Childhood and adult-onset xeroderma pigmentosum: clinical evaluation with striking new findings

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Background: Xeroderma pigmentosum variant (XP-V) is a genetic disorder that starts in early childhood with a mild disease course. The aim of study was to record all cases of XP-V that were seen and examined over a specific period.

Methods: This descriptive study included 48 patients; there were 4 (8.33%) patients with xeroderma pigmentosum (XP) and 44 (91.66%) patients with XP-V. Patients with XP-V were divided into childhood and adult-onset types.

Results: Childhood-onset type was detected in 34 patients, including 20 (58.82%) males and 14 (41.17%) females. Their ages ranged from 3-25 years, with a mean of 15 years. Freckling and solar keratosis were observed in 100% and 23.68% of patients, respectively, while non-melanoma skin cancer (NMSC) was detected in 8 (21.05%) patients, including one case with squamous cell carcinoma (SCC) and 7 with keratoacanthoma. In the adult-onset type, ten cases were seen, half of each gender. Their ages ranged from 23-60 years, with a mean of 32 years. Patients gave a history of early adult onset of their disease. Skin hyper-photosensitivity was the first problem, followed gradually by other features of solar damage to the face, including freckles and solar keratosis. SCC and keratoacanthoma were each observed in two patients.

Conclusions: The clinical picture of XP-V was similar to ordinary XP but with late age onset and a slower course. The clinical picture of adult-onset XP-V was similar to the childhood type.

Keywords: Xeroderma pigmentosum, DNA, DNA Repair

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INTRODUCTION

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder characterized by photosensitivity, pigmentary changes, premature skin aging, and malignant tumor development, with an impaired ability to repair ultraviolet (UV)-induced DNA damage [1]. Xeroderma pigmentosum is caused by mutations in one of eight different genes, seven of which are related to classic complementation groups (XP-A to XP-G) that affect nucleotide excision repair (NER). In contrast, the eighth one, xeroderma pigmentosum variant (XP-V), results from defective translesion synthesis (TLS) [2,3]. It is more common in Japan and the Middle East, but patients have been recorded worldwide across all races, including white Asians, blacks, and Native Americans; it is also relatively common in communities like Iraq, where intermarriages are common [4-6]. A large series of patients with XP-V have been described in the Iraqi population since 1997, appearing to be more common than classic XP 5. The median age of onset of the skin manifestations is between 1-2 years [4,5,7,8].

Patients with XP who are below 20 years of age have a greater than 10,000-fold increased risk of cutaneous basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or malignant melanoma (MM) [9]. The median age of onset of non-melanoma skin cancer (NMSC) recorded in patients with XP is eight years [10].

Light eye testing for photophobia is a crucial differential point between ordinary XP and its variants, as light exposure to the eyes will cause immediate blinking and eye closure in ordinary XP but does not do so in its variants [5,8]. XP-V patients have a late onset of symptoms, comparatively milder phenotype, and delayed progression. Typically, XP-V patients do not have ophthalmic or neurological involvement [11]. Several studies suggested that this form of XP is underdiagnosed [12,13]; therefore, XP-V cases constitute about 20 to 30% of all XP patients [14].

In 1970 Jung *et al*. discovered a disorder similar to XP, which they named 'pigmented xerodermoid' [15]. The disease showed a similar XP phenotype but was characterized by a significantly later onset, generally milder symptoms, a prolonged course of the disease, and normal NER [15-17]. Cases of both pigmented xerodermoid and XP-V were reported for almost a decade [18-21] until 1980, when Cleaver *et al.* showed that the biochemical and molecular defects in cells derived from pigmented xerodermoid and XP-V are similar and indistinguishable. Consequently, the term pigmented xerodermoid was announced to be redundant [22].

Two published studies regarding childhood XP-V were conducted in Iraq; the family history was positive in 72% and 86% of studied patients [5,23]. The present literature had reported limited cases of XP-V, with no well-documented clinical evaluation. Hence, this present study was planned. Although classic XP is generally a rare autosomal recessive disease in the Iraqi population, we have observed XP-V cases, which might be much more commoner than XP. For this reason, the present study was arranged to record these cases and obtain a complete clinical picture.

