Therapeutics of xeroderma pigmentosum: A PRISMA-compliant systematic review

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Abstract

Xeroderma pigmentosum is a rare hereditary autosomal recessive genodermatosis. At present, there are many treatment options for xeroderma pigmentosum, covering medical/procedural, surgical and combined modalities. However, the quality of these interventions has not been assessed. Our study aimed to perform a systematic review of the literature regarding the treatment of xeroderma pigmentosum. Multiple medical databases were accessed with the Medical Subject Headings terms; "xeroderma pigmentosum," "therapeutics" and "surgical procedures, operative" from January 2000 to April 2019, including articles published in Portuguese, Spanish and English (PROSPERO-CRD42018114858). Two hundred and ninety-eight studies were found in the databases researched, of which, after applying the inclusion criteria, only 33 studies remained. The 33 complete articles were read by three of the authors, having been found: 16 reported medical/procedural and 17 reported surgical treatments. Only one clinical study presented a good level of evidence (EL: 2): a randomized clinical trial using a T4 endonuclease V (T4N5) liposome lotion which reduced the development of skin lesions in patients with xeroderma pigmentosum. Amongst surgical modalities, all studies presented low evidence level (EL: 4). Three illustrative cases are also presented, to emphasize the multiple number of times that surgical modalities may be required in these patients. The therapeutic modalities, both clinical and surgical, for xeroderma pigmentosum presented a low level of scientific evidence which did not allow meta-analysis. More therapeutic studies, both clinical and surgical, with better scientific evidence are needed.

Key words: Carcinogenesis, operative, surgical procedures, therapeutics, xeroderma pigmentosum

Introduction

Xeroderma pigmentosum is a rare inherited autosomal recessive genodermatosis, first described in 1874 by Hebra and Kaposi.[1] In 1932, de Sanctis and Cacchione reported neurological degenerative diseases associated with xeroderma pigmentosum.[2] In 1968, Cleaver established the molecular origin of the disease, demonstrating numerous DNA repair defects in fibroblast cultures irradiated with ultraviolet light.[3,4] In particular, the *p53* gene mutation was identified in skin tumors in xeroderma pigmentosum patients.[3,4]

The estimated global incidence of xeroderma pigmentosum is 1:1,000,000.[5] In Japan, the prevalence is 1:22,000,[6] and in countries in North Africa[7-9] and the Middle East[10,11] the prevalence is increasing, especially where consanguinity is common.[12] However, there is no predilection for any gender.[12] In Brazil, 48 cases of xeroderma pigmentosum were reported between 1953 and 1995 with consanguinity reported in eight of them.[13-15] The poor prognosis of this genodermatosis is due to the high incidence of skin tumors, approximately 1,000 times higher than the population mean, with a predominance of basal cell carcinoma and squamous

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cell carcinoma.[12] Melanoma in xeroderma pigmentosum usually occurs in adolescence, with patients having a worse prognosis and shorter survival time.[12]

In clinical practice, xeroderma pigmentosum is characterized by severe skin sensitivity to sunlight, resulting in burns, dry skin, depigmentation, poikiloderma, early skin aging and skin malignancies.[16] Systemic changes may also occur which compromise development and growth in childhood.[12,13,16] Thus, patients with xeroderma pigmentosum must initiate aggressive protective measures against sunlight exposure as soon as the diagnosis is made.[12,16,17]

Currently, there are many treatment options for xeroderma pigmentosum, covering medical/procedural, surgical and combined modalities.[12,18,19] In clinical practice, antioxidant drugs, retinoic acid derivatives,[20] isotretinoin,[20,21] imiquimod 5%,[22] acitretin,[22] 5-fluorouracil,[12,23] immunomodulators,[12,22,23] topical liposome lotion containing T4N57 bacteriophage endonuclease,[24] photodynamic therapy[25] with aminolevulinic acid[18] and cryotherapy[26] have been used. The surgical approaches most often performed include excision of skin lesions with primary closure or the use of skin grafts and local flaps, simple or composite, or distant flaps.[27] However, the literature is silent with regard to the efficacy of various treatment options in xeroderma pigmentosum. The objective of the present study was to perform a systematic review of the literature regarding the medical/procedural and surgical treatment of xeroderma pigmentosum.

Methods

A systematic review of the literature was performed in EMBASE/Elsevier, Scopus, Medline, PubMed, BVS, SciELO and Lilacs, following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[28] The search strategy was as follows: *("xeroderma pigmentosum"[MeSH Terms] OR ("xeroderma"[All Fields] AND "pigmentosum"[All Fields]) OR "xeroderma pigmentosum"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR ("surgical"[All Fields] AND "procedures"[All Fields]) OR "surgical procedures"[All Fields])*.

The present review was registered in the international prospective register of systematic reviews (PROSPERO-CRD 42018114858). All articles found, based on the title and abstract, were tabulated, then read and separated into two categories, medical/procedural and surgical treatment and analyzed in detail. The article selection and reading process was carried out by two of the authors. All articles selected by the two authors (FAGA and FCI) were definitively included in the systematic review. Articles selected by only one of the authors were analyzed by a third (senior) author (LMF) and included only if there was concordance between all three authors. The full text was obtained for complete evaluation and final inclusion of the articles.

The inclusion criteria comprised randomized clinical trials, prospective and retrospective cohort studies, case-control studies, case series and case reports, published from January 2000 to April 2019.

The study design classification was based on the definition described by Dekkers *et al*.[29] The level of evidence of the studies were scored by the authors according to the levels determined by the 2011 Oxford center for evidence-based medicine.[30]

The data contained in the included articles was extracted by the researchers independently and evaluated together to obtain consensus on the information. Experimental studies using cell culture and animal models were not included, even if applicable as xeroderma pigmentosum treatment strategies. Articles published in languages other than Portuguese, Spanish and English were not included. Studies involving transplant patients, preliminary and pilot studies and studies with conflicts of interest of any nature were excluded. The data collected is summarized in Table 1.

Results

Totally, 298 articles on the treatment of xeroderma pigmentosum, published between 2000 and 2019, were found [Figure 1]. Of these, 86 articles were selected for their relevance to the topic of the systematic review according to the title and abstract, after removing duplicates. Of these 53 studies were excluded because they did not meet the inclusion criteria, while the remaining 33 studies were included, after complete reading and analysis. [Table 1].

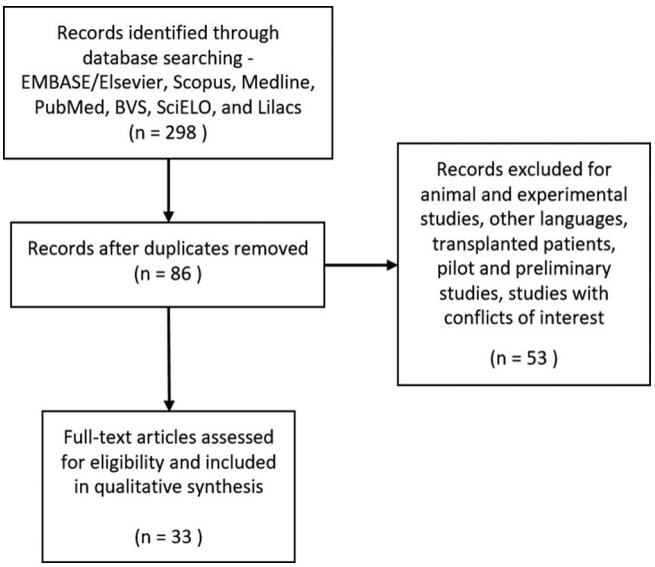

Figure 1: Study recruitment details

Table 1: Description of included studies (*n*=33)

