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LETTER TO THE EDITOR

Variant subtype of xeroderma pigmentosum with multiple basal cell carcinomas diagnosed in a Chinese woman

As a rare autosomal recessive genetic disease, xeroderma pigmentosum (XP) can be categorized into eight different subtypes (XP-A to XP-G and XP-V) and is caused by mutations in one of eight different genes.[1] The subtypes XP-A to XP-G are genetic disorders caused by mutations in genes involved in the nucleotide excision repair (NER) pathway, making the responses of XP cells to photoproducts induced in DNA by ultraviolet (UV) rays from sunlight defective. Due to this diminished DNA repair activity, patients with this syndrome have a high possibility of developing skin cancers when exposed to sunlight.[2-4] The XP-V subtype has normal NER and is caused by mutations in the XP-V gene, also known as *POLH*, *POLH* encodes for Pol η, a member of the Y-DNA polymerase family, which is associated with the synthesis of DNA after injury (translesion synthesis process). In XP-V cells, the ability to replicate DNA after UV exposure is reduced by *POLH* mutations. As a result, UV lesions are highly mutagenic and lead to skin cancers.[5-9] Classic XP phenotypes include noticeable freckles, acute sunburn, persistent erythema under minimal sun exposure, keratitis, and even nervous abnormities. Compared with the general population, patients with XP develop both non-melanocytic cancer and malignant melanoma at higher frequencies of 10 000 and 2000 fold, respectively.[4,10,11] Among all XP patients worldwide, XP-V patients account for approximately 20% and the number of XP-V patients reported so far is relatively limited.[12] Most patients with a clear diagnosis are older, especially in developing countries. Here we report a Chinese XP-V patient with multiple basal cell carcinomas (BCCs). The application of dermatoscopy was important to early diagnosis and treatment of accompanied skin cancers and then improve the prognosis of this disease.

A 27-year-old female patient was admitted to our dermatology department twice, January 2019 and November 2019, with a history of progressive skin pigmentation, widespread freckles, multiple lentigines, and xerosis mainly on sun-exposed areas. She had experienced numerous sun-induced skin changes since she was 5 years old.

On physical examination, the patient's general condition and vital signs were normal, and her superficial lymph nodes were negative. Laboratory examinations, including routine blood, urine, liver function, kidney function, thyroid function, glycated hemoglobin, coagulation function, and tumor marker tests, showed nothing abnormal. Eye examinations, including a corneal endoscope, optical coherence tomography, color fundus photography, and slit lamp examination, showed nothing abnormal, but intraocular pressure was slightly high. The left eye intraocular pressure was 23.2 mm Hg (11 ~ 21 mm Hg) and right eye intraocular pressure was 26.7 mm Hg (11 ~ 21 mm Hg), the patient had no eye discomfort. Imaging examinations, including electrocardiograms, ultrasound examinations of liver, bile, pancreas, spleen, kidney, bladder and ureter, lung CT, brain CT, and brain MRI, showed nothing abnormal, and no nervous abnormities were identified in the patient. She was an abandoned child brought up by her adoptive parents.

On dermatologic examination, Fitzpatrick skin phototype III, widespread freckles, multiple lentigines, xerosis, capillary telangiectasias, hyperpigmented, and hypopigmented lenticular macules (2-5 mm) were identified (Figure 1A). These lesions were mainly located in UV exposed areas, including the parietal region, face, upper thorax, upper limbs, trunk, and back. The palms, soles, and mucosae were unaffected. We used a dermoscopy (Dermlite DL4, USA) without immersion oil for examination, and dermoscopic evaluation demonstrated typical criteria of BCC (Figure 1B-H). Careful skin inspection revealed the presence of seven BCCs on the parietal region, face, and neck. On the first visit, we found four BCCs and the second time we found three. All seven lesions were surgically excised with clear resection margins and histologic analysis confirmed all of them as BCCs.

For the first visit, when combiningwith the patient's history and clinical manifestations, we diagnosed the patient with xeroderma pigmentosum. After 10 months, the patient returned to the hospital for treatment of malignant skin lesions. This time, we suggested genetic counseling to the patient in order to make a clear diagnosis. A homozygous splicing mutation, c.490G > T (p.Glu164*) in exon 4 of *POLH* was identified by whole-exome sequencing and verified by Sanger sequencing. This mutation has been reported in many XP patients from Korea and Japan[13-15] and included in the human gene mutation database (HGMD). Based on the clinical, histological, and genetic findings, a diagnosis of XP-V in combination with multiple BCCs was made.

