Case Report

# Xeroderma Pigmentosum with Malignant Transformation in a 2-Year-Old Boy

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## Abstract

Xeroderma Pigmentosum (XP) is a rare autosomal recessive disorder characterized by photo sensitivity and increased propensity for development of skin malignancies in affected individuals. We report a 2year 6months old boy who was diagnosed with XP with unusual malignant transformation of his facial ulcers into squamous cell carcinoma (SCC) at such a young age. He received 3 courses of chemotherapy comprising of cisplatin, cyclophosphamide and adriamycin at 3weekly intervals with remarkable clinical improvement. The boy's two older female siblings were also diagnosed with XP and their biological parents are first cousins. This case emphasizes the role of consanguinity in disease transmission and the effectiveness of multidisciplinary team management in patient care for optimal outcome.

**Keywords**: Xeroderma Pigmentosum, Malignancy, Squamous cell Carcinoma, Consanguinity, Child

## INTRODUCTION

Xeroderma Pigmentosum (XP) is an extremely rare autosomal recessive disorder characterized by increased sensitivity to sunlight and tendency to develop skin malignancies due to defect in the enzyme system that repairs DNA after damage from ultraviolet rays. Over 50% of affected individuals show exaggerated and prolonged sunburn response, particularly in sun exposed areas of the body.[1] This exaggerated response is greatest on the skin of the face, upper extremities, eyelids and the surface of the eyes, though the tip of the tongue may also be damaged.[2] The incidence of XP ranges from 1:250,000 in the USA to 1:20,000 in Japan, though it may be found in all racial groups with equal sex distribution, reflecting the underlying autosomal recessive pattern of its inheritance. [2, 3, 4]A recent survey also reported an estimated 2.3 million live births in the incidence of XP in Western Europe.[5]

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Data on the incidence of XP in Africa and the Middle East is rather scanty, however consanguinity plays an important role in these regions from the few available reports.[6,7] We present a 2-year-old male child with xeroderma pigmentosum and consequent malignant transformation of his facial ulcers into squamous cell carcinoma.

## CASE REPORT

A 2-year 6 months-old male child was brought to the Plastic surgery unit of our hospital by his parents who are first cousins. The parents narrated complaints of photosensitivity, multiple and generalized non itchy painless pigmented skin lesions which were worse on sun exposed areas shortly after the boy's birth. A year after birth, the boy developed non healing bilateral temporal facial ulcers which had been gradually increasing in size. Occasionally, the ulcers bled spontaneously with attendant purulent discharge. The parents sought traditional herbal treatment with no improvement and the ulcers subsequently increased substantially in size with occlusion of the right eye. He also had recurrent fever and progressive generalized body weakness with no constitutional symptoms of cough or respiratory difficulty. There was no history of seizures, altered sensorium, abdominal or genitourinary symptoms. He had normal developmental milestone and childhood immunizations without any known drug allergy. The parents also confirmed similar photosensitivity and generalized pigmented lesions without ulcers in the boy's two older female siblings aged 7 years and 4 years. The parents decided to seek medical intervention because of the non-healing ulcers on the boy's face. Both parents had no skin lesions or history of photosensitivity.

Clinical examination of the boy showed a rather sad stoic ill child with a height of 82 cm and weight of 8Kg which was 67% of expected for his age and a body mass index (BMI) of 10.8. He was pale and dehydrated and had multiple generalized pigmented skin lesions with a few scaly and raised lesions from scratching. His temperature was 36. 8C and he was anicteric. There were two ulcers in both temporal regions and a satellite ulcer on the scalp. The right temporal ulcer measured 8 x 5 cm in dimension and extended from the right cheek to the lateral canthus of the right eye while the left ulcer measured 11 x 10 cm and extended from below the left ear lobe to the parietal and left cheek (Figures 1& 2). Both ulcers had rolled everted edges, dirty floor and indurated base that bled on touch. Other systems were unremarkable. He had no focal neurological deficit.

A clinical working diagnosis of epidermodysplasia verruciformis was entertained with differential diagnosis of congenital ichthyosiform erythroderma and malignant ulcers.

At this stage, the pathologists and dermatologists were invited to review the patient with the plastic surgeons on the further management of the boy. The two older siblings were also invited and examined clinically. Both siblings had similar multiple hyperpigmented skin lesions distributed floridly on the face and upper limbs with sparing of the trunk, abdomen, and lower limbs (Figure 3). Incisional biopsies were taken from the facial ulcers of the boy, and from intact pigmented raised lesions from all three siblings for histopathological assessment. Tissue biopsies of the raised pigmented lesions from the three siblings showed distinctive features of hyperkeratosis, mildly atrophic epidermal layer, melanin incontinence spilling into the papillary dermis and mild superficial perivascular inflammation with vascular telangectesia confirming the diagnosis of xeroderma pigmentosum and moderately differentiated squamous cell carcinoma of the facial ulcers (Figures 4 &5). Consequent to this histopathological diagnosis, the multidisciplinary management team was expanded to include the paediatricians, radiologists, radiation oncologists and radiation nurses as well as social workers. A philanthropist also took up the financial aspect of his hospital stay and clinical management due to the parents' financial constraints.

