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Skin cancers, blindness, and anterior tongue mass in African brothers

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CASE SUMMARY

History

Two Northern African brothers presented to the National Institutes of Health for evaluation of severe damage to sun-exposed areas of the skin, eyes, and mucosae; multiple skin cancers; a tongue mass; and photophobia with loss of vision.

The patients were born full term after uncomplicated pregnancies and achieved age-appropriate developmental milestones. Patient XP393BE (Fig 1, *A*), 23 years old, was noted to have freckle-like pigmented lesions on his face at 2.5 years and photophobia by age 3 (Table I). A squamous cell carcinoma (SCC) had been removed from his nose at age 13 and the site was grafted with sun-shielded skin from his thigh. His brother, patient XP394BE (Fig 1, *D*), 17 years old, developed freckle-like lesions on his face by 8 years of age. At age 13, an SCC was excised from his right cheek. Both boys had bilateral progressive loss of vision with unilateral blindness since the age of 12 to 14 years (Fig 1, *B*).

Abbreviations used:

BCC:	basal cell carcinoma
NER:	nucleotide excision repair
SCC:	squamous cell carcinoma
UV:	ultraviolet radiation
XP:	xeroderma pigmentosum

Patient XP393BE had a 10-year history of a slowly enlarging, painful, bleeding mass on the tip of his tongue (Fig 2, *A*). He denied weight loss, excessive consumption of alcohol, or chewing of tobacco or betel quid.

Living in Kuwait, Sudan, Libya, and Egypt, neither patient had a history of sunburns or use of sun protection. The patients have a 21-year-old unaffected brother. Their parents were second cousins and members of the same tribe in the Sudan. There was no family history of cancer.

Physical examination

Skin examination of both patients revealed numerous 1- to 5-mm hyperpigmented macules on the cheeks and scalp (see Figs 1 and 2) and sun-exposed portions of the chest and extremities with sparing of sun-protected sites. Patient XP393BE had a 1.3- × 1.7-cm stellate, indurated, black, brown and gray plaque on his left cheek (Fig 1, *A*). Dermatoscopy revealed characteristic leaf-like structures and blue-gray ovoid nests that distinguish pigmented basal cell carcinoma from melanoma (Fig 1, *C*). A 1-cm nodular, ulcerated mass was present on the base of his nose, and there were multiple translucent black lesions on his face. Patient XP394BE had a crusted, darkly pigmented plaque on the left ala and tip of the

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Conflicts of interest: None declared.

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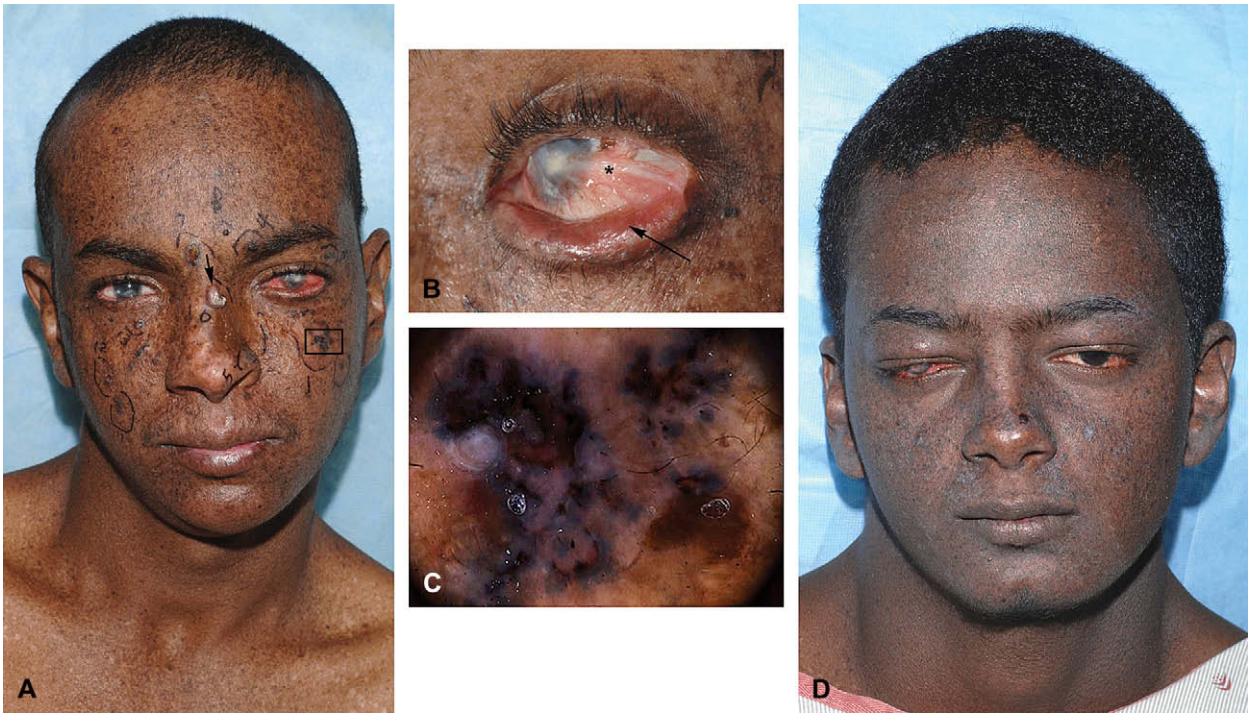

