Cutaneous Squamous Cell Carcinoma and Multiple Basal Cell Carcinomas in Xeroderma Pigmentosum-Variant Type Treated with Imiquimod 5% Cream and Radiotherapy: A Case Report

Amanda T. Chung, MD-MBA, Jerson N. Taguibao, MD-MBA, Arunee H. Siripunvarapon, MD and Ma. Lorna F. Frez, MD

Department of Dermatology, Philippine General Hospital, University of the Philippines Manila

ABSTRACT

Xeroderma pigmentosum (XP) is a rare DNA repair disorder characterized by sensitivity to sunlight and predisposition to cutaneous malignancies. There are various types, including the Variant type, which does not manifest with acute sunburn reactions. This results to the development of multiple malignancies that are often discovered at late stages, making management more challenging. This is a case of a 54-year-old Filipino female presenting with multiple basal cell carcinomas (BCCs) on several areas of the face and advanced cutaneous squamous cell carcinoma (cSCC) on the right zygomatic area, treated with imiquimod 5% cream and external beam radiation therapy, respectively. There was an excellent response of the BCCs to imiquimod 5% cream and good tumoral response of the SCC to radiation therapy, with tolerable side effects, highlighting the use of these palliative treatment modalities for XP patients with multiple, unresectable, or difficult-to-treat cutaneous malignancies.

Keywords: xeroderma pigmentosum, basal cell carcinoma, squamous cell carcinoma, imiquimod, radiation therapy

INTRODUCTION

Xeroderma pigmentosum (XP) is a rare autosomal recessive DNA repair disorder characterized by extreme sensitivity to ultraviolet radiation and increased risk of cutaneous malignancies.[1] XP-variant (XP-V) arises from mutations in DNA polymerase η, encoded by the POLH gene, whose role is to replicate DNA damaged by ultraviolet radiation through the translesion synthesis pathway.[2]

In the United States and Europe, prevalence of XP is about 1 in 1,000,000. In Japan, XP is much more common, affecting 1 in 22,000. Majority of XP cases are due to pathogenic variants in the XP-A (30%), XP-C (27%), and POLH (23.5%) gene.[3] In the Philippines, cases of XP are rare with only 17 reported cases from 2011-2021 based on local data from the Philippine Dermatological Society - Health Information System.[4] It is also unknown how many of these patients constitute XP of the variant type.

Herein, we present a case of XP-V in a middle-aged Filipino female with multiple cutaneous malignancies to highlight the late manifestations of XP-V and present imiquimod 5% cream and radiation therapy (RT) as alternative treatment modalities for such cases.

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Corresponding author: Amanda T. Chung, MD-MBA
Department of Dermatology
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: amanda.chungmd@gmail.com
ORCiD: https://orcid.org/0009-0002-0163-733X

CASE PRESENTATION

A 54-year-old Filipino woman, with no known comorbidities, consulted at our institution due to a cutaneous mass on the right zygomatic area. She presented with a 7-year history of multiple, black papules and nodules on the face and a 2-year history of a solitary, light pink tumor on the right zygomatic area. The patient is the first child in a brood of three, born to non-consanguineous parents. Her younger sister and a paternal aunt present with similar skin changes while both her children do not (Figure 1). The patient recalls spending most of her childhood swimming in the ocean without any form of sun protection, noting transient erythema within hours of exposure with no blistering, swelling, or tenderness.

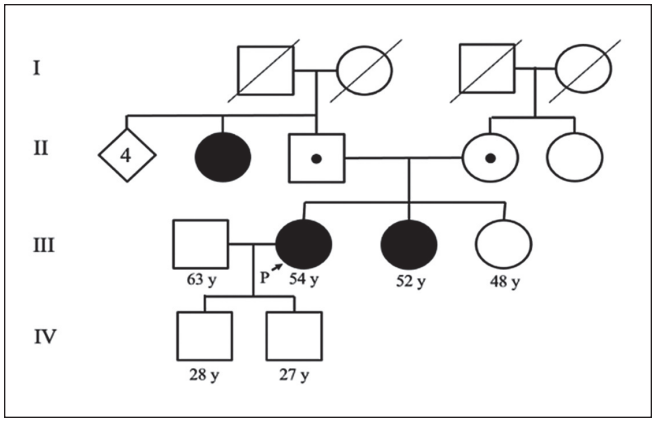

Figure 1. Pedigree of the family with xeroderma pigmentosum-variant.

