

## Case of xeroderma pigmentosum with well differentiated squamous cell carcinoma in the eye

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### Abstract

A seven year old female child presented with complaints of increased freckling over the face since the age of two years and a rapidly growing mass over the right eye. She underwent excisional biopsy of the mass over the eye which on histopathological examination was diagnosed as squamous cell carcinoma.

**Keywords:** Xeroderma pigmentosum, freckles, malignant tumour, excision biopsy, squamous cell carcinoma of eye

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Xeroderma pigmentosum (XP) is a group of rare inherited skin disorders characterized by photosensitivity and premature skin aging with early onset of freckle-like pigmented macules limited to the sun exposed areas and later development of skin cancers. Chronic sun exposure causes marked alterations in the skin leading to keratosis, telangiectasia, atrophy and development of malignant tumours like squamous cell carcinomas, basal cell carcinoma, malignant melanoma, fibrosarcoma etc. The pathogenesis in a majority of these cases involve a defect in the mechanism of DNA repair due to an inability to initiate excision repair of pyrimidine dimers and other photoproducts.

A case of xeroderma pigmentosum who presented with ophthalmic problems is presented.

### Case history

G.C, a seven year old female child was brought by her father to the Ophthalmology OPD at Kathmandu Medical College, Kathmandu in September, 2003 with complaints of increased freckling over the face since the age of two years and a rapidly growing mass over the right eye for the last one and a half months.

She was apparently well till two years of age when her parents noticed multiple discrete, dark pigmented lesions over her forehead. Similar lesions gradually appeared over the subsequent years over her face, neck, forearms and legs. Since early childhood, she was unable to open her eyes in bright light and there was constant watering from both eyes. She was taken to various eye hospitals and was prescribed various drop and ointment preparations.

There was no history of seizures or difficulty in hearing. She had a good appetite with normal bowel movements. There was no history of consanguinity in the family and no history of similar skin condition in the family. She was the youngest among three siblings and the two older brothers were in good health. There was a history of poor vision in two of her first cousins on the paternal side of the family, but the cause for this could not be ascertained.

On general examination, she was pale, underweight and short for her age. There was increased freckling of the skin over all the exposed areas like face, neck, arms and legs. The skin over the covered areas was normal.

Ocular examination revealed that the patient was highly photophobic. The ocular movements were normal. The skin over both the lids was markedly pigmented. The conjunctiva was congested with and there were vascular pterygium on the medial side in both eyes.

There was a round, non-pigmented growth on the temporal side of the limbus measuring 1 cm horizontally and 0.5 cm vertically, encroaching over about 2mm of the cornea.

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**Fig. 1:**



The cornea was clear and rest of the anterior segment was normal in both eyes. Detailed fundal examination could be done only under general anaesthesia after dilating the pupil with mydriatics and revealed no abnormality.

On CNS examination, the child was intelligent with normal higher mental functions. Cranial nerves were intact. Motor examination including deep tendon reflexes was normal and all sensory modalities were intact. ENT evaluation showed normal hearing.

Systemic examination for respiratory system, cardiovascular system and abdomen revealed no abnormality.

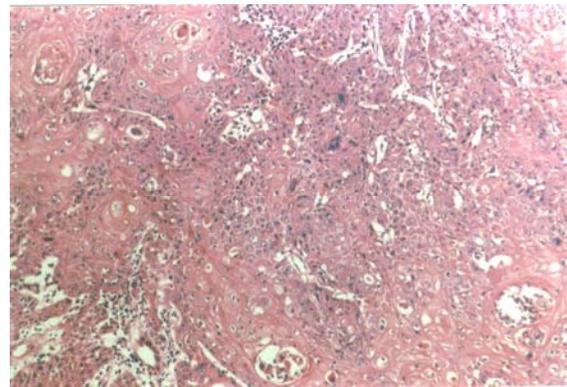
Excision biopsy of the growth in the eye was performed under general anaesthesia. The pre and post operative periods were uneventful.

**Fig. 2:**

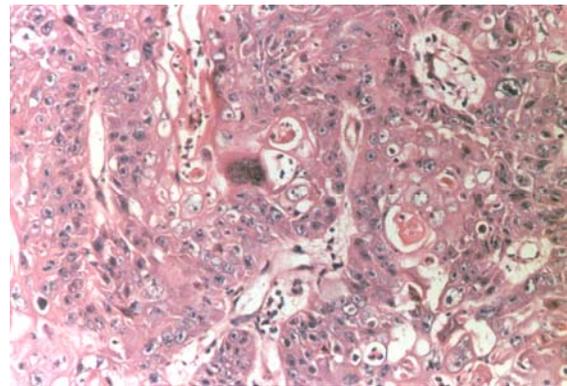


Histopathological examination of the excised mass showed features of a well differentiated squamous cell carcinoma. The tissue was lined by dysplastic stratified squamous epithelium showing severe dysplasia. The basement membrane was interrupted and tumour cells were seen in the sub-epithelium. These cells were arranged diffusely, in nests and in cords. The tumour cells were highly pleomorphic with abundant eosinophilic cytoplasm and central round to oval vesicular nuclei with prominent nucleoli. Atypical keratotic cells and keratin pearls were also seen. Marked inflammation was seen in the stroma (Fig 3 & 4).

**Fig. 3**



**Fig. 4**



In order to avoid further recurrence, the margins were well cauterized after removal of the growth.

Prior to discharge, the patient was advised strictly to avoid sun exposure by not going out into the sun, keeping rooms darkened by keeping curtains drawn at all times and wearing clothes covering as much of the body as possible. Use of sunblocks, hats and dark goggles was also advised. The father was explained in detail about the chances of recurrence of the growth and the importance of the above mentioned

preventive measures. The need for regular follow up was also emphasized and since they hailed from a long distance away, follow up after three months was advised.

### Discussion

Xeroderma pigmentosum was first described in 1874 by Hebra and Kaposi.<sup>1</sup> In 1882, Kaposi coined the term “xeroderma pigmentosum” for the condition referring to its characteristic dry pigmented skin. It was also named as atrophoderma pigmentosum by Crocker.<sup>2</sup>

Xeroderma pigmentosum (XP) is a group of rare inherited skin disorders characterized by a heightened reaction to sunlight (photosensitivity) with skin blistering occurring after exposure to the sun. In some cases, pain and blistering may occur immediately after contact with sunlight. Acute sunburn and persistent redness or inflammation of the skin (erythema) are also early symptoms of XP. In most cases, these symptoms may be apparent immediately after birth or occur within the next three years. In other cases, symptoms may not develop until later in childhood or, more rarely, may not be recognized until adulthood. Other symptoms of XP may include discolorations, weakness and fragility, and/or scarring of the skin.

XP affects the eyes as well as the skin and has been associated with several forms of skin cancer. In some cases of XP may occur along with dwarfism, mental retardation, and/or delayed development.

Several subtypes of XP (i.e., XP complementation groups) have been identified, based upon different defects in the body’s ability to repair DNA damaged by ultraviolet light (UV). According to the medical literature, the symptoms and findings associated with the classic form of xeroderma pigmentosum, known as XP, type A (XPA), may also occur in association with the other XP subtypes. These include: XP, type B (XPB); XP, type C (XPC); XP, type D (XPD); XP, type E (XPE); XP, type F (XPF); and XP, type G (XPG). These XP subtypes are transmitted as an autosomal recessive trait. In addition, another subtype of the disorder, known as XP, dominant type, has autosomal dominant inheritance.

In addition to the XP subtypes discussed above, researchers have identified another form of the disorder known as XP, variant type (XP-V). As with the other XP subtypes, symptoms and findings associated with the classic form of XP may also be seen in individuals with XP-V. XP-V cells have a normal or near normal ability to repair UV-induced

DNA damage (nucleotide excisional repair); however, they are defective in replicating UV-damaged DNA during the division and reproduction of cells. Although the disorder’s mode of inheritance is unknown, most researchers suspect that XP-V is transmitted as an autosomal recessive trait.