Fig 1. Northern African brothers with xeroderma pigmentosum. **A**, Patient XP393BE, 23 years old, with multiple hyperpigmented macules and papules on photodistributed areas of face and neck. Nodular BCC (*arrow*) on left base of nose. Pigmented BCC on left cheek (*rectangle*). **B**, UV-induced ocular damage in patient XP393BE, showing left eye ectropion (*arrow*), and conjunctival pterygium (*asterisk*). **C**, Dermatoscopy of pigmented lesion on lateral left cheek of patient XP393BE (*rectangle* in **A**) reveals characteristic leaf-like structures and blue-gray ovoid nests that distinguish pigmented BCC from melanoma. **D**, Patient XP394BE, 17 years old, with similar features to his brother including pigmented BCC on left ala and severe involvement of eye.

nose (Fig 1, *D*). Ocular examination of both patients revealed increased freckle-like pigmentation of the lids, conjunctival injection, and corneal scarring with neovascularization, which occluded vision. Patient XP393BE's left eye had pigmented areas on the bulbar and palpebral conjunctiva, a left lateral pterygium, and an ectropion with keratinization of the lower lid (Fig 1, *B*). Patient XP394BE had blepharitis, ptosis, and prominent vessels on his right eye. The lips of patient XP393BE had mild cheilitis, loss of vermilion border, and hyperpigmented macules (Fig 2, *A*). Oral examination revealed an ulcerated 1.5- × 3-cm fungating mass on the left-sided anterior tip of his tongue, and he had a bleeding pedunculated mass in his right nostril (Fig 2, *A*). Neither brother had cervical, axillary, or inguinal lymphadenopathy. Their neurological examinations yielded normal findings.

Diagnostic studies and treatment

Patient XP393BE had iron deficiency anemia (hemoglobin, 10.1 g/dL [reference range: 12.7-16.7]; hematocrit, 31.5% [reference: 36.7-48.3]; serum iron, 35 μg/dL [reference: 50-150]; transferrin, 384 mg/dL [reference: 204-345]; 6% saturation [reference: 15%-62%]; ferritin, 6 μg/dL [reference: 18-370]). Both patients were vitamin D deficient (25-OH-Vit D, 9-10 ng/mL [<10 severe deficiency]). Computed tomography of the head, neck, and posterior thoracic inlet were negative for metastasis for both brothers. Panorex radiography revealed that patient XP393BE had a 2.5-cm multilocular lesion with radiolucent and radio-opaque areas on the right mandible containing an inverted displaced tooth (#32). Sequencing of DNA from both patients revealed a homozygous two nucleotide deletion (c.1643_1644delTG, p.Val548Alafs*25) in exon 9 of the *XPC* gene [NM_004628.3].

Biopsy specimens of the facial lesions showed 10 pigmented basal cell carcinomas (BCCs) in patient XP393BE and two pigmented BCCs in patient XP394BE (see Fig 1). The pedunculated tongue mass of patient XP393BE (Fig 2, *A*) was excised at the stalk followed by a wedge-shaped excision of the base of the lesion. Histologic examination of the

Table I. Clinical features of Northern African brothers with XP

	Patient XP393BE	Patient XP394BE
Age (y)	23	17
Skin and mucous membranes		
Acute photosensitivity on minimal sun exposure	No	No
Hypopigmentation and hyperpigmentation in sun-exposed areas	Yes	Yes
Sunlight-induced skin cancer	Yes (at 13 y)	Yes (at 13 y)
Sunlight-induced tongue tumor	Yes	No
Eyes		
Photophobia	Yes	Yes
Corneal opacity with neovascularization	Yes	Yes
Lower lid ectropion	Yes	No
Impaired vision	Yes	Yes
Nervous system		
Developmental delay/neurologic disease	No	No
Disease mechanism		
DNA repair defect	Yes—XPC	Yes—XPC

XP, Xeroderma pigmentosum.

resected tongue mass revealed a central core of inflamed granulation tissue, surfaced by a layer of focally ulcerated, severely dysplastic squamous mucosal epithelium. Histopathologic examination of the wedge-shaped excision specimen at the base of the lesion revealed a well-differentiated, superficially invasive SCC (Fig 2, *B*) arising in a background of moderately to severely dysplastic squamous mucosal epithelium. The surrounding area of dysplasia was treated with carbon dioxide laser ablation. Biopsy findings of the bleeding mass in the right nasal septum of patient XP393BE were consistent with pyogenic granuloma. The lesion of the right mandible was enucleated, and histologic examination of the resected lining showed a keratocystic odontogenic tumor.

Diagnosis

Xeroderma pigmentosum (XP).

Follow-up

The brothers were instructed to avoid sun exposure and to practice rigorous sun protection. The skin cancers in both brothers will be treated with excision and Mohs surgery. The tongue and mandible of patient XP393BE healed well; his anemia resolved with iron supplementation. The area of his right mandible will be followed up periodically because of the potentially high recurrence of keratocystic odontogenic tumors.[1] The vitamin D deficiency in both patients resolved with oral vitamin supplementation.

DISCUSSION

XP is a rare, autosomal recessive inherited disease characterized by increased susceptibility to cancer of sun-exposed mucocutaneous and ocular structures due to defective repair of ultraviolet (UV)-induced DNA damage.[2-4] XP patients develop skin cancers at a mean age of less than 10 years,[5,6] a 50-year reduction in age at onset compared to the U.S. general population. Sunlight-induced malignancies in XP patients occur at a 1000-fold greater frequency than in the general population. XP is present worldwide and has a prevalence of about 1:1,000,000 in the United States and Europe.[7] It is more common in countries with high levels of consanguinity, including Japan,[8] Northern Africa, and the Middle East. There is no race predilection.

Important clinical features of XP are cutaneous photosensitivity, xerosis, poikiloderma, actinic keratosis, and malignant lesions in sun-exposed areas, including BCC, SCC, and melanoma. Approximately 50% of XP patients report a history of acute burning on minimal sun exposure.[5] The other half tan easily instead of burning, as did the patients in this report. The development of increased freckle-like pigmentation occurs in all XP patients following sun exposure and may occur before 2 years of age.[2,9]

Ocular abnormalities in XP are limited to the anterior (UV-absorbing) surfaces of the eyes and adnexa. They include photophobia, conjunctivitis, inflammatory masses, keratopathy that can progress to corneal opacification, and ocular neoplasms. Atrophy of the skin of the lids results in ectropion, entropion, or complete destruction of the lids.[2,9,10]