PATIENTS AND METHODS

This descriptive study included 48 patients (XP and XP-V) from different Iraqi regions. The study was conducted from August 2012 to April 2020. The patients ranged in age from 3 to 60 years, with a mean of 21 years. There were 28 (58.33%) males and 20 (41.66%) females.

The cases were diagnosed as XP or XP-V according to the following characteristics: age of the patient, clinical picture of the disease, ophthalmic and neurologic involvement, photophobia, and light eye testing. Accordingly, we observed 44 (91.66%) XP-V cases and 4 (8.33%) XP cases.

Subsequently, we divided the XP-V patients into childhood and adult-onset types according to the age at onset.

A full history was taken from each patient, including age, sex, occupation, address, parental consanguinity, family history, outdoor activities, drug history, and past medical and surgical history. A complete clinical examination was performed to evaluate the morphological distribution and extent of the skin lesions besides a complete systemic examination. Light eye testing for photophobia was done for all patients as to whether or not the patient blinked and immediately closed their eyes. Skin biopsies with a pathological stained section (Hematoxylin and Eosin [H&E]) were obtained when necessary in many patients. General laboratory tests were carried out for all patients, including a complete blood count, urine analysis to exclude porphyria, and blood biochemistry.

Statistical analysis

Data were statistically described in terms of range, mean, median, frequencies (No. of cases), percentage(%), disease duration, and male to female ratio. All statistical calculations were done using Statistical Package for the Social Science (SPSS) version 22.

Ethical considerations

The study followed the Declaration of Helsinki principles, and informed consent for photography and the skin biopsy was obtained in writing from all patients or their parents prior to beginning the study and after explaining the nature of the disease, duration, course, prognosis, and follow-up.

RESULTS

Forty-eight patients were included (44 XP-V

cases and 4 classic XP cases). Their ages ranged from 3-60 years, and their skin type was Fitzpatrick III and IV. According to the age at onset of the disease, XP-V cases were divided into two types:

1. Childhood-Onset

34 patients were detected, including 20 (58.82%) males and 14 (41.17%) females. Their ages ranged from 3-25 years, with a mean of 15 years. The mean age of onset was 3 years. The family history was positive in 28 (82.35%) patients. All patients had a history of sunburns as the first manifestation, followed by freckling. Then, other skin lesions like solar keratosis and recurrent keratoacanthoma (KA) gradually appeared, followed by the appearance of SCC or, rarely, BCC (Figures 1, 2, 3). With the exception of one case appearing in childhood, all other NMSCs appeared in early adulthood. Pigmented macules and solar keratosis were observed in 100% and 23.68% of patients, respectively, while NMSCs were detected in 8 (21.05%) patients (1 SCC and 7 KA). Some patients had a rapidly progressive course, though most had a slow disease course, probably related to the time of outdoor activities. Eye involvement was detected in two patients as solar keratosis of the sclera in one patient and corneal opacity in the other. Neither neurologic nor systemic involvement was detected in any childhood XP-V patient.

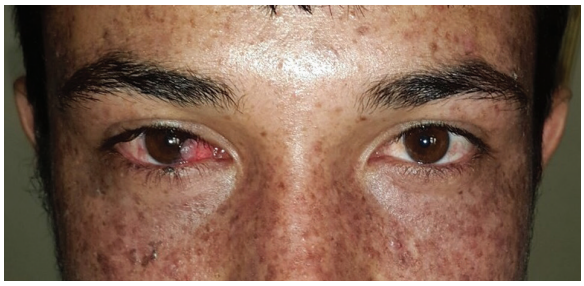

Figure 1. A 17-year-old patient with childhood-onset xeroderma pigmentosum variant showing multiple hyperpigmented solar keratoses affecting the entire face.

2. Adult-onset

10 cases, including 5 (50%) females and 5 (50%) males. Their ages ranged from 23-60 years, with a mean of 32 years. All patients gave a history of

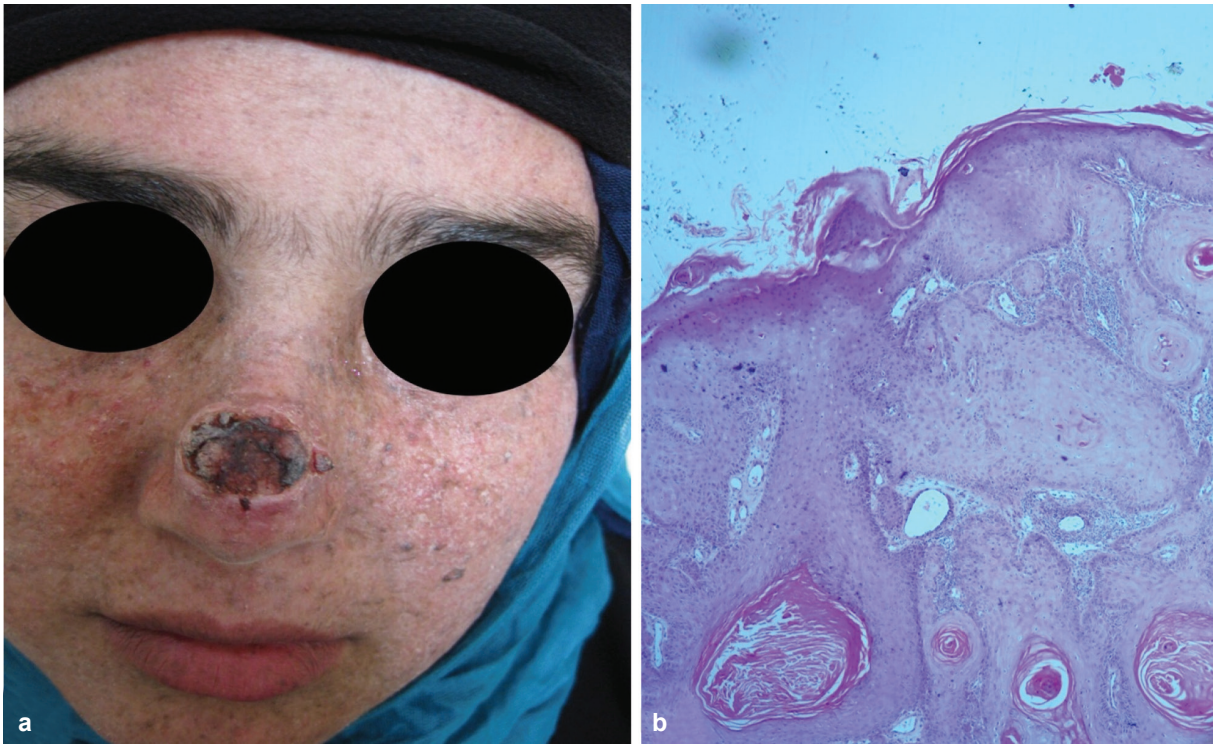

Figure 2. (a) A 21-year-old female patient with childhood-onset xeroderma pigmentosum variant showing freckles and solar keratosis involving the entire face associated with keratoacanthoma on the nose and normal eyes; (b) H&E stained section from the lesion on the nose showing features of keratoacanthoma (×10).

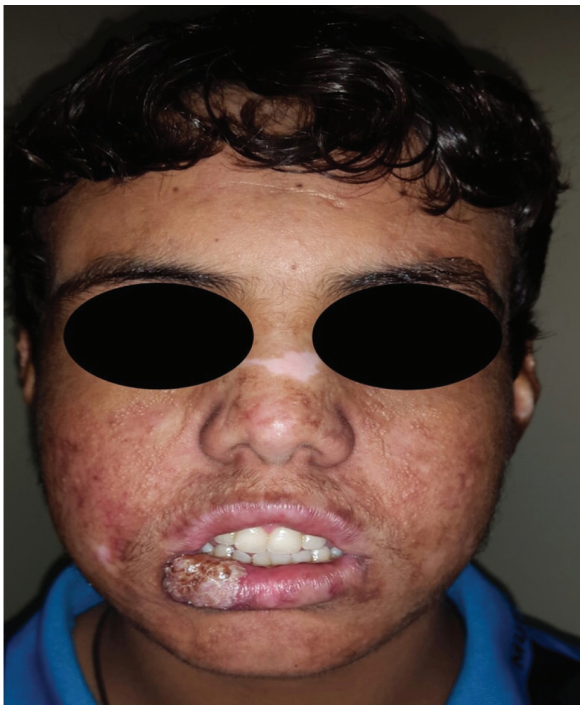

Figure 3. A 15-year-old patient with childhood-onset xeroderma pigmentosum variant showing sun-damaged skin with multiple squamous cell carcinomas (some excised). Eyes were normal.

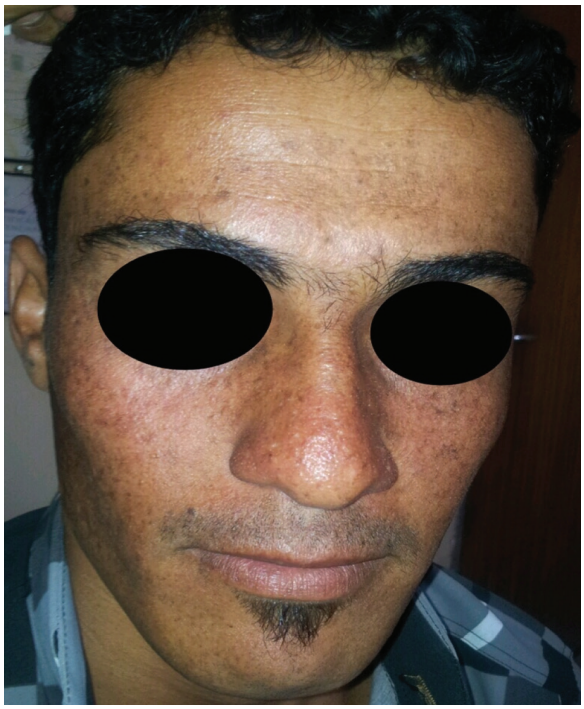

Figure 4. A 25-year-old patient with adult-onset xeroderma pigmentosum variant showing multiple hyperpigmented macules and solar keratosis on the top of sun-damaged skin affecting the entire face. Eyes were normal.

early onset of their disease during their twenties. Photosensitivity to UV light was the first early skin problem, followed gradually by other features of solar skin damage to the face. Pigmented macules and solar keratosis were reported in all cases, while SCC developed in two cases and recurrent KA was seen in another two patients (Figures 4, 5, 6, 7). Hence, 4 cases of NMSC were detected (40%), but no malignant melanoma was recorded. The family history of adult-type XP-V was positive in one case (Figure 5). Neither neurologic nor eye involvement was detected in any case of XP-V of adult type. No systemic involvement was seen in this type.

Overall, the frequency of skin tumors in all 42 VP-V patients was as follows: solar keratosis in 18 (40.90%), KA in 9 (20.45%), and SCC in 3 (6.81%) patients.

Regarding classic XP, four cases were diagnosed, including three males and one female. Their ages ranged from 12-18 years, with a mean of 15 years. The age period at onset was early infancy. Evident photosensitivity of the face was the first manifestation noticed by the parents of the patients during early infancy; two to three years later, pigmented macules started to appear on the

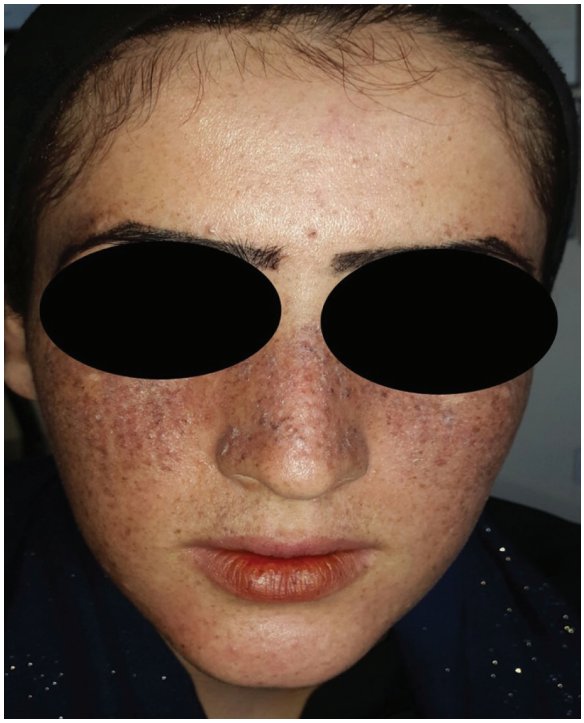

Figure 5. A 23-year-old female with adult-onset xeroderma pigmentosum variant, mainly showing solar keratosis on sun-damaged skin. Eyes were normal.

