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Xeroderma pigmentosum at a tertiary care center in Saudi Arabia

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BACKGROUND: Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder caused by defective DNA repair that results in extreme sensitivity to ultraviolet (UV) rays. Depending on the type of XP, the disease may affect the skin, eyes and nervous system.
OBJECTIVES: Describe the dermatologic manifestations in patients suffering from XP.
DESIGN: Retrospective, descriptive review of medical records.
SETTING: Dermatology clinic at tertiary care center in Riyadh.
PATIENTS AND METHODS: This study included Saudi patients with clinically confirmed XP.
MAIN OUTCOME MEASURE(S): Demographic and clinical data including pathology and associated conditions and outcomes.
RESULTS: Of 21 patients with XP, the most common manifestation was lentigines, affecting 18 patients (86%). The most common skin cancer was basal cell carcinoma followed by squamous cell carcinoma (SCC) affecting 15 (71.4%) and 9 (42.8%), respectively. Other skin findings included neurofibroma, trichilemmoma and seborrheic keratosis. Ocular involvement included photophobia, which was the most common finding followed by dryness and ocular malignancies. Two patients showed neurological involvement, which correlated with the type of mutation.
CONCLUSION: Considering that XP is a rare genetic disease, this description of our patient population will aid in early recognition and diagnosis.
LIMITATIONS: Retrospective and small number of patients. Genetic analyses were done for only 5 of the 21 patients.

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease. It was first described in Vienna 1874,[1] but its link to defective DNA repair was reported nearly a century later by James Cleaver.[2] The specific defect lies within the nucleotide excision repair (NER) pathway and is characterized by hypersensitivity to ultraviolet (UV) light, specifically UVB and UVC. As of now, there are seven known complementation groups, XPA through XPG, with an additional variant type known as XPV.

The clinical manifestations of this disease are predominantly cutaneous, presenting as pigmentary changes and early cutaneous malignancies. Other manifestations include ocular and neurological symptoms such as photophobia and cognitive impairment. There is an established association with consanguinity, and thus, the prevalence of this disease is highest in areas where consanguinity is common, such as in North Africa and the Middle East.

PATIENTS AND METHODS

We conducted a retrospective examination of the medical records of Saudi patients who had been diagnosed clinically or genetically with XP at the Dermatology Clinic, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. This study was conducted after obtaining approval from the Office of Research Affairs. Images are reproduced on consent of the parent or guardian. Data was collected between the months of February and June 2016 from medical records.The prevalence estimate was based on a report of the General Authority for Statistics, Saudi Arabia, 2016.

RESULTS

The earliest and most common manifestation in our review was lentigines, affecting 18 of 21 patients (86%) on sun-exposed areas (**Table 1**). Nineteen patients (90%) exhibited non-melanoma skin cancer (NMSC) (**Table 2**). BCC was the most common NMSC finding, which affected 15 patients (71%). Nine patients (42%) had SCC; 7 patients were male and 2 female. The most common location of NMSC was the face, mainly over the nose. Moreover, the two patients without NMSC at the time of writing were aged 1 year and 18 months, respectively. Four patients (19%) had malignant melanoma; two on the scalp, with invasive superficial spreading of malignant melanoma and invasive nodular melanoma. The other two had lentigo maligna melanoma over the cheeks. Other skin findings observed in 7 patients (33%) included seborrheic keratosis, affecting 3 of the 21 patients (14%), neurofibromas in 3 (14%), trichilemmomas in 3 patients (14%) and actinic cheilitis in 1 (4.7%) (**Figure 1**).

Two brothers (9%) suffered from neurological involvement in the form of mild mental retardation and speech impairment. Internal neoplasms were only found in one patient, a young female who suffered from a right breast phyllodes tumor. Two of the 21 patients (9%) had oral involvement; one in the form of gingivitis and inflammatory granulomas and the other with acute gingivitis, gingival hyperplasia and oral pyogenic granulomas. Many of our patients reported ocular involvement as well, mostly in the form of photophobia, which affected 13 patients (61%) and dryness, which affected 5 patients (23%). Pterygium was also noted in 4 patients (19%). Four patients (19%) had ocular squamous cell carcinoma, 3 of which affected the limbus, and 1 patient had melanoma in the limbus.

In the five patients who had genetic testing, two brothers with neurological symptoms had a homozygous missense mutation in the XPA gene, which results in c.682C>T (p.R228X). The patient with the breast tumor and two sisters in our review had homozygous missense mutations in the XPC gene which results in c.856A>T (p.R286X).

