ORIGINAL ARTICLE

Xeroderma Pigmentosum

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ABSTRACT

Objective: To describe the features of Xeroderma pigmentosum observed in the stage 3 of the disease.
Study Design: Case series.
Place and Duration of Study: Mayo Hospital Lahore, from December 2001 to September 2008.
Methodology: All patients diagnosed with Xeroderma pigmentosum stage 3 in the outpatient department of the study centre, were included. The age at first presentation, tumour sites, histology, recurrence rate, new tumour formation rate and the number of biopsies taken in a single session were recorded. The follow-up time was seven years.
Results: There were 25 patients including 15 males and 10 females. The mean age at initial presentation with the tumour was 20.4 years. The maximum number of biopsies taken from one patient during the same operation was 15 (mean=4). Complete tumour clearance was achieved in 15 patients and 3 patients were inoperable. Altogether, 70% tumours were basal cell carcinomas (BCC). The average interval for the development of a new tumour was 6 months. Twenty (80%) of the tumours were on the face, one was on the back and 3 on the forearms. Thirteen patients had ocular complications. Fifteen had a first degree relative afflicted. All wounds were closed primarily or with split grafts.
Conclusion: There was a family history. The tumours were mostly BCCs. The rate of new tumour formation and recurrence was exceptionally high.

Key words: *Xeroderma Pigmentosum (XP). Xeroderma pigmentosum genes (XPA - XPV). Basal cell carcinoma. Stage 3 tumours. Complications. Excision.*

INTRODUCTION

The term Xeroderma Pigmentosum (XP), meaning "pigmented dry skin", was coined in 1882.[1] The initial report of this disease was made by Hebra and Kaposi in 1874.[2] It is an autosomal recessive genetic disorder in which patients are unable to repair the DNA damage inflicted by UV radiation.[3] Unrepaired DNA presents as a mutation in the normal DNA structure. A mutation in the p53 gene results in multifocal and aggressive cancers from a very young age. These usually present in various stages of progression, causing cosmetic and functional grievances, apart from threatening life expectancy. The course of the disease is divided into 3 stages. In stage 1, which usually occurs around 6 months of age, skin erythema, scaling and freckling appear. Stage 2 is the stage of poikiloderma while stage 3 is the stage of tumour formation. Apart from skin tumours, intraoral tumours have also been reported.[4] Stage 3 patients are those that actually concern the plastic surgeon with an intention of extirpating the tumour. Siblings of the patients are usually affected too.

Since the disease is rather uncommon, relevant local literature regarding the disease is lacking. The purpose of the study was to describe the pattern, tumour pathology and complications of this rare disease in the local setup.

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METHODOLOGY

All patients of XP Stage 3 presenting in the outpatient department of Mayo Hospital Lahore from December 2001 to September 2008 were included. Patients in stage 1 and 2 of the disease were excluded. Though the data of affected first degree relatives in stage 1 and 2 was enquired into, they were not included in the study cases.

Data of the patients including age, gender, any previous admissions, tumours, clinical signs and symptoms at presentation and complications was entered. The age at first presentation with tumour was recorded. Sites of tumour growth, gender predilection and histology of the tumours were studied. In order to emphasize the multifocal nature of the tumours, the total number of biopsies taken from a patient during a single operative session was recorded. The time period between the excision of a previous tumour and presentation with a new tumour was noted.

The follow up time designated for this study was the total duration of the study. According to the prescribed protocol, squamous cell carcinomas are to be followed-up at 3 month intervals for the first two years and then at 6 month intervals. Basal cell carcinomas are advised follow-up at 6 month intervals for 5 years. As this study was related to xeroderma pigmentosum patients, who are at a perpetual risk of developing aggressive

malignant tumours, the follow-up visits were advised for life. However, only 18 of the patients presented for follow-up. At each follow-up the excised lesion was examined and the patient was investigated for the presence of new lesions. Patients were also asked to report immediately if a new lesion appeared. Complications were also studied.

The data was analyzed using SPSS version 11. Age groups, biopsies taken at a single operation, tumour histology and site of tumour were given in the form of frequency tables and percentages.

RESULTS

The mean age was 20.4 years ranging from 4 to 70 years (Table I). There were 15 males and 10 females showing a ratio of 1:1.5. Five patients were aged above the age of 40 years at first presentation with a tumour (Figure 1). At first presentation 23 patients had more than one tumour. The number of biopsies taken from each patient in one sitting is described in Table II. Reconstruction was done with either primary closure or split skin grafts in all the cases. Tumour clearance, confirmed by histological evidence, was ultimately achieved in 22 of the 25 patients. On the basis of advanced disease and distant metastasis, 3 patients were termed inoperable and referred to oncology and radiotherapy departments. Out of the three inoperable cases, two had basisquamous carcinoma and one patient had malignant melanoma.