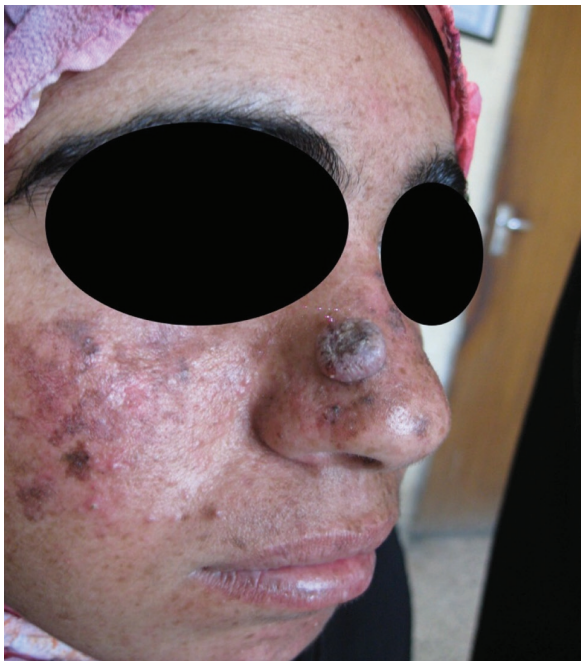

Figure 6. A 27-year-old female patient with adult-onset xeroderma pigmentosum variant showing multiple freckles and solar keratosis involving the entire face associated with keratoacanthoma on the side of the nose on the top of sun-damaged skin. Eyes were normal.

face and exposed areas. After that, as a result of continuous exposure to sunlight, dry and pigmented skin appeared (Figure 8). Non-melanoma skin cancer was detected in all cases of XP, but no MM was observed. Ocular involvement was identified in two cases: corneal opacity in one and keratitis in the other.

Light eye testing for photophobia was negative in both types of XP-V (albeit some patients had mild blinking after light exposure) but was strongly positive in XP patients. The comparison between our XP and XP-V patients is shown in Table 1.

Histopathological examination of tumoral lesions showed pathological features related to each type of tumor, such as SCC or KA (Figure 2B).

The results of all laboratory investigations requested for patients in both types of XP-V were within normal limits.

DISCUSSION

This is the first study of XP-V to report 44 patients, including 25 (56.81%) males and 19 (43.18%) females. According to the age of onset,