On examination, the patient presented with multiple, well-defined, round to irregularly shaped, grey-black papules and nodules over the face (Figures 2A and B). Dermoscopy of the lesions demonstrated a combination of blue-grey ovoid nests, white blotches and strands, and brown dots, consistent with BCC. On the right zygomatic region, there was a solitary, light pink, irregularly-shaped, firm, non-movable tumor measuring approximately 7.0 x 5.0 x 3.0 cm with ulceration at the right lateral canthus draining yellow, non-foul-smelling seropurulent discharge (Figure 2B). There were multiple well-defined, mottled, brown papules admixed with hypopigmented macules in a symmetric distribution on sun-exposed areas of the face and body (Figure 2C). Ophthalmologic examination revealed ptosis and lower lid retraction on the right eye, and a solitary, oval, red mass, measuring 0.9 x 0.4 x 0.3 cm on the lower palpebral conjunctiva of the right eye. Corneal opacification and limitation of extraocular muscle movement were not noted. There was trismus, which made oral examination difficult. There were lip lesions and no palpable lymph nodes. The rest of the systemic and neurologic examinations were unremarkable.

Biopsies from the forehead and right zygomatic region were consistent with BCC and SCC, respectively. Genetic testing revealed a homozygous mutation (c.1066 C>T (p.Arg356*) in exon 9 of the POLH gene. Contrast-enhanced cranial and neck magnetic resonance imaging (Figure 3) showed a cutaneous-subcutaneous predominantly solid mass on the right zygomatic region with extensions and mass effects to the right orbital and masticator space, with possible perineural spread. A round focus was seen in the left aspect of the clivus, intimately related to the left petrosal

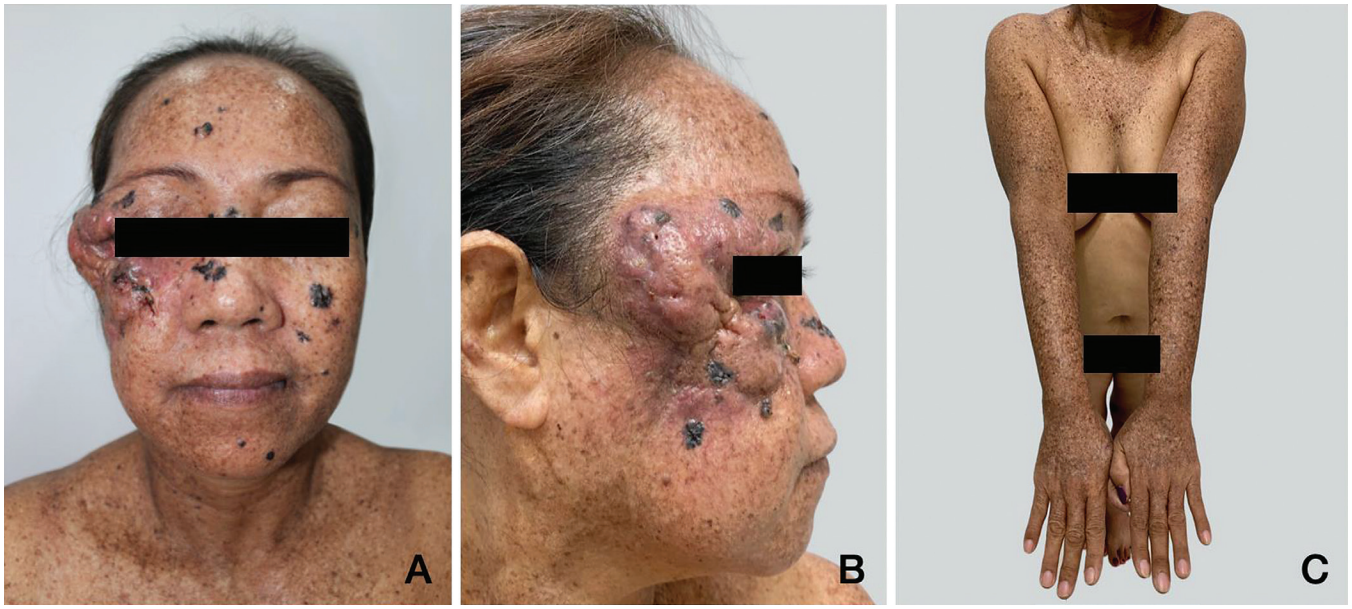

Figure 2. Baseline photos. **(A,B)** Multiple, round to irregularly shaped, grey-black papules and nodules with rolled borders on the face. **(B)** Solitary, pink, irregularly shaped tumor on the right zygomatic region. **(C)** Freckle-like macules on sun-exposed areas of the body.

sinus. Prominent, enhancing lymph nodes were detected in the right parotid gland and along the bilateral upper, mid, and lower jugular chains, submental, and submandibular regions. Contrast-enhanced chest and abdominal computed tomography scan showed no findings suggestive of metastasis. The tumor on the right zygomatic and periorbital area was classified as SCC, stage IV (T4cN2cM1).[5]

For management, surgery was offered as a first-line treatment option for the BCCs. However, since removal of multiple BCCs would also lead to high risk of disfigurement, imiquimod 5% cream was recommended as an alternative treatment strategy. The patient was instructed to apply the cream uniformly over lesions once daily at bedtime, three times a week. The patient was not fully compliant to the treatment regimen, skipping application on some weeks. The cream was applied, albeit intermittently, for 10 months. There was decrease in size of the grey-black papules on the root and bridge of the right ala (Figure 4). Local erythema, irritation, erosion, and atrophic scars were the only observed side effects.

A multi-disciplinary conference involving oncology, otolaryngology - head and neck surgery, and ophthalmology was held to discuss the most appropriate management for the patient's SCC. Given the involvement of pterygoid muscles and metastasis to the clivus seen on imaging, the patient was not a good surgical candidate. Neoadjuvant chemotherapy with pembrolizumab, followed by radiotherapy, was the proposed treatment plan. However, due to the inaccessibility of pembrolizumab in the local setting, chemotherapy with carboplatin and paclitaxel was considered. Given the possible adverse effects of cisplatin in XP patients, we opted to defer chemotherapy and prioritize radiation therapy instead.

The patient received external beam radiation with 6600 cGy in 33 fractions by intensity modulated radiotherapy planning with 6 MV photons, at 200 cGy per fraction over 51 days (December 2022 to February 2023) similar to the protocol of Mankada et al.[7] Radiotherapy was tolerated well until completion of treatment. There was development of grade 1 radiation dermatitis, right periorbital swelling, chemosis, and conjunctival injection two months after initiation of RT