Table I: Age, site distribution and histology of tumours.

Variables	Number of cases	Percentage
Age group (years)		
Birth-10	13	52%
11-20	05	20%
21-40	02	8%
41-70	05	20%
Tumour histology		
BCC	18	72%
SCC	04	16%
Basisquamoid	03	12%
Malignant melanoma	01	04%
Fibroangioma	01	04%
Site of tumour		
Scalp	15	60%
Face and neck	20	80%
Upper limb	03	10%
Intraoral	02	08%
Back	01	04%

Table II: Quantitative analysis of biopsies taken in a single operative session.

Number of patients	Number of biopsies taken at a single operation
05	01
15	2-4
03	5-8
01	15
01	20

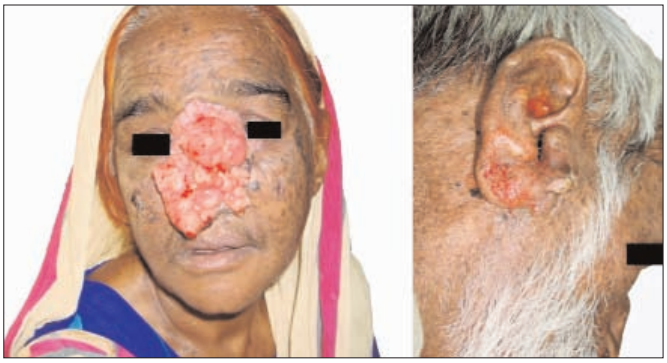

Figure 1: Two patients of Xeroderma pigmentosum in the older age group (70 and 59 years respectively) with squamous cell carcinoma. The one on the nose of the female was inoperable.

In total, 18 (70%) of the tumours were basal cell carcinomas (Table I). There was a fibroangioma on the tongue in one patient. Keratoacanthomas and actinic keratosis were present in all the cases. As depicted in Table I, most of the tumours occurred on sun exposed areas. Recurrence rate after complete removal was 5%; one patient for basal cell carcinomas and in 2 cases of squamous cell and basisquamoid carcinomas. The interval between excision of a tumour and new tumour development was on an average 6 months.

Ocular complications were present in 18 of the 25 (72%) patients. Photophobia and conjunctivitis being the most common, were present in all 18 cases. Ectropion was seen in 2 of the 18. Macular pigmentation on the conjunctiva was present in 08 and corneal opacities were present in 15 of the 25 patients with eye complications. However, no neurological complication, was found in any patient.

The series behavior had a strong genetic link, with 20 patients having one or more first degree relatives affected. Of the 25 patients, only 18 presented again for any kind of a follow-up over a 7-year period. The minimal follow-up time was 2 months and the maximum was 12 years, albeit at irregular intervals. The mean follow-up time was 6 months. Of those, 8 developed a new tumour within 6 months of excision of the previous tumour. Over a 7 year period, 15 of the 18 followed-up patients developed new tumours. Eighteen had a first degree relative afflicted. Fourteen of them were still tumour free. All the other affected relatives had skin changes of stages 1 and 2.

DISCUSSION

Xeroderma pigmentosum is a potentially life threatening and disfiguring, autosomal recessive congenital disorder characterized by photosensitivity, pigmentary changes, premature skin aging, and malignant tumour development at a very young age.[5] It is relatively rare, with an epidemiology of 1 in 250000 in the USA.[6,7] However, this differs widely and the incidence is 6 times more common among the Japanese.[6] The most

common defect in XP is an autosomal recessive gene deficiency. The process whereby DNA is removed and replaced with new DNA using the intact strand as a template, involves the products of various genes. Each gene (of which XPA to XPG have been identified), encodes for specific proteins that are involved in nucleotide excision and repair. Each protein has a specific role in the incision, removal and replication of the damaged DNA segments.[8] Collectively they are known as the nucleotide excision repair (NER) enzymes e.g. endonucleases. Thus, seven variants of the disease, known as complementation groups, from XPA to XPG have been described, depending on the XP gene deficient. The various types of XP show clinical and epidemiological differences, the reason for which is not clear as yet. For example the XPC group, which is most prevalent in Europe, shows no neurological defects. The XPA groups exhibit neurological disorders before the age of 7 but the XPD group after this age. A variant of the disease known as XPV has also been described and is present in 20% of the patients.[9] This is due to a mutation in the gene encoding for DNA polymerase, such that the repaired DNA chains are lighter than normal.