Approximately 30% of XP patients have progressive neurodegeneration.[5] The earliest manifestations of XP neurological disease may be diminished or absent deep tendon reflexes and high-frequency hearing loss. Intellectual impairment and loss of motor control can occur in later stages. Magnetic

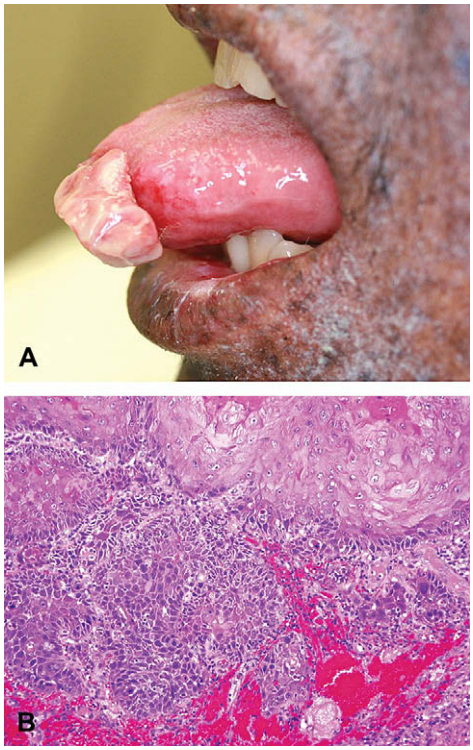

Fig 2. Squamous cell carcinoma on tongue (patient XP393BE). **A**, Ulcerated 1- × 3-cm fungating mass on left anterior tip of the tongue. Note loss of vermilion border of lips with cheilitis and marked freckle-like pigmentation. **B**, Histologic examination reveals a well-differentiated, keratinizing, superficially invasive SCC at base of pedunculated lesion, characterized by prominent cytologic atypia of lesional keratinocytes showing infiltrative growth pattern. A dense inflammatory infiltrate consisting predominantly of lymphocytes is also present. (Hematoxylin-eosin stain; original magnification: ×200.)

resonance imaging studies may reveal cerebral and cerebellar atrophy and enlarged ventricles.[2] The primary histologic finding is neuronal degeneration without inflammation or abnormal depositions.[2,11]

The clinical manifestations of XP are determined by a combination of both environmental and genetic factors. Skin, mucous membrane, and ocular involvement is strongly linked to environmental sun exposure. Severity of skin disease is greatest on portions of the body exposed to the most amount of sunlight.[5] The DNA nucleotide excision repair (NER) system plays a major role in prevention of cutaneous neoplasia. XP patients have cellular hypersensitivity to UV radiation secondary to faulty DNA NER.[3,4,12] To date, there are 8 genes associated with clinical disease: *XPA*, *XPB*, *XPC*, *XPD*, *XPE*, *XPF*, *XPG* (with defective NER), and XP variant (*XP-V*) (with defective DNA polymerase eta that bypasses DNA photoproducts). Mutations in *XPA*, *XPC*, *XPD* and polymerase eta account for more than 90% of XP.[13] Functional assays may be used for laboratory diagnosis of XP.[3]

Consistent with the history of parental consanguinity, the patients presented in this report were homozygous for a mutation in the *XPC* gene. This TG deletion frameshift mutation is predicted to result in premature termination of the encoded protein 25 amino acids downstream. The mutation might be a founder mutation since it was reported in other Northern African XP patients (Algeria and Morocco).[14] It might also be a mutation hotspot in the *XPC* gene since it occurs in a run of 3 TG's and was reported in patients in different parts of the world (Italy, Honduras, and United States.)[14-16]

These two brothers with similar genetic make-up and environmental exposure have similar clinical features of XP. They were not sun protected and had substantial exposure to UV rays because of their environment in Northern Africa. Dark-skinned individuals have a lower incidence of skin cancer than the general population due, in part, to the photoprotective effects of melanin.[17,18] However, these XP patients sustained photodamage on their skin and non–melanin-containing structures—the tip of the tongue and the anterior surface of the eyes. This demonstrates the importance of a normally functioning DNA repair system in protection against skin cancer even in darkly pigmented individuals.[5]