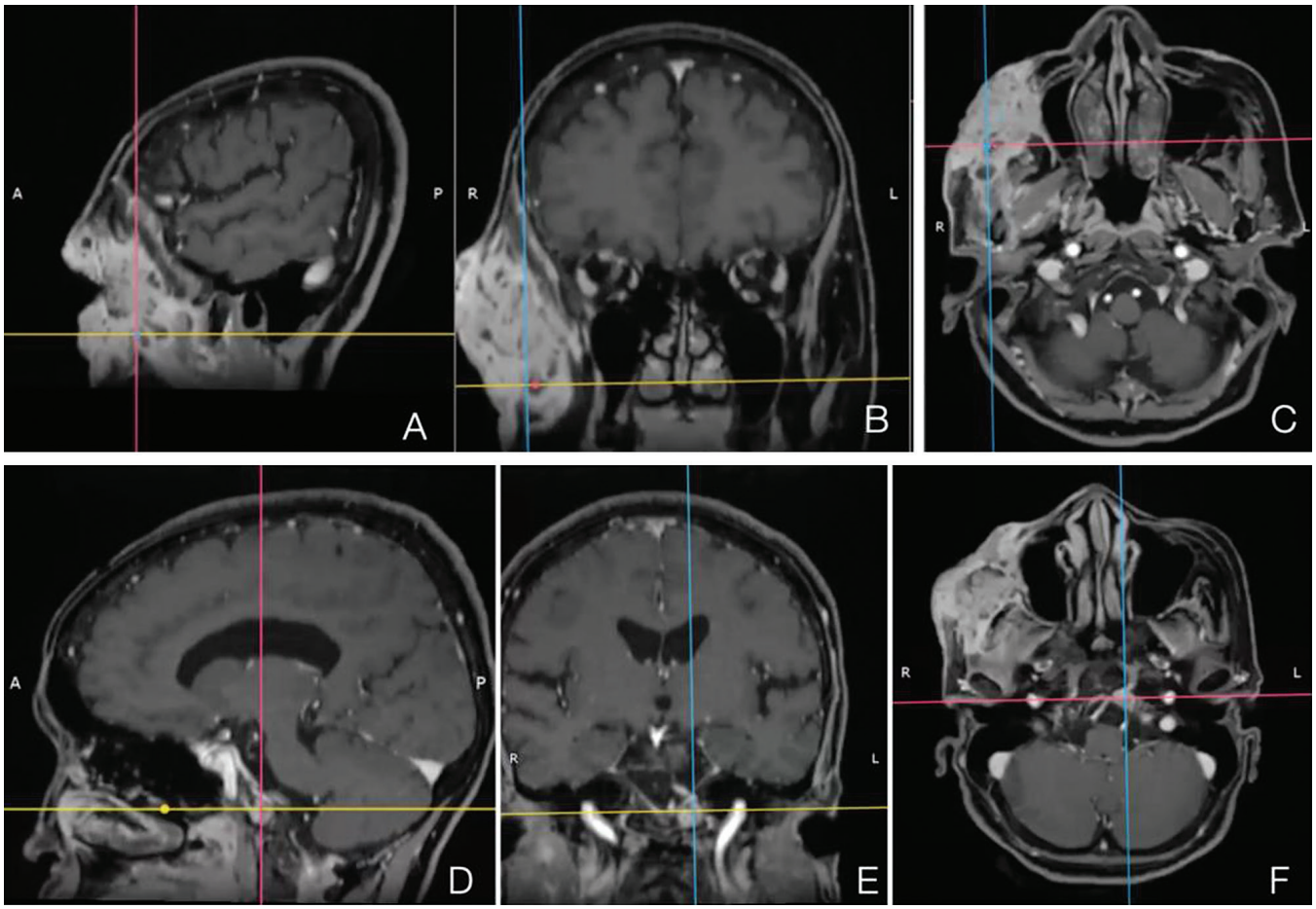

Figure 3. Contrast-enhanced cranial MRI. Sagittal **(A)**, coronal **(B)**, and axial **(C)** T1-weighted images showing extension of the mass to the masticator space. Sagittal **(D)**, coronal **(E)**, and axial **(F)** T1-weighted images showing heterogenous (predominantly hyperintense) signals in the left aspect of the clivus measuring approximately 1.0 x 1.0 x 1.0 cm (CC x W x AP). The focus is intimately related to the petrosal sinus.