Patient commenced nutritional rehabilitation, infection control with regular dressing of wound sites. He also had blood transfusions to optimize and ensure his fitness for chemotherapy. With a body surface area of 0.4$m^2$, he commenced three- weekly courses of chemotherapy comprised of cisplatin - 50 mg/$m^2$, Adriamycin- 50 mg/$m^2$ and cyclophosphamide -500 mg/$m^2$ in appropriate volume of paediatric saline, after ensuring patient fitness on day 1 of each course. He has received 3 of the 6 scheduled courses along with other supportive care. Chemotherapy was well tolerated with minimal side effects as evidenced by reduction in tumour size, reduced facial ulceration and discharge, with significant reduction in compression of the right eye (Figures 6 & 7) and overall improvement in quality of life of patient. Both parents were counseled on the illness and management protocol for the boy.

## DISCUSSION

Xeroderma pigmentosum (XP) was first described in 1874 by Moriz Kaposi in Vienna. It is an autosomal recessive genodermatosis characterized by increased sensitivity to sunlight and risk of skin cancers such as malignant melanoma (MM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The main defects in XP is in the nucleotide excision repair (NER), which leads to deficient repair of DNA

damaged by ultraviolet radiation.[8] Overall, nine gene mutations namely XPA, ERCC3, XPC, ERCC2, DDB2, ERCC4, ERCC5, ERCC1 and POLH have been reported. The most common of these in United States, Europe and North Africa is XPC.[6,9,10] The particular defect in this case was not identified due to absence of facility for genetic study and analysis.

Consanguinity confers higher risk as seen in these 3 children who are products of a monogamous consanguineous marriage with parents that are also children of siblings from the same parents. Consanguinity plays a significant role in the transmission of this disease in settings where consanguineous marriage is rife as evidenced by documented reports from Egypt, Pakistan and Nigeria.[11,12] The 2 year old in our case had more severe clinical manifestation with malignant transformation into squamous cell carcinoma (SCC) unlike the older siblings. 1.4% cases of XP has been documented to progress into SCC from several reports. [1, 12, 13] The clinical manifestation of XP appears to be more severe in the males though there is equal sex affectation as seen in these children.[3]

The diagnosis requires clinicopathological correlation with assessments of skin biopsies and genetic studies which will aid in differentiating from other genodermatosis such as epidermodysplasia verruciformis characterized by hyperkeratosis, mild to moderate acanthosis, and large intraepidermal cells with blue-gray cytoplasm having perinuclear halos[14] while icythyosis is characterized microscopically by hyperkeratosis, parakeratosis, mild acanthosis with a normal or slightly thickened granular layer and separation of edematous keratinocytes.[15] . Whereas, XP has distinctive hyperkeratosis, atrophic epidermal layer, melanin incontinence spilling into the papillary dermis and mild superficial perivascular inflammation with vascular telangectesia as seen in the three siblings' tissue biopsies. Genetic studies is also desirable in confirming the particular mutational defect involved. However, we do not have the facility for genetic analysis.

Squamous cell carcinoma with background xeroderma pigmentosum in paediatric age is very rare and presents multiple clinical management dilemma because of paucity of standardized guideline for children, however, treatment generally follows the pattern instituted in adults.[16, 17] In early localized disease, surgery is the mainstay of treatment with either wide local excision with clear margin or Mohs micrographic surgery for invasive tumour in the face region.[18,19] Wide local excision was not considered for this boy because of involvement of the eyes and ears and the resultant huge cosmetic defect that would be left following the surgery. However, it is recommended that surgical excision could be followed by adjuvant radiotherapy or cyclical chemotherapy to improve locoregional control in high-risk patients.[18,19] Radiotherapy in this patient was also not considered because of the extensive spread of the tumour in the face and neck regions with involvement of critical structures of the eyes and ears. Radio-therapeutic tumour control in this instance did not justify the significant damage that would have resulted to these critical structures. Also, the young age of the patient and background genetic disorder of xeroderma pigmentosum with increased risk of developing other cutaneous malignancies which may be precipitated by radiotherapy negated radiotherapy. Chemotherapeutic agents such as oral capecitabine, 5-fluorouracil, cisplatin, cyclosphosphamide and adriamycin have been used in extensive, widespread tumour or metastatic condition with varying degrees of responses in other patients.[18-21] This boy had 3 courses of chemotherapy and responded well with significant tumour and ulcer reductions and improved general condition. Also, targeted therapy such as alpha interferon, cetuximab and gefitinib have been used in selected patients with promising results of increase in survival rates.[18-21]

The main goal of management in this boy was palliation to reduce tumour burden and improve his quality of life, which were both achieved. Furthermore, this achievement would have been impossible without the philanthropic gesture and multidisciplinary management team approach.

## CONCLUSION

In conclusion, cutaneous malignant transformation though common in xeroderma pigmentosum is rare in paediatric age as seen in this case. The associated parental consanguinity also significantly increased the risk of developing this uncommon disease.

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