Case Report
Olgu Sunumu

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Navigating diagnostic challenges in Xeroderma Pigmentosum variant type

Kseroderma Pigmentozum varyant tipinde tanısal zorluklara bakış

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Abstract

Xeroderma pigmentosum (XP) is a rare autosomal recessive genodermatosis caused by mutations in the DNA repair system, leading to impaired repair of ultraviolet (UV) radiation-induced damage. XP is classified into seven nucleotide excision repair-deficient types (XPA to XPG) and a variant type (XPV). Diagnosis can be made at a later age in the XPV subtype, where sunburn reactions are known to be less severe. In this case, a 33-year-old male patient with a history of freckling that began at age 10 and basal cell carcinoma and squamous cell carcinoma in the head and neck region over the past 5 years presented with a suspicious non-pigmented 6 mm nodular lesion in the left subauricular region. Pathological examination revealed a diagnosis of malignant melanoma (MM). Concurrent genetic analysis revealed a homozygous c.491-6T>G mutation in the POLH gene, confirming a diagnosis of XPV. The mild clinical features of XP in our patient made the XPV diagnosis challenging, and the atypical dermoscopic features of the lesion complicated the clinical diagnosis of MM. It is reported that the age of onset of malignant skin tumors in XPV patients is later than in other groups, and the frequency of MM is higher. This case highlights the frequent delay in diagnosis and the diagnostic challenges of skin tumors in XPV patients.
Keywords: Xeroderma pigmentosum, malignant melanoma, dermatoscopy

Öz

Kseroderma pigmentozum (XP), DNA onarım sistemindeki mutasyonlar nedeniyle ultraviyole ışınlarına bağlı hasarın tamirinin bozulduğu nadir bir otozomal resesif genodermatozdur. XP, yedi nükleotid eksizyon onarım eksikliği tipi (XPA'dan XPG'ye) ve bir varyant tip (XPV) olarak sınıflandırılır. Güneş yanığı reaksiyonunun daha az olduğu bilinen XPV alt tipinde tanı daha geç yaşta konulabilmektedir. Sunulmakta olan 10 yaşında başlayan çillenme, son 5 yıldır baş ve boyun bölgesinde ortaya çıkan bazal hücreli karsinom ve skuamöz hücreli karsinom öyküleri olan 33 yaşındaki erkek olguda sol subaurikular bölgede pigmente olmayan 6 mm çapında şüpheli nodüler lezyon tespit edilmiş, patolojik inceleme sonucunda malign melanom (MM) tanısı konulmuştur. Beraberinde yapılan genetik incelemede POLH geninde homozigot c.491-6T>G mutasyonu tespit edilmiş ve hastaya XPV tanısı da konulmuştur. Olgumuzun XP'ye ait hafif klinik bulguları XPV tanısını, lezyonun atipik dermatoskopik özellikleri de klinik olarak MM tanısını zorlu kılmıştır. XPV hastalarında malign deri tümörlerinin görülme yaşı diğer gruplara göre daha geç, MM görülme sıklığının ise daha yüksek olduğu bildirilmektedir. Bu olgu, XPV hastalarında tanının gecikme sıklığını ve deri tümörlerinin tanısal zorluklarını vurgulamaktadır.
Anahtar Kelimeler: Kseroderma pigmentozum, malign melanom, dermatoskopi

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Introduction

Xeroderma pigmentosum (XP) is a rare autosomal recessive genodermatosis caused by mutations in the DNA repair system, leading to impaired repair of UV radiation-induced damage. This deficiency results in early-onset actinic damage and the development of skin tumors. XP is classified into seven nucleotide excision repair-deficient types (Xeroderma pigmentosum complementation group A through Xeroderma Pigmentosum, complementation group G) and a xeroderma pigmentosum variant type (XPV). The manifestation of sunburn reactions and actinic damage varies according to the complementation group, affecting the timing of diagnosis and the frequency of skin cancer development based on cumulative UV radiation exposure[1]. Nevertheless, differentiating malignant lesions in the actinically damaged skin of all these patients is challenging. Although dermoscopy is indispensable in this context, it requires greater attention, and the threshold for biopsy should be low.

Case Report

A 33-year-old male patient, with no skin findings at birth, reported a history of freckling around the age of 10. In his twenties, he experienced febrile convulsions, requiring medication for 4-5 years. Consanguinity was noted in his parental lineage. The patient exhibited actinic damage inconsistent with his age, numerous seborrheic keratoses, and fibroepithelial polyps, and from the age of 27, he began developing non-melanoma skin tumors. Over five years, during his sporadic visits to the dermatology clinic, he underwent multiple excisions of basal cell carcinoma (BCC) and squamous cell carcinoma from the head and neck region. Despite occupational sun exposure, the patient exhibited inadequate adherence to sun protection practices. Comprehensive evaluations revealed no accompanying ophthalmological, neurological, or cardiological pathology. During follow-up, a newly developed erythematous, centrally crusted nodular lesion measuring 6 mm in diameter was identified in the left subauricular region of the patient's neck (Figure 1). Dermoscopic examination revealed a non-pigmented, irregularly bordered neoplasm featuring linear-irