
LAPORAN KASUS

Case Report: Developed Infraocular Squamous Cell Carcinoma and Nasal Basal Cell Carcinoma in Xeroderma Pigmentosum

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ABSTRACT

Introduction: Xeroderma pigmentosum (XP) is a rare autosomal recessive disease caused by a gene defect in nucleotide excision pathway named nucleotide excision repair (NER), characterized by photosensitivity of the skin. **Case:** A 5 year old girl, 15 kgs, came with brown and black spots on the entire body since she was 7 month old. These complaints were accompanied with itchiness and burning sensation. Since two years ago, a small bump appeared on the nose and below the left eye, increasingly enlarged, also easily bled. She complained red and watery eyes since two weeks ago. Patient often felt glare. Physical examination all over the body found obtained multiple hypopigmented and hyperpigmented macules unsharply marginated with varying size from pinpoint to few cm and also dry skin. Right and left ophthalmic region showed red, watery eye, and photophobia. Nasal region showed nodules about 1 cm in size, accompanied by erosion and crusting. **Histopathology** examination result of left infraoculi region was malignant squamous cell carcinoma and nasal region was malignant basal cell carcinoma. Patient were diagnosed with XP with infraocular squamous cell carcinoma and nasal basal cell carcinoma. Patient was treated with natrium fusidic 2% cream, sunscreen with sun protecting factor (SPF) 30, moisturizer, chlorpheniramine maleate, chemotherapy, and also educated to avoid sun exposure. **Discussion:** XP causes a variety of clinical manifestations, often with a skin malignancies. Skin biopsy is mandatory to establish the diagnosis

Key words: xeroderma pigmentosum, photosensitivity, skin malignancies.

ABSTRAK

Latar belakang:

Xeroderma pigmentosum (XP) merupakan penyakit autosomal resesif yang jarang, disebabkan oleh defek gen pada jalur eksisi nukleotida bernama *nucleotide excision repair* (NER) ditandai dengan fotosensitivitas kulit. **Kasus:** Anak perempuan usia 5 tahun dengan berat badan 15 kg datang dengan keluhan bercak coklat dan hitam pada seluruh tubuh sejak berusia 7 bulan disertai rasa gatal dan terbakar. Sejak 2 tahun yang lalu, muncul bentol kecil pada hidung dan dibawah mata sebelah kiri yang semakin membesar dan mudah berdarah. Keluhan mata merah dan berair sejak 2 minggu yang lalu. Pasien sering tampak silau. Pemeriksaan fisik pada seluruh tubuh didapatkan makula hipopigmentasi dan hiperpigmentasi, batas tidak jelas ukuran bervariasi dari ukuran yang sangat kecil sampai beberapa cm dan kulit kering. Pada regio optalmika dekstra dan sinistra didapatkan mata merah, berair, dan fotofobia. Regio nasal didapatkan nodul diameter 1 cm, disertai erosi dan krusta. Pemeriksaan histopatologi didapatkan karsinoma sel skuamosa pada regio infraokular sinistra dan karsinoma sel basal pada regio nasal. Pasien didiagnosis dengan XP dengan karsinoma sel skuamosa infraokular dan basal sel karsinoma nasal. Pasien mendapat terapi krim natrium fusidat 2%, tabir surya SPF 30, pelembap, klorfeniramin maleat, kemoterapi, dan edukasi untuk menghindari pajanan sinar matahari. **Diskusi:** XP menyebabkan berbagai manifestasi klinis, sering disertai dengan keganasan pada kulit. Biopsi kulit diharuskan untuk menegakkan diagnosis.

Kata kunci: xeroderma pigmentosum, fotosensitivitas, keganasan kulit.

