Variant subtype of xeroderma pigmentosum diagnosed in a 77-year-old woman

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INTRODUCTION

Xeroderma pigmentosum (XP) is a rare, autosomal recessive disease that results in sensitivity to ultraviolet (UV) radiation with characteristic cutaneous pigmentary changes and a high frequency of sunlight-induced cutaneous and ocular neoplasms. Phenotypic changes in XP arise from defective repair of UV-induced DNA damage including cyclobutane pyrimidine dimers and 6-4 photoproducts.[1,2] The nucleotide excision repair (NER) pathway is the primary mechanism for excising these UV-induced lesions, and pathogenic mutations within the NER pathway result in one of the 7 classical XP complementation groups (XP-A to XP-G).[2]

About 50% of XP patients present in the first weeks of life with sunburn and extreme sensitivity to sunlight.[2,3] Poikilodermatous changes develop on sun-exposed areas, and first skin cancer occurs by a median 9 years of age.[3] Patients younger than 20 years with XP have a 2,000-fold increase in melanomas, a 10,000-fold increase in the frequency of nonmelanoma skin cancer, and a 12-fold increased risk of internal malignancy, particularly brain neoplasms.[3] Certain XP complementation groups (A, B, D, G, and F) are associated with progressive neurologic degeneration. Patients with XP have a median mortality of 32 years.[3]

Abbreviations used:

BCC:	basal cell carcinoma
NER:	nucleotide excision repair
UV:	ultraviolet
XP:	xeroderma pigmentosum
XP-V:	xeroderma pigmentosum variant

In contrast, patients with XP variant (XP-V) retain a normal NER pathway and have a defect in, *POLH,* which encodes the protein DNA polymerase *eta*. First described in 1970 as pigmented xerodermoid,[4] XP-V may comprise 25% of the XP patients in selected genetic populations.[5-7] Patients with XP-V may have a distinct clinical presentation from their counterparts with NER-deficient XP and may display delayed onset, lack of neurologic findings, and variable severity.[5,6,8] Herein, we illustrate this with a patient diagnosed with XP-V late in life, highlighting the need to consider a diagnosis of XP-V in patients of all ages who have multiple cutaneous malignancies of different histologic types.

CASE

A 77-year-old Mexican woman presented to a dermatology clinic that provides care for the medically underserved. She requested management of a

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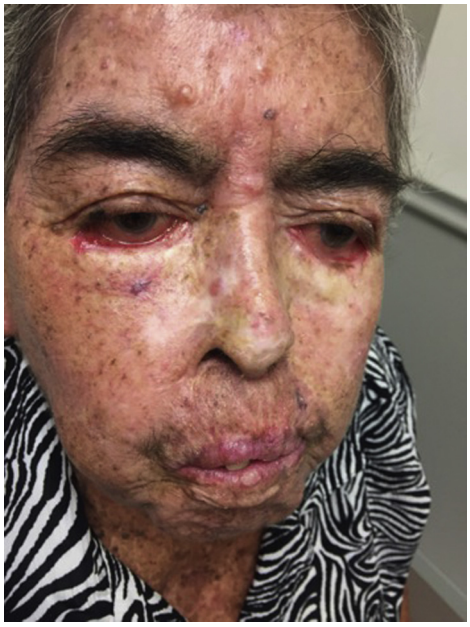

Fig 1. Patient's face at presentation with diffuse freckle-like pigmentation, tight atrophic skin admixed with surgical scars, and numerous pearly papules concerning for BCC. There is loss of lower eyelids and corneal inflammation.