Author	Year	Title	Type of Article	Resume
Medical / Procedural Therapeutics Studies (*n*=16)				
Yang *et al.*[35]	2015	Multiple facial BCCs in XP treated with topical imiquimod 5% cream	Case report EL: 4 Medical	Topical application of imiquimod 5% cream is effective in treating multiple BCCs in XP
Lambert and Lambert[19]	2015	Development of effective skin cancer treatment and prevention in XP	Review and case report EL: 4 Medical	Effective protocol prevents most skin cancer development in XP patients using either topical 5-fluorouracil or imiquimod
Sahai *et al.*[39]	2013	BCC in a child with XP: clinical response with electron beam radiation therapy	Case report EL: 4 Procedural	Radiation therapy is an effective therapeutic modality for the treatment of cutaneous neoplasms with XP
Larson and Cunningham[41]	2012	Photodynamic therapy in a teenage girl with XP Type C	Case report EL: 4 Medical	Individuals with XP may be the ideal candidates for PDT treatment because of the profound posttreatment photosensitivity and strict post-therapy sun avoidance
Schaffer and Orlow[42]	2011	Radiation therapy for high-risk squamous cell carcinomas in patients with XP: report of two cases and review of the literature	Case report EL: 4 Procedural	XP patients generally have normal cellular and clinical responses to ionizing radiation which reflects the specificity of their nucleotide excision repair defect for ultraviolet radiation-induced DNA damage
Segura *et al.*[43]	2011	Noninvasive management of nonmelanoma skin cancer in patients with cancer predisposition genodermatosis: a role for confocal microscopy and photodynamic therapy	Case report EL: 4 Medical	Methyl-aminolevulinate photodynamic therapy may be useful for the treatment of superficial BCCs in VV XP
Rubió Casadevall *et al.*[49]	2009	XP: neck lymph node metastasis of a squamous cell carcinoma of the skin treated with cetuximab	Case report EL: 4 Medical	Neck node recurrence of an SCC had good response and survival with cetuximab
Malhotra *et al.*[50]	2008	Multiple BCCs in XP treated with imiquimod 5% cream	Case report EL: 4 Medical	Successful treatment of multiple BCCs was described with imiquimod 5% cream
Pyun *et al.*[51]	2008	XP treated with an advanced phenol-based peeling solution	Case report EL: 4 Procedural	XP patient was treated with chemical peels using time peel solution. The face was resurfaced using the sharplan silk touch flash scanner CO2 laser and then, on average, two times of applications of each time peel solution. The triangular-shaped sponge was applied with stroking motions until it appeared frosted
Nijsten *et al.*[52]	2005	A patient with XP treated with imiquimod 5% cream	Case report EL: 4 Medical	The mechanism of imiquimod's antitumor activity is not clear. In XP, it may be caused by the stimulation of the impaired immune responses in these patients
Unlü *et al.*[54]	2004	Phenol intoxication in a child	Case report EL: 4 Procedural	The case of an 11-year-old boy with a diagnosis of XP who underwent mechanical dermabrasion and chemical peeling with phenol and then developed severe cardiac arrhythmias is reported
Roseeuw[55]	2003	The treatment of basal skin carcinomas in two sisters with XP	Case report EL: 4 Medical	They were treated with imiquimod 5% cream three times weekly, one for 6 weeks and the other for 10 weeks. Both sisters temporarily discontinued the treatment due to severe erythema and erosion. However, successful long-term clearance was observed with no recurrences in both cases
Nagore *et al.*[56]	2003	The excellent response of BCCs and pigmentary changes in XP to imiquimod 5% cream	Case report EL: 4 Medical	Excellent clinical response of multiple small pigmented BCC and pigmentary changes using imiquimod 5% cream with only minor side-effects, were described
Weisberg and Varghese[59]	2002	Therapeutic response of a brother and sister with XP to imiquimod 5% cream	Case report EL: 4 Medical	Imiquimod 5% cream was effective in treating facial BCC in these siblings with XP

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Table 1: Contd...

Author	Year	Title	Type of Article	Resume
Hamouda *et al.*[23]	2001	Topical 5-fluorouracil to treat multiple or unresectable facial squamous cell carcinomas in XP	Case report EL: 4 Medical	Topical 5-fluorouracil may be a helpful palliative treatment in multiple and superficial squamous cell carcinoma of the face. It avoids the extensive scars of abrasive surgery; however, leaves the regrettable risk of persistent tumor
Yarosh *et al.*[60]	2001	Effect of topically applied T4 endonuclease V in liposomes on skin cancer in XP: a randomized study. XP study group	RCT EL: 2 Medical	The topical application of DNA repair enzymes to sun-damaged skin of patients with XP. This treatment lowered the rate of development of two forms of these lesions during a year of treatment
Surgical Therapeutics Studies (*n*=17)				
Lemaître *et al.*[31]	2018	Outcomes after surgical resection of lower eyelid tumors and reconstruction using a nasal chondromucosal graft and an upper eyelid myocutaneous flap	Case series EL: 4 Surgery	They found a single local tumor recurrence and this was a BCC in an XP patient. After surgery, none of the patients had lagophthalmos or ocular surface complications. Only 4 patients had a 1 mm scleral show postoperatively; 3 other patients developed a small retraction of the eyelid after adjuvant radiotherapy and a 1 mm scleral show occurred
Sibar *et al.*[32]	2016	Technical aspects and difficulties in the management of head and neck cutaneous malignancies in XP	Case series EL: 4 Surgery	The most common type and tumor locations were SCC and orbital region. The transfer of free tissue was the most commonly performed surgical intervention. Six patients were siblings of each other and five patients had local recurrences. There is no definitive treatment algorithm. Early surgical intervention and rigorous follow-up are gold-standard modalities
Chappell *et al.*[33]	2016	Atypical fibroxanthoma in a 13-year-old guatemalan girl with XP	Case report EL: 4 Surgery	The tumor was excised by amputation just distal to the proximal phalanx. Atypical fibroxanthomas are rarely associated with children with XP
Sánchez Cañal *et al.*3[4]	2016	Eyelid reconstruction in a child with XP	Case report EL: 4 Surgery	BCC in the lower eyelid affecting its free edge created a secondary ectropion. A resection of the eyelid tumors and the conjunctival lesions were reconstructed by placing a skin graft and amniotic membrane, respectively
Lasso *et al.*[36]	2014	Invasive BCC in an XP patient: facing secondary and tertiary aggressive recurrences	Case report EL: 4 Surgery	Free flaps are good solutions for reconstruction and should proceed from non-sun-exposed areas of the body. Complications are frequent when reconstructed areas are highly radiated and/or skin tumors affect deep anatomical areas
Adu[37]	2014	XP in Ghanaians: a report of three cases and review of literature	Case report EL: 4 Surgery	Early recognition of the disease is necessary to avoid morbidity and mortality from malignant complications
Sadaf and Yazdanie[38]	2013	XP with melanoma of face and its prosthetic management	Case report EL: 4 Surgery	Prosthodontist was able to construct a nasal prosthesis via conventional technique by using the patient's sibling nasal form as a template
Ozmen *et al.*[40]	2012	Facial resurfacing with a monoblock full-thickness skin graft after multiple malignant melanomas excision in XP	Case report EL: 4 Surgery	Complete resurfacing of exposed skin with full-thickness skin graft provides acceptable results
Tayeb *et al.*[44]	2011	Facial resurfacing with split-thickness skin grafts in XP variant	Case report EL: 4 Surgery	One of the most effective treatment options for the malignant lesions is full-face resurfacing with skin grafts
Jan *et al.*[45]	2011	XP	Case series EL: 4 Surgery	There was a family history. The tumors were mostly BCCs. The rate of new tumors formation and recurrence was exceptionally high. Twenty (80%) of the tumors were on the face, one was on the back and three on the forearms. All wounds were closed primarily or with split grafts
Amin *et al.*[46]	2010	Living related hemi-face skin transplant using radial forearm free flap for an XP patient: early outcome	Case report EL: 4 Surgery	Although we cannot comment on long-term results due to graft rejection, our early cosmetic result was very promising. In addition, the patient did not develop skin lesions in the operated site but developed one in the virgin hemi-face

Contd...

Table 1: Contd...