As an autosomal recessive genetic disease, XP has various clinical manifestations, among them, the most characteristic feature is patients' predisposition to skin cancers.[16] Overlapping clinical features

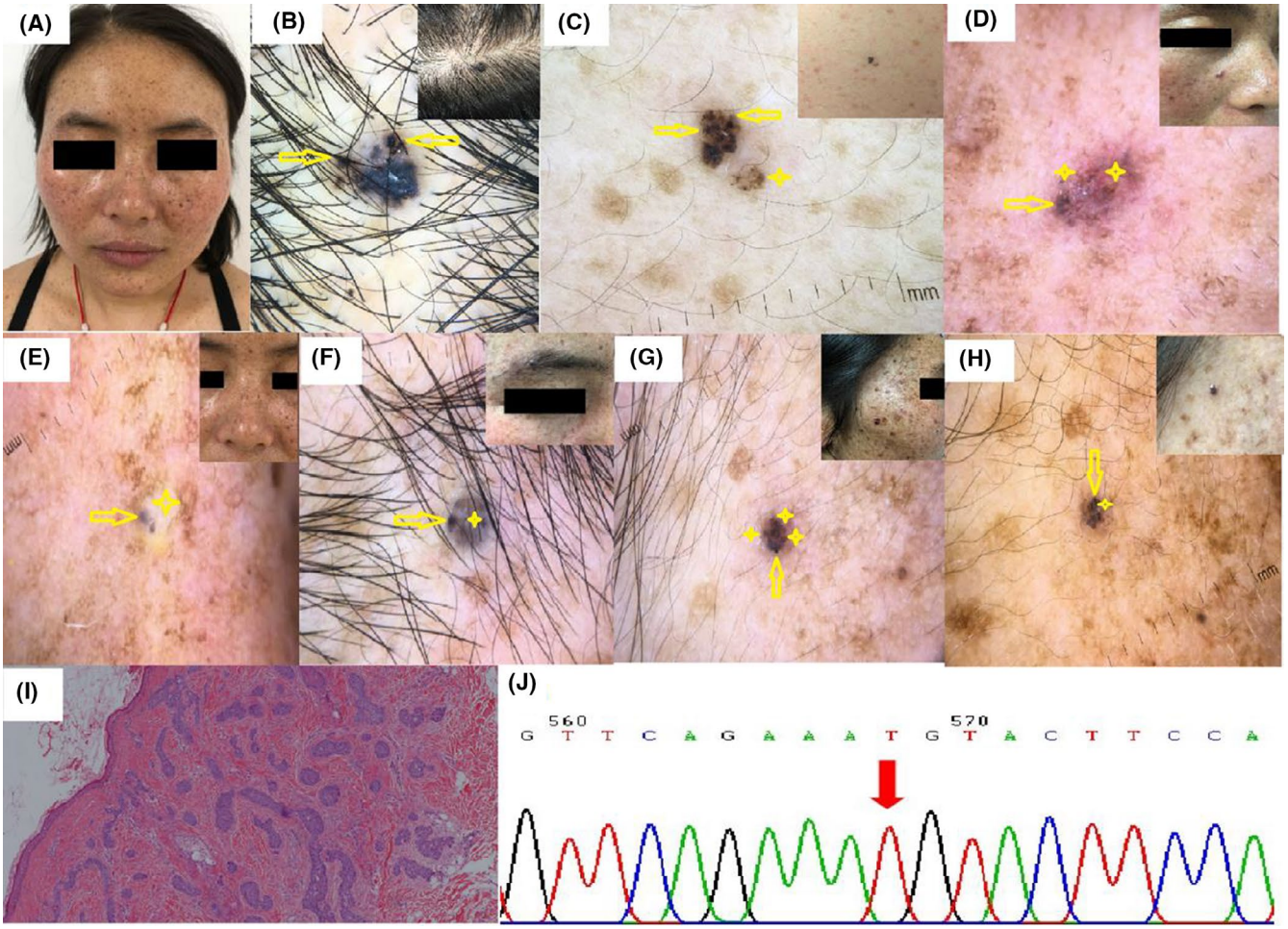

FIGURE 1 Patient with xeroderma pigmentosum. (A) Widespread freckles on the face and xerosis mainly on sun-exposed areas. (B) Dermatoscopy (original magnification × 10): BCC with blue ovoid nests (arrow). Inset: clinical image. (C) Dermatoscopy: BCC with blue ovoid nests (arrow) and leaf-like structures (asterisk). Inset: clinical image. (D) Dermatoscopy: BCC with blue ovoid nests (arrow) and arborizing vessels (asterisk). Inset: clinical image. (E) Dermatoscopy: BCC with blue ovoid nest (arrow) and shiny white structures (asterisk). Inset: clinical image. (F) Dermatoscopy: BCC with blue ovoid nest (arrow) and shiny white structures (asterisk). Inset: clinical image. (G) Dermatoscopy: BCC with blue ovoid nest (arrow) and short-fine telangiectasia (asterisk). Inset: clinical image. (H) Dermatoscopy: BCC with blue ovoid nest (arrow) and erosion (asterisk). Inset: clinical image. (I) Microscopically, The tumor shows micronodules scattered throughout the dermis and subcutis. Tumor nests are typically irregular, tentacular, and infiltrative deep or peripheral edge, composed predominantly of small discrete nodules. (hematoxylin and eosin, original magnification × 70). (J) Sequencing of genomic DNA from this patient identified a homozygous splicing mutation (c.490G > T) in *POLH* in exon 4 (arrow). BCC, basal cell carcinomas

have been observed among the XP patients. In XP-V patients, skin symptoms such as skin cancers and solar lentigines occur later in life compared to the classical XP patient. These mildly ill patients usually cannot be diagnosed early on and have a higher predisposition for malignancies, especially melanoma, SCC, and BCC.[10] So the dermatologic examination was important to early diagnosis the malignant lesions. When considering patients with XP clinically, Nishigori [16] summarized the process of diagnostic procedures for each complementation group of XP and variant type. After the causative mutations are clearly identified, subsequent targeting treatment can be done.

Dermatoscopy is a noninvasive technique for the diagnosis of skin lesions that helps clinicians differentiate benign from malignant lesions with its higher sensitivity and specificity for skin cancers detection than the naked eye examination.[17] The dermoscopic findings in skin cancers were similar to those previously described in patients not affected by XP.[18] In this case, we used dermatoscopy to check all suspicious lesions in order to minimize the possibility of missing a malignant lesion. Skin cancers can be better evaluated when combined with dermoscopic images, which is desirable for patients who are subjected to repeated biopsies for improving quality of life.