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INTRODUCTION

Xeroderma Pigmentosum (XP) is a rare autosomal recessive condition characterized by the failure of deoxyribonucleic acid (DNA) nucleotide excisional repair (NER) after sun induced damage from ultraviolet B (UVB) light (a spectrum of 280 to 320

nm), it is called as dry pigmented skin.¹ XP is characterized by photosensitivity, freckly pigmented changes, premature skin ageing, telangiectasis, warty and papillomatous growth, and malignant tumor development in later stage.^{2,3}

Patients develop early sun sensitivity, which

usually manifests as prolong erythema and blistering at one to two years of age. Freckling and poikiloderma develop as evidence of sun damage. These patients develop multiple precancerous actinic keratosis and skin cancers (non-melanoma and melanoma) early in life. In fact, a risk of skin cancer development in these patients is more than 1.000 times greater than in the general population.^{4,5}

XP is defined by extreme sensitivity to sunlight, resulting in sunburn, pigment changes in the skin, and a greatly elevated incidence of skin cancers. It is an autosomal recessive disease with the potential of causing more than 1000 fold increase in the frequency of all types of major skin cancers (basal cell cancers, squamous cell cancers, and malignant melanoma) in areas exposed to sunlight compared to normal population.^{6,7}

XP has been identified in people of every ethnic group all over the world. XP is a rare disorder transmitted in an autosomal recessive manner. The frequency is approximately 1 case per 250.000 population. An equal incidence has been reported in male and female.^{8,9}

Disease causing mutations have been identified in 8 different genes in patients with XP: 7 of these genes (XPA, XPB, XPC, XPD, XPE, XPF, and XPG) are involved in NER, and the eighth gene, polymerase-eta, involved in the replication of damaged DNA and is mutated in patients with the XP variant form.¹⁰⁻¹²

Estimated incidences vary from 1 in 20.000 in Japan to 1 in 250.000 in the United States (USA), and approximately 2.3 per million live births in Western Europe. Diagnosis is made clinically by the presence of unusual sunburns or lentiginosis or onset of cancers at an early age.^{10,13} A more recent survey in Western Europe suggests approximately 2.3 per million live births. Anecdotally, the incidence in North Africa and the Middle East, where there is a high level of

consanguinity, is substantially higher.^{14,15}

Approximately 60% of XP patients in Japan belong to the XP-A complementation group, twice the proportion seen in other countries, 90% of patients are homozygous for the XP-A founder mutation, carried by 1% of the Japanese population. In 2010, Soufir et al reported that 85% of XP families in the Maghreb region (Algeria, Tunisia and Morocco) carried a founder mutation in the XP-C gene. More recently, it has been reported that 1 in 5.000 individuals of the black Mahori population in the Comoro Islands have XP-C.^{6,16}

CASE REPORT

A 5-year-old-girl, weighted 15 kg weight, came to the Dermatology and Venereology Outpatient Clinic, Dr. Soetomo General Hospital Surabaya complained about brown and black spots appeared on the entire body since the age of 7 months. Spots initially appeared on the face and neck, then spreads to chest, hands, and feet. These complaints were accompanied with itchiness and burning sensation. There were small bumps on her nose and below the left eye since 2 years before admission, became eroded and crusted. Lesion on her nose was getting wider, and easy to bleed. She also complained of photophobia. There was history of applying alternative medication but wasn't improvement.

She was born at 38 weeks of pregnancy, delivered spontaneously by midwife, with birth weight 3200 gram. There was lesion on the skin when she was born. She did not have any significant perinatal history. She was the second child from healthy parents, she has healthy brothers. There was a history of consanguinous marriage, which her father and mother were cousin. There was no abnormality of physical and mental development, also no history of same disease in the family.

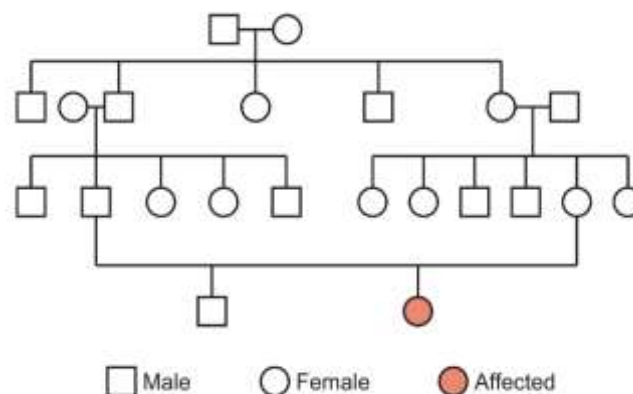


Figure 1. Pedigree

From physical examination, the general condition was compos mentis, vital sign (pulse, respiratory rate, and temperature) were within normal limit. Body weight was 15 kgs. Head and neck were within normal limit. There were no abnormalities found in chest, abdomen, also extremities. On dermatological state, all over the body, there were multiple hypopigmented and hyperpigmented macules (lentiginos/freckles-like skin