Author	Year	Title	Type of Article	Resume
Wei *et al.*[47]	2010	Re-irradiation of metastatic disease in the neck from XP	Case report EL: 4 Surgery	This report is the first to describe re-irradiation to treat cervical and intraparotid metastatic disease in an XP patient
Terziqi and Tarpila[48]	2009	Reconstruction of large defect of lower lip and commissure using Karapandzic flap: a case report	Case report EL: 4 Surgery	Karapandzic circumoral advancement-rotation flap for earlier resections of recurrent BCC and SC of lower lip because of scars. These followed natural folds of the face and, despite a slight microstomia, the aesthetic appearance is acceptable
Brunner and Jöhr[53]	2004	Anesthetic management of a child with XP	Case report EL: 4 Surgery	Resection and replacement by a transposition-flap of the skin covering the nose was planned and associated with a forehead skin expander, in a second step
Sönmez Ergün[57]	2003	Resurfacing the dorsum of the hand in a patient with XP	Case report EL: 4 Surgery	Although conservative surgical resection is primarily preferred in XP patients, in cases in whom radical surgical intervention is necessary, the technique should be individualized, to minimize undamaged skin
Ergün *et al.*[58]	2002	Is facial resurfacing with monobloc full-thickness skin graft a remedy in XP?	Case report EL: 4 Surgery	Harvesting skin grafts were chosen based on the least sun-exposed and pigmentation-free areas
Hadi *et al.*[61]	2000	Squamous cell carcinoma of the lower lid in a 19-month-old girl with XP	Case report EL: 4 Surgery	SCC on the right lower lid was surgically excised with no evidence of recurrence after 2-year follow-up

BCCs: basal cell carcinomas, EL: evidence level – EL 1: Systematic review of randomized trials; EL 2: Randomized trial; EL 3: Non -randomized controlled cohort/follow-up study; EL 4: Case-series, case-control, or historically controlled studies; EL 5: Mechanism-based reasoning, SCC: squamous cell carcinoma, XP: xeroderma pigmentosum, RCT: randomized controlled trial

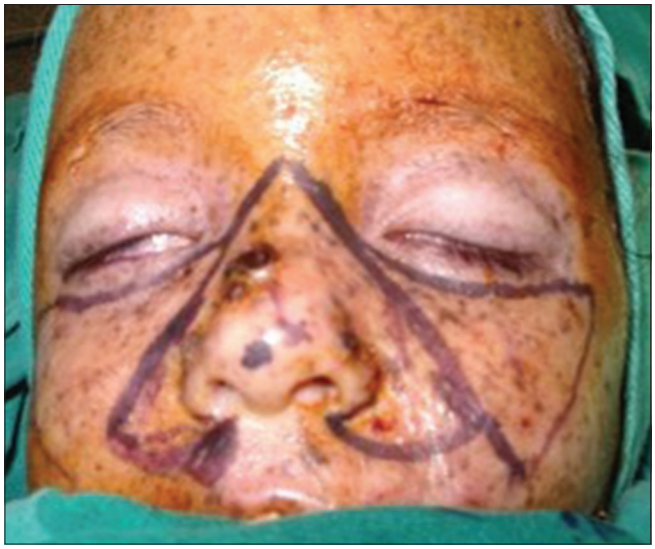

Figure 2a: Preoperative image of the lesion in the nasal dorsum and surgical marking of the nose esthetic unit and medial subunit of the genic unit

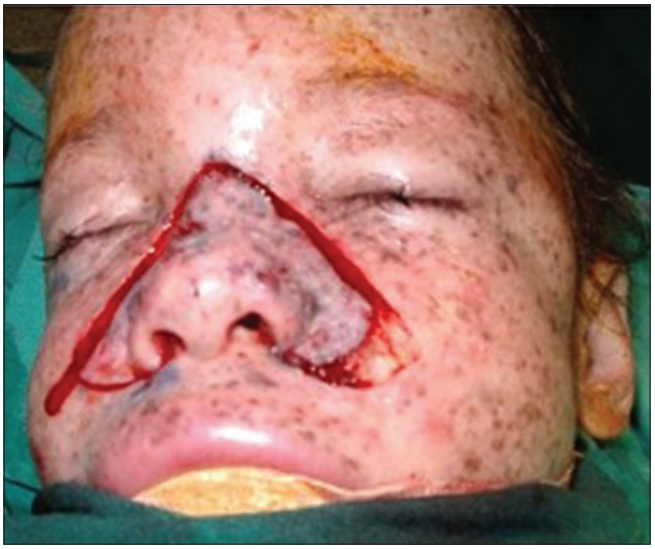

Figure 2b: Patient under tarsorrhaphy, demarcation of the total skin graft needed

Of the 33 articles included, 16 reported medical/procedural and 17 surgical treatments of xeroderma pigmentosum, as depicted in Table 1 Studies reporting medical and procedural treatments were evaluated and classified with a low evidence level, except one.[60] As for studies with surgical treatments, all were evaluated and classified with a low evidence level.

Three illustrative cases are described below, in which the patients presented malignant neoplastic lesions, mainly in the face. The therapeutic proposal was the complete resection of each lesion followed by closure by second intention surgeon-assisted healing. These cases serve to demonstrate the multiple number of times that surgical intervention may be required, as well as the efficacy of this procedure.

Illustrative case 1

L.S.S., is a Caucasian female, born in 2001 in Maceió, Alagoas, Brazil. Her parents are first cousins. In 2003, at 2 years of age, the patient was seen at the Plastic Surgery

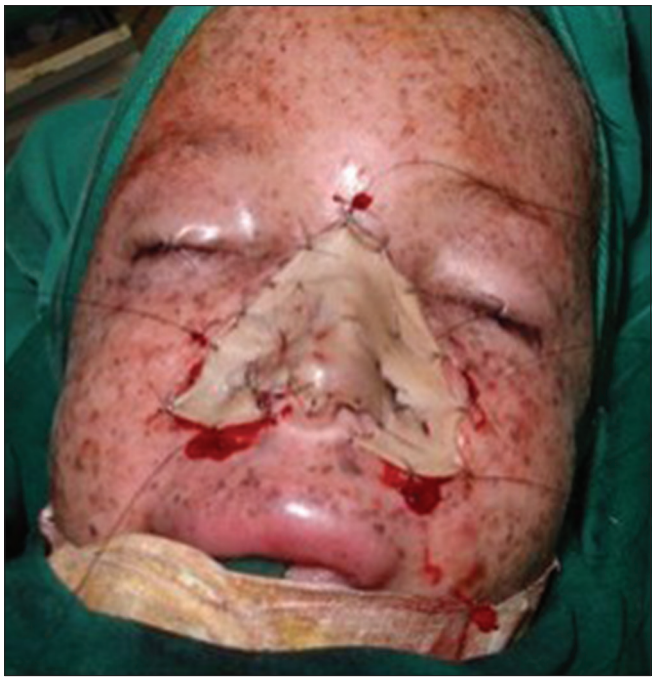

Figure 2c: Inguinal area hyposensitized to the sun as a donor area of the total skin graft

