SKIN CANCERS IN VIETNAMESE XERODERMA PIGMENTOSUM PATIENTS

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ABSTRACT

Objectives: Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder caused by defects in DNA repair, leading to severe photosensitivity and significantly increased risk of skin cancer. This study aimed to investigate the clinical features and characteristics of skin cancers in newly diagnosed XP patients in Vietnam from 2018 to 2022, with the goal of improving diagnosis and management.

Methods: We conducted a descriptive cross-sectional study on 36 newly diagnosed XP patients. Diagnosis was based on medical history and clinical examination. Data on the presence of skin cancers, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), were collected and analyzed.

Results: Among the 36 patients, 8 (22.22%) had one or more skin cancers. Six patients had BCCs, and two had SCCs. The mean age at first BCC appearance was 44 ± 18.72 years. One patient presented with multiple BCCs (3 lesions). All BCC cases were treated surgically with good outcomes. The highest number of SCCs (4 lesions) was observed in a 55-year-old man, who also had 20 actinic keratoses (AKs). All patients with BCC or SCC had concurrent AKs. A 16-year-old male, who developed skin cancer at age 9, died due to a giant tumor on his head, representing the youngest case of skin cancer in this cohort.

Conclusions: Early diagnosis and management of XP, including sun protection and regular monitoring for skin cancers, are essential for improving patient outcomes. The findings from this study contribute to the development of practical guidelines for diagnosing and managing XP in Vietnam.

Keywords: Actinic keratosis, basal cell carcinoma, skin cancer, squamous cell carcinoma, xeroderma pigmentosum.

1. INTRODUCTION

Xeroderma pigmentosum (XP) is a very rare disorder characterized by skin and ocular manifestations due to increased photosensitivity, caused by a deficiency in DNA repair resulting from genetic defects. XP patients often come to the clinic with early-onset cutaneous symptoms such as sunburn, freckles, dry skin, telangiectasias, poikiloderma on sun-exposure areas along with the appearance of multiple cutaneous malignancies[1,2]. In addition to cutaneous manifestations, XP patients also present with various ocular and neurological disorders. Approximately half of XP patients present with severe sunburn with minimal

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sun exposure and more than 30% of them present with progressive neurodegeneration included intellectual impairment and hearing loss[3,4]. The disease can occur in all races and in both men and women, usually manifest as early as first two years of age. XP is a very rare genetic disease with an estimated incidence in Europe, America, and Japan of 1 : 250 000 to 1 : 1 000 000 000 and 1 : 22 000, respectively[5,6].

The genetic abnormalities found in XP patients are often related to genes that recognize and repair UV-induced DNA damages. Most genetic defect are found in the nucleotide excision repair (NER) pathway, which is regulated by a group of genes with autosomal recessive inheritance[7]. XP subgroups are divided based on specific mutated NER pathway genes ranging from XPA to XPG, each subgroup has different clinical manifestations and severity[8]. NER can be subdivided into two pathways: the transcription-coupled repair (TCR) and the global genome repair (GGR). XPC and XPE mainly affect the GGR pathway while XPA, XPB, XPD, XPF, XPG can affect both TCR/GGR pathways[9]. Unlike XPA to XPG, genetic defect in xeroderma pigmentosum 'variant' (XPV), another variant of XP, does not affect the NER pathway but is associated with a defect in post replication repair system due to mutations in the gene encoding enzyme DNA polymerase η (polη)[10]. Because the TCR system is still preserved in XPC, XPE and XPV patients, in these cases, photodamages are usually not severe and appear later, but it also leads to delays in diagnosis and the long-term accumulation of UV-induced DNA damages resulting in higher incidence of skin cancer[9].

The presence of malignancies is the major factor influencing prognosis in patients with XP. Previous reports have documented in XP patients both cutaneous malignancies and other internal cancers (e.g., gastric, breast, bladder, colorectal, lung, endometrial, brain, head and neck, prostate cancers)[11]. Deficiency in UV-induced DNA damage repair has resulted in accumulation of oncogenic mutations and earlier formation of tumors. Bradford et al reported that among XP patients with skin cancers, non-melanoma skin cancer (NMSC) was increased 10 000-fold and melanoma was increased 2 000-fold in patients under age 20, in addition skin cancer was also the major cause of mortality (34%) beside neurologic degeneration (31%) and internal cancer (17%).[3] XPC, XPE and XPV are often the subgroup at higher risk of skin cancer due to delayed diagnosis and lack of necessary photodamage prevention in the early stage of life.

2. SUBJECTS AND METHODS

2.1. Study subjects

This study involved newly diagnosed Vietnamese patients with xeroderma pigmentosum (XP) from 2018 to 2022. Patients were diagnosed based on medical history and clinical presentations. Subjects were recruited through convenient sampling, with suspected cases initially screened by primary care physicians and subsequently re-evaluated by dermatological specialists.

2.2. Study methods

Study design

A descriptive cross-sectional study was conducted to assess the clinical features and skin cancer characteristics of XP patients in Vietnam.

