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Case Report

Xeroderma Pigmentosum with Ocular Squamous Cell Carcinoma-A Case Report

Farida Tabri

Dermatology and Venereology Department, Medical Faculty of Hasanuddin University, Wahidin Sudirohusodo Hospital, Makassar, Indonesia

ABSTRACT

Xeroderma pigmentosum (XP) is a rare autosomal recessive genodermatoses characterized by increased cellular photosensitivity to ultraviolet radiation and early onset of skin malignancy. XP may occur in any race or gender. This disease is usually acquired in infancy or childhood and is usually detected at the age of 1-2 years when sun exposure commonly starts. Clinically, the first abnormality found is extreme sensitivity to sunlight, abnormal lentigo can be found in areas exposed to sunlight. This is followed by an increase or decrease in pigmentation, aging of the skin and an increase in the incidence of skin cancer. A clinical diagnosis is confirmed by a cellular test to repair damaged DNA. We report a case of XP in a 2-year-old boy with clinical symptoms of lentiginous spots in the sun-exposed area, accompanied by Squamous Cell Carcinoma (SCC) in the eye based on histopathological examination. Multidisciplinary approach with the ophthalmology department was done to remove the SCC. The patient was given education about lifetime sun protection measurements and the importance of regular follow-up to detect the occurrence of new lesions or worsening of preexisting lesions.

Key words: Xeroderma pigmentosum (XP), Ocular squamous cell carcinoma, genodermatoses

INTRODUCTION

Xeroderma pigmentosum (XP) is a rare autosomal recessive genodermatoses characterized by increased cellular photosensitivity to ultraviolet radiation and early onset of skin malignancy. [1] XP was first described in 1874 by Hebra and Kaposi. In 1982, Kaposi coined the term XP for skin conditions that referred to characteristics: rare, genetically inherited, characterized by photosensitivity, pigmentary changes, premature aging and development of malignant tumor. This skin disorder is caused by cellular hypersensitivity to ultraviolet (UV) radiation due to defects in DNA repair. In 1998, Thompson identified eight genes in patients with XP, seven involved as repair of nucleotide excision (XP A-XP G) and one variant of XP not cloned, involved in replication of damaged DNA in leading strands. [2-3]

XP may occur in any race or gender. This disease is usually acquired in infancy or childhood and is usually detected at the age of 1-2 years when sun exposure commonly starts. The reported frequency in Europe and United States is about 1in 250,000. Group XP C is the most common type found in the United States. In Japan, the frequency is as high as 1 in 40,000, XP Group A is the most common form in Japan. The XP A and XP C groups are the most commonly found. [1,3] About 1 in 2.3 million live births in Western Europe, less than 40% of patients with XP survive until the age of 20, and only a few patients with XP show non-progressive clinical symptoms that can last up to 40 years of age. [4]

Clinically, the first abnormality found is extreme sensitivity to sunlight, abnormal lentiginosis can be found in areas exposed to sunlight. This is followed by an increase or decrease in pigmentation, aging of the skin and an increase in the incidence of skin cancer, if the individual is not protected from sunlight. In a small percentage of patients, they show progressive neurological abnormalities.

The diagnosis is clinically made by the reaction of the skin to acute and prolonged sunburn in all exposed sites, from birth, early lentiginosis which is unusual in areas exposed to sunlight or the appearance of skin cancer at a young age. A clinical diagnosis is confirmed by a cellular test to repair damaged DNA.

We report a case of XP in a 2-year-old boy with clinical symptoms of lentiginous spots in the sun-exposed area, accompanied by Squamous Cell Carcinoma (SCC) in the eye based on histopathological examination.

METHODS

A patient with XP was examined by conducting a thorough history taking and physical examination supported by relevant laboratory tests. Multidisciplinary approach in cooperation with the ophthalmology department was carried out to ensure a holistic management. A review of the latest literatures was then conducted to ensure an evidence-based and updated management approach.

CASE REPORT

A 2-year-old boy was brought by his parents with a chief complaint of multiple brownish spots in the face, neck, upper chest, and limbs. These patches were seen on sun exposed area and some were grouped and form blacklumps under the left eye and nuchal area. The black lumps were in the size of quail egg with uneven surfaces. White spots appeared on areas that are unexposed to the sun. The patient also winces when exposed to the sun. This complaint was accompanied by burning sensation, pain and itching. According to the mother, brownish spots started to appear when the patient was 1.5 years old and increased in number along with time. The patient is the first child of two siblings. The patient's sister was 7 months old and did not present with similar condition. He has normal birth history and complete immunization. Both parents were cousins and the father was a heavy smoker. Family history with the same complaint was denied. There was no history of drug or food allergy. The family has not sought any treatment for the skin complaints.