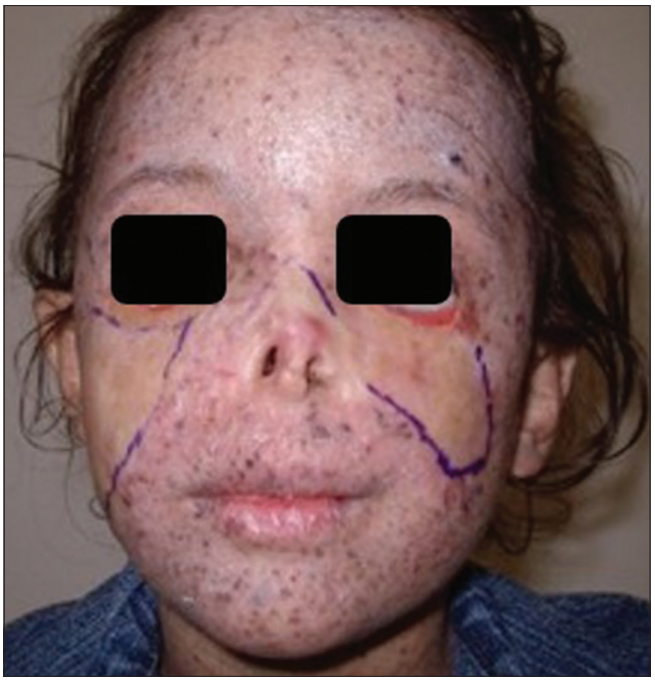

Figure 3a: Frontal postoperative image of 3 months

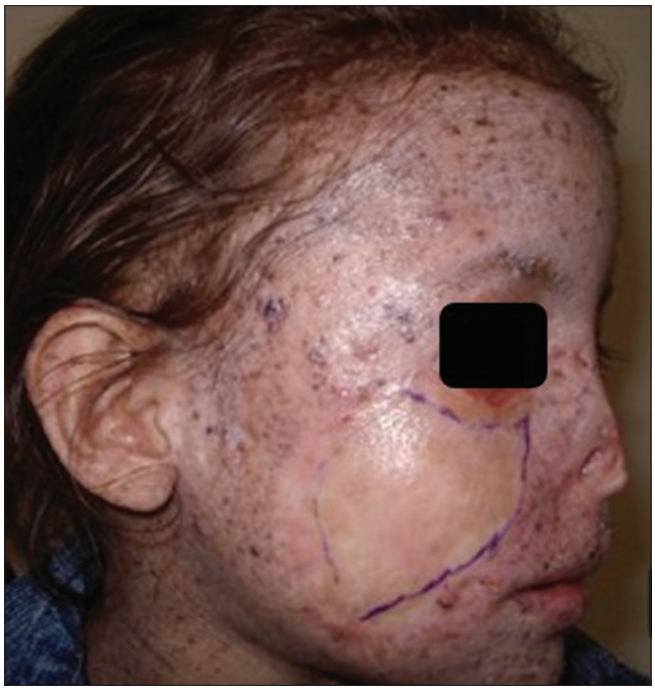

Figure 3b: Right profile postoperative of 3 months

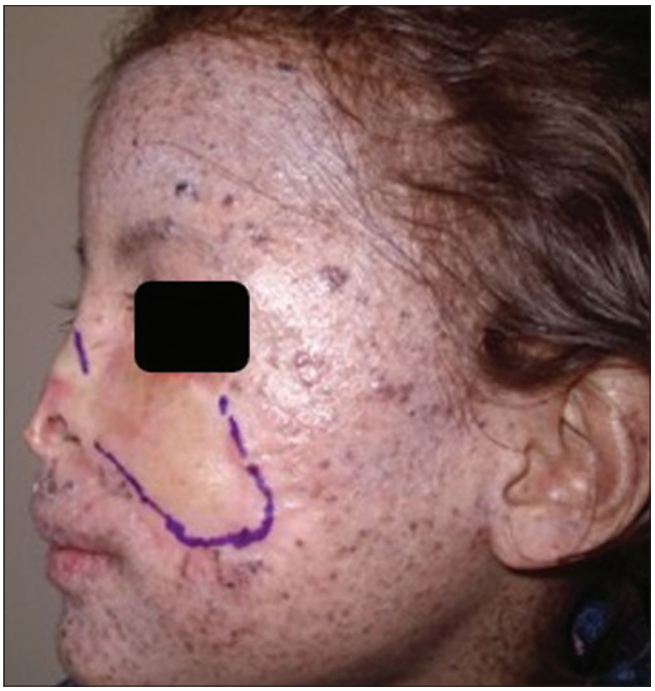

Figure 3c: Left profile postoperative of 3 months

Outpatient Clinic of the Professor Alberto Antunes University Hospital (UFAL HUPAA), Federal University of Alagoas, where a diagnosis of xeroderma pigmentosum was made. On the same date, instructions for continuous solar photoprotection were emphatically given but not followed by the parents or relatives. Almost 3 years after diagnosis, in October 2006, at 4 years of age, the patient underwent incisional biopsy and subsequently, regular excision of multiple basal cell carcinomas and actinic keratoses on the nose, back and nostrils. The entire aesthetic unit of the nose (dorsum, sidewall, ala, lobule, soft triangle facet and columella) was operated and the material was sent for histopathology during surgery which showed that the margins were not compromised. The wound area was closed with a full-thickness skin graft taken from the inguinocrural region (sun-hyposensitized region) [Figure 2]. In November

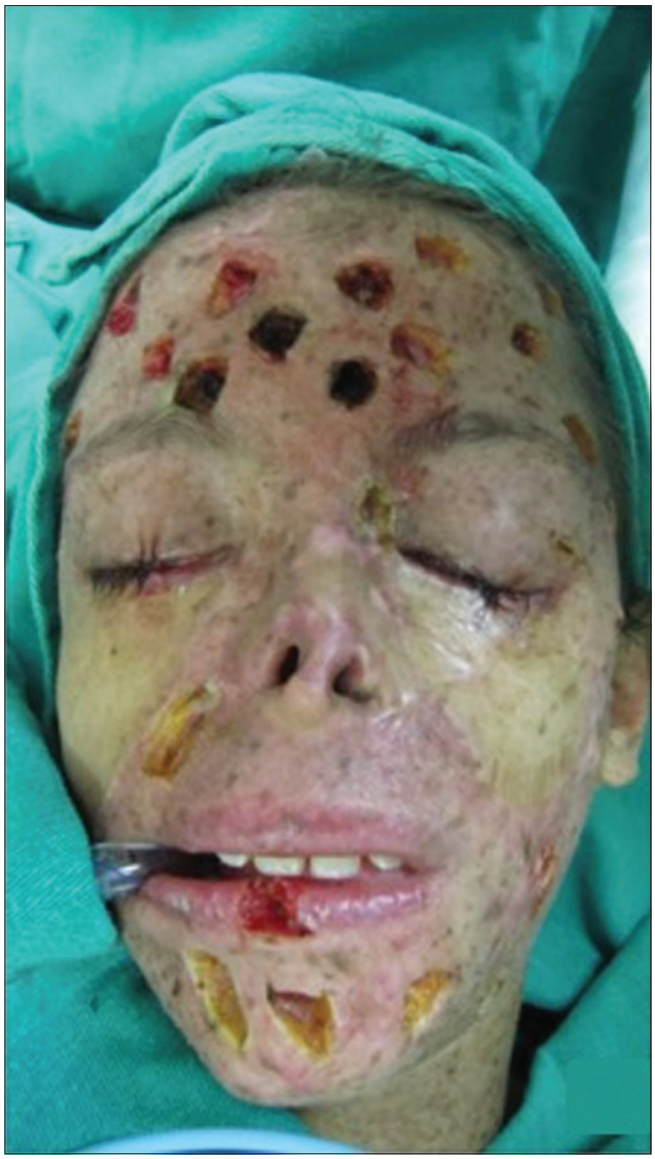

Figure 4a: Frontal intraoperative photograph - frontal, left eyelid and mental lesions

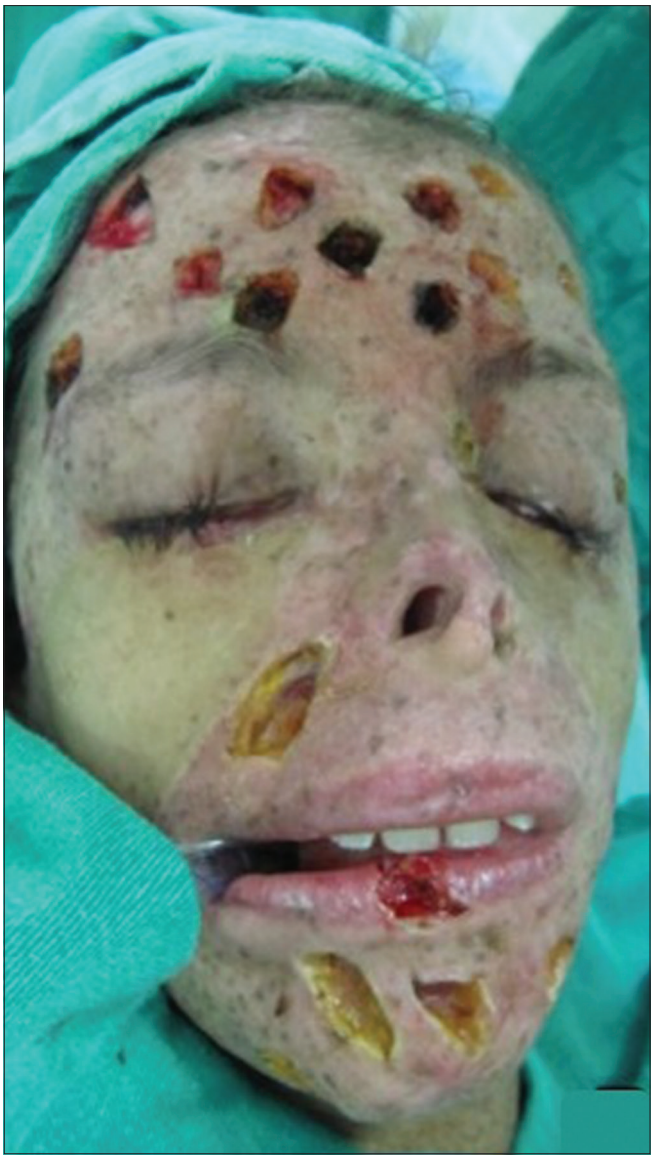

Figure 4b: Right profile intraoperative - frontal, left eyelid and mental lesions

