Xeroderma pigmentosum presenting as a diffuse midline glioma in a patient with skin of color

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INTRODUCTION

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder of DNA repair with cutaneous and systemic manifestations.[1,2] Here, we discuss the unique case of a patient diagnosed with XP after presenting with a brain tumor.

CASE REPORT

An 18-year-old black female presented to the emergency department with a 2-week history of headaches, nausea, and vomiting. Hearing and intellect were normal, and no other neurologic symptoms were present. Brain imaging revealed a right ventricular mass, and subsequent biopsy demonstrated a grade IV H3K27M-mutated diffuse midline glioma. The tumor was excised with the resolution of symptoms, and adjuvant chemoradiation therapy with temozolomide was completed.

At initial presentation, corneal clouding and scattered pigmentation on bilateral conjunctivae were observed. Diffuse hypopigmented macules with poikilodermatous changes throughout sun-exposed areas were also noted and had been present since early childhood with a progressive increase in size and number (Fig 1). The patient had no siblings, and there was no family history of similar skin findings. Although her unusual complexion had been followed by physicians during routine care for years, a diagnosis of freckles was made, and no further workup was initiated.

Dermatology was consulted and provided the diagnosis of XP clinically. Sun-protective behavioral counseling was provided with close follow-up every 3 months for skin cancer surveillance.

Abbreviation used:

XP: xeroderma pigmentosum

Over the year following her diagnosis, the patient received 8 additional cycles of temozolomide monotherapy without developing new symptoms. She was also diagnosed with porokeratosis of the left distal extremity, and a squamous cell carcinoma of the chest was cleared in one stage by Mohs micrographic surgery.

Shortly thereafter, she was diagnosed with a recurrence in the left side of the thalamus after experiencing headaches and somnolence. Lomustine, bevacizumab, and carboplatin therapies were then provided over the next several months, resulting in slowed but continued disease progression. Worsening balance, coordination, and weakness in the lower portion of the left extremity led to several falls, and she required assistance in activities of daily living. She eventually became severely lethargic and experienced one seizure-like episode.

During this time, facial field treatment with 5-fluorouracil was provided but with minimal effect. A squamous cell carcinoma on the left cheek was also identified (Fig 2). However, due to the patient's poor neurologic condition, she did not undergo scheduled Mohs micrographic surgery. Palliative radiation therapy was soon administered for her

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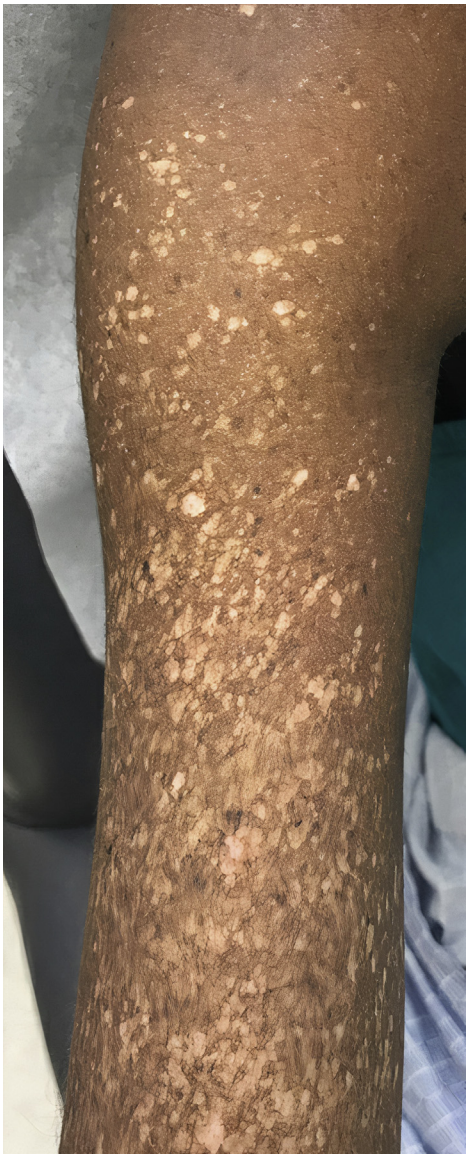

Fig 1. Poikilodermatous changes of the upper extremity.

glioma, and she ultimately succumbed to the disease approximately 1.5 years after her initial diagnosis.

DISCUSSION

The diagnosis of XP is based on clinical and molecular features.[3-6] Several papers have suggested that the diagnosis can be established using clinical features alone,[3,4] with functional assays and genetic analysis serving a more complementary role. Key clinical features include early-onset poikiloderma in sun-exposed areas, a history of severe sunburn following minimal sun exposure (acute sun sensitivity), skin cancer development at a young age, and consistent family history.[3,4] However, only 60% of patients exhibit acute sun sensitivity, and the negative family history does not exclude the diagnosis.[3-5]

Fig 2. Squamous cell carcinoma of the left cheek (*arrow*).

Ocular and neurologic manifestations used to support a clinical diagnosis include corneal and conjunctival changes and progressive neurodegeneration, cognitive impairment, and sensorineural hearing loss.[3,4,6] Criteria used for a clinical diagnosis do not currently contain well-defined parameters, such as a minimum set of features necessary for confirmation.

Certain guidelines that provide more structured diagnostic criteria suggest that a diagnosis of only possible or probable XP can be made in the presence of characteristic clinical features alone, with some form of molecular testing required for a definitive diagnosis.[6] Other authors support the notion that XP cannot be confirmed without functional assays or genetic analysis.[5] Our patient was diagnosed clinically by the combination of early-onset poikiloderma, the development of skin cancer at a young age, and the presence of corneal opacification with conjunctival melanosis. Genetic testing to assess the patient's complementation group was recommended. However, due to her significant neurologic deterioration at the time, further testing was declined by the family to avoid additional stress to the patient.

Genetic testing classifies patients into one of eight distinct subtypes (XPA − XPG, XPV).[6] In addition to its diagnostic utility, significant implications for prognosis and management warrant routine use.[3] For example, neurodegeneration is rare in XPC, the most common subtype in the United States.[7] In contrast, patients with XPA, the most common subtype in Japan, frequently experience neurodegeneration and have an extremely poor prognosis.[6] Subtype differentiation may lead to more effective, targeted management strategies, as early neurologic rehabilitation and follow-up may be used to maximize the quality of life in patients with XPA, whereas these interventions may be unnecessary for subtypes such as XPC.[6]

In addition to XP's cutaneous, ophthalmologic, and neurologic features, patients with XP are more likely to develop central nervous system tumors, with those under 20-years-old at a 50-fold increased risk.[1,2,7] Previously documented tumors include medulloblastomas, glioblastomas, spinal cord astrocytomas, and schwannomas.[1,2] To the authors' knowledge, this is the first case of a diffuse midline glioma reported in the literature. In light of this association, providers should maintain a high index of suspicion when XP patients present with signs and symptoms concerning central nervous system malignancy, especially in younger populations.

Despite her providers' long-term awareness of her unusual complexion, our patient experienced a significant diagnostic delay. This could potentially be attributed to the rarity of this condition,[1,7] an issue further exacerbated by the relatively small percentage of recorded cases in populations with the skin of color.[8] Our patient's darker complexion may have also facilitated the persistent misinterpretation of her actinically damaged skin as common freckling. Diagnostic delay and misdiagnoses in dark-skinned patients are not uncommon in dermatology and have been attributed to nonclassic disease presentations and disparities in provider education.[9] In addition, misconceptions of this population's resistance to actinic damage have led to inadequate sun-protective practices and behavioral counseling.[10]

In conclusion, practitioners should be aware of XP's association with central nervous system tumors and provide appropriate management when encountering symptomatic patients. Dermatologic conditions may also present differently or less obviously in those with darker skin types, prompting the need for an increased representation of this population in the literature.

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Conflicts of interest

None disclosed.

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