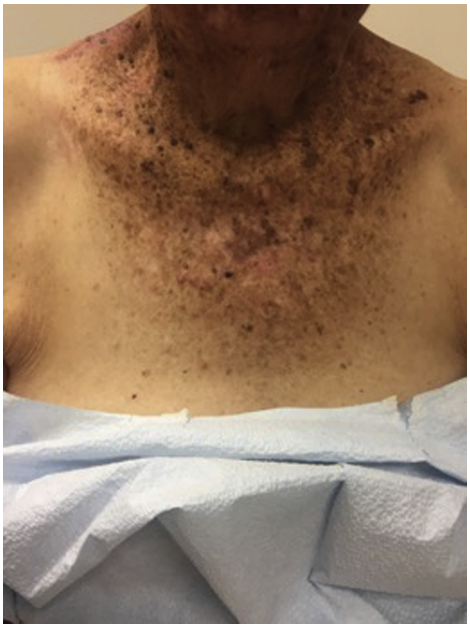

Fig 2. Patient's chest at presentation. In this image of the patient's chest, note the striking difference between sun-exposed and sun-protected skin.

painful growth behind her right ear. Her medical history was significant for type 2 diabetes mellitus and dyslipidemia. The patient had a history of sporadic and infrequent medical care before her presentation to our clinic. She indicated that she had her first skin cancer after the age of 50. She denied blistering sunburns. She had a history of outdoor labor as a young woman, but relays she always tried to practice sun protection with clothing when possible. She had 5 sisters and 1 brother. By history, 2 of her sisters also had frequent skin cancers, one of whom died in middle age of an unknown cancer type. She denies consanguinity between her parents, but both were from the same small town in Mexico. She had 2 daughters and 3 sons, all alive, healthy and without skin cancer.

On examination, the patient had diffuse freckle-like pigmentation, xerosis, and actinic damage in sun-exposed areas, with skin in sun-protected areas strikingly normal in appearance (Figs 1 and 2). There was loss of the lower eyelids from past surgical resection and corneal inflammation. Numerous pearly papules and plaques were present on the face and arms admixed with irregularly pigmented dark macules and patches. An ulcerated, 3.5- × 2.9-cm foul-smelling plaque was present in the right retroauricular sulcus (Fig 3). Her neurologic examination was normal and lymph node examination was negative.

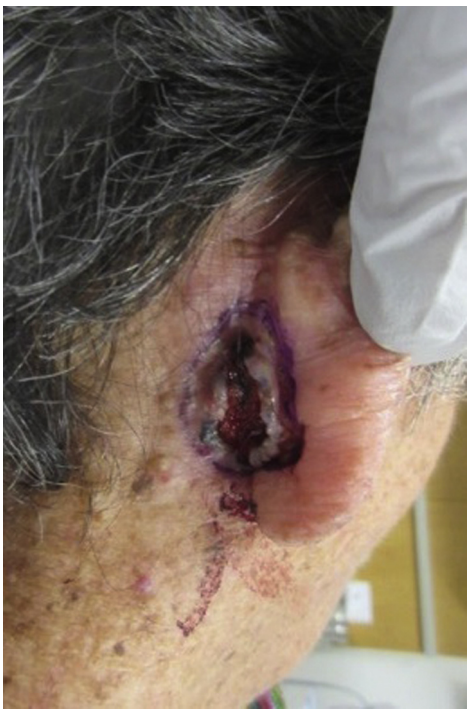

Fig 3. Ulcerated plaque that brought patient to medical attention. The ulcerated, 3.5- × 2.9-cm plaque in the right retroauricular sulcus with rolled borders that brought the patient to medical attention was later found to be BCC.

Biopsies at her initial visit found 5 basal cell carcinomas (BCC) (retroauricular sulcus, jawline, tragus, anterior scalp, and clavicle); 1 invasive squamous cell carcinoma on the cutaneous lip, and

1 melanoma in situ of the right side of the neck. She underwent Mohs micrographic surgery for the BCC and squamous cell carcinoma, with coordinated care with plastic surgery for the lesion on the right retroauricular sulcus, she underwent wide local excision of the melanoma in situ. She received extensive counseling that she and family members would benefit from sun protection and early, regular dermatologic intervention. For chemoprevention of the nonmelanoma skin cancers, acitretin, 17.5 mg daily, was prescribed, with strict sun avoidance. Given the extensive presence of cutaneous carcinomas, she was included in a National Institutes of Health natural history study of XP, which includes sequencing known XP genes.

Sanger sequencing was performed on DNA harvested from peripheral blood mononuclear cells. All *POLH* and *XPC* gene exons, including splice donor and acceptor sites, were polymerase chain reaction–amplified using intronic primers flanking these sequences and sequenced as previously described.[5] Sequencing found a novel homozygous 2-nucleotide deletion [c.1643_1644delCA, p.Ser548Cysfs*13] in exon 11 of the *POLH* gene [NM_006502.2]. The 2-base deletion leads to a frame shift and creation of a premature stop codon that is expected to encode a truncated POLH protein, assigning the patient to the XP variant subtype. Functional testing of cultured cells was not performed.

DISCUSSION

The defect in XP variant lies in loss of the protein DNA polymerase *eta,* which is encoded by the *POLH* gene.[5,9] Polymerase *eta* has the unique capacity to replicate through UV-damaged segments of DNA (translesional DNA synthesis). The absence of functional polymerase *eta* leads to the use of alternate, error-prone polymerases, thereby promoting replication of mutated segments of DNA.[10]

Patients with XP-V typically do not sunburn or present with extreme sunlight sensitivity. They tend to be spared the neurologic findings often seen in NER-deficient XP[3,5,6,8] and often have a better prognosis and longer life expectancy.[5] Reports of patients with XP-V having their first skin cancer range from as early as 7 years of age[8] to as late as 71.[6] In one study, up to 40% of patients with XP-V had melanoma and most had a nonmelanoma skin cancer.[5,8] Occasionally, severe phenotypes resulting in early death have also been reported.[3] The degree of clinical involvement may be dependent on the type of *POLH* mutation and UV exposure, with mutations in exon 11 having milder phenotypes.[6]

We described a case of a woman with multiple skin cancers of different histologic types who was found to have XP-V late in life. She presented without the internal neoplasms or neurologic degeneration seen in some other XP types; this case illustrates the spectrum of XP disease.

REFERENCES

1. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. *Arch Dermatol*. 1987;123(2):241-250.
2. DiGiovanna JJ, Kraemer KH. Shining a light on xeroderma pigmentosum. *J Invest Dermatol*. 2012;132(3 Pt 2):785-796.
3. Bradford PT, Goldstein AM, Tamura D, et al. Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. *J Med Genet*. 2011;48(3):168-176.
4. Jung EG. New form of molecular defect in xeroderma pigmentosum. *Nature*. 1970;228(5269):361-362.
5. Inui H, Oh KS, Nadem C, et al. Xeroderma pigmentosum-variant patients from America, Europe, and Asia. *J Invest Dermatol*. 2008;128(8):2055-2068.
6. Ben Rekaya M, Messaoud O, Mebazaa A, et al. A novel POLH gene mutation in a xeroderma pigmentosum-V Tunisian patient: phenotype-genotype correlation. *J Genet*. 2011;90(3):483-487.
7. Munford V, Castro LP, Souto R, et al. A genetic cluster of patients with variant xeroderma pigmentosum with two different founder mutations. *Br J Dermatol*. 2017;176(5):1270-1278.
8. Broughton BC, Cordonnier A, Kleijer WJ, et al. Molecular analysis of mutations in DNA polymerase eta in xeroderma pigmentosum-variant patients. *Proc Natl Acad Sci U S A*. 2002;99(2):815-820.
9. Lerner LK, Francisco G, Soltys DT, et al. Predominant role of DNA polymerase eta and p53-dependent translesion synthesis in the survival of ultraviolet-irradiated human cells. *Nucleic Acids Res*. 2017;45(3):1270-1280.
10. Masutani C, Kusumoto R, Yamada A, et al. The XPV (xeroderma pigmentosum variant) gene encodes human DNA polymerase eta. *Nature*. 1999;399(6737):700-704.