

Suspected case of stage 3 Xeroderma pigmentosa: a case report

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SUMMARY

Xeroderma pigmentosum (XP) is a condition inherited as an autosomal recessive trait and is characterized by photosensitivity, pigmentary changes, premature skin ageing and malignant tumour development resulting from a defect in DNA repair. A case of stage 3 Xeroderma pigmentosum affecting a young girl and her siblings is presented. This is a rare medical condition which may cause difficulties in making a timely diagnosis.

Keywords: Xeroderma Pigmentosum; Squamous Cell Carcinoma; Hyperpigmentation; Photophobia; Sub-Saharan Africa.

INTRODUCTION

Xeroderma pigmentosum (XP) first described by Kaposi and Hebra in 1874, is a rare hereditary familial skin condition which usually begins in early childhood. ^{1,2} It is multigenic, multiallelic, autosomal recessive condition, characterised by photosensitivity, pigmentary skin changes, premature skin aging and malignant tumor development. ³⁻⁵ Its prevalence in the general population ranges from 1/40,000 to 1/250,000. The basic defect in XP is mutations in various genes and eight of them have been identified XPA to XPG and XPV. These genes are involved in Nucleotide excision repair (NER) of carcinogen adducts after UV irradiation, and mutations will lead to deficient repair of DNA. They differ with respect to disease severity, frequency and clinical feature e.g. XPG is very severe, whereas XPF is mild, XPA appears to be more common and XPE fairly rare. ⁶⁻¹⁰ Individuals with XP have severe sun sensitivity that leads to degeneration of the skin and eyes and the development of cutaneous squamous cell and basal cell carcinomas and melanomas. Associated ocular abnormalities include keratitis, opacification of the cornea, iritis with synechia formation and melanoma of the choroid. ¹¹⁻¹⁵ Neurological manifestations include progressive cognitive impairment, ataxia, choreoarthrosis, sensorineural hearing loss, spasticity, seizure and peripheral neuropathies. We report a case of

suspected stage 3 XP.

CASE REPORT

HISTORY

Patient LK was a 12 year old female who presented with a 10 year history of skin nodules and 4 year history of visual loss. She was well until 2 months of age when the mother noticed excessive tearing when the child was taken out in the sun. There would be accompanying redness and scaling of the skin over the face. At eight months she developed hyperpigmented and hypopigmented macules and papules around the eyes. This spread to the face, neck, arms and legs. Some of the papules on the forehead, nose and lip enlarged to become nodules. At 5 years, the mother noticed erosions over the nodules giving way to ulceration of some of the nodules. The ulcerated nodules progressively got larger and developed bleeding insidiously. There was no itching. There was no pain until the ulcers formed. The mother sought treatment about 5 years prior to referral to our facility at local health centres with no resolution and gave up. Neighbors accused the mother of neglect and reported her to the authorities and media and that is when she got a referral to our tertiary referral facility in the capital city, Kenyatta National Hospital (KNH) in June 2013.

LK is the third born in her family. She has never attended school due to her illness. The family lives in eastern Kenya where the mother is a farmer of maize and beans and the father is a mason. Her two older siblings both female aged 16 and 13, are alive and well and show no signs of any illness. However, three other siblings all males aged 9, 7, 5 all have similar illness. All four children have visited multiple hospitals but no diagnosis was made. There is no history of consanguinity, and no history of exposure to benzene.

PHYSICAL EXAMINATION

The young girl looked pale with a severely disfigured face. Her hair was sparse and brown. The scalp had multiple nodules measuring 1-2 cm in diameter and premalignant cutaneous horns or keratoacanthomas with associated scaling and freckling (Figure 1A). Her limbs showed hypopigmented and hyperpigmented macules (Figure 1B). Her vitals were: temperature 38.8°C; pulse rate 97 beats/min regular, normal character; respiratory rate 17/min; and BP 120/70. Her weight was 31 kg with a height of 1.52 m and a body mass index of 13.4 Kg/m² (severely underweight). She had no lymphadenopathy. She had poor vision with perception of light only. This was because the cutaneous lesions on the face had involved the eye with nodules and subsequent infections. The central nervous system, the cardiovascular, abdominal and respiratory systems were normal. The working diagnoses were a febrile illness and xeroderma pigmentosum and the patient was investigated along

these lines.

INVESTIGATIONS

Full blood count showed an isolated microcytic hypochromic anaemia with haemoglobin level of 7.8 g/l, MCV 53.9 fl. Liver function tests, BUN and serum creatinine were normal. ELISA for Human Immunodeficiency Virus, Hepatitis B and Hepatitis C were negative. Pus swab on the ulcerated nodules cultured *Staphylococcus aureus* sensitive to cefuroxime, ceftazidime and imipenem. Skin biopsy done revealed a well differentiated keratinizing squamous cell carcinoma with solar keratosis. Considering a compatible history and clinical presentation, the skin biopsy findings though not necessarily typical of XP were highly suggestive of the same. CT scan 3D with reconstruction of the head showed multiple scalp and facial masses of different sizes as would be seen in stage 3 XP. Genetic testing was not available at the time.

