

CASE REPORT

Xeroderma pigmentosum: a case report and review of the literature

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Key words

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Summary

Inherited molecular defects in nucleotide excision repair genes cause the autosomal recessive condition xeroderma pigmentosum. Xeroderma pigmentosum is characterized by photo-hypersensitivity of sun-exposed tissues, and by a several thousand-fold increase in the risk of developing malignant neoplasms of the skin and of the eyes.

Mutations in xeroderma pigmentosum genes that regulate nucleotide excision repair, not only predispose persons with xeroderma

pigmentosum to multiple malignancies, but also promote premature cutaneous and ocular ageing, and in some cases promote progressive neurodegenerative changes.

This paper describes a case of xeroderma pigmentosum with advanced cutaneous squamous cell carcinoma, actinic cheilitis and ocular lesions in a 19-year old black woman. The extensive ultraviolet radiation-induced skin and eye damage are evidence of neglect of sun-protection and lack of appropriate medical care from childhood.

Introduction

Xeroderma pigmentosum ('dry pigmented skin') (XP) is a hereditary autosomal recessive disorder characterized by mucocutaneous and ocular hypersensitivity to UV radiation with irreparable DNA damage and subsequent malignant changes; and in some subjects also by progressive neurological degeneration [1-6]. The prevalence of XP is 1:1,000,000 in the United States and Europe, and is 1:100,000 in Japan. It is more common in populations where marriage of close blood-relatives is common. There is no sex or race predilection [1, 2].

Xeroderma pigmentosum occurs in subjects with molecular defects in the genes involved in nucleotide excision repair (NER) of ultraviolet-induced DNA lesions leading to premature skin and ocular ageing consequent upon cellular apoptosis and other UV-induced degenerative changes. If sufficient DNA damage occurs, there will be cellular transformation and the development of malignancies [7-9].

The NER pathway is associated with at least 28 genes, some of which are also part of the multi-protein basal transcription factor, TFIIF; and some participate in somatic growth and development [7]. Mutation in any of the NER genes XPA, XPB, XPC, XPD, XPE and XPF cause most of XP [2, 10, 11].

Twenty percent of cases of XP are caused by defects in the XPV gene encoding an error-prone DNA polymerase pol eta that bypasses unrepaired DNA damage. Cells derived from persons with XP owing to XPV mutation have a normal NER pathway but have de-

fective DNA replication after UV-induced DNA damage, thus showing deficient DNA translation synthesis [1, 8, 12].

In subjects destined to have XP, fibroblasts and keratinocytes have normal karyotypes without expressing excessive DNA lesions. However following UV-radiation, XP fibroblasts and keratinocytes show a higher level of genomic mutations compared to normal cells. It is noteworthy that subjects with XP have a 10 to 20-fold increase in various internal neoplasms that have no UV aetiology compared to the general population [1], suggesting that the repair of endogenous oxidative DNA damage may also be dysregulated in some subjects with XP [13].

Case report

A 19-year old black female with XP who was under the treatment of the Department of Dermatology, School of Health Sciences, was referred to the Medunsa Oral Health Centre at Ga-Rankuwa, South Africa, for evaluation of a red lesion on the anterior tongue (Fig. 1). She had severely damaged facial skin (Figs 1, 2), 'salt and pepper' pigmentary changes all over her body (Fig. 3) and bilateral ocular ulcerations (Fig. 4).

There was no history of other family members having XP. The sequence of pathological events in the patient were the appearance of irregular hyperpigmentation of the skin at 2 years of age, early ocular lesions at 3 years, significant visual impairment by 7 years, and the appearance of multiple cancers of the facial skin at the age of

Fig. 1. Severe actinic cheilitis of the upper and lower lips and erosions of the anterior one third of the tongue.



17. The patient does not suffer from any neurodegenerative abnormalities or impairment of intelligence. Until the age of 17 she received neither education regarding protection from sun-exposure nor treatment for

Fig. 2. Severely damaged facial skin, depigmentation, and scattered exophytic lesions, one on the right cheek, confirmed to be squamous cell carcinoma.



Fig. 3. 'Salt and pepper' pattern of depigmentation/hyperpigmentation.

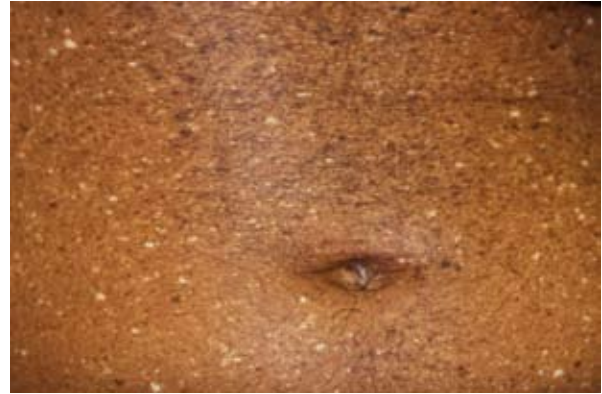


Fig. 4. Severe ulcerations of eyelids and conjunctiva.



her ocular and skin conditions. When the facial skin cancers were diagnosed some were excised. Many of the lymph nodes of the head and neck were enlarged. The lesions of the eyelids and conjunctivas were probably squamous cell carcinoma (SCC), and there was

Fig. 5. Large ulcerated squamous cell carcinoma of the right lower cheek, photographed 3 months after Figure 2.



