



Case Report

A SCITECHNOL JOURNAL

Xeroderma Pigmentosum: A Case Report of Two Siblings

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Abstract

Xeroderma pigmentosum (XP) is a rare disorder, inherited as an autosomal recessive genodermatosis. It is characterized by photosensitivity, freckly pigmented changes, premature skin ageing, teleangiectasis, warty and papillomatous growth and malignant tumor development in later stage. It results from mutation in seven nucleotide excision repair gene (XP-A to XP-G complement groups) and post replication repair defect (XP-Variant). We present a case of two siblings. The first 5 year old and the other is 3 year old male child, both affected by Xeroderma Pigmentosum.

Introduction

Xeroderma Pigmentosum (literally means dry pigmented skin) is defined by extreme sensitivity to sunlight, resulting in sunburn, pigment changes in the skin and greatly elevated incidence of skin cancers (Alan R Lehman et al.). Herberich and Kaposi first described Xeroderma Pigmentosum in 1974 [1,2]. Kramer et al. found an equal sex predilection and significant parental consanguinity, confirming an autosomal recessive inheritance pattern [3]. The incidence of XP seems to vary across the globe. The incidence reported in US and Europe is 1:250000 and in Japan and other countries at a higher frequency 1:40000. Its incidence is not that significant in context to the other part of the world [4]. The basic defect underlying the clinical manifestations is a nucleotide excision repair (NER) defect leading to a defective repair of DNA damaged by ultra violet (UV) radiation [5] [3]. Historically, the disease was classified as classical XP with only skin abnormalities and the De-Sanctis-Cacchione syndrome with skin abnormalities and extreme neurological degeneration was evident [1]. Xeroderma Pigmentosum is variably also known as Kaposi Disease, Xeroderma Pigmentosum Variant Type, XP-V and XP. At least eight inherited forms of xeroderma pigmentosum have been identified till date. They are

1. Xeroderma Pigmentosum, Type A, I, XPA, Classical Form
2. Xeroderma Pigmentosum, Type B, II, XPB
3. Xeroderma Pigmentosum, Type C, III, XPC
4. Xeroderma Pigmentosum, Type D, IV, XPD
5. Xeroderma Pigmentosum, Type E, V, XPE
6. Xeroderma Pigmentosum, Type F, VI, XPF
7. Xeroderma Pigmentosum, Type G, VII, XPG
8. Xeroderma Pigmentosum, Dominant Type [6,7]

XP is an autosomal recessive disorder with 100% penetrance and

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Received: August 20, 2012 Accepted: September 17, 2012 Published: September 24, 2012

can result from mutation in any one of eight genes. The products of seven of these genes i.e. XP-A through G are involved in the repair of UV induced photoproducts in DNA by the process of nucleotide excision repair. Defects in the eight XP gene (XP-V) do not affect NER. Instead these so called XP variants have hitch replicating DNA containing UV induced damage. The molecular defects in XP cells result in an elevated induction of mutations in sun exposed skin of affected individuals. This mutation probably is the reason for the pigmentation change and the skin cancer. The causes of the neurological abnormalities are yet not known. It has been suggested that it may be due to oxidative DNA damage generated during normal metabolism in the central nervous system. This type of damage may be repaired by NER. Thus in the absence of normal functional repair by NER, neurological deficit takes place [4]. In general the signs and symptoms of xeroderma pigmentosum starts from the age of 1-2 years. The disease begins with photosensitivity and burning sensation after nominal sun exposure in 60% of cases. Cutaneous manifestations include dryness of skin (Xeroderma), pigmentation (pigmentosum), freckling and telangiectasis. Ocular abnormalities include photophobia, ectropion, conjunctival infection, keratitis with incidence of tumors like SCC, melanoma and epithelioma. There is a 10000 fold increased risk of skin cancer on sun exposed sites. A one-fifth of patients (20-30%) have associated abnormalities such as gait disturbance, aflexia, difficulty swallowing, deafness, growth delay, and low intelligence [4,8].

Case Presentation

Case 1

A 5 year old male child was diagnosed with xeroderma pigmentosum when he reported to the Department of Oral and Maxillofacial Pathology and microbiology, Sharad Pawar Dental College and Hospital, Wardha, Maharashtra, India in the year 2011. At the age of 8 months he presented with numerous brownish-black pigmentation of the face, which was initially less in number and progressed with the age (Figure 1). Gradually the pigmentation started to appear on the hands, neck, trunk, groin, thighs and legs. Pigmentation was sparse on the unexposed area to sun like trunk, groin, thighs and legs where as on sun exposed area of the body like face, neck and hands the pigmentation was abundant and darker in colour (Figure 2). Dry skin of the face and hand was also observed. At the age of 4 years he presented with a growth on left side of the face whose surface was ulcerated. The growth was approximately 7x7cm in size, round to oval in shape with a central depression giving umbilicated appearance. The growth covers the left eye sparing the



Figure 1: Case # 1: Ulceroproliferative lesion on right side of the face.

upper eyelid. The left upper eyelid is pushed upwards due to the growth. On asking the relevant history to his parents it was found that the patient had difficulty in walking. His IQ was also low as he was not oriented to time, place and person. Incisional biopsy was taken from the face for the histopathological diagnosis. Histopathological diagnosis was moderately differentiated squamous cell carcinoma (Figure 3). Immunohistochemistry staining for p53 was also carried out and was found to be positive. The patient was advised for the surgical resection of the tumor. The patient was also advised to apply sun block on exposed skin and to avoid exposure to sunlight.

