Xeroderma pigmentosum with XPC gene mutation. A case report

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Background
Xeroderma pigmentosum is an autosomal recessive gerodermatosis with an incidence of 1 to 4 in 1,000,000 live births. Its genetic condition is autosomal recessive. This disease is caused by mutations in the ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, POLH, DDB2, XPA and XPC genes, involved in the repair of damaged DNA, which is why it is characterized by an inability to repair lesions in the DNA strand, presenting mainly skin lesions in photo-exposed regions. A 9-year-old male patient, product of consanguinity and with a history of a mother carrier of xeroderma pigmentosum with ephelides-type skin lesions and café-au-lait spots predominantly on the face and upper extremities, is presented. Genetic result with mutation in the XPC gene and histopathological results of skin lesions compatible with squamous cell carcinoma, basal cell carcinoma and Bowen's disease. The importance of early diagnosis and treatment in this pathology with sun protection measures lies in prognostic improvement of the patient and increase in the years of survival.

Keywords: xeroderma pigmentosum.

Case Report

Genetics

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Case report

9-year-old male patient, history of consanguinity, son of first cousins; mother carrier of xeroderma pigmentosum, father carrier of HIV. It has a genetic load by maternal branch of cervical cancer and type 2 diabetes; by paternal side of type 2 diabetes and systemic arterial hypertension. 23-year-old brother with asthma and 13-year-old sister with allergic rhinitis, both alive.

Current immunizations for age. Blood group O Rh positive.

Product of the fifth pregnancy (G5, C3, P0, A2) of a 34-year-old mother, prenatal control since 10 SDG, presented with cervicovaginitis, preeclampsia without severity data, and gestational diabetes. She was born by caesarean section due to lack of progression of labor, fetal distress, short umbilical cord and mother with preeclampsia: a single live child of 41 weeks of gestation, weight of 3200 grams, height 47 cm, APGAR 8/9, Silverman Anderson 0, the healthy binomial was discharged.

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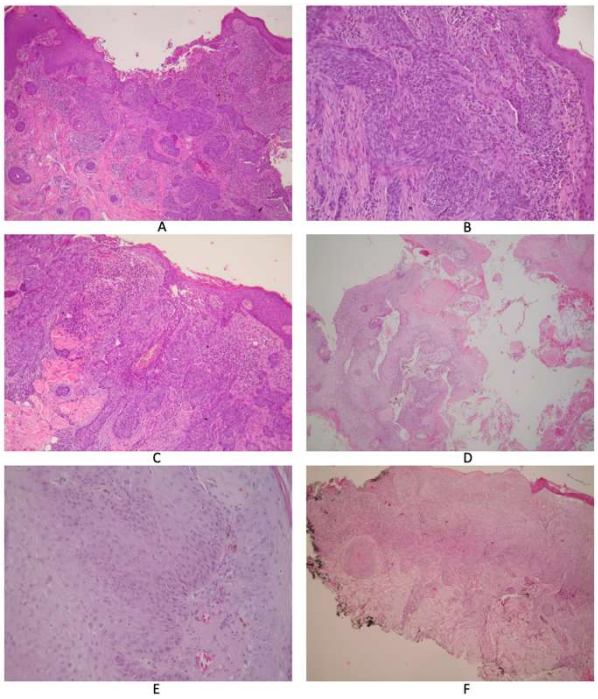