pigmentation) unsharply margined, varying in size from pinpoint to a few cm. On nasal region and left infraoculi region, there were nodules about 1 cm in size with erosion and crusting. On orbital region there were redness and watering on both of the conjungtivas. There were no oral mucosal lesions and no abnormalities on hair and nails.



Figure 2. Regio all over the body there were multiple hypopigmented and hyperpigmented macules (lentiginos/freckles like skin pigmentation) unsharply margined, with varying in size from pinpoint to a few cm. There were no oral mucosal lesions and no abnormalities on hair and nail. On nasal region and left infraoculi region, there were nodules 1 cm in size with erosion and crusting. On orbital region there were redness and watering on both of the conjungtiva.

The laboratory examination results: white blood cells 8.01 cells/mm³, platelet count 525.000 cells/mm³, hemoglobin level 11.5 g/dl, hematocrit 37.2%, albumin 3.5, SGOT 31, and SGPT 26. The urine examination result was pH 5, leucocytes (-), protein (-), erythrocytes (-), keton (-), urobilinogen 0.2, bilirubin (-), nitrite (-), glucose (-).

In most cases, the initial diagnosis of XP is made on the basis of clinical findings and family history. Manifestation of either the extreme sensitivity to UV in those individuals who show this feature, or appearance of lentiginosis on the face at an unusually early age may guide diagnosis.

Fine needle aspiration biopsy (FNAB) was

performed on left nasal region. The result showed group of squamous epithelial cells. The cells had dysplasia, N/C ratio increased, the core was atipic, bluish background cytoplasm contained a lot of polymorphonuclear cells. The conclusion was squamous epithelium with moderate dysplasia. On left infraoculi region examination was not performed because the patient was not cooperative. The histopathology examination showed hyperkeratosis, hyperpigmentation, and focal degeneration of basal cell. Fewer cell infiltration perivascular of lymphocytes and histiocytes, there was no sign of malignancy. The conclusion was xeroderma pigmentosum.

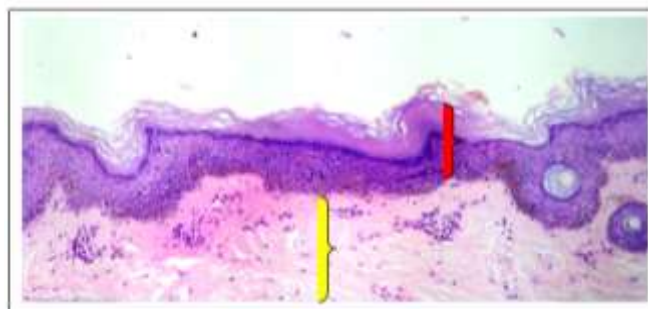


Figure 3. Histopathology result with 100x magnification. Showed hyperkeratosis, hyperpigmentation and focal degeneration of basal cell. Fewer cell infiltration of perivascular lymphocytes and histiocytes.

In order to treat the patient, we did multidisciplinary approach with other departments. This patient was consulted to Surgery Department and the answer was non melanoma skin tumors with malignant clinical, patient were followed up for further diagnostic. She was also consulted to Ophthalmology Department and the answer was right and left oculi showing ocular surface squamous neoplasia and conjungtivitis.

The answer of consultation from Pediatric Department was XP with microcephaly, underweight and severely stunted. Current developmental abnormalities could not be evaluated because patient refused the examination. They suggested a hematology examination and bone age x-ray (manus sinistra). Hematology examination result were atipic cell and toxic carelling. Bone age x-ray (manus sinistra) result photos of bone age of a to the 2 year old girl.