DISCUSSION

Under normal circumstances, DNA repair pathways are able to correct damage caused by endogenous or exogenous factors such as breaks, bulky adducts and oxidative lesions. However, in XP this process is deficient. The complementation groups affect various stages of the NER pathway resulting in mutations which affect the incision and repair processes. XP variant is caused by postreplication due to exposure to UV rays. The skin is the primary organ involved and cutaneous signs are often first to appear upon sun exposure. Initially they present as sunburns, which eventually turn into pigmentary changes and later into skin cancers.

XP prevalence is highest in areas with increased consanguinity rates such as in North Africa and the Middle East. In Japan, the prevalence is around 1:22 000,[3] in the United States and Europe, it is estimated to be around 1:1 000 000.[4] Higher rates were observed in Morocco.[5] In Saudi Arabia, although it is difficult to determine an exact number, Alfawaz et al[6] estimated the incidence to be around 15-20:1 000 000,[6] which is about the same rate as in Libya.[7] However, in our case series, we estimated an incidence of 1:1000 000, which is the same as in the United States and Europe. It affects men and women equally,[4] which is consistent with our series. Consanguinity plays a major role in autosomal recessive disorders. As in our study, almost all parents are first-degree relatives.

The most common manifestation in our study was lentigines, which affects sun-exposed areas with a line of demarcation. The incidence of NMSC in XP patients is about 10 000 fold that of an unaffected individual. Ninety percent of our patients exhibited NMSC. In previous studies a rate of 60% has been reported.[8] Taking into consideration the two unaffected individuals were less than two years of age, we expect that at the time of puberty the incidence of NMSC would be 100%. The risk of melanoma is increased by 2000 fold in XP patients. Four of our patients had melanoma. Contrary to that reported in previous studies, the distribution of melanoma in XP was more on the scalp and face rather than the extremities. Other skin manifestations included trichilemmoma, affecting three patients (14%). A potential correlation with XP was reported by Mane, et al in which neurological manifestations were estimated to affect 25% of XP patients.[8] However, lower incidences have been reported, which can be explained by the predominance of the XPC type in regions including our region. Neurological manifestations occur more in XPA, XPB, XPD and XPG types.[9] It has been reported that there is a 12-fold increase in internal malignancies younger than the age of 20 in sun-protected areas.[10] In another study, the occurrence of internal malignancies were 10-20 times greater.[11] In this study, internal neoplasms were only found in one patient, a young female who suffered from a right breast phyllodes tumor.

Ocular involvement in our study included photophobia, dryness and pterygium. Moreover, four patients (19%) had ocular SCC and one (4%) had limbal melanoma. Oral changes ranged from gingivitis to squamous cell carcinoma of the oral cavity.[12,13] In our study, two

Table 1. Demographic and clinical characteristics of the 21 patients.

Case	Gender	Age at diagnosis	Lentigines +/-	NMSC (SCC or BCC)	Cutaneous MM	Other skin findings	Ocular involvement	CNS
1	F	11 y	+	BCC	-	-	Dryness	-
2	M	9 mo	+	BCC	-	Neurofibroma	Photophobia	-
3	F	10 y	+	BCC	-	Seborrheic keratosis	SCC, photophobia, dryness	-
4	M	26 y	-	BCC+SCC	+	-	Photophobia, Pterygium	-
5	F	14 y	+	BCC+SCC	+	-	Dryness,SCC	-
6	M	1 y	+	-	-	-	-	-
7	M	19 y	+	BCC+SCC	-	Actinic cheilitis	Photophobia, Pterygium	-
8	F	23	+	BCC	-	-	Pterygium	-
9	M	6 mo	+	BCC	-	-	Photophobia	+
10	M	6 mo	+	SCC	-	-	Photophobia	+
11	M	1 y	+	BCC+SCC	+	Neurofibroma Trichilemmoma	Pterygium, photophobia, dryness	-
12	M	2 mo	+	SCC	-	-	Photophobia	-
13	F	2 y	+	BCC	-	Gingival involvement, gingivitis.	Photophobia	-
14	F	3 y	+	BCC	-	Trichilemmoma	Photophobia	-
15	M	-	-	BCC	-	-	SCC	-
16	F	15 y	+	BCC	-	Neurofibroma, seborrheic keratosis	Photophobia, dryness, SCC	-
17	M	-	-	SCC	-	-	-	-
18	F	8 y	+	SCC+BCC	-	Seborrheic keratosis, trichilemmoma,	Limbal melanoma	-
19	M	Referred to KFSH at 30y	+	SCC	+	-	Photophobia	-
20	F	2 y	+	BCC	-	Gingival involvement- pyogenic granuloma	-	-
21	F	18 mo	+	-	-	-	Photophobia	-

NMSC: non-melanoma skin cancer, BCC: basal cell carcinoma, SCC: squamous cell carcinoma

Table 2. Frequency of skin cancers in the 21 patients.

