Archive of Obstetrics, Gynecology and Reproductive Medicine
AOGRM, 3(3): 101-103
www.scitcentral.com

ISSN: 2640-2297

Case Report: Open Access

High Risk of Developing Cancer in Young Patients with Fanconi Anemia

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Received April 23, 2020; Revised May 17, 2020; Accepted May 19, 2020

ABSTRACT

Background: Fanconi anemia (FA) is a genetic disorder, autosomal recessive or linked to the X chromosome, which presents with pancytopenia, congenital malformations and predisposition to develop cancer.
Methods: We present the case of a 20-year-old female patient with Fanconi Anemia who developed gynecological and hematological neoplasm's that were treated with surgery, radiotherapy and chemotherapy treatment in a limited manner due to the toxicity presented.
Results: The patient developed vulvar cancer and multiple clinical complications that prevented the application of full treatment leading to a fatal outcome.
Conclusions: Individuals with FA are at increased risk for a number of solid tumors and this risk is likely to be increased in those who have undergone hematopoietic cell transplantation (HCT). Routine cancer screening and preventive interventions e.g., human papilloma virus (HPV) vaccination must be recommended. If a patient with FA develops a malignancy that requires chemotherapy and/or radiation therapy, dose reductions or alternative regimens are likely to be necessary.

Keywords: Fanconi anemia, Pancytopenia, Vulvar carcinoma, Acute myeloblastic leukemia

CASE

Fanconi anemia (FA) is an autosomal recessive chromosomal instability syndrome characterized by a hypersensitivity of DNA to clastogenic agents. Clinically, it presents progressive spinal cord insufficiency, various congenital anomalies and increased susceptibility to malignant diseases [1-3]. Among epithelial tumors, head and neck and lower genital tract tumors, especially vulvar cancer, are frequent and are usually associated with high risk human papillomavirus (HPV), genotypes (16/18) [4,5].

The laboratory diagnosis is made with the analysis of spontaneous and induced chromosomal aberrations with diepoxibutane in the peripheral blood, in the bone marrow or in the fibroblasts. This analysis is considered the gold standard [6]. There are 15 known complementation groups related to defects in 15 different genes involved in the AF/BRCA pathway, which is responsible for the DNA damage [7].

The prevalence of FA ranges from one to five affected per million, with a carrier frequency of 1/300 in Europe and the United States. A higher incidence in certain population groups has been described due to the presence of founder mutations or those with a high rate of consanguinity, such as the case in question, which, being of gypsy ethnicity is carrier of inter-family genetic crosses with cultural roots. The treatment of FA is the object of intense research that is currently focused on the transplantation of hematopoietic progenitors, preferably from HLA-identical sibling donors, and on gene therapy, still under clinical investigation [8]. Current therapies for oncohematological complications show marked limitations due to the high incidence of grade 3-4 toxicity manifested by these patients.

CASE REPORT

We report a retrospective case of a 22-year-old woman diagnosed in another center of spinal anemia type FA in 1993,

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Citation: Quiñonero PO, Gutiérrez AT & Ortega CM. (2020) High Risk of Developing Cancer in Young Patients with Fanconi Anemia. Arch Obstet Gynecol Reprod Med, 3(3): 101-103.

at the age of seven. Among the notable personal history for the development of the disease only family consanguinity was found, as she was of gypsy ethnicity. As clinical manifestations of the disease, our patient presented: hyperpigmentation (although due to her race her skin was dark, showing typical café- au-lait spots), low height, prominent forehead, small almond-shaped eyelid fissures, strabismus, prominent and low-implantation auricular pavilions and some degree of hearing loss. At the musculoskeletal level she showed hands with tenar hypoplasia, and slight xiphosis, as well as, varus equinus foot. The diagnostic suspicion arose from a bone marrow failure syndrome, primary hematological feature present in more than 90 percent of those affected. This is followed by pallor, bleeding and repeated infections as secondary complications. Anabolic agents were started as treatment, maintaining stable hemoperipheral figures. The patient did not have a compatible donor for allogeneic hematopoietic progenitor transplant (TPH), the treatment of choice.

Therefore, staged treatment with androgens was initiated, without the need for cytokines or a transfusion regime. It remains stable until the age of 20 when she consults for discomfort in the vulva and vagina. On gynecological examination an indurated and ulcerated lesion of 1 cm is observed on the right side of the vulvar fork, which is biopsied with the result of moderately differentiated and infiltrating squamous cell carcinoma of 6 mm in diameter and 16 mm thick originating on VIN 3. (pT1a).