Fig. 6. Squamous cell carcinoma on the right cheek showing progression 3 months after Figure 2.



severe corneal scarring. There were no neurological abnormalities, and microscopical examination of a biopsy specimen of the tip of the tongue showed no evidence of epithelial dysplasia.

The patient was supposed to undergo surgical removal of the multiple skin SCC and biopsy of the suspicious ocular lesions and of the enlarged right sub-mandibular lymphnode, but for personal and administrative reasons this was delayed.

Three months after our initial examination the facial skin malignancies were worse (Figs. 5, 6). Magnetic resonance imaging of the head and neck showed associated lymphnodes involvement, but there was no infiltration of major vessels or metastases to the brain. Because of the severity and of the extent of the carcinomatous disease, the treatment will be palliative.

Molecular events associated with nucleotide excision repair of UV-induced DNA damage

The nucleotide excision repair (NER) pathway is the mechanism responsible for repairing UV-induced helix-distorting lesions of DNA. NER comprises two sub-pathways, the global genome NER and the transcription-coupled NER [14-16]. Global genome NER recognises and repairs UV-induced DNA lesions in non-transcribed DNA throughout the genome, while transcription-coupled NER is initiated by damaged DNA-induced arrest of transcribing RNA-polymerase II on the transcribed strand of an active gene [10, 13, 15, 16].

The DNA repair pathway of NER is a multi-step mechanism comprising recognition of the UV-induced DNA lesion, unwinding of the DNA from around the lesion, and finally re-synthesis and ligation [15, 16]. XPC protein recognises the DNA lesion and recruits TFIIH to the DNA-damaged site where XPG protein binds it. XPB and XPD helices are two sub-units of TFIIH that open the DNA double helix around the lesion. Subsequently XPA

protein is recruited to the region to stabilize the intermediately open repair site, and positions XPF and XPG endonucleases, enabling them to excise the damaged strand. The cellular replication machinery then fills the remaining gap which is later sealed by ligase [9, 10, 14, 17-20]. The exact rôle of XPE protein in NER activity is unknown, but it has been suggested that it participates in damaged DNA recognition [7, 11, 19]. Thus, subjects with XP have molecular defects in cellular DNA repair mechanisms because of mutations in one or more NER XP genes, leading to hypersensitivity to UV radiation. This results in the accumulation of unrepaired UV-induced DNA damage which either promotes cell death contributing to accelerated skin ageing, or promotes cellular transformation resulting in the development of cancer [9, 16, 17, 19]. Persons with XP are at a several thousand-fold increased risk of skin cancer compared to healthy subjects [13]; and show many features of photo-ageing including corneal opacity, atrophy of both the epidermis and the dermis, poikiloderma (dyspigmentation) and skin laxity [14].

However, clinical manifestations of XP are not predictable according to the type of the XP gene defect: some subjects with different molecular defects may manifest the same clinical features, while other subjects with the same molecular defects may manifest different clinical features [7, 14, 16].

In addition, genetic polymorphism in XP genes may have a functional impact on DNA repair mechanisms modifying cancer risk [21]. Epigenetic diversity and differences in the stochastic nature of the accumulated damaged DNA may contribute to the substantial phenotypic variance among persons with XP carrying the same causative molecular defect [16]. Although XP disorders exhibit phenotypic variability, there are common denominators to all XP variants (photosensitivity, susceptibility to cancer) since the NER mechanism is a multistep sequence, and a molecular defect at one step dysregulates the function of the downstream steps and subsequently of the whole system [7].

Clinical features of Xeroderma Pigmentosum

SKIN

The hallmark of XP is UV-induced skin hypersensitivity manifesting as degenerative and proliferative cutaneous changes, including hyperpigmentation, skin atrophy, poikiloderma, actinic keratosis, basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma [2, 3, 7, 14].

About 50% of persons with XP experience acute sunburn on minimal exposure to UV radiation and tend to develop neurological abnormalities [7].

Cutaneous signs and symptoms usually emerge in children under the age of 2 years [1, 3, 7], and up to 60% of persons with XP will eventually develop skin cancer [3], in many cases with multiple primary lesions [1, 14]. The mean age at diagnosis of XP-associated skin cancer is 8 years, 50 years younger than in the general population [1].

Although dark-skinned people have a lower incidence of skin cancer compared to light skinned people, most probably owing to the photoprotective properties of melanin, dark-skinned and light-skinned people with XP, have similar incidences of skin cancer emphasizing the essential rôle of DNA repair mechanisms even in the presence of protection by melanin [2].