Figure 1. (A) Biopsy of a left cheek lesion, completely resected ulcerated and adenoid basal cell carcinoma. 10x field, histological sections with routine HE staining: ulcerated epidermis is observed accompanied by a basal cell-dependent neoplasm, which infiltrates the superficial and deep dermis. This neoplasm is arranged forming nests with peripheral palisades, in addition to periadnexal inflammatory infiltrate. (B) Biopsy of a lesion on the left cheek, completely resected ulcerated solid basal cell carcinoma. 40x field in the histological sections of the skin with routine HE staining, a solid pattern is observed that infiltrates the dermis. (C) Biopsy of a lesion on the left cheek, completely resected adenoid and ulcerated solid basal cell carcinoma. 10x field, histological sections of the skin with routine HE staining show ulcerated epidermis and an infiltrating basal cell-dependent neoplasm that alternates with chronic inflammatory infiltrate. (D) Skin biopsy of the lower eyelid, squamous cell carcinoma in situ (Bowen's disease) with microinvasion without lesion on the edges. In histological sections of the skin with routine HE staining, neoplasia is observed arranged in a solid pattern of cells with squamous characteristics which do not exceed the basement membrane accompanied by keratin pearls. (E) Skin biopsy of the tip of the nose, Superficial infiltrating squamous cell carcinoma. 40x field, histological sections of the skin with routine HE staining, infiltrating neoplasm with the appearance of squamous cells arranged in nests, cells with moderate amount of cytoplasm with hyperchromatic nuclei with irregular contours. Nose tip skin biopsy, Basal cell carcinoma. 10x field, histological sections of skin with routine HE staining. In panoramic view, a solid-nodular pattern is observed that covers the reticular dermis, but does not touch the edge.

Exclusively breastfed for 3 months, complementary feeding at 6 months of age.

Developmental milestones: language delay, with difficulty in pronunciation, for which she went to speech therapy.

Traumatic history, transfusion, allergy and contagious infection denied.

The condition began at 4 months of age with the appearance of café-au-lait spots on the trunk and extremities, later, at 5 months of age with ephelides on the face, the pediatric service consulted the dermatology service, who found disseminated dermatosis characterized by the following lesions: ephelides located on the face, both hypermelanotic and hypomelanotic lesions, compatible with poikiloderma, in addition to finding darker basal skin on the forehead; 8 café-au-lait spots measuring 1-2 millimeters distributed on the left arm, abdomen, and left leg; rounded scaly lesions on the elbows and a scale on the scalp. Rest of the physical examination apparently without alterations.

Study protocol with multidisciplinary treatment begins, counting to date with 1188 evaluations by the following services: anesthesiology, audiology, reconstructive surgery, dermatology, genetics, dentistry, ophthalmology, pediatric oncology, otorhinolaryngology, pediatrics and emergencies; and three hospitalizations: May 27, 2019, October 28, 2019, and December 19, 2020 for surgical management of injuries.

Surgical history:

05-27-19 Wide resection of centrofacial lesions + primary closure and right nasolabial bilobed flap

10-30-19 Excisional biopsies of lesions on the face (frontal region, right supraorbital region, cheeks and left forearm)

12-18-20 Excisional biopsies of 14 lesions on the face, including a lesion on the lower left eyelid.

Report of histopathological results of performed biopsies (02-07-2019)

Nose tip skin biopsy (revision block "A"):

• Superficial infiltrating squamous cell carcinoma associated with actinic keratosis.
• No edge injury or surgical bed.

Lower eyelid skin biopsy (revision block "B"):

• Squamous cell carcinoma in-situ, hyperkeratotic, without border lesion or surgical bed.

Right side outer edge supraciliary skin biopsy (revision block "C"):

• Basosquamous carcinoma, ulcerated and fragmented with tumor in one of the surgical edges (18-12-2020)

Excisional skin biopsies

• Slide A- Invasive well-differentiated keratinizing squamous cell carcinoma with a lesion a few microns from the surgical bed.
• Slide B- Invasive moderately differentiated keratinizing squamous cell carcinoma without border lesion.
• Lamella C- Ulcerated hypertrophic actinic keratosis and colonized by coccoid bacteria and without border lesion.
• Lamella D- acanthotic seborrheic keratosis without border lesion.