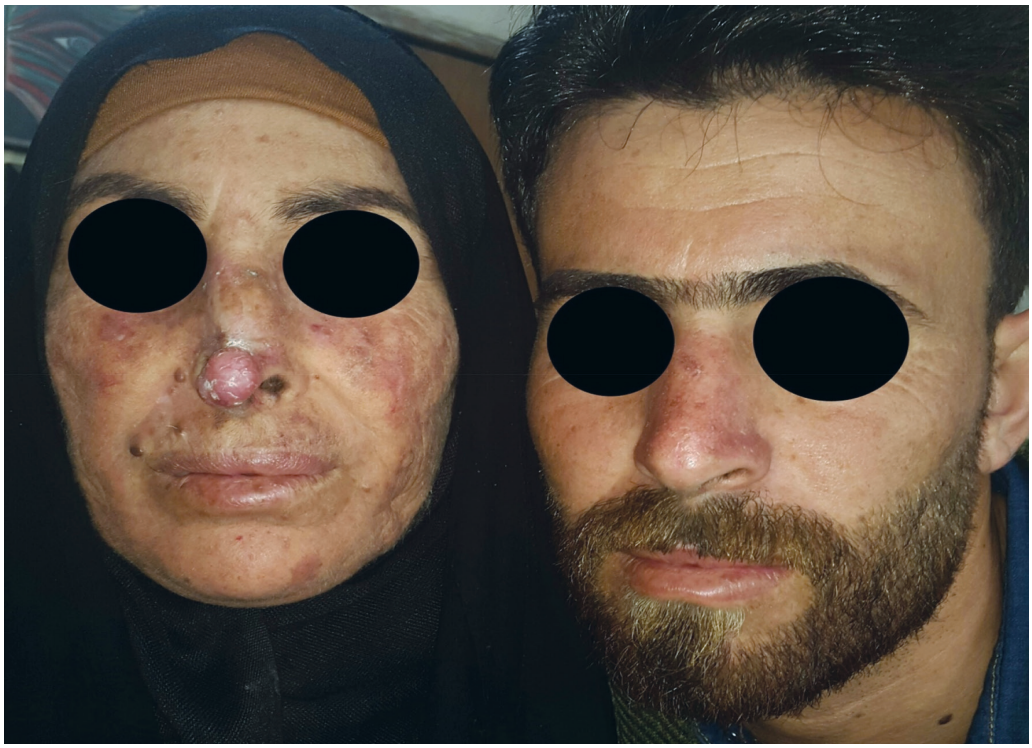

Figure 7. Familial adult-onset xeroderma pigmentosum variant: a 50-year-old mother and her 22-year-old son. The clinical picture was severe in the mother, including squamous cell carcinoma of the nose, but was early-onset and had a mild clinical picture (mainly solar keratosis) in the son. The eyes were normal in both patients.

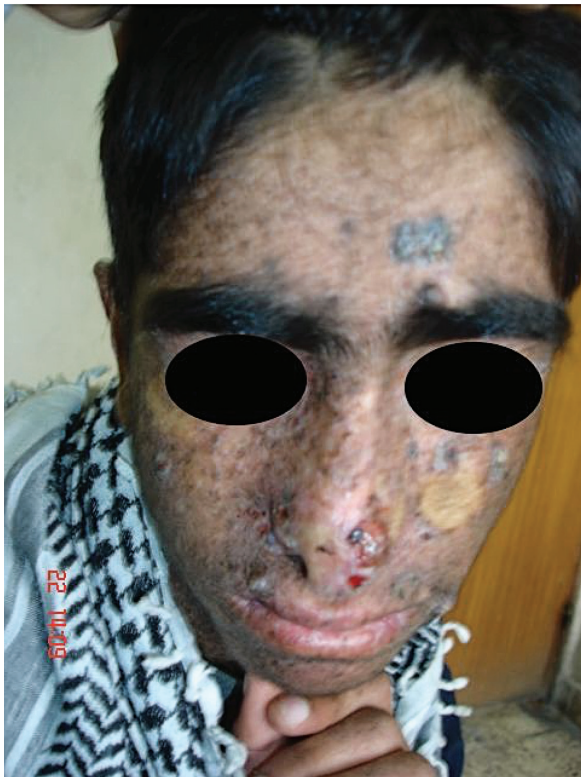

Figure 8. A 16-year-old male with classic xeroderma pigmentosum showing pigmentary changes admixed with scarring, pigmented macules, dryness, and multiple non-melanoma skin cancers involving different face sites (including the nose), with severe eye damage.

they were divided into childhood and adult types. The present study showed that XP-V had a late age of onset, usually after infancy and early childhood. The mean age was 15 years in the childhood type, which is somewhat comparable to other published studies [24]. While in the adult type XP-V, the onset was during early adult life, with a mean age of 32 years. The family history in childhood type was positive in 82.35%, and this is consistent with other studies where family history ranged from 72% to 86% [5,23].

While the most common NMSC among the XP-V patients in our study was KA, other studies showed the predominance of BCC, followed by SCC and KA [23-25]. However, when we compare these results with the ordinary XP, the most common tumors are SCC and BCC, followed by KA and, less frequently, MM [9]. Still, the frequency of these tumors in XP-V was much less when compared with ordinary XP [9]. Accordingly, patients with XP-V can have almost a good life with sunlight protection, mainly by wearing big hats and using sunblock. Also, the course of the disease was slower and less progressive without ophthalmological and neurological complications. This is mainly because XP-V patients have a late onset of symptoms and a milder phenotype [11]. In the present study, all NMSCs appeared in childhood and adulthood. These results differ from classic XP, in which NMSCs are high frequent and more severe with an earlier age of onset and a very high mortality rate [10]. Still, XP-V could be more severe in sunny countries like Iraq when compared with a less sunny atmosphere [5,6].