A month later, Surgery Department did the FNAB examination again on left nasal region and left infraoculi region. The results obtained from left nasal region consisted of atipic epithel cells, round cored, hyperchromatic, thin cytoplasm, palisade of edge. There was a few of eosinophilic matrix. The conclusion was suspected basal cell carcinoma. The results obtained from the left infraoculi region consisted of atypical squamous cell oval cored, pleomorphic, hyperchromatic, blueish cytoplasm. The conclusion was suspected squamous cell carcinoma. Department of Pathology Anatomy suggested to do wide excision for histopathology confirmation. Histopathology examination on the left nasal region showed malignant basal cell carcinoma and on the left infraoculi region showed malignant squamous cell carcinoma. According to the result, Surgery Department suggested to perform chemotherapy.

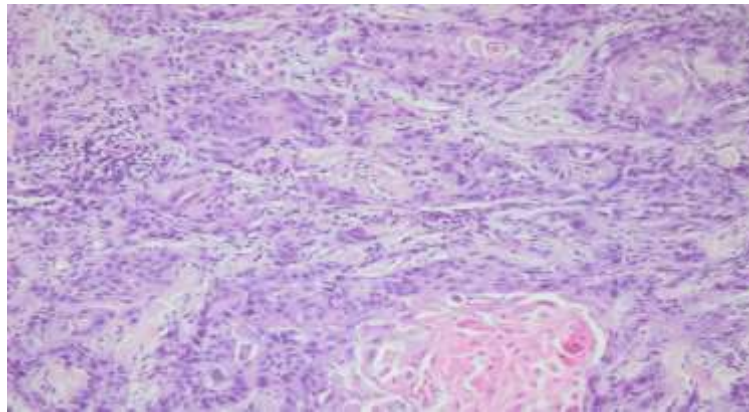


Figure 4. Histopathology examination with 200x magnification. Nasal tissue region showed pieces of tissues covered skin with neoplasm growth consist of proliferation of anaplastic basal epithel cells, oval cored, pleomorphic, hyperchromatic, composed in nets with palisade edge.

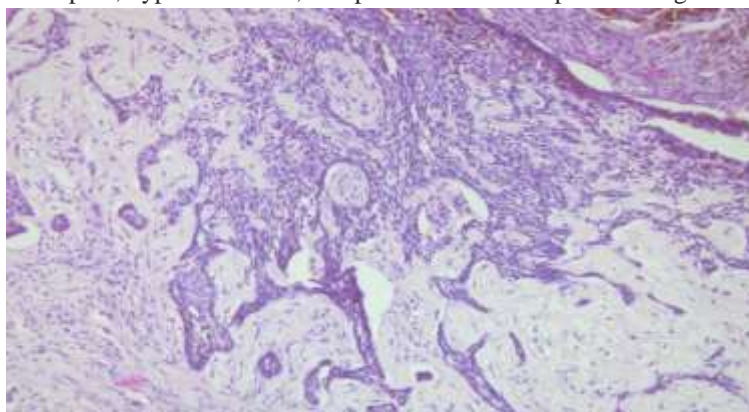


Figure 5. Histopathology examination with 200x magnification. Left infraocular tissue region showed pieces of tissues covered skin with squamous anaplastic cells, oval cored, pleomorphic, hyperchromatic, composed in nets and also appear pearl ceratin, neoplasm grew invasion in stroma.

The first assessment of this patient was xeroderma pigmentosum with premalignant lesion, then reassessed to be xeroderma pigmentosum with squamous cell carcinoma on left infraocular region

and basal cell carcinoma on nasal region, microcephaly, underweight, severely stunted, ocular surface squamous neoplasia, and left and right conjunctivitis. Treatment of XP for this patient were application of natrium fusidic 2% cream, sunscreen with SPF 30, moisturizer, chlorpheniramine maleate 3x

0,25 mg/day, was suggested to undergo chemotherapy and was educated to avoid sun exposure. The other treatments from Ophtalmology Department were levofloxacin 4x1 drops right eye and left and cendo cenfresh 4x1 drops right eye and left.