Procedures

All patients underwent comprehensive clinical evaluations, including screening for skin

lesions and tumors. This included dermoscopic examination and, where necessary, skin biopsies. The study focused on identifying precancerous lesions, including actinic keratosis (AK), and non-melanoma skin cancers such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Melanoma cases were also noted. Additionally, patients were examined by specialists for ocular and neurological manifestations.

Statistical analysis

Data were entered, managed, and analyzed using SPSS version 20.0. Comparative analyses between groups were conducted using chi-square tests for categorical variables and t-tests for continuous variables. Statistical significance was set at $p < 0.05$.

2.3. Ethics

Personal information of patients was kept confidential and used solely for the purpose of this study, in accordance with the Helsinki Declaration of 2013. This research was approved by the National hospital of Dermatology and Venereology.

3. RESULTS

3.1. General characteristics of XP patients

We identified 36 new XP cases during the study period. The patients predominantly resided in poor, mountainous areas across 11 northern provinces of Vietnam. The general characteristics of all XP patients are summarized in Table 1.

Table 1. General characteristics of XP patients (N = 36)

Characteristic		
Age (years)		24.3 ± 20.3
Gender	Male	23 (63.9%)
	Female	13 (36.1%)
Geography	City	1 (2.8%)
	Rural, mountainous	35 (97.2%)
Familial history of XP		22 (61.11%)
Age of onset (months)		25.3 ± 34.9 (1 - 120 months)
The first symptom	Skin	100%
	Ocular, neurology, others	0%
Symptoms of disease onset	Sunburn	15 (41.7%)
	Hyperpigmentation	21 (58.3%)

The patients had a mean age of 24.3 years, of which 63.9% were male. 22/36 patients had family members who were also diagnosed with XP. Among 36 patients in this study, there are 7 families with many people suffering from the disease, in which the family with the most people infected is 2 people.

The mean age of onset is 25.3 ± 34.9 months, in which 13/36 patients have symptoms in the first year of age, especially 8 cases onset in the first 3 months after birth. All cases presented initially with cutaneous lesions included sunburn (41.7%) and hyperpigmented lesions (freckles, lentigines) (58.3%).

3.2. General characteristics of XP patients

At the time of our clinical examination, patients were fully symptomatic with various cutaneous lesions such as sunburn, freckles, lentigines, seborrheic keratosis, xerosis, atrophy, poikiloderma, telangiectasias, and skin cancers (table 2).

Table 2. Cutaneous features of XP (N = 36)

Features		
Location of lesions	Exposure areas only	21 (58.3%)
	Both exposure and unexposed areas	15 (41.7%)
Incidence of cutaneous lesions		
Sunburn		34 (94.4%)
Freckle-like hyperpigmentation		36 (100%)
Xerosis		36 (100%)
Hypopigmentation		33 (91.7%)
Telangiectasia		21 (58.3%)
Seborrheic keratosis		12 (33.3%)
Poikiloderma		20 (55.6%)
Actinic keratosis		24 (66.7%)
Skin cancers		8 (22.2%)

3.3. Clinical features of actinic keratosis and skin cancers

At the time of diagnosis, 15/36 patients had skin lesions in both exposure and unexposed areas. Sunburn, pigmentation lesions and xerosis are the most common cutaneous symptoms, seen in most cases. We also detected 24 cases of actinic keratosis and 8/36 cases (22.22%) had malignant lesions at the time of diagnosis. Skin cancer detected in XP patients in this study included basal cell carcinoma (6/8) and squamous cell carcinoma (2/8), there were no melanoma among our XP patients. Each of these cases had only one type of skin cancer. The clinical characteristics of patients with AK and skin cancer are presented in Table 3.

Table 3. Clinical features of actinic keratosis and skin cancers

Characteristic	AK (n = 24)	BCC (n = 6)	SCC (n = 2)
Age (years)	33.2 ± 19.2	53 ± 15.4	35.5 ± 27.6
Time of skin cancer appearance (years old)	-	44 ± 18.7	30.5 ± 30.4
Number of lesions	6.0 ± 4.2	1.5 ± 0.8	2.5 ± 2.1
Mortality	0/24	0/6	1/2

In the group of patients with skin cancers, the youngest age at onset of skin cancer was in the case with a giant SCC tumor on the head that appeared at 9 years old. The mean age of onset of BCC was 44 years old, of which the smallest was a case with a hyperpigmented papule near his right eye appearing at 21 years old. The highest number of AK we detected on a case was 20 lesions in a 55-year-old man who also had 4 SCC lesions at the time of our examination. The highest number of BCC lesions was 3 lesions (in 1 case). All BCC and SCC patients had multiple AKs concurrently with skin cancer.

For XP patients with AK or BCC, these lesions were detected at the stage that available for topical or surgical treatment, so we treated these patients and followed up after treatment. No mortality was recorded among this patients (Table 3). Particularly the only case of death from skin cancer was a 16-year-old male patient, when be diagnosed he had a giant tumor covering the entire face area with biopsy results as low-differentiated SCC. This lesion was diagnosed at the advanced stage and was no longer suitably indicated for surgery and the patient also died not long after.