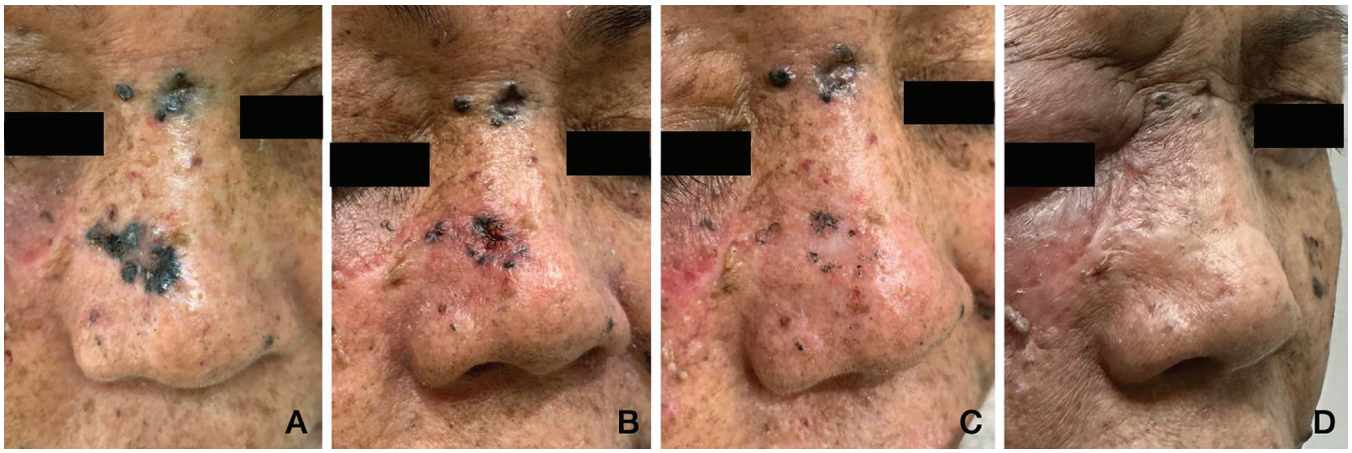

Figure 4. Representative lesions where imiquimod 5% cream was applied. **(A)** Prior to treatment, multiple basal cell carcinomas on the root and right nasal bridge of the nose were present. **(B)** Two months after treatment, erythema on the right nasal bridge and decrease in size of the papules were seen. **(C)** Six months after treatment, few black nodules were replaced by hypopigmented atrophic scars. **(D)** Ten months after treatment, there was further decrease in black nodules and improved texture of the skin.

(February 2023). Application of hydrocortisone 1% cream and tobramycin 3% ophthalmic ointment, and cleansing with povidone-iodine solution were advised with noted relief. Clinically, there was noted further decrease in size and erythema of right zygomatic mass, resolution of right periorbital swelling and yellow seropurulent discharge draining from the mass, and soft tissue atrophy of the right temple and cheek following radiotherapy (Figure 5). Patient also noted improvement of trismus.

The patient was advised to apply imiquimod 5% cream three times a week over the remaining nodules and to follow-up every four weeks for reassessment of clinical clearance. The patient refused further chemotherapy treatment and management is now mainly supportive aside from strict sun protection measures and full body skin examinations at regular intervals.

DISCUSSION

XP is diagnosed on the basis of clinical, family history, and/or molecular features. Suggestive cutaneous findings include acute sun sensitivity, marked freckle-like pigmentation, and skin cancers at an early age. The manifestations of XP largely vary between the type, nature of the mutation, and cumulative UV exposure of the patient, with only 60% exhibiting acute sunburn reactions.[3] Our patient was diagnosed clinically based on her presentation of freckle-like hyperpigmentation and multiple malignancies before the age of 50 years. The case was confirmed to be a definite case through genetic testing, wherein a homozygous pathogenic variant (c.1066 C>T) in exon 9 of the POLH gene was detected. A homozygous mutation indicates that both copies of the gene have the same mutation; therefore, confirming a definite case of XP.

Cutaneous manifestations of XP may be divided into two: exaggerated sunburn reaction type and abnormal pigment change type. The exaggerated sunburn reaction type is seen in XP-A, B, D, F, G and presents as intense erythema, swelling, blistering, and erosions after 3-4 days of exposure. In contrast, the abnormal pigment change type seen in XP-C, E, and V presents as freckle-like macules without any exaggerated sunburn reaction on sun-exposed sites.[8] Our patient presented with the latter type and was not diagnosed with XP until she presented at our institution with a right zygomatic mass. By this time, she had already exposed herself to a substantial amount of UV and developed multiple BCCs and a high-risk SCC on the face. Early diagnosis of XP-C, E, and V is a challenge as freckle-like hyperpigmentation, in the absence of blistering, is often brushed off as solar lentiginosis from intense UV exposure. In countries where XP is very rare, the diagnosis is often overlooked.