Figure 6. Three month after the therapy. Lentigines/freckles like skin pigmentation, xerosis cutis, ectropion in left oculi, and red eyes on left and right oculi were still persist. Basal cell carcinoma and squamous cell carcinoma after wide excision (arrow).

DISCUSSION

XP is autosomal recessive genetic disease caused by defects in the normal repair of DNA of various cutaneous and ocular cell types damaged by exposure to sunlight. The basic defect underlying the clinical manifestations is a nucleotide excision repair defect leading to a defective repair of DNA damaged by UV radiation.¹⁷ Consanguinity has been implicated as an etiological factor. This has been reported to varying degrees of up to 92.8% in XP patients in Libya. Other studies reported from Egypt, Pakistan, and Nigeria, have a high incidence of XP.

Many persons with XP will get unusually severe sunburn after a short sun exposure. The sunburn will last much longer than expected, perhaps for several weeks. This type of sunburn will usually occur during a child's first sun exposure, and it may be a clue to the diagnosis of XP. Continued sun exposure will lead to further changes in the skin, including irregular dark spots, thin skin, excessive dryness, rough surfaced growths (solar keratoses) and skin cancers. The eyes of a person with XP are often painfully sensitive to the sun and may easily become irritated, bloodshot, and clouded. Non cancerous and cancerous growths on the eyes may occur.^{1,18}

UV irradiation is composed of both the UVA spectrum (320–400 nm) and the UVB spectrum (280–320nm), UVB plays a more pivotal role in the etiology of XP. UV irradiation causes two major photoproducts

in DNA: cyclobutane pyrimidine dimers (CPD) and (6–4) pyrimidine-pyrimidone photoproducts (6–4PP). These DNA lesions influence cellular death, aging, mutagenesis, and carcinogenesis when they are not fully corrected by the DNA repair machinery of the cells. XP is an autosomal recessive disorder resulting from mutations in any one of eight genes. The products of seven of these genes (XP-A through G) are involved in the repair of ultraviolet induced photoproducts in DNA by the process known as NER.¹⁸

The disease typically passes through 3 stages. The skin is healthy at birth. Typically, the first stage makes it appearance after the age of 6 months. This stage is characterized by diffuse erythema, scaling and freckle like areas of increased pigmentation present on the sun exposed area beginning on the face and progressing to lower limbs, the neck, and even the trunk in extreme cases. The second stage is characterized by poikiloderma consisting of skin atrophy, telangiectasias, and mottled hyperpigmentation and hypopigmentation. The third stage is heralded by the appearance of numerous malignancies including squamous cell carcinoma, malignant melanoma, basal cell carcinoma, and fibrosarcoma. These malignancies may occur as early as age 4 to 5 years and are more prevalent in sun exposed area.^{4,19}

This patient suffered from lentigines or freckles like skin pigmentation, photosensitivity, and xerosis cutis. This is according to the literature that states there

is marked freckling of sun exposed areas in a child before the age of 2 years old. Photosensitivity approximately 50% of XP patients show acute sun sensitivity and also complaint about xerosis.^{1,6,18}

From the literature there were diffuse erythema, scaling and freckle like, areas of increased pigmentation on over sun exposed areas, such as face, extremities and neck. Poikiloderma consists of skin atrophy, telangiectasias, and mottled hyperpigmentation and hypopigmentation. In the absence of sun protection, the skin ages, dry, rough and atrophic. Lentigines increase in number small hypopigmented macules among lentigines giving rise to the characteristic mottled hyperpigmentation and hypopigmentation known as salt and pepper pattern of skin.^{1,18} In my case, similar with the literature, there were freckle-like areas of increased pigmentation on over sun exposed, the characteristic of mottled hyperpigmentation and hypopigmentation known as salt and pepper pattern of skin.