Light eye testing for photophobia was negative in both types of XP-V, which is an important test as it is always positive in ordinary XP, and this

Table 1. Comparison between classic xeroderma pigmentosum and xeroderma pigmentosum variant patients

	XP	XP-V
Age at onset	Early infancy	Early adulthood
Sex	Males=females	More common in males
Distribution of skin lesions	Cheeks, nose, and exposed parts	Cheeks, nose, and exposed parts
Early manifestations	Photosensitivity and sunburns	Photosensitivity and sunburns but milder than classic XP
Types of tumor	SCC, BCC, KA; less frequently MM	KA, SCC; less frequently BCC, but no MM
Median age of the first NMSC	8 years	19 years
Photophobia and light eye test	Strongly positive in all cases	Mostly negative
Ocular abnormalities	About 40%	About 4.5%
Neurological involvement	About 30%	Usually no involvement
Affected gene	XPA through XPG	POLH
Defective pathway	NER	TLS
Prognosis	High mortality	Low mortality; could live a normal life

Abbreviations: XP, xeroderma pigmentosum; XP-V, xeroderma pigmentosum variant; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; KA, keratoacanthoma; MM, malignant melanoma; NMSC, non-melanoma skin cancer; NER, nucleotide excision repair; POLH, polymerase (DNA) eta; TLS, translesion synthesis

observation has not been mentioned as an important differential point.

Sharquie *et al.*, in 1997, reported 25 cases in a well-localized area (Ramadi city in the west of Iraq), where they found that most of the cases did not follow the clinical picture of classic XP and suggested the name XP-V [5]. The present work is also in agreement with the previous study, but the majority (91.3%) were XP-V, and this decrease in the number of classical XP could be attributed to the high mortality rate among these patients and the low rate of marriage among those affected. This great decline in the frequency of XP could also be seen elsewhere in other countries. Hence we expect that cases of XP will almost completely vanish over time, apart from a few new cases from a novel mutation.

Xeroderma pigmentosum-V seems to be not a rare disease in the Iraqi population when compared with other countries. This could be attributed to more consanguineous marriages or a stronger racial element with lighter color skin types [5,23,24].

In our study, the adult-onset type of XP-V was reported for the first time as it was not recognized before or mentioned in the medical literature; hence, one aim of our work was to evaluate the clinical picture of this type of disease. The frequency of XP-V seems to be higher than classic XP in the Iraqi population in contrast to what has been reported in other countries [5]. As Iraq is a sunny country, the course of classic XP is rapidly progressive; the death rate is very high, and patients rarely live beyond the age of 20 years [5,6]. The skin becomes dry and parchment-like, with multiple hyperpigmented macules and freckles. Patients with classic XP who are below 20 years of age have a greater than 10,000-fold risk of BCC, SCC, or MM [9].

There are some cases of XP-V that can not easily be differentiated from mild to moderate XP, though photophobia may represent an important differential point. In challenging cases, genetic studies are essential.

The limitation of this study was the unavailability of genetic analysis at our laboratories at the time of the study.

CONCLUSIONS

Childhood-onset XP-V is not a rare disorder in the population where intermarriages are present. The clinical picture mainly includes sunburn, freckling, solar keratosis, and skin cancers, depending on the patient's age. The skin lesions are similar to those with XP but with a late age of onset, and the disease course is less rapid with milder skin lesions. Adult-onset XP-V cases were reported for the first time as a new unrecognized type, and its clinical picture was similar to the childhood-onset type but with a later onset and milder course.

Early diagnosis accompanied by early full protection of XP-V patients against UV light exposure will lead to a normal life without or with few skin cancers. Light eye testing for photophobia is very important to differentiate between classic XP and XP-V. Based on the results obtained from this study, XP-V is more common than classic XP in the Iraqi population. We suggest using the term 'xerodermoid pigmentosum' rather than XP-V as it is more straightforward and descriptive.

Conflict of Interest: None declared.

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