Carcinoma of the tip of the tongue has been reported in XP patients, including patients of African and Middle Eastern descent,[5,6,9,19,20] representing a 3000-fold increase in tongue tumors over the general population.[6] In the general population, tongue cancer is associated with excessive alcohol consumption or chewing of tobacco, betel quid, or vinyl plastic wire. The location is generally on the posterior lateral tongue and the disease course is aggressive, requiring extensive treatment, and usually results in metastasis and early death.[21] The overall 5-year relative survival rate for 1996-2004 for black men with tongue cancer was only 33.3%.[22] In XP patients, severe cheilitis of the lips and precancerous lesions such as leukoplakia may precede carcinoma of the tongue. Sun exposure may result from licking of the lips. Early age of occurrence, risk factors (UV exposure), location at the tip of the tongue, and indolent course differentiate the oral carcinomas associated with XP from their homologues in adults in the general population. The mass on the anterior tip of the tongue of patient XP393BE was reported to be slowly growing and predominantly consisted of inflamed granulation tissue. In view of the slow growth and minimal invasiveness of the SCC, we elected to treat the tongue tumor conservatively. After excising the base of the lesion, we used a

carbon dioxide laser, which produces infrared radiation, for treatment of the surrounding dysplasia. In treating XP patients, it is important to avoid using UV-emitting modalities, such as UV lamps, lasers or light-curing units, which could pose risk of further damage.

Education and sun protection are important in the management of XP. Early diagnosis and extensive sun protection have the potential to prevent skin cancers in XP patients and prolong their life expectancy.[2,3,23,24] Sun protection can be achieved by wearing protective clothing, UV-absorbing sunglasses with side shields and using topical sunblocking agents. UV-absorbing films and filters can be placed over windows and fluorescent or halogen lamps. Thorough skin self- and dermatologic examinations to monitor any skin changes and ensure early detection and treatment of skin cancers should be performed regularly. Active XP patients who practice sun protection and maintain a good diet may have adequate vitamin D levels.[25] However, XP patients who are protected from UV radiation early in life may be at risk for vitamin D deficiency. Normal vitamin D levels can be maintained by oral vitamin D supplements. Genetic counseling is also an important component of patient management for this inherited disease, especially if a family has an affected child and is considering having additional children.[3] Information about the availability of genetic testing for XP can be found at the Web site, http://genetests.org. XP patient support groups are a valuable resource for educational and support services.

KEY TEACHING POINTS

- XP is an autosomal recessive inherited disease seen in all races throughout the world.
- Patients with XP have defective repair of UV-induced DNA damage resulting in markedly increased susceptibility to cancer of sun-exposed skin and mucous membranes, including the eyes and tip of the tongue. Defects in at least 8 different genes have been identified in XP patients.
- The diagnosis of XP can be made on the basis of clinical features. While some patients may be exquisitely sun sensitive and experience severe sunburn after minimal sun exposure, others do not. All patients develop freckle-like pigmented lesions at an early age with poikilodermatous changes.
- Early diagnosis of XP and rigorous sun protection are important for prevention of cancer.

Editor's note: Dr Kraemer is an authority on DNA repair deficiency diseases, including XP, trichothiodystrophy, and Cockayne syndrome. Clinicians can refer interested patients to the NIH patient recruitment and referral office at 800-411-1222 or by E-mail at kraemerk@nih.gov. XP support groups include the XP Society (http://www.xps.org); the XP Family Support Group (http://www.xpfamilysupport.org/); the Xeroderma Pigmentosum Support Group (United Kingdom) (http://xpsupportgroup.org.uk); Enfants de la lune (France) (http://asso.orpha.net/AXP/); and XP-Freu(n)de (Germany) (http://www.xerodermapigmentosum.de/).

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