According to the theory, ocular abnormalities are almost as common as the cutaneous abnormalities, but they are strikingly limited to the anterior, UV exposed structures of the eye (lids, cornea, and conjunctiva). Photophobia is often present and may be associated with prominent conjunctival injection. Continued sunlight exposure may result in severe keratitis, leading to corneal opacification and vascularization, and neoplasia. Oral manifestations of this disorder are rare.^{1,19} In this case there were photophobia, ectropion in left oculi, left and right ocular surface squamous neoplasia, conjunctivitis, and no oral manifestation.

In 20-30% of patients XP have neurological problems and intellectual deficiency. The time of onset can vary from the age of two to middle age. The neurological abnormalities are the result of progressive neuronal degeneration resulting in sensorineural deafness, ataxia, areflexia, microcephaly and intellectual deficiency as well as impaired eyesight. This patient had microcephaly, underweight, and severely stunted.^{1,6}

XP patient under 20 years of age have greater than 1000 times increased risk of cutaneous basal cell carcinoma or squamous cell carcinoma or melanoma.⁶ In this case there were basal cell carcinoma on left nasal region and squamous cell carcinoma on left infraoculi region, dysplasia of squamous epithelium, at 3 of age. In most cases, the initial clinical diagnosis can be made on the basis of either the extreme sensitivity to UV in those individuals who show this feature, or in the appearance of lentiginosis on the face at an unusually early age. The diagnosis can be confirmed definitively by employing robust cellular

tests for defective DNA repair that are available in several countries. The most commonly used test is the measurement of unscheduled DNA synthesis in cultured skin fibroblasts.^{1,6}

Diagnosis XP can be confirmed since the start of visible signs or symptoms at the age of 1-2 years. Usually patients with XP will die at a young age due to skin cancer. However, if the patient is diagnosed early, do not suffer from neurological symptoms that are harmful, and take precautions against sun exposure, the possibility of life expectancy will be higher. In general, 60% of patients XP only lived to the age of 20 years.^{1,6} Prenatal diagnosis of XP has been done in research laboratories, but it is not a routine test. Parents of a child with XP should seek genetic counseling before considering having another child. Researchers in the United States and throughout the world are learning about XP and trying to correct the DNA repair defect in laboratory grown cells from patients with XP. The genes causing most types of XP have been identified. Many laboratories in the United States, Europe, and Japan are studying XP genes and trying to understand what they do. Clinical studies on skin cancer prevention with oral medications and evaluating patients with unusual features are also being conducted at the National Institutes of Health.

As with all genetic disorders, genetic counselling and psychological support is appropriate for the families, to discuss aetiology, probability of occurrence in future pregnancies, increased likelihood of occurrence in communities in which consanguineous marriages are common, feelings of isolation and concern about career prospects.

Children with XP should not play outdoors during the day unless they are under ultraviolet light blocking shelters and away from reflective surfaces such as snow, sand, or water. Clouds do not block out harmful rays. Special arrangements for children with XP should be made at school to ensure that they are not exposed to sunlight from an open window, that they are not exposed to any unfiltered fluorescent light bulbs, and that they are not permitted outside for gym, recess, fire drills, or other activities.²⁰

When patients with XP are outdoors in daylight, they should wear long sleeves, long pants, and wide brimmed hats. Two layers of clothing protect more than one layer. Tightly woven fabrics generally give more sun protection than loose weaves. This patient have to wear clothing that they can not see the light through. Choose eyeglasses or sunglasses specifically labeled to block ultraviolet light completely.²⁰

While sun protection by clothing is most effective, any skin not covered by clothing or hair

should be protected by sunscreen contains zinc oxide, titanium dioxide or sun blocking makeup. Sunscreens with a sun protection factor of 15 or higher should be used. They should be applied at least 30 minutes before going out in the sun. Lip moisturizers containing sun blocking agents also give protection.²⁰ UV protected glasses should be worn. In this case, the treatment XP for this patient were natrium fusidic 2% cream, sunscreen SPF 30, moisturizer, chlorpheniramine maleate 3x0,25mg/day. Patient was suggested to undergo chemotherapy, and educated to avoid sun exposure.

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