	Number of patients	%
No cancer	2	9.5
SCC only	3	14.2
BCC only	10	47.6
Concurrent SCC and BCC	2	9.5
Concurrent SCC and MM	1	4.7
Concurrent SC, BCC and MM	3	14.2
Total	**21**	

Number of each type of cancer not shown. BCC: basal cell carcinoma, SCC: squamous cell carcinoma, MM: malignant melanoma.

patients (9%) had oral involvement; one in the form of gingivitis and inflammatory granulomas and the other with acute gingivitis, gingival hyperplasia and pyogenic granulomas.

In managing this disease, prevention is critical and early diagnosis and close follow up are key. Patients are instructed to adhere to photo-protective measures such as wearing sunscreen and protective gear (sunglasses, gloves, etc.). Regular visits to a dermatologist and ophthalmologist are vital for early detection and management. Due to the high likelihood of psychological stress and social withdrawal, a psychiatrist should also be involved as well as a genetic counselor.

Patients must also be given vitamin D supplements to compensate for strict sun avoidance. Vitamin A derivatives have been shown to reduce the frequency of skin cancers by about 63%.[14] However, rebound phenomenon, which is the rapid appearance of malignancies after cessation of treatment, is usually encountered. Topical immunotherapy and chemotherapy haven been used to treat superficial types of skin cancers. In our center, these patients undergo chemical peelings at six-month intervals with 35% trichloroacetic acid under general anesthesia with or without curettage and electrodessication for any suspected superficial skin cancer. We use topical 5-fluorouracil 5% cream twice a week on the face as prophylaxis and twice a day on any suspected skin cancers in between peeling sessions. Trials in progress with gene therapy are showing promising results.[15]

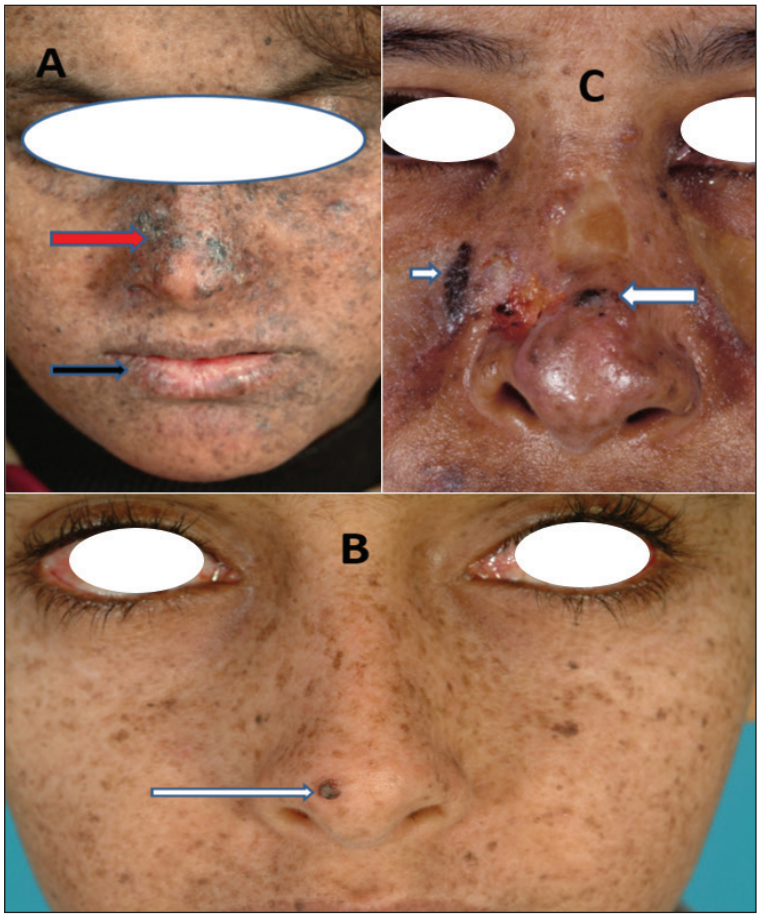

Figure 1. Clinical presentation of some patients with xeroderma pigmentosum. All showing multiple lentigines. White arrow: basal cell carcinoma; Black arrow: actinic cheilitis; Red arrow: hypertrophic actinic keratosis and squamous cell carcinoma

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