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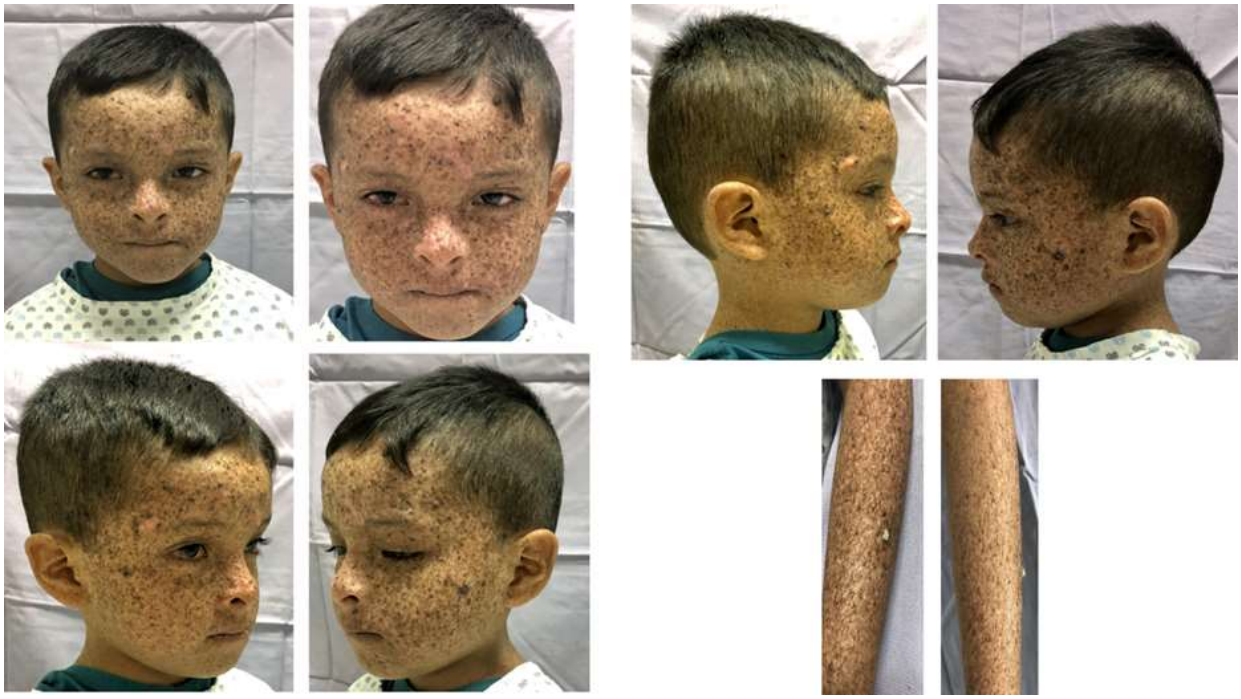

Figure 2. 8-year-old male patient with stage 3 xeroderma pigmentosum with sun damage lesions in various stages.

• Slide E AND F- Squamous cell carcinoma in situ (Bowen's disease) with microinvasion without border lesion.
• Slide H- Solid and keratotic basal cell carcinoma with a lesion in the surgical bed.
• Lamilla I- Bowenoid actinic keratosis with border lesion.
• Slide J- Solid basal cell carcinoma with lesion in the surgical bed.
• Slide K- Basosquamous carcinoma without border lesion

Genetics

• Molecular study with a homozygous mutation in the XPC gene.
• Explained by the condition of the parents
• Base deletion that conditions a change in the reading frame.
• Autosomal recessive mode of inheritance.
• Sunscreen to prevent and delay the development of skin cancer (melanoma, basal cell and squamous cell).
• Occurs 10 thousand times more frequently.

Discussion

Xeroderma pigmentosum is an autosomal recessive disorder with an incidence of 1 to 4 in 1,000,000 live births. Its autosomal recessive genetic condition is frequently associated with parental consanguinity, as in the clinical case presented above, product of first cousins.

Its age of presentation is usually from six months of age, with a mean age of presentation of two years, however in our patient it presented at a more premature age, four months.

This disease is caused by mutations in the ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, POLH, DDB2, XPA and XPC genes, involved in the repair of damaged DNA. Therefore, this pathology is characterized by an inability to repair lesions in the DNA strand due to the hereditary loss of cleavage endonucleases (proteins involved in the cleavage of nucleotides whose function is to prevent DNA damage). in DNA repair, photosensitivity, changes in skin pigmentation, neoplasms in areas exposed to the sun and in 20% of cases it is accompanied by neurodegenerative disorders.