The patient was in a good general condition with normal vital signs. Dermatologic examination showed hyperpigmented, crustal, lentiginous, multiple macules on the face and upper and lower limbs; necrotic abscess was seenon the left periorbita region. (Figure 1).

Figure 1. (a-d) Hyperpigmented macules, multiple lentigenes at sun exposure areas and necrotic abscess in left periorbita.

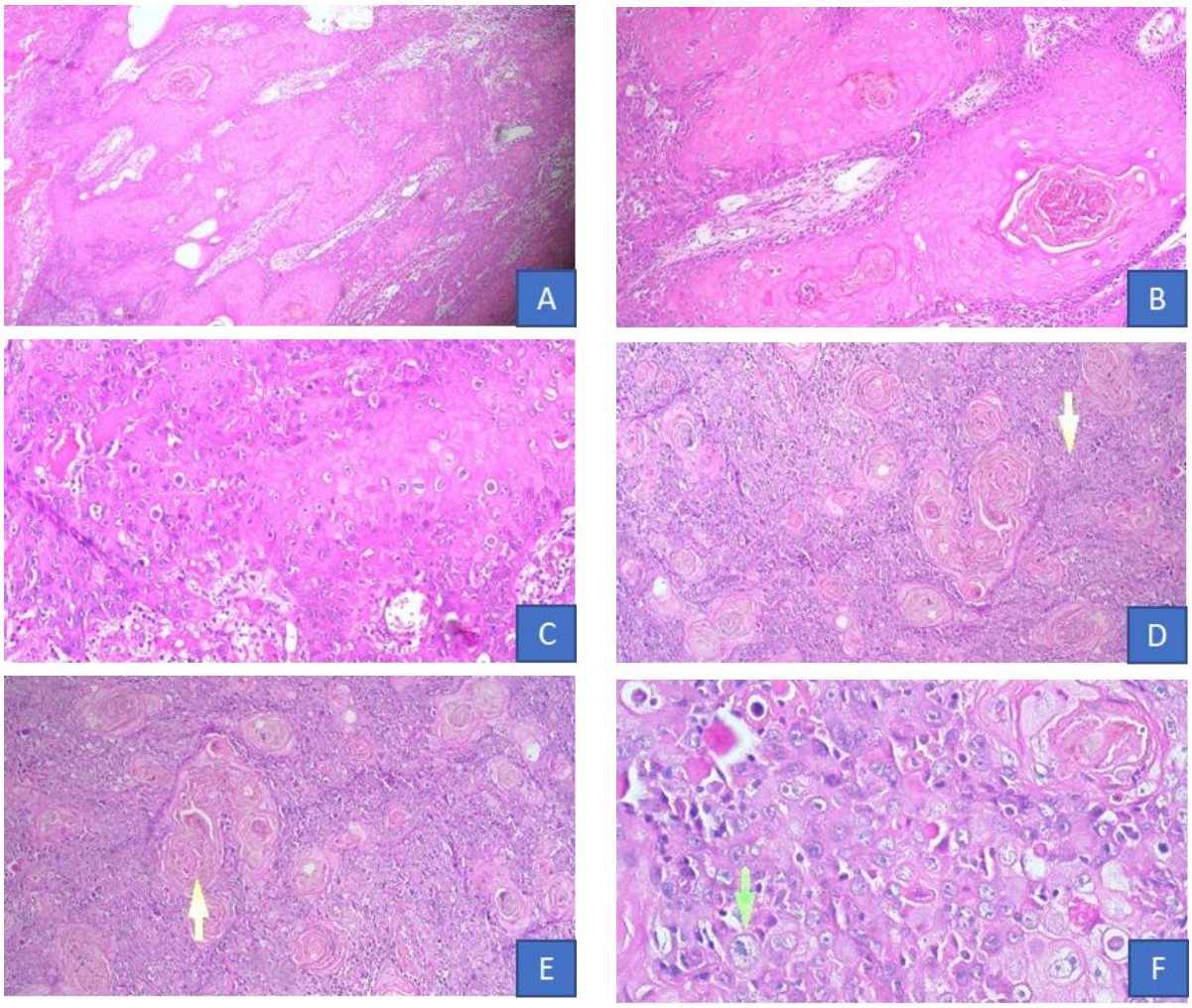

Figure 2. Histopathology
(A-C) Show inflammatory cell with necrotic tissue (magnification 4;10;20 times)
(D) Keratinizing; arrow show keratin mass, magnification 10 times;
(E) Atypical squamous cell proliferation, magnification 10 times;
(F) Atypical squamous cell, pleomorphic, prominent nucleoli, eosinophilic cytoplasm (SCC), magnification 40 times.