In patients with xeroderma pigmentosum, 80% show a defect in the initiation of DNA excision of ultra violet radiation byproducts e.g. Cyclobutamide or pyrimidine diamers.[10] The continued presence of repair proteins at sites of DNA damage may also contribute to the pathogenesis of cutaneous cancer.[11]

This series followed a very strong hereditary pattern as 20 of the 25 patients had at least one first degree relative in some stage of the disease. There is a strong tradition of intermarriages in our society which may be the cause of this finding. In the present series,[16] patients were offspring resulting from such marriages. Anderson and Bregg in 1950, found an autosomal dominant form of the disease among Scottish kindred.[12]

A slightly higher ratio of males presented, though literature states sex incidence to be equal.[7] This may be due to the greater exposure of the male gender of this society to the outdoors compared with their female counterparts. In the study group, 70% of the patients had BCC, and 15% had SCC. Also, 23 of 25 patients had more than one tumour at first presentation, highlighting the tendency of XP patients to form multiple tumours simultaneously. Tumour clearance rates were satisfactory though development of new tumours within 6 months was inevitable in almost all the patients. The two most common causes of death are metastatic squamous cell carcinoma and malignant melanoma.[10]

Age at first tumour presentation is 1-2 years, the disease is often fatal before the age of 10 years and worldwide two-thirds die before the age of ten.[7] Almost half of these patients were above the age of 10 at first presentation. The oldest in the study group was a 70 year old female with her first tumour. According to literature, survival beyond the third decade of life is unusual and the longest living survivor is assumed to be no more than 46 years of age.[13] The dark skin of our race may be responsible for the late onset of tumours in these patients as compared to their white counterparts, even though sun protection measures are hardly ever practiced. Though the study ended in the September of 2008, it may be pertinent to mention that in the year since, 90% of XP patients presented to us with a first tumour were above the age of 15 years.

Ocular complications were found in 72% of the patients, the most common complaints being conjunctivitis and photophobia. The incidence of ocular complications is reported to be 80%.[7] Neurological complications like growth retardation, deafness and cortical atrophy, otherwise reported to be present in 20% of XP patients,[7] especially in the XPA and XPD subgroups, were not found at all in the study group. It was inferred that these subgroups are not endemic in this region.

Following excision, all defects were reconstructed either by primary closure or with split skin grafts. Excision of tumours followed by total resurfacing by split thickness grafts on the face, has been reported to arrest new tumour formation for 5 years.[14] The technique was tried in one case, using skin from a yet unaffected site, but there was new tumour growth on the forehead within 4 weeks. Though chemical peeling and dermabrasion are known to be helpful entities in the treatment of lesions especially actinic keratosis,[15] they have not used at the study centre.

Prenatal diagnosis by amniocentesis is possible, as post repair replication is reduced in amniotic fluid cells as well,[6,16,17] but is not available currently at the study setup. Parents were educated about and asked to look out for and detect any tell tale signs of the disease in siblings. Great emphasis was laid on the prevention of tumour formation by sun etiquette counselling which can be quite a daunting task.

Patients were advised regular follow-up and application of 5 FU cream on all new lesions. At the study centre, it is as yet the only nonsurgical weapon in the arsenal for treatment of small size new lesions. It has shown satisfactory results in halting tumour progression in the series. Oral retinoids have been shown to decrease the incidence of skin cancer in patients with XP.[18,19] Gianotti *et al*. have suggested the topical use of 5% imiquimod and acitretin (20 mg/day) for 4-6 weeks as a successful alternative to surgery.[20] Once the DNA damage has occurred, a new modality in treatment is to deliver the repair enzyme T4 endonuclease V via engineered liposomes in lotion form and has shown encouraging results when used regularly for one year.[21-23] The enzyme, obtained from *E. coli* bacteria has

glycosylase activity and cleaves the pyrimidine diamers produced after DNA damage. Gene therapy to supply the missing NER using viral vectors (adeno and retroviruses) is still in its experimental stage.[23,24] Ex vivo gene therapy, in which grafted skin that has the genetic defect corrected, is also being tried.[22] The future strategy will be to procure topical T4 endonuclease V and study its efficacy in preventing tumour formation.

CONCLUSION

Xeroderma pigmentosum stage 3 was characterized by disfiguring and potentially life threatening tumours mostly including basal cell carcinomas. There was a marked familial tendency. The higher melanin content of skins in this part of the world protecting from lethal damage at a young age, may be the cause of the higher age at first presentation. With limited resource-set up, surgery is the best option. However, the rate of new tumour formation and recurrence was exceptionally high.

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