Protection from UV through environmental modifications, protective clothing, and diligent sunscreen use is emphasized in the management of XP. Despite these precautionary measures, patients inevitably develop multiple and extensive cutaneous malignancies. Skin cancers that are recurrent or in high-risk locations such as the face, are best treated by Mohs micrographic surgery. However, given the number of BCCs and extensive involvement of the SCC in our patient, this would lead to significant scarring and cosmetic disfigurement.

Imiquimod is an immune response enhancer that demonstrates compelling antitumor effects. Its mechanism involves the activation of Toll-like receptor 7 (TLR7), which triggers the production of inflammatory cytokines. These cytokines stimulate natural killer cells and boost antigen-presenting cell activity promoting the elimination of tumor cells. It has been used successfully to treat XP-

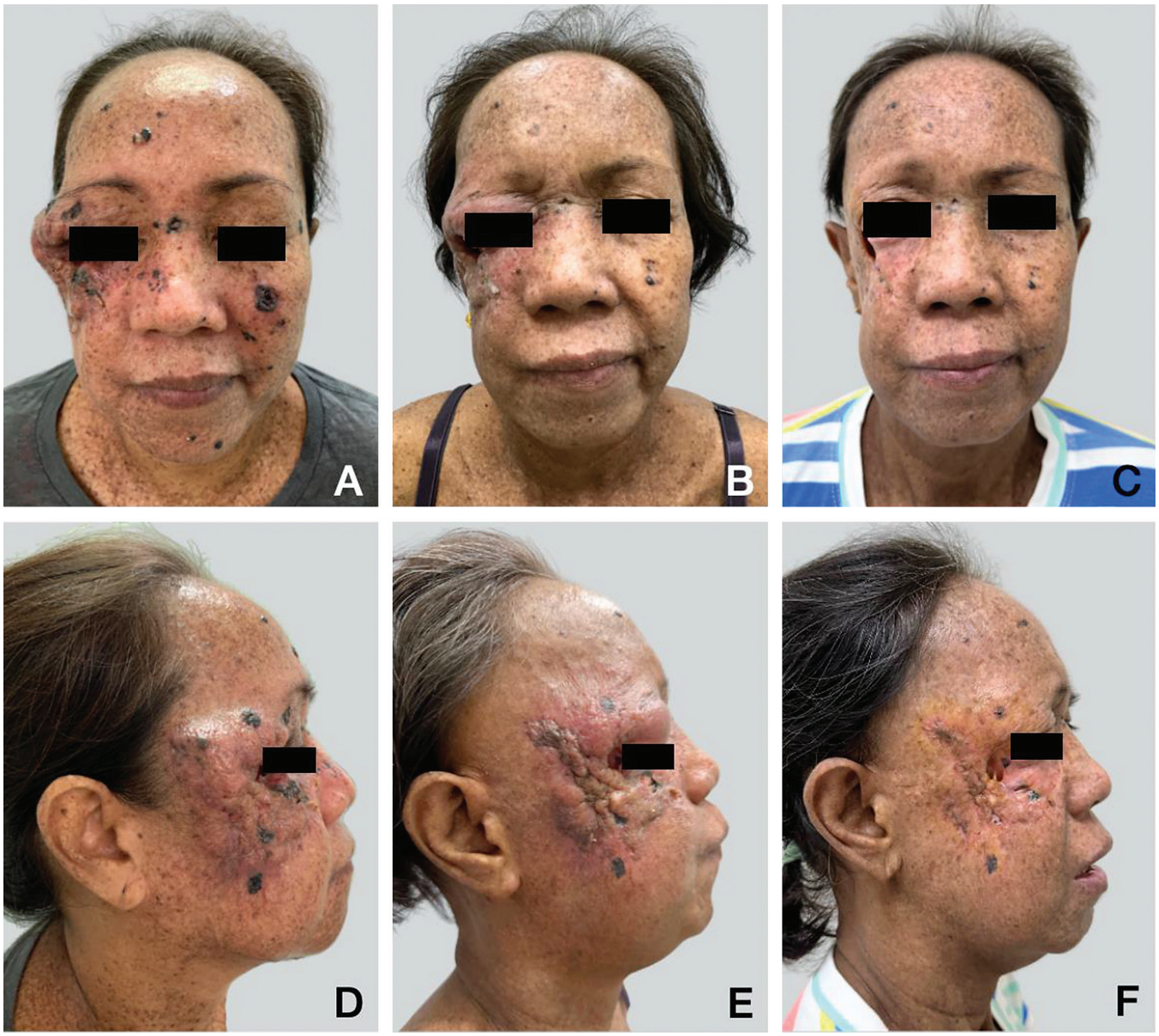

Figure 5. **(A,D)** Baseline photos prior to radiotherapy and ongoing application of imiquimod. **(B,E)** Three months after the last radiotherapy session, periorbital swelling, decrease in size, and erythema of right zygomatic mass were observed. **(C,F)** Nine months after the last radiotherapy session, there were resolution of periorbital swelling, further decrease in size and erythema of right zygomatic mass, and soft tissue atrophy of the right temple and cheek. BCCs have also decreased in size.

associated pigmented BCCs with only minimal side effects (e.g., erythema, erosions, scaling). Dosage and frequency of application varies from three to five times a week to once daily.[9,10]

In our patient, there was observed significant improvement in terms of size and thickness of the BCCs on the forehead, right nasal bridge, chin, and cheek where imiquimod was applied. There was also overall improvement in skin texture and pigmentation. Aside from treatment of cutaneous BCCs, imiquimod has a potential prophylactic role against the development of premalignant and malignant lesions in XP. It is suggested that application be once daily for three weeks, at intervals of 3-6 months, as soon as XP is diagnosed.[11] As a self-administered topical therapy with minimal systemic side effects, it offers more advantage over retinoids.

