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. 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. The XP-V subtype has normal NER and is caused by mutations in the XP-V gene, also known as POLH, which 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. Classic XP phenotypes include noticeable hyperpigmentation, 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 mucosa 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 combining with 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 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. Overlapping clinical features...
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.\textsuperscript{10} So the dermatologic examination was important to early diagnosis the malignant lesions. When considering patients with XP clinically, Nishigori\textsuperscript{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.\textsuperscript{17} The dermoscopic findings in skin cancers were similar to those previously described in patients not affected by XP.\textsuperscript{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.\textsuperscript{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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