### Pathophysiology

The basic defect in XP is in the nucleotide excision repair (NER), leading to deficient repair of DNA damaged by UV radiation. This intensively studied process consists of the removal and replacement of damaged DNA with new DNA. Two types of NER exist- global genome (GG-NER) and transcription coupled (TC-NER). The last decade has seen the cloning of the key elements of NER, and the process has been reconstituted *in vitro*.<sup>3</sup>

Seven XP repair genes, XPA through XPG have been identified. These genes play key roles in GG-NER and TC-NER. Both forms of NER include a damage sensing phase, performed in GG-NER by the product of the XPC gene complexed to another factor. In addition, the XPA gene product has been reported to have an affinity for damaged DNA. Therefore, XPA likely plays a role in the damage sensing phase as well.

In addition to the defects in the repair genes, UV-B radiation also has immunosuppressive effects that may be involved in the pathogenesis of XP. Although typical symptoms of immune deficiency such as multiple infections are not usually observed in patients with XP, several immunologic abnormalities have been described in the skin of patients with XP. Clinical studies of the skin of patients with XP indicate prominent depletion of Langerhans cells induced by UV radiation. Various other defects in cell mediated immunity have been reported in XP.

The incidence of XP in the US is 1:2,50,000, with group XPC being the most common form.<sup>4</sup> In Japan, the incidence is higher and occurs in 1: 40,000 individuals. The XPA form is the most common form in Japan.

In Nepal, few cases of XP have been reported. One study by Karmacharya et al in 1987, most of the cases of XP were found to be from Western Kathmandu and Lumbini zone.<sup>5</sup> Another interesting case report presented a whole family including both parents and their five children, in Tunisia, were affected by Xeroderma pigmentosum.<sup>6</sup>

XP is transmitted in most cases as an autosomal recessive manner but in our case, the pedigree did not reveal a family history. However, genetic

counselling can help to reduce the incidence of the disease in the community. The disease can be diagnosed prenatally by genetic counselling in which cells from amniotic fluid are cultured to establish the diagnosis and if indicated, termination of pregnancy is carried out.<sup>7</sup>

XP is seen either in infancy or early childhood especially around the age of two.<sup>8</sup> It has been reported in all races, including the Negro despite the protective nature of skin pigmentation found in this race. The incidence has also found to be equal in both sexes.

The clinical course of the disease can be divided into three stages. The skin is healthy at birth. Typically, the first stage makes its appearance after the age of six months. This stage is characterized by diffuse erythema, scaling and freckle-like areas of increased pigmentation in sun-exposed areas, with initial involvement of the face. With progression of the disease, the skin changes appear on the lower legs, neck and arms. While these features tend to diminish during the winter months with decreased sun exposure in the initial stage of the disease, they become permanent as time passes. The second stage is characterized by poikiloderma, which consists of skin atrophy, telangiectasias and mottled hyper and hypo pigmentation.

The third stage is heralded by the appearance of numerous malignancies, including squamous cell carcinomas, malignant melanomas, basal cell carcinomas and fibrosarcomas. These malignancies may occur as early as at 4-5 years of age, and are more prevalent in sun-exposed areas.<sup>9,10</sup>

Ocular problems occur in nearly 80% of individuals with XP. The initial problems begin with photophobia and conjunctivitis. Eyelid solar lentigenes occur in the first decade of life and may transform later into malignant melanomas. Other ocular findings include ectropion, symblepharon with ulceration, repeated conjunctival inflammations, infections and scarring. In addition, vascular pterigia, fibrovascular pannus of the cornea and epitheliomas of the lids, the conjunctiva and the cornea can occur. Finally, the propensity for malignancies, such as squamous cell carcinomas, basal cell carcinoma, sebaceous cell carcinomas and fibrosarcomas can also involve the eye of the patient with XP. In our case also, the child had well differentiated squamous cell carcinoma near the limbal region in the right eye.

Neurologic problems are seen in nearly 20% of patients with XP, more commonly in groups XPA and XPD. The severity of these problems is proportional to the sensitivity of XP fibroblasts to

UV radiation. The problems include microcephaly, spasticity, hypo or areflexia, ataxia, chorea, motor neuron signs, sensorineural deafness, supranuclear ophthalmoplegia and mental retardation. The neurologic problems might overshadow the cutaneous manifestations in some patients with XP.