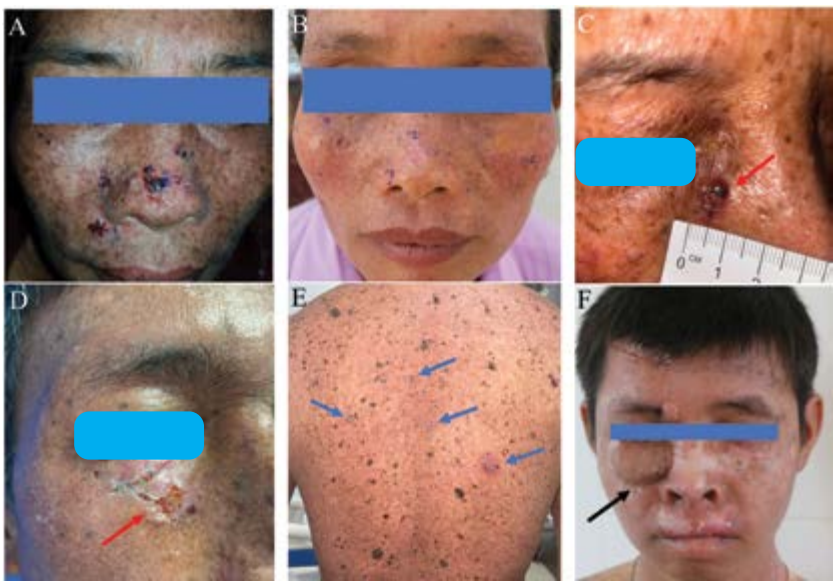

Figure 1. A, B: *XP patients with multiple facial BCCs.* ***C, D:*** *Facial BCC along with multiple freckle-like hyperpigmentations (red arrow: BCC lesion).* ***E:*** *Patient with multiple freckle-like hyperpigmentations and actinic keratosis in unexposed area (blue arrow: actinic keratosis).* ***F:*** *Post BCC removal surgery on the face with multiple freckle-like hyperpigmentations and atrophic scars due to sunburn (black arrow: Skin graft after BCC removal)*

4. DISCUSSION

Xeroderma pigmentosum is a rare genetic disorder, however many variants of the disease have been identified. Each subgroup of the disease is characterized by a different mutation in genes involved in DNA repair process, thereby presenting a different phenotype. The correlation between genotype and phenotype in XP patients has been reported in many previous studies[9,12-15].

During the course of this study, we detected 36 newly diagnosed cases of XP in northern Vietnam, of which about one-fifth of the cases were associated with skin cancer lesions at the time of diagnosis. The majority of skin cancer lesions were found to be basal cell carcinoma (6/8 cases). The average age of onset of BCCs in this study was 44 years old, much older than the average age

of onset of NMSC in the US. This age is also not much younger than the average age of patients diagnosed with BCC at our National Hospital of Dermatology and Venereology as previously reported by Sau Huu Nguyen. Most of the BCC in our study are at early stage, patients only go to the doctor when they observe the appearance of the first suspected BCC lesion. However, the age of first SCC in this study was 9 years old in a male patient with giant tumor, this age is relatively consistent with the reports available in the literature. The patient had this tumor at very young age and the tumor grew very quickly to become a giant lesion at the age of 16 years, this was main cause of the patient's death within 1 year after being diagnosed. Although skin lesions may appear at early stage, the prognosis of XP depends mainly on the presence of skin tumors, internal cancers or neurologic degeneration, three major causes of death in XP.[3] There are two main subgroups of XP, those with deficiency in the TCR pathway (including mutations in genes XPA, XPB, XPD, XPF, XPG) and those without TCR defect (including XPC, XPE, XPV). In the subgroups with disorder of the TCR pathway, although there was a risk of developing skin lesions and skin cancer at an early stage, but this also prompted patients to go to the doctor and receive early prevention, when the number of skin and DNA damages is not much. In contrast, in the subgroups without TCR gene disorder, the later formation of skin lesions leads to late diagnosis and treatment, malignant lesions may appear later, but in more numbers and at an advanced stage. However, in general, XP is a genetic disease with a high risk of skin cancer with multiple lesions and early onset. Cleaver reported that in XP patients, the median age of first non-melanoma skin cancer was 8 years old, 50 years earlier than the general population in the United States[16]. This age is also much younger than the mean age of first melanoma appearance in XP patients in the US at 22 years, suggesting a different carcinogenic mechanism between NMSC and melanoma[17].

In our study, 1 patient died from skin cancer with a SCC at terminal stage when be diagnosed. The main reason for this poor outcome is that: this patient, like most of the other patients in our study, lived in difficult mountainous areas (35/36 cases, 97.22%), accessibility to health care services is very limited. Most of the cases were discovered by chance or through screening of family members of previously detected cases in some clusters of cases in the same family. This is also the main purpose that led us to conduct this study, thereby providing a diagnosis and management guideline for xeroderma pigmentosum that is easy to apply and suitable to the conditions in Vietnam, helping to detect early and improve prognosis of our XP patients, with particular emphasis on the prevention of malignancy.

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