The previously mentioned clinical case presented a mutation in the XPC gene, located on the short arm of chromosome 3 (3p25.1). The XPC protein helps verify DNA damage and stabilizes it by repairing it. This gene is associated with the largest number of mutations causing xeroderma pigmentosum, so far at least 40 mutations have been reported in this gene. Mutations result in a non-functional protein or reduce the amount of this protein that is encoded in cells. A partial or complete loss of the protein prevents cells from repairing DNA damage normally. As a result, abnormalities accumulate in the DNA, causing cells to eventually become cancerous or die.

Skin lesions may present as sunburn, erythema, scaling, blistering, scabbing, ephelides, telangiectasia, and keratoses; the predominant lesions in our patient were ephelides, sunburn and keratosis.

This genetic mutation in most cases is usually associated with a clinical form with oculocutaneous involvement, however, the patient only presented skin involvement.

20% of patients with neurological disorders present with mental retardation, deafness, ataxia, spasticity and atrophy of the cerebral cortex. DeSantis-Cacchione syndrome occurs in the minority of cases, which includes skin lesions, microcephaly, delayed weight-height growth, and sexual maturation.

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Neurological alterations can be found in patients with XPC gene mutation, however, none of the neurological alterations were found in the presented patient.

Different phases of presentation of xeroderma pigmentosum have been described: phase 1, also called erythematopigmentation, which is characterized by erythema, edema, vesicles or blisters after sun exposure; phase 2 or atrophic-telangectatic phase: characterized by pearly atrophic lesions, presenting areas of telangiectasia on the surface, poor-quality surrounding skin, with data of dryness and presence of scales: poikiloderma; and phase 3, of skin tumor proliferation. The patient presented was in phase 3 with histopathological results of facial lesions compatible with squamous cell and basal cell carcinoma.

Regarding diagnosis, it is important to know that an early prenatal diagnosis can be made in carrier parents by amniocentesis, as well as various ultrastructural tests in a specialized cytogenetic laboratory, to determine cellular hypersensitivity, chromosomal abnormalities, and DNA repair defects. In this case, a prenatal diagnosis could be made due to the history of a mother with xeroderma pigmentosum.
Postnatal diagnosis is mainly clinical and can be confirmed by the frequency of sister chromatid exchange in peripheral blood lymphocytes, which can be high in the cells of these patients. In addition, fibroblast cultures may be performed which, in this disorder, will be unable to repair excisions.
Timely diagnosis will improve the prognosis in these patients with rigorous protection against light-solar radiation.

In the treatment of this pathology, it is essential to use physical protection measures such as appropriate clothing, hats, umbrellas, and the application of filters and sunscreens every 2 to 4 hours. Systemic derivatives of retinoic acid, isotretinoin or acitretin, have been found to be effective in preventing malignant tumors.

Despite the fact that its incidence in Latin America is reported to be low, it is important to detect it early in our patients, due to the high risk they present of developing different skin carcinomas such as melanoma, squamous cell and basal cell carcinoma, as well as increased risk of other cell lines, thus decreasing the half-life of these patients with an average life of only 40 years due to mortality associated with these skin carcinomas. Its early detection and treatment will improve the survival of these patients.

Conclusion

Xeroderma pigmentosum, despite being a pathology with a low incidence of presentation, presents a high risk of developing skin carcinomas, so timely diagnosis and treatment is essential to improve the prognosis of patients.

In this case, the timely detection of the disease in this patient in his assigned unit with his early referral to a tertiary unit allowed a multidisciplinary and comprehensive approach and management by pediatric, plastic surgery, genetics, audiology, ophthalmology and oncology services, with care for the patient's affectations and prevention of possible complications, in addition to genetic counseling for his relatives, and periodic follow-up for the patient.

The importance of its early diagnosis and treatment with sun protection measures lies in prognostic improvement of the patient and increase in the years of survival.

Conflicts of interests

The authors have no conflicts of interest to disclose.

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