De Sanctis- Cacchione syndrome refers to the combination of XP and neurological abnormalities including mental retardation and cerebellar ataxia, hypogonadism and dwarfism.

Fortunately, none of the above mentioned neurological problems were seen in our patient.

A few studies have also shown a co-relation between the risk of primary lung cancer and polymorphism of the DNA repair gene, especially among smokers in group A and group G of XP.<sup>11,12</sup>

No consistent routine lab abnormalities are present in XP. The diagnosis is based mostly on clinical findings and biopsy analysis. However, many studies can be performed in specialized laboratories to help in diagnosing the condition. These studies include cellular hypersensitivity to UV radiation, chromosomal breakage studies, complementation gene sequencing to identify the specific gene complementation group.

Antenatal diagnosis is possible by amniocentesis or chorionic villi sampling. A faster technique is the alkaline comet assay (single cell gel electrophoresis assay)<sup>13</sup>. Sometimes, electroencephalographic findings may also be abnormal.

In our case, however, the diagnosis was made on the basis of history, clinical features and the histopathological reports on the lesion.

Malignant melanomas and squamous cell carcinomas are the two most important causes of mortality in patients with XP. Patients younger than twenty have a thousand fold higher incidence of non-melanoma skin cancer and melanomas. The mean age at which XP patients develop skin cancer is eight years while the mean age for the same in a healthy population is sixty years. Actinic damage occurs in XP patients by age of one to two years.

Although XP is ultimately fatal, life can be prolonged by paying strict attention to simple preventive measures to minimise sun exposure. The aim of the treatment is to educate the patient regarding these measures, to provide regular check ups with a dermatologist and to detect and treat early any malignancies that may occur.

The use of sunscreens in conjunction with other sun-avoidance methods e.g. protective hats, eyewear etc. can minimize UV induced damage in patients with

XP. Oral retinoids have been shown to decrease the incidence of skin cancer in patients with XP, but the therapy is limited by dose-related irreversible calcification of ligaments and tendons<sup>14</sup>. Chemical therapy with 5-fluorouracil may be useful for actinic keratoses and a new approach to photoprotection is to repair DNA damage after UV exposure, which is accomplished by delivery of a DNA repair enzyme into the skin by means of specially designed liposomes. A topical formulation of a bacterial T<sub>4</sub> endonuclease is being investigated<sup>15</sup>.

Similarly, equally important aspects of the treatment of the patient with XP include the provision of surgical care for the complete excision of malignancies associated with XP, consultation with ophthalmologists for ocular problems and with neurologists for the neurological problems.

Follow up care should be provided through outpatient visits every three months. The health care provider must seize the opportunity provided by these visits to educate the patient and their parents regarding the importance of sun protection and early detection of skin cancers.

Genetic counselling should be offered to families at risk.

The prognosis of this disease is poor with fewer than 40% of patients surviving beyond the age of twenty. Individuals with milder forms of the disease, may however, survive beyond middle age.

In the United States, the Xeroderma Pigmentosum Society was founded by Caren and Dan Mahar, whose youngest daughter has XP. It is a charitable non-profit organization dedicated to helping XP patients and their families.

### Conclusion

XP is a rare genetic disease characterized by defective DNA repair leading to clinical and cellular hypersensitivity to ultraviolet radiation. General features of the disease include parental consanguinity, onset of symptoms in the first two years of life, pigmentation or freckles in the sun exposed parts of the body and later, development of premalignant and malignant skin lesions. Ocular and neurological manifestations may also occur. Ocular features include lid freckles or atrophic skin lesions, lower lid tumours, chronic conjunctival congestion, corneal opacification, squamous cell carcinoma of the limbus, bilateral pterygium, visual impairment, etc. Treatment is aimed at education to minimize sun exposure and regular follow up for early detection and treatment of skin cancers. Prognosis is poor with

less than 40% of those affected surviving beyond the second decade.

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