Treatment is difficult for those with multiple lesions. In this case, all the lesions were BBCs, we had standard excision, Mohs micrographic surgery, cryosurgery, and other therapies to choose from.[2] We chose plastic surgery twice. When the patient was discharged from the hospital, we suggested that the patient carry out a stringent protection regimen from sunlight, including the use of sunglasses,

hats, long-sleeve garments, installing UV ray filters on the windows of her car and home, and avoidance of daytime outdoor activities. Broad-spectrum chemical and physical sunscreens were also cost-effective. For XP patients, numerous skin cancers will arise and early detection and excision are essential. We encouraged the patient to see a dermatologist every 3-6 months so a doctor could assess if the protection measures were successful. Also, close follow-up by ophthalmology and dermatology was recommended to monitor for ocular and skin damage. Each patient must be managed individually.[2,19,20] Treatments for skin also include retinoids, photodynamic therapy, 5-fluorouracil (5 FU), imiquimod,[2] and nicotinamide.[20]

Because of the different molecular mechanisms, patients with XP-V, in comparison with other genes, present with decreased UV sensitivity and intensity of sunburns, longer survival, and a lack of neurological degeneration and they normally have a better prognosis.[21-23] In XP-V patients the mean age of onset of BCC is 41.5 years old.[19] Andrew reported a variant subtype of xeroderma pigmentosum diagnosed in a 77-year-old woman with basal cell carcinoma, squamous cell carcinoma, and malignant melanoma.[24] So far, XP-V frequently occurs in combination with skin cancers, including BBC, SCC, melanoma, and angiosarcoma.[25]

In managing this disease, prevention is critical and early diagnosis and regular follow-ups are key for the health of patients and their families. Genotyping can be determined through genetic testing, and genetic counseling and prenatal diagnoses can be used to reduce XP mutations in following generations. Early patient education and appropriate protection measures can minimize XP damage and improve the quality of life and prognosis of XP patients.

CONFLICT OF INTEREST

All of the authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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