2006, 1 month later, a basal cell carcinoma in the malar region and a squamous cell carcinoma in the eyelid were excised. Total skin grafting of the left inguinal region was also performed to cover the defects. In March 2007, 4 months later, resection of a posterior cervical basal cell carcinoma with primary suture was done. Another basal cell carcinoma and multiple squamous cell carcinomas located in the left malar region were treated by excision and total skin grafting with skin taken from the inguinal region [Figure 3]. In September 2007, May 2008, March and September 2009 and October 2010, basal cell carcinomas and a squamous cell carcinoma on the face were excised. Circular tumor excision was performed. The wound area was left open for second-intention healing [Figures 4 and 5]. In December 2010, May and December 2011, March and September 2012, June and October 2013 and February 2014, other lesions were excised with diagnoses of cutaneous hemangioma, basal cell carcinoma, actinic keratosis and pyogenic granuloma. Total skin grafting was then performed in the aesthetic unit (dorsum, sidewall and ala) of the nose and malar regions using the inguinocrural region as the donor area. After 7 years of follow-up, the skin grafted in these regions remains distinct from the adjacent "natural" skin.

Illustrative case 2

D.L.S.S., a caucasian female, born in 2005,the sister of L. S. S. (case 1), presented at 3 months of age, with a gradually progressive poikiloderma mainly on the face, shoulders and anterior thoracic region. The mother denied excessive sun exposure and claimed significant use of sun protection when outside the home. At 3 years of age, the patient underwent excision of lesions on the right thigh and side of the face, with a histopathological diagnosis of junctional melanocytic nevi. In March 2012, at 7 years of age, seven basal cell carcinomas

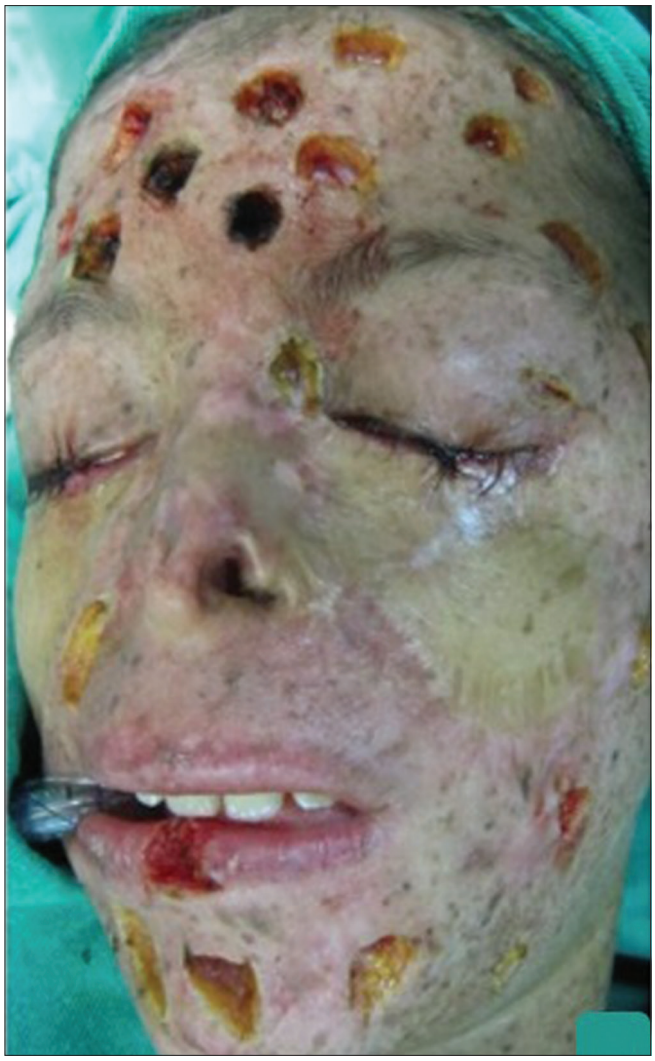

Figure 4c: Intraoperative patient: lesion exertion in frontal region, left eyelid and mental region (left profile view)

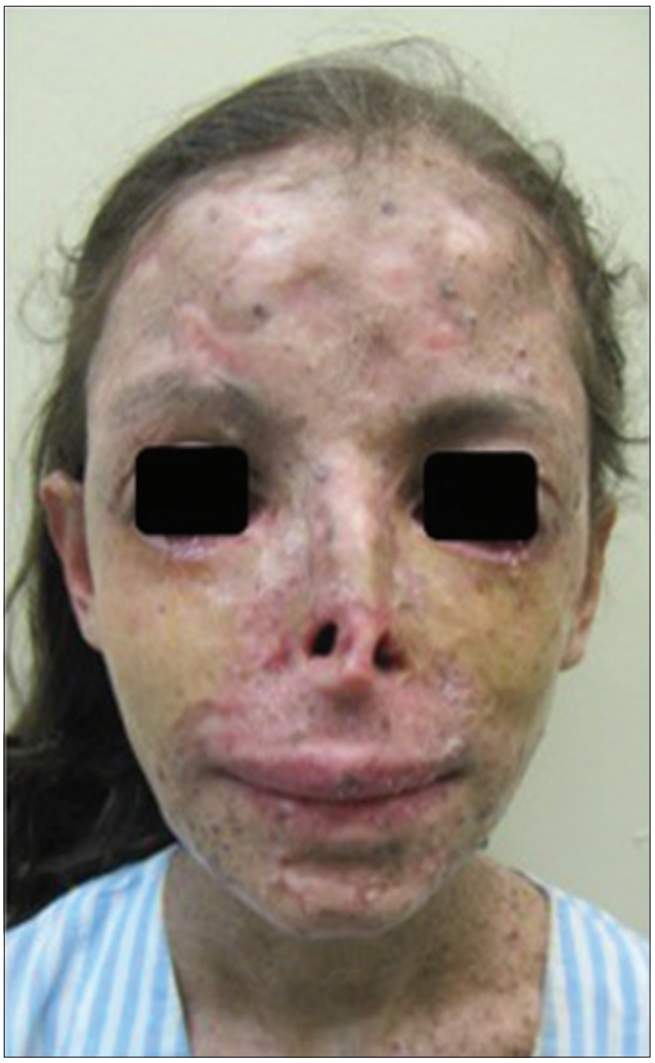

Figure 5a: Patient at the postoperative period of 5 months, showing the result of surgeon-assisted healing in frontal view

were excised with tumour free surgical margins [Figure 6]. In December 2012, 9 months later, another nine basal cell carcinomas on the face were excised with free margins. In July 2013 and February 2014, solid basal cell carcinomas were excised in the right and left temporal regions. The patient receives monthly outpatient follow-up.

Illustrative case 3

M.A.S., is a female patient, born in 2006 . There was no report of consanguinity between parents. The patient presented with gradually progressive hyperpigmented lesions and dry skin after sun exposure since the first year of life. In 2011, at 5 years of age, the patient was referred to the university hospital, where a diagnosis of xeroderma pigmentosum was made and specific therapy started, on the basis of information about the pathology and the use of sunscreen was advised. In May 2011, a multicentric basal cell carcinoma on the nose and left malar region and a squamous cell carcinoma on the lower lip were excised, with tumour-free surgical margins [Figure 7]. In July, September and December of the same year, multiple lesions on the face and lips were excised with a diagnosis of basal cell carcinoma. Three months later, in March 2012, a new ulcerated squamous cell carcinoma on the lower lip was excised with tumour-free margins. In April 2013, at 6 years of age, the patient underwent excision of solid basal cell carcinomas in the right infraorbital and glabellar regions, superficial basal cell carcinoma in the right temporal region and carcinoma *in situ* in the upper lip with tumour-free surgical margins. Five months later, in September 2013, the patient underwent excision of an ulcerated basal cell carcinoma in the right periorbital region, pigmented basal cell carcinoma in the lower right eyelid and solid basal cell carcinomas in the upper lip and left malar region with tumour-free surgical margins. In August 2014, 11 months later, the patient underwent excision of squamous cell carcinomas in the left malar and periorbital regions treated by second-intention healing. The patient is on a monthly outpatient follow-up schedule.