Based on the history and clinical examination, the differential diagnoses are XP and SCC. The patient was consulted to the oncology department, given the importance of management of suspected malignancy in the left eye.

Education about sun protection measures such as wearing polyester clothing, hats, sunglasses, and long-sleeved clothing during daytime activities was given to the parents. The patient was prescribed SPF 30sunscreento be applied in morning, noon, and afternoon.

On the 30th day the patient was referred back to the dermatology department. The necrotic abscess had been removed and the result of the histopathological examination was SCC (Figure 2).

Dermatological examination showed hyperpigmented, crusty, lentiginous, multiple macules in the facial region, neck, and upper and lower limbs. (Figure 3)

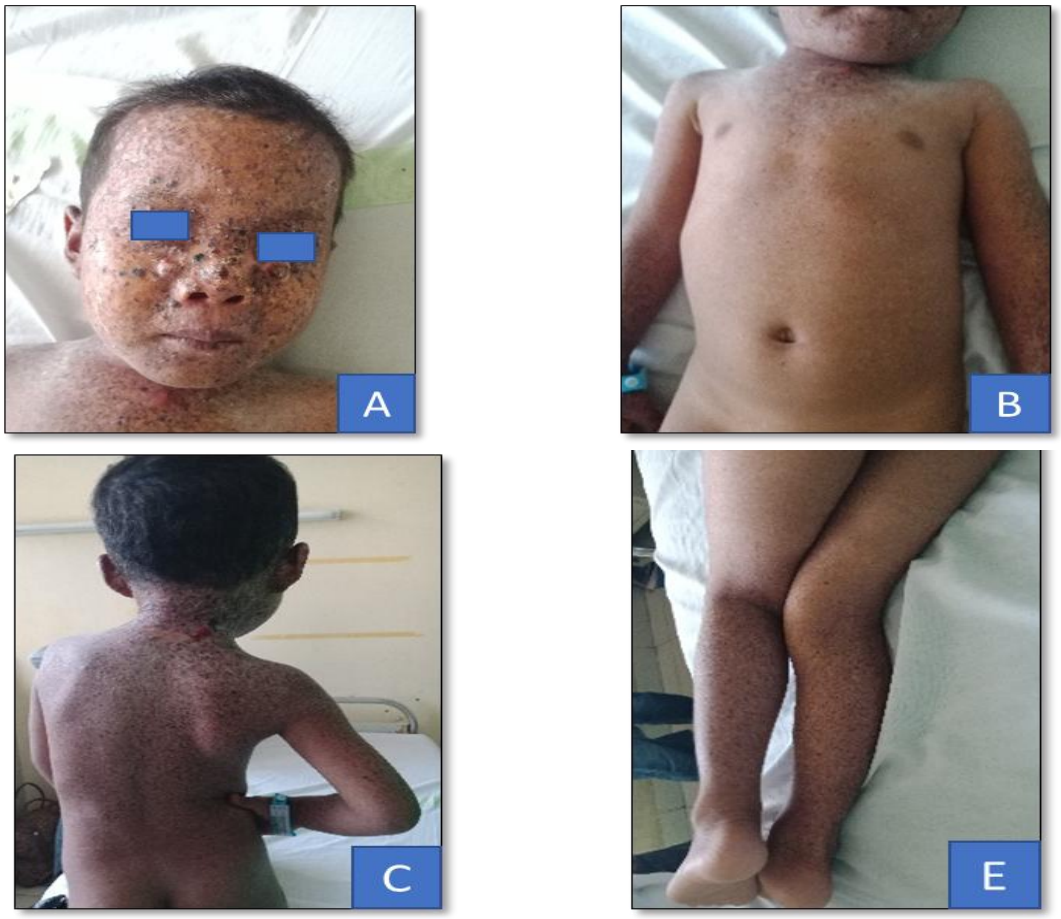

Figure 3.(A-E) after 30th day of treatment, Hyperpigmented macules, multiple lentigenes at sun exposure are still existed

Based on the history taking, physical examination, and supporting examination, a diagnosis of XP with SCC of the eye was eventually made. The patient was given education on sun protection measures and SPF 30 sunscreen. The patient is advised to do a regular monthly control to our department.

