu. Rev. Cancer Biol.*, mars, 2019; 3(1): 457‑478.
5. D. Papadopoulo et E. Moustacchi, « [Fanconi anemia: genes and function(s) revisited] », *Med. Sci. MS*, 2005; 21(8‑9): 730‑736.
6. pubmeddev et S. A. and A. BP, « Pathophysiology and management of inherited bone marrow failure syndromes, Blood Rev, 2010; 24(3): 101-22.
7. L. Bouguenouch *et al.*, « Anémie de fanconi au CHU Hassan II Fès: à propos de 6 observations », *Pan Afr. Med. J.*, déc, 2017; 28.
8. H. Dong, D. W. Nebert, E. A. Bruford, D. C. Thompson, H. Joenje, et V. Vasiliou, « Update of the human and mouse Fanconi anemia genes », *Hum. Genomics*, nov, 2015; 9: 32.
9. K. B. Kuchenbaecker *et al.*, « Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers », *JAMA*, 2017; 23(317): 2402‑2416.