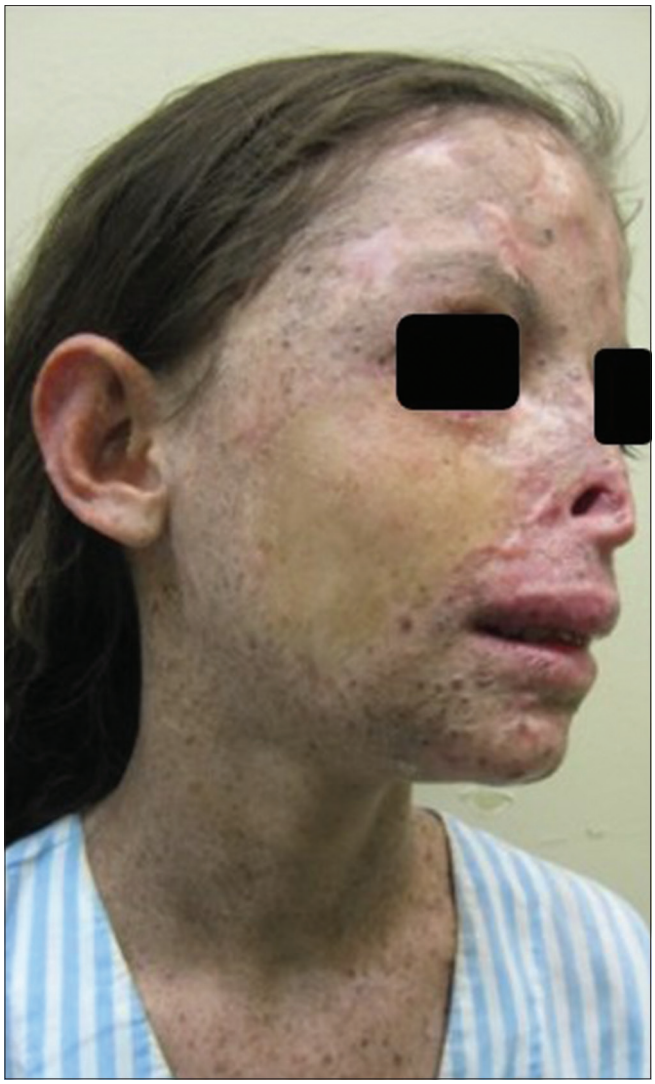

Figure 5b: Patient at the postoperative period of 5 months, showing the result of surgeon-assisted healing in right profile view

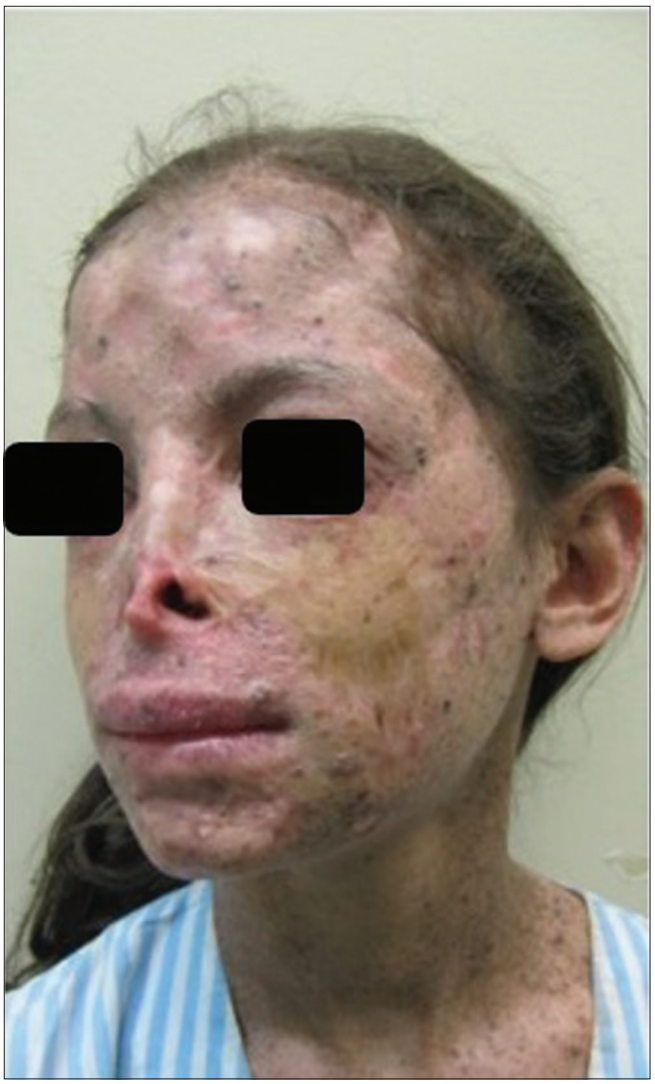

Figure 5c: Patient at the postoperative period of 5 months, showing the result of surgeon-assisted healing in left profile view

Discussion

Xeroderma pigmentosum is an autosomal recessive disorder in which patients exhibit impaired DNA repair.[12,18] Skin lesions are caused by the effect of ultraviolet light on cellular genetic material, causing uncontrolled mutations and proliferation due to the heterogeneity of defects in cell repair mechanisms. This multiplicity is evidenced by the wide variety of genetic variation associated with xeroderma pigmentosum: XPA, XPB/ERCC3, XPC, XPD/ERCC2, XPE/DDB2, XPF/ERCC4, XPG/ERCC5 and XPV/POLH.[6,12] Patients are therefore classified according to the type of genetic mutation they carry (XPA or XPB, for example). Patients in the XPA to XPG groups have defects in nucleotide excision repair.[6,12] Patients with the XPV mutation have normal nucleotide excision repair but have a deficiency in allowing DNA replication after DNA damage caused by ultraviolet light.[12], Photosensitivity is thus a cardinal characteristic of this genodermatosis.[12,18,25]

Approximately 60% of patients with xeroderma pigmentosum report an acute reaction to sunburn after minimal ultraviolet exposure.[25,62] The mean age for the onset of cutaneous signs and symptoms is between the first and second year of life, limited to sun exposed areas.[10,12,25] Continuous sun exposure generates actinic keratoses, and these lesions develop into skin carcinomas. Melanomas also develop but with lower incidence.[12,25]

Bradford *et al*. concluded that individuals up to 20 years of age with xeroderma pigmentosum are at a higher risk for malignant neoplasms of the skin compared to the general population.[63] For carcinomas (basal cell carcinomas and squamous cell carcinomas), the risk of developing the disease is approximately 10,000 times higher with a mean age for the onset of lesions at nine years, almost 60 years earlier than in the general population. For melanoma, the risk increases 2,000 times with the mean age for the first lesion at 22 years which is approximately 30 years earlier than in the general population.