TREATMENT

She was put on intravenous cefuroxime and ofloxacin eye drops. Wound care for the ulcerating nodules was instituted. Multidisciplinary approach consisting of plastic surgeons, dermatologists, ophthalmologists and oncologists was adopted. They considered various approaches such as administration of intralesional 5-fluorouracil, radiotherapy, and surgical excision of the massive nodules. It was concluded that this would not be beneficial to the patient as the interventions



Figure 1. (A) Multiple ulcerated nodules on the scalp and face, and nasal septum destruction; (B) Hypopigmented and hyperpigmented macules in the lower limbs

would accelerate rate of DNA damage worsening the situation. Genetic counseling for the parents was recommended and they were advised on the importance of UV light protective sun screens and protective clothing for the other siblings of the patient whose conditions were not as bad.

DISCUSSION

XP being a diagnostic challenge in most health facilities is also difficult to manage in severe cases. With a mortality rate of 40% before the age of 20, mostly due to melanoma and metastatic squamous cell carcinoma, not many treatment options are available.

Frequent reports have emanated from other countries including Europe, Egypt, Israel, Korea, China, India and Pakistan. Bhutto et al¹⁶ when he reported 36 cases of XP including sporadic and familial cases in Pakistan, emphasized the tropical nature of the climate. Although skin types need to be considered, Africa has predominantly a non-Caucasian population with the majority having dark pigmentation. Due to the inherent defect the XP affected African patients possess, they are more prone to malignancy. A recent case series from Kenya reported 5 cases, 2 of whom presented with craniofacial tumours.¹⁷

The basic defect in xeroderma pigmentosum is in nucleotide excision repair (NER), leading to deficient repair of DNA damaged by UV radiation.³ A xeroderma pigmentosum variant has also been described. The defect in this condition is not in NER, but is instead in postreplication repair. In the xeroderma pigmentosum variant, a mutation occurs in DNA polymerase.^{5,6}

Seven complementation groups, XPA through XPG, corresponding to defects in the corresponding gene products of XPA through XPG genes, have been described. These entities occur with different frequencies (e.g., XPA is relatively common, whereas XPE is fairly rare), and they differ with respect to disease severity (e.g., XPG is severe, whereas XPF is mild).⁷ In XPD, the continued presence of repair proteins at sites of DNA damage may also contribute to the pathogenesis of skin cancer.⁸

Over and above its defects in the repair genes, UV-B radiation also has immunosuppressive effects that may be involved in the pathogenesis of xeroderma pigmentosum. Although typical symptoms of immune deficiency, such as multiple infections, are not usually observed in patients with xeroderma pigmentosum, several immunologic abnormalities have been described in the skin of patients with xeroderma pigmentosum. Various other defects in cell-mediated immunity have been reported in xeroderma pigmentosum. These include reduced natural killer cell activity, decreased ratio of circulating T-helper cells to suppressor cells, impaired cutaneous responses to recall antigens, impaired lymphocyte proliferative responses to antigens and impaired production of interferon in lymphocytes. In addition to their role in DNA repair, xeroderma pigmentosum proteins also have additional functions. For example, Fréchet et al⁹ have shown that matrix metalloproteinase 1 is overexpressed in dermal fibroblasts from patients with XPC. They also demonstrated accumulation of reactive oxygen species in these fibroblasts in the absence of exposure to UV. They concluded that the XPC protein has roles in addition to NER. Matrix metalloproteinase 1 overexpression has been shown to occur in carcinogenesis.

No consistent routine laboratory abnormalities are present in xeroderma pigmentosum cases. The diagnosis of xeroderma pigmentosum is usually established by studies performed in specialized laboratories. These include cellular hypersensitivity to UV radiation and chromosomal breakage studies, complementation studies, and gene sequencing to identify the specific gene complementation group. Prenatal diagnosis is possible by amniocentesis or chorionic villi sampling. Unscheduled DNA synthesis is the classic method for diagnosis. None of these are available in our setting as well as majority of countries in sub-Saharan Africa.

We largely rely on histopathological findings derived from skin biopsy. The findings of the first stage of the disease include hyperkeratosis and increased melanin pigment (this corresponds to the clinical freckling) in the basal cell layer (not necessarily accompanied by an increase in the numbers of melanocytes). These findings may be accompanied by a chronic inflammatory infiltrate in the upper

dermis.

In the second stage, atrophy ensues, with more marked hyperkeratosis and hyperpigmentation. Telangiectasia is prominent. Findings usually correspond to poikiloderma. In addition, the epidermis may exhibit architectural disorder and atypia, and the dermis may be elastotic. Therefore, the histologic picture might be indistinguishable from that of actinic keratosis. The histologic appearances of the various tumours that complicate xeroderma pigmentosum are seen in the third stage of xeroderma pigmentosum. This stage of XP is virtually diagnostic in the appropriate setting of compatible history and the likelihood of an alternative diagnosis is remote. However earlier stages may mimic skin conditions like acanthosis nigricans, acute systemic lupus erythematosus, epheles and hydroa vacciniforme.

This case presented at an advanced stage of disease and available options for treatment like radiotherapy would further damage and complicate DNA repair predisposing her even to more malignancies. Genetic testing to determine the exact gene mutation was not available at our facility and this was a hindrance in further classifying her disease and being able to foresee more complications. Other affected siblings were advised on ways to protect their skin from UV irradiation by wearing caps and wearing clothing that would cover their limbs. They would be followed up 3 monthly at our ambulatory dermatology clinic.

In conclusion, recommended management should be focused on educating the patient and the parents about effective sun protection and early recognition of cancers. Genetic counseling should be offered for families at risk.

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