Melanin is always thought to be the agent which provides such protection against UV-induced DNA damage as to be responsible for the difference in the incidence of premalignant and malignant skin lesions in light skinned and dark skinned people. However, the observation that dark skinned persons with XP develop carcinomas on the pigmented parts of the skin as frequently as light skinned persons with XP, brings the importance of the protective rôle of melanin into question.

It may well be that when NER mechanisms are intact, the levels of UV-induced molecular damage in pigment-protected dark skin can be effectively repaired so that cellular transformation and malignant transformation do not occur; but in XP where the NER mechanisms are defective and therefore dysfunctional, the same amount of UV penetration of the pigmented skin produces the same quantum of UV-induced molecular damage, but in this case it is beyond the repair capabilities of the defective NER system, and malignancy may ensue.

By contrast, in light skin, the greater penetration of the UV in the absence of a heavy pigment layer, can bring about molecular damage of an extent that even an intact and fully functioning NER system cannot cope and cellular transformation and malignancy will ensue.

EYES

Between 40% and 80% of persons with XP have ocular abnormalities caused by UV-induced DNA alteration to epithelial cells of the conjunctiva, the cornea, and the eyelid [14, 22]. They also have photophobia, conjunctivitis, keratitis that may lead to corneal opacification, hyperpigmentation of the eyelids, loss of eyelashes, and malignancies including SCC, basal cell carcinoma and melanoma [1-4, 7].

NERVOUS SYSTEM

Between 20% and 30% of persons with XP have neurological abnormalities [2, 5, 7] which may be mild or severe, including loss of fine motor control, ataxia, spasticity, rigidity, loss of hearing and progressive mental retardation [14]. It is presumed that as a consequence of defective DNA pathways associated with mutated XP genes, neurons accumulate endogenous genotoxic-induced DNA damage, and undergo apoptosis leading to loss of neurons [14].

MOUTH

Leukoplakia, erythroplakia and SCC of the tip of the tongue, actinic cheilitis and SCC of the lips are associated with XP. The precancerous and cancerous lesions of the tip of the tongue, sites seldom affected in the normal population group, are presumed to be induced by UV radiation. This is not a convincing explanation but it is the only one offered [1-3, 23].

In the general population, SCC most frequently affects the postero-lateral and ventral surfaces of the tongue and floor of the mouth of elderly users of tobacco and alcohol, and runs an aggressive course. By contrast XP associated SCC affects the tip of the tongue of persons younger than 20 years of age and runs a slowly progressive course [2, 3].

Treatment

The treatment of XP is challenging because it is a multi-organ and multi-system disease, and because usually by the time of diagnosis, significant tissue damage has already occurred [23]. Malignant tumours may already have developed by the third or fourth year of life [24]. Early diagnosis and immediate implementation of rigorous sun-protection measures may prolong the lives of persons with XP [7, 23]. About two thirds of unmanaged subjects die before the age of 20 years [24], but as reported by Clever and Revet [6], in climates with intense sunlight exposure, children with XP who do not implement sun-protection measures and have limited access to modern medical care, have a life expectancy of about 10 years.

Persons with XP must avoid exposure to any sources of UV light including sunlight, fluorescent, halogen and mercury-vapour lights [2], and must wear protective clothing and UV-absorbing eye glasses, and must use high protection factor sunscreens [1].

XP associated cutaneous, ocular and oral lesions and disorders should be treated as in any other person. Topical application of 5-fluorouracil or imiquimod is appropriate for premalignant and surgical excision for malignant neoplasms of the skin, tongue, eyelids, conjunctiva and cornea. Methyl cellulose or quinodine-containing eye drops, and bland ointment at night, constitute correct eye-care [1, 3].

It must be remembered that persons with XP who are properly protected from sun-light may suffer consequential vitamin D deficiency, and they should routinely take vitamin D supplements [2].

Comments

This paper describes a typical case of xeroderma pigmentosum in a young woman of 19 years who had advanced SCC of the skin, actinic cheilitis, and ocular lesions such that she has been declared legally blind, but she does not have neurological abnormalities. Her extensive and striking UV-induced skin and eye damage are tragic evidence of the consequences of the lack of sun-protection, and of appropriate medical care from an early age.

Considering the sunny climate where she lives and her complete lack of protective measures and the reported life expectancy of sufferers from XP living in similar circumstances, it is remarkable that she has lived so long. Patients with rare photodermatoses such as xeroderma pigmentosum are put at risk by exposure even to sources

of low-level ultraviolet radiation (UVR). This risk has increased in recent years, with the increased use of high-intensity discharge light sources such as energy-saving fluorescent lamps which emit higher levels of UVR and blue light than do low-intensity incandescent light sources which emit light towards the yellow/red end of the spectrum [25, 26].

Prolonged exposure to high-intensity discharge light-sources, in particular at short range may constitute a health

risk not only to photosensitive people, but even to the general population [27], making this a public health concern. There is evidence that exposure to indoor electrical light sources, aggravates photosensitive-related skin conditions including xeroderma pigmentosum and lupus erythematosus [27, 28], so photosensitive individuals should avoid exposure to high-intensity discharge light sources; and should implement light protection measures even indoors.

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