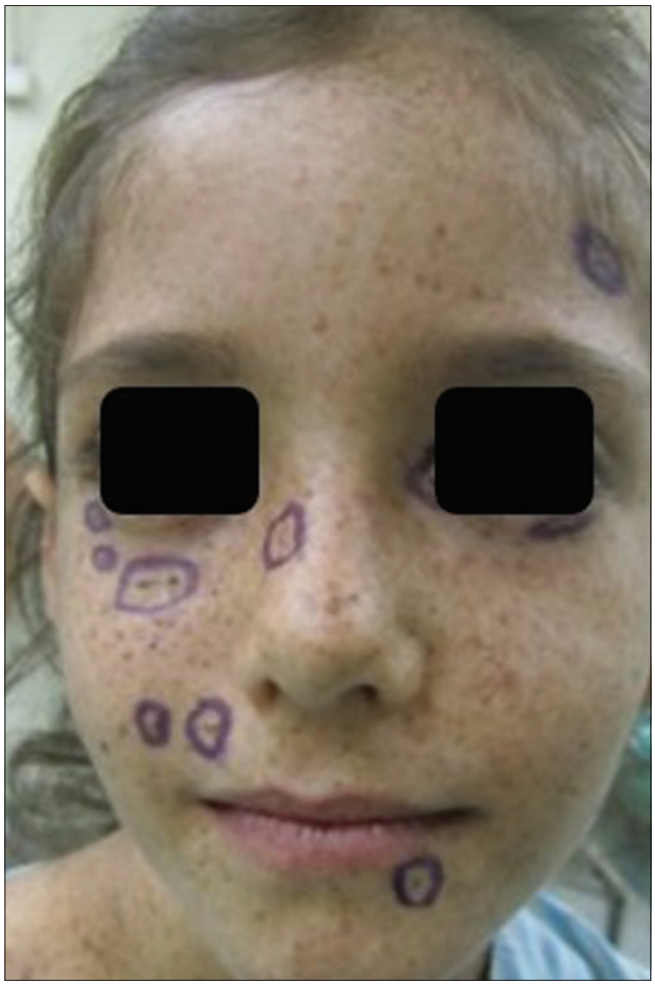

Figure 6a: Preoperative photo showing several lesions in the face

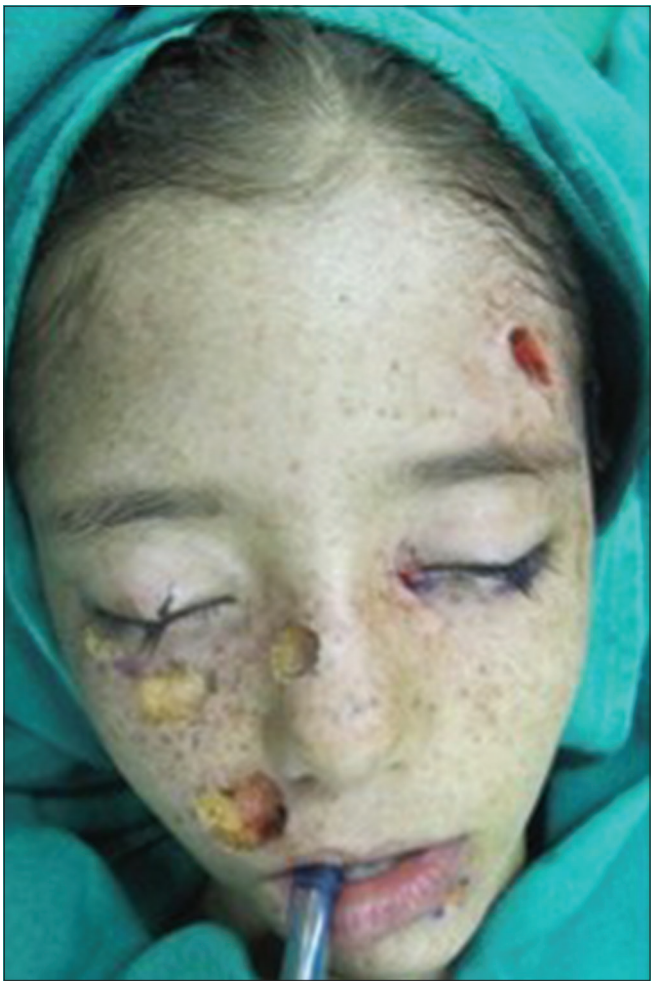

Figure 6b: Intraoperative photo after lesion excision

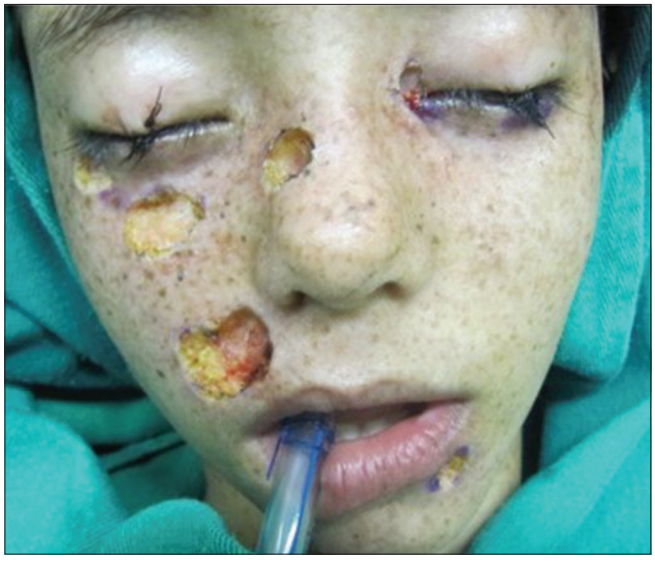

Figure 6c: Close-up view

The treatment of xeroderma pigmentosum depends on early diagnosis, starting with immediate and strict prevention of sun exposure and other ultraviolet sources.[64] This involves minimizing or avoiding staying outdoors without proper protection, even on cloudy days. Even with a clinical suspicion of xeroderma pigmentosum, sun protection measures must be initiated until confirmation or negative diagnosis.[25] In addition, because of the extensive ultraviolet protection, patients should be supplemented with vitamin D,[65] in addition to being given adequate nutritional guidance.[18]

The present study is a systematic review of xeroderma pigmentosum treatment, both medical/procedural and surgical. There were 33 included studies. Of these, 17 studies addressed surgical treatment. All studies have a low level of scientific evidence, as they were case reports and case series (level of evidence 4). However, there was consensus regarding skin-sparing resections and the use of skin grafts from donor areas that were not exposed to the sun and/or were poorly pigmented.[36,46,57,58] No study reported continuous, long-term follow-up to determine the incidence of recurrence or new lesions in the grafts or flaps used.

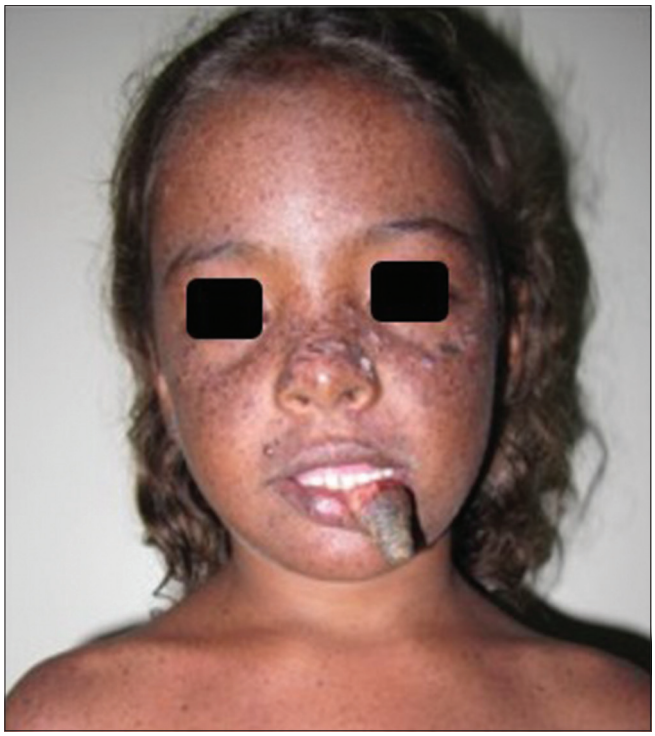

Figure 7a: Patient preoperatively showing lesions on the back and wings of the nose, on the left malar region and on the lower lip in frontal plane

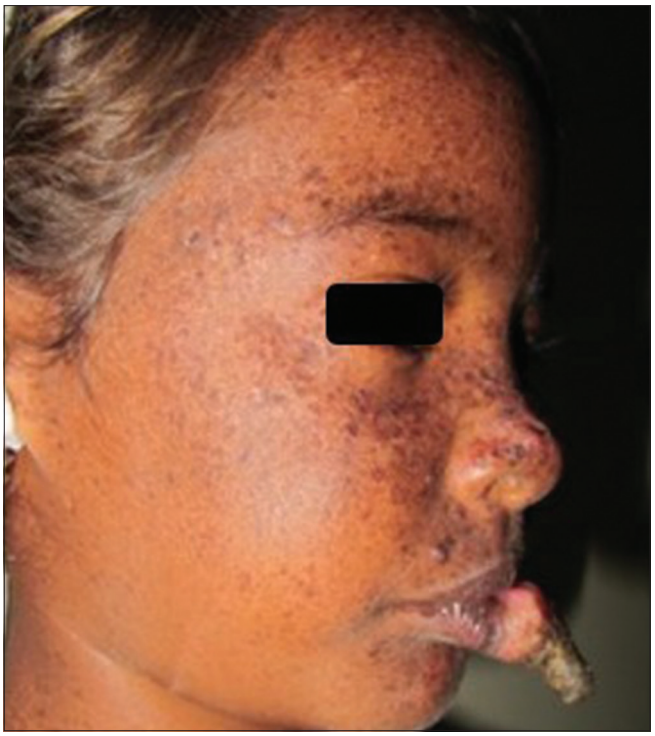

Figure 7b: Patient preoperatively showing lesions on the back and wings of the nose, on the left malar region and on the lower lip in right profile view

This scientific scenario could be explained by the rarity of xeroderma pigmentosum, making it difficult to perform large randomized clinical trials and meta-analyses. Thus, the long-term follow-up of patients with ongoing surgical treatment, and documenting the evolution of the postoperative period should be encouraged.