DISCUSSION

XP (XP) was first described in 1874 by Hebra and Kaposi. [1] XP is an autosomal recessive disorder due to DNA gene mutation abnormalities characterized by dry and hyperpigmented skin. [1,6,7] XP is usually detected at the age 1-2 years when children start to have sun exposure. There is no ethnic or gender predilection. [4] The prevalence of XP is higher in the Middle East where marriages between close relatives are common. XP patients have also been reported in various parts of the world and various races including whites, Asians, blacks and Americans. [1]

We report a case of XP in a 2-year old boy who presented with black lumps

under the left eye and nuchal area which slowly developed from brownish spots 6 months prior to admission. These lesions were clearly seen on sun-exposed areas which are not covered with clothes. Generally, from an early age, patients with XP are sensitive even to minimal sun exposure. Initially, the lesions presented as erythema, vesicles, and edema. At the age of two years, solar lentigines, xerosis and pigmentation are often found which may be followed with the development of actinic keratosis, keratoacanthoma, basal cell carcinoma, SCC and malignant melanoma. [8] A study shows the average age for developing melanoma malignancies at the age of 8 years. [9] In a study involving 830 patients, 45% of patients had basal cell carcinoma or SCC with majority of tumors found on the head and neck. [2,4]

The cause of XP is the failure of DNA which is needed especially after excessive exposure to UV light. As many as 80% of patients with XP have defects in initiating DNA repair. [8] The majority of patients with XP have a history of previous sun exposure. A history of sun exposure should be focused on the relationship between sun exposure and the occurrence of abnormalities and the length of sun exposure. Usually a family history is absent because XP is an autosomal recessive disease. [5] This is in line with our findings as skin lesions started to appear when the patient began to have sun exposure with no family history.

Sunburn is a normal finding in patients of XP. Clinical features such as erythema and edema are caused by vasodilation and inflammation. This response is likely triggered by UV exposure which triggers DNA damage. Patients with XP will suffer from a feeling of intense sunburn. This will result in persistent DNA UVR photoproducts. [11] Similar complaint was observed in this case where heat and pain are felt after exposure to the sun.

The basis for the occurrence of XP is in DNA repair defects, especially in nucleotide excision repair (NER), [8] this is due to damage caused by UV radiation. There are two types of NER in our body, the global genome NER (GG-NER) and transcription coupled NER (TC-NER). Recent study shows that in vitro NER cloning can replace damaged NER. [1] NER itself is a process that aims to replace damaged DNA by placing new DNA using strand as a buffer and involving 30 different types of genes. [8]

A total of seven repair genes in XP have been identified, namely the XPA gene. This gene plays a role in GG-NER and TC-NER. It has been reported that the XPA gene has an affinity for DNA that is damaged; XPA can also detect damage to DNA. When DNA damage is detected by the XPA gene, a complex will be formed. This complex will repair DNA. Other gene products needed in the formation of complexes are XPB and XPD, which are both part of the 9 protein complex subunits (TFIIH). After the damaged DNA is removed, the XPG and XPF genes encode the endonucleus to activate new DNA through cell polymerization. [6]

Ultraviolet absorption by DNA results in the formation of photoproducts (CPD and 6-4PPs) which are recognized and repaired by NER. If left untreated, they can cause classic UVB mutations found in skin cancer. Molecular defects in XP cells lead to the recognition and abnormal repair of UVR-induced DNA damage, and the induction of UVB mutations that increases significantly in sun-exposed skin in affected individuals. The increased frequency of these mutations tends to account for pigment changes and skin cancer in XP patients. It is thus not surprising thatp53 gene examination from XP patients shows characteristic mutations. [4]

In approximately 60% of XP cases, hypersensitivity to sun exposure is the first presentation. Sunburn may occur in the first week and can be misdiagnosed as cellulitis or impetigo. Approximately 40% of other individuals do not show sunburn. In the first 2 years, the skin appears as hyperpigmented spots such as seen in lentigo, particularly in

areas exposed to sun exposure. These manifestations arise in the nasal region, zygoma, and forehead before appearing on the neck. Hypopigmented macules often appear at first and are followed by telangiectasia in the later phase. [4,5] Approximately 50% of patients with XP has a history of sunburn although only briefly exposed to the sun. Some patients reported lesions in the form of hyperpigmented macules, especially in areas experiencing exposure to sunlight. Continuous exposure will cause the skin to become dry with parchment-like appearance. [1]