Case 2

His 3 year old brother was also diagnosed with xeroderma pigmentosum on clinical examination. The clinical examination included evaluation mucosa, eye and psychiatric analysis. Other than dermatological findings, no other clinical findings were present. He presented with brownish-black pigmentation on the sun exposed part of the body like face, hands and neck at the age of 2 years (Figure 4). Dry skin was also evident. He also complained of burning sensation on exposure to sunlight. On asking relevant history to his parents, he did not have difficulty on walking. Psychiatric analysis revealed that the patient was oriented to time, place and person and his mental IQ was average. The patient was advised to apply sun block on exposed skin and avoid exposure to sunlight. Patient was recalled for follow up every month. Unfortunately, both the patient did not turn up to our institution. Thus, we do not have follow up record for the patient.

Discussion

Xeroderma pigmentosum is autosomal recessive genetic disease caused by defects in the normal repair of DNA of various cutaneous and ocular cell types damaged by exposure to sunlight [8]. The basic defect underlying the clinical manifestations is a nucleotide excision repair (NER) defect leading to a defective repair of DNA damaged by ultra violet (UV) radiation [9]. Defects in NER are result in rare, autosomal recessive syndromes xeroderma pigmentosum (XP), Cockayne syndrome (CS), and trichothiodystrophy (TTD). Inherited defects in NER causes Xeroderma pigmentosum (XP) [10]. This



Figure 4: Case 2: Showing pigmentation of face.

disease is pigeonholed by photosensitivity, hyperpigmentation and ichthyosis (dry, scaly skin) in sun exposed areas, a 1000-fold increase in the risk of basal and squamous cell carcinomas and melanomas of the skin and eyes [11]. Increased mutagenesis is accepted as the basis of elevated skin cancer incidence in XP [10]. Roughly 30% of XP patients develop progressive neurologic symptoms. There are seven complementation groups of XP (XP-A to -G) caused by defective NER, corresponding to mutations in the genes encoding XPA, XPB, XPC, XPD, XPE, XPF and XPG. The rigorosity of symptoms in XP varies broadly, with the age at diagnosis ranging from early infancy to adulthood, and for the most part correlates with the extent to which the mutation affects NER [12]. Mutations in genes encoding three of the ten components of the multifunctional protein complex TFIIH—XPB, XPD, and p8/TTD-A—are associated with the widest clinical diversity, ranging from XP to XPCS, TTD, and XP/TTD. In DNA repair via the NER pathway, the XPB and XPD helicase subunits of TFIIH, together with p8/TTD-A, cooperate to unwind DNA surrounding the lesion. TFIIH also opens promoters for RNA polymerase (Pol)II, and RNA PolI transcription and mediates some forms of activated transcription. In addition, TFIIH has putative roles in p53-dependent apoptosis, cell cycle regulation, and resistance to oxidative stress [10]. XP is more commonly seen in populations where marriage of close blood relatives is common [11]. Xeroderma Pigmentosum has been reported worldwide in all races with an overall prevalence of 1-4% per million [13]. Treatment of the disorder includes avoidance of Ultra violet radiation, topical application of 5- fluorouracil to treat actinic keratoses, and regular evaluation by an ophthalmologist, dermatologist, and neurologist. Genetic counseling is an important aspect as an increased incidence of consanguineous marriages has been reported with this disorder [11]. A case of xeroderma pigmentosum should be give utmost importance by the panel of doctors, to improve the life expectancy of the affected individual. There are very few cases of xeroderma pigmentosum reported in literature from India. Reporting every case might help us to know the incidence and prevalence of XP in India which is yet unknown.



Figure 2: Case # 1: Pigmentation on neck, trunk, groin and thighs.

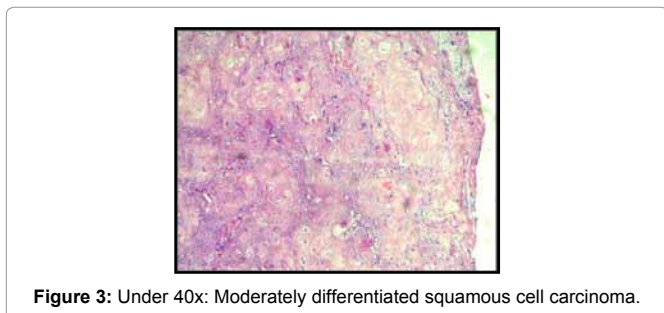


Figure 3: Under 40x: Moderately differentiated squamous cell carcinoma.

Conclusion

Xeroderma pigmentosum is a life threatening disorder, as various malignancies may occur at an early age, so early diagnosis and management may prove fruitful. Genetic counseling implicating the effect of consanguineous marriages should be emphasized.

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