As for studies with medical/procedural treatments, most prevalent was the use of topical imiquimod and 5-fluorouracil. Similar to surgical treatment studies, most of the studies presented a low level of scientific evidence. Only one study was a randomized clinical trial. Yarosh *et al*. tested the ability of the T4 endonuclease V (a bacterial DNA repair enzyme) in a liposomal delivery vehicle applied topically (T4N5 liposome lotion) to lower the rate of new skin cancers in xeroderma pigmentosum patients.[60] Twenty patients were assigned T4N5 liposome lotion daily for 1 year. The annual rate of new actinic keratoses was 8.2 among the patients who used the lotion and 25.9 for the patients in the control group ($P = 0.004$). For basal cell carcinomas, the annual rates of new lesions were 3.8 in the treatment group and 5.4 in the control group (difference 1.6 [0.38–2.82], $P = 0.006$). No significant adverse effects were found among patients. The hypothesis of this study is based on the fact that xeroderma pigmentosum originates in modifications in the genome, and thus a focused treatment could be effective.

For the cutaneous lesions that originate from the failure of DNA repair, there are several studies with a multiplicity of treatments, both medical surgical and combined. Preference is given to less invasive treatments. For example, premalignant lesions are treated with cryotherapy.[26] In larger areas of sun-damaged skin, called the cancerization field, topical preparations of 5-fluorouracil or imiquimod may be used.[12,19,23] Isotretinoin or acitretin[20-22] are used for the prevention of skin neoplasms in patients with xeroderma pigmentosum.[66,67] However, due to their toxicity (hepatic, hyperlipidemic and teratogenic effects), these drugs are reserved for patients who are actively developing a large number of new skin tumors.[12,19]

When malignant lesions occur, the treatment is similar to that of patients without xeroderma pigmentosum. This involves electrocautery and skin resurfacing, curettage or surgical excision.[44,57,68] Skin cancers that are recurrent or in places with a high risk of recurrence, such as the face, are best treated by Möhs micrographic surgery.[12] Moreover, because a high percentage of these patients undergo multiple surgical procedures, removal of the undamaged skin adjacent to the lesion should be minimized.[57,58] In severe cases or cases needing extensive resections, complete excision followed by skin grafting should be used with a donor area protected from sun exposure.[58] When the neoplasia is inoperable, the therapeutic option is the use of radiotherapy, such as X radiation and electron therapy , since most patients with xeroderma pigmentosum are not sensitive to this radiation.[69,70]

Autologous skin transplantation is not free of risk, and skin previously not exposed to the sun can develop

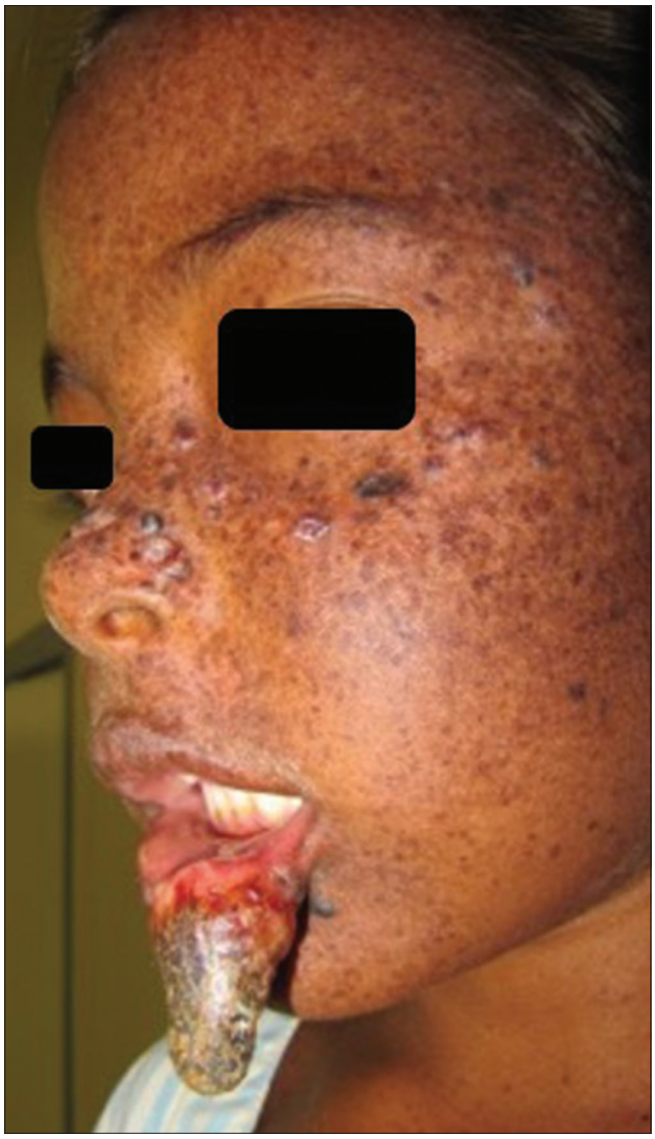

Figure 7c: Patient preoperatively showing lesions on the back and wings of the nose, on the left malar region and on the lower lip in left profile view

Figure 7d: Intraoperative patient after resection of the lesions in frontal plane

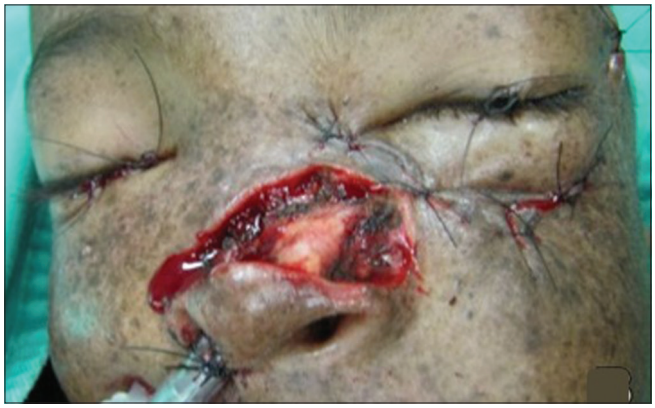

Figure 7e: Intraoperative patient after resection of the lesions, midface close-up

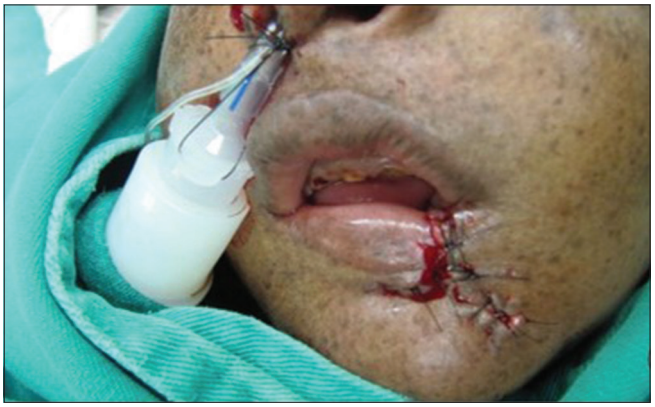

Figure 7f: Intraoperative patient after resection of the lesions, lower face close-up

lesions when exposed to ultraviolet light. We emphasize second-intention healing for the closure of wound areas, called "surgeon-assisted healing," especially for small lesions, which aims to salvage tissue and ensure skin integrity. Furthermore, scar tissue at the site where the lesion was excised may not be affected by neoplasms, preventing the progression of xeroderma pigmentosum, although this tactic limits the aesthetic aspect.

The present study had some limitations, firstly, regarding its methodology, in which only studies since January 2000 were included and with restrictions on their idiom. As for the results, the literature only threw up studies with low evidence levels. For this reason, it was not possible to perform a meta-analysis that could direct treatment guidelines.

Conclusion

Studies with better scientific evidence are needed. Randomized trials or prospective cohort studies should be encouraged in care centers of patients with xeroderma pigmentosum.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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