Ocular manifestations include the development of scar tissues and skin cancers that require excision. Ocular abnormalities in XP can be accompanied by dry eyes, red conjunctiva, swelling, and early pterygium. Prolonged exposure can cause scarring and impaired vision. Ocular cancer, especially SCC, has been reported in patients with significant sun exposure and poor ocular photoprotection. Patients with neurodegeneration related to XP can also develop neuro-ophthalmological features, photosensitivity, nystagmus and strabismus. Photophobia is also common and is often the earliest ophthalmic symptom in XP. [10-13] Neurological complications occur in about 30% of cases and can worsen the patient's condition. [8,14]

The diagnosis of XP is based on history, physical examination and laboratory examinations. XP usually takes place in three phases. The first phase appears after 6 months of age and is characterized by diffuse erythema, scales and hyperpigmented spots on areas exposed to sunlight. In very severe, lesions may also occur in other areas such as the lower limbs, neck and body. Clinical manifestations in XP are usually being permanent even in the winter with minimal sun exposure. [6,11] The second phase is characterized by poikiloderma which consists of skin atrophy, telangiectasia, hyperpigmentation and hypopigmentation. Although telangiectasia is more commonly found in sun-exposed areas, telangiectasia may also appear on non-exposed skin such as the buccal mucosa. [6,11] The third phase of this disease is the appearance of malignancies, including basal cell carcinoma, SCC, malignant melanoma, and fibrosarcoma. This malignancy can occur at the beginning of the age of 4-5 years and more commonly found in areas that are heavily exposed to sunlight. [6,11]

The diagnosis of XP can be established by a special laboratory examination that includes cell culture to see cellular hypersensitivity. [1,2] In this examination, fibroblasts from patients with XP are exposed to various doses of UV radiation and the chromosome damage is evaluated in at least 100-200 cells. The cells from patients are then compared with cells from their parents to see whether there are heterozygotes for XP. Cells from healthy individuals are used for control. Furthermore, to eliminate the XP subject, evaluate of damaged chromosome can be done. Prenatal diagnosis can be done by measuring exposure to UV light which will trigger DNA synthesis in amniotic fluid cell cultures. The diagnosis of XP is established by finding trophoblast cells obtained early in pregnancy. Another test that can be useful is electroencephalography examination. [6]

Histologic findings in the first phase of XP were hyperkeratosis and an increase in melanin pigment. Some rete ridges can extend where other rete ridges may show atrophy. This is due to the chronic inflammatory process that infiltrates the upper part of the dermis. [1,2] Another feature was apoptosis of keratinocyte cells. [11] The histologic features in the third phase are not specific because there are varieties of tumors that are complications of XP. [6] The histologic findings in this case are inflammatory cells accompanied by tissue necrosis, keratinizing, atypical squamous cell proliferation, pleomorphic, prominent nucleoli, and eosinophilic cytoplasm, which supports a diagnosis of squamous cell carcinoma.

Management of patients with XP includes lifetime protection from

sunexposure and early detection and treatment of neoplasms. Diagnosis is based on the characteristics of the clinical appearance and is confirmed by laboratory tests of cellular hypersensitivity to UV and failure of DNA repair. [7] Sun protection measures, such as face coverings, hat, sunglasses, and in many patients with XP can cause social isolation and may lead to psychological adverse effects such as depression and anxiety. [4] Patients must be educated to protect all body surfaces from sun exposure by wearing protective clothing and UV-absorbing glasses and long hairstyles. They must adopt a lifestyle to minimize sun exposure and use sunscreen with high SPF (minimum SPF 30). Patients must be frequently examined by family members who have been trained to assess the occurrence of new lesions or worsening of preexisting lesions. A set of color photographs of the entire surface of the skin with a focus on lesions is often very useful for patients and doctors in detecting new lesions. A doctor must examine the patient approximately every 3-6 months depending on the severity of the skin disease. Premalignant lesions such as actinic keratosis can be treated with liquid nitrogen, topical 5-fluorouracil, or imiquimod. [1,4] Patients are given education regarding prevention of sunlight and use of sunblock.

Patients who are diagnosed early and carry out strict protective measures as shown I this case have a good prognosis. They can expect a relatively normal life span but need to maintain protection against the sun for life time. The neurological disorder may cause progressive disability, which may vary in severity between patients and may result in a shorter life span.

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