RT is recognized for its ability to induce DNA damage directly through ionizing radiation (IR). This form of radiation primarily results in various types of DNA lesions, including double-strand breaks, single-strand breaks, and

base lesions. RT is used as an adjunct treatment option for high-risk squamous cell carcinomas with invasion of deep tissues, perineural involvement, or regional lymph node metastases.[12] Patients with XP are not expected to have abnormal reactions to IR on the basis that IR is repaired by base excision repair and nonhomologous end joining, and not nucleotide excision repair.

Technique and total dose are highly individualized. Majority of patients treated with RT tolerated treatment and reported good outcomes. Acute reactions consisted of mild erythema, erosion, conjunctivitis.[7,12-14] It must be emphasized that XP patients and its complementation groups may have varied sensitivity to radiation, in vivo and in vitro. One study suggested impairment of DNA damage repair function of XP-V patients after ionizing radiation exposure, implying possible involvement of polymerase η in cell cycle checkpoint pathways.[15] Caution in initiating treatment, particularly doing a small initial test dose is still suggested to check for clinical signs of hypersensitivity. Moreover, caution must be taken when treating areas adjacent to mucosal surfaces as the severity of complications among XP patients is still relatively unpredictable, as with our patient who developed conjunctival inflammation and chemosis following RT.

CONCLUSION

This case of XP-V with late complications from chronic sun exposure highlights the importance of maintaining a high index of suspicion for XP in patients with skin of color who present with multiple freckle-like macules over sun-exposed areas. Delays in diagnosis may result in the development of complex cutaneous malignancies that are more difficult to treat.

Due to the nature and pathophysiology of XP, other treatment modalities, such as topical imiquimod 5% cream and radiation therapy can be considered as alternative treatment options for multiple BCCs and advanced SCC, respectively. As protocols for treatment with imiquimod 5% cream and radiation therapy in XP patients have not been established and are largely based on case reports, there should be close coordination with a multidisciplinary team and close follow-up during treatment.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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