Biopsy margins contacted with infiltrating lesion and VIN 3. DUAL (CINtec Plus: Positive, [9], what did it mean high probability of progression to high grade lesion. PCR was positive for HPV 16 (high risk) with a cervical biopsy reported as High-Grade Squamous Intraepithelial Lesion (H-SIL). Indication for surgery was ruled out due to the appearance of a left pleuropneumonia due to probable pneumococcus with subsequent pancytopenic sepsis and menigoencephalitis, with bad clinical evolution developing an extensive left carotid stroke (left cerebral artery and middle cerebral artery) in probable relation with prothrombotic state secondary to severe sepsis due to pneumococcus and neoplasia of the lower genital tract. After this episode, she presented motor aphasia (adequate language comprehension, exclusively emits some monosyllables) and right hemiparesis (brachial 1/5, crural 4/5). Two months later, the patient's general condition being stable and gynecological surgery was performed. Cervical conization with diathermy loop was performed in the first stage and vulvectomy with bilateral inguinal lymphadenectomy in the second stage, as the selective sentinel lymph node biopsy was positive. Vulvectomy piece reported as well-differentiated and ulcerated squamous cell carcinoma, originated on high-grade squamous intraepithelial lesion (VIN III) TNM stage: pT1b pN2b. FIGO stage: III B. The study for HPV typing by PCR has been positive for genotype 16 (high risk). Cervical conization piece: High-grade pavement intraepithelial lesion/CIN III. pTis. Location: anterior and posterior lip. Surgical margins: endocervical: affected and exocervical: in contact. The patient started adjuvant radiotherapy for infiltrating carcinoma of the vulva but had to be interrupted after the second session due to the appearance of a severe pancytopenia which in the bone marrow study is labelled as AML (Acute Myeloid Monocytic Leukemia M5b). In view of the poor clinical status of the patient and the poor prognosis, it was decided to start conservative treatment with a hypomethylating agent, azathioticin, from which she received only one cycle, since she developed as a third complication, a case of septic shock and finally died.

DISCUSSION

Patients with FA have a proven propensity for cancer and marked limitations to support specific oncohaematological therapy, making them particularly fragile in front of these pathologies [10,11]. Prevention and strict monitoring are particularly useful for them. The intrinsic genetic inestability to ionising radiation, environmental carcinogens and chemotherapeutic agents entails extreme risks for these patients.

Adolescent girls should have a visual examination of the external genitalia beginning at menarche and a comprehensive gynecologic evaluation including cervical cytology once they become sexually active or by the age of 18 years, whichever comes first.

Human papilloma virus (HPV) vaccination should be given to all patients prior to the onset of puberty. Some researchers conclude that FA is associated with increased susceptibility to HPV-induced carcinogenesis, perhaps due to a homozygosis for Arg72, a p53 polymorphism [12]. Our patient should have had gynecological examinations from the age of 18, with visual inspection of the external genitalia and cervical cytology. Colposcopies and biopsies should be performed if lesions are seen during an inspection or if the results of the cytology exam were abnormal, due to the high risk of squamous cell carcinoma in the lower genital tract associated with FA. But for family reasons, people of gypsy tradition and low socio-cultural level, these tests were not performed in order to have detected as soon as possible any incipient neoplastic process that would have been easier to manage with less toxic procedures. The patient should have received HPV vaccine to prevent associated cancers.

The patient followed controls in the hematology service on an irregular basis. Any patient diagnosed with FA without bone marrow failure should have a complete hemetry with reticulocyte count 3 or 4 times a year. When any cytopenia is observed, the analysis should be performed monthly to assess the progression of the cytopenia until bone marrow failure is established. An annual bone marrow aspiration should be performed to more safely define the relationship between cytogenetic abnormalities and the onset of leukemia or myelodysplastic syndrome. Once the clonal alteration has

appeared, bone marrow aspiration should be performed every 3 or 6 months.

The patient was a candidate for allergenic transplant but it was not performed because she did not have an HLA-identical relative and the search for an unrelated donor was not initiated because she maintained good hemoperipheral figures without the need for transfusion of blood products. Despite the low incidence of acute myeloid leukemia (AML) of 10% in FA, our patient evolved to acute leukemia possibly as a complication of previous gynecological processes with coadjuvant radiotherapy treatment [13].

CONCLUSION

Gene therapy offers a therapeutic alternative for Fanconi anemia patients who do not have a histocompatible donor. The goal is to introduce at least one functional copy of the affected gene into the patient's cells. The hematological problem is the most relevant in this disease and this makes the hematopoietic stem cell the ideal target. As it is an autosomal recessive disease, the introduction of a single copy of the affected gene can potentially reverse the disease. With the insertion of FANC genes, it facilitates the correction of the hypersensitivity of these cells to the action of cytoclastic agents.

Due to the susceptibility of chromosome breaks, leukemias and other cancers, it is necessary to provide these patients with guidelines on the importance of screening for cancers most frequently associated to FA, as well as avoiding certain environmental carcinogens including tobacco. HPV vaccine must be recommended both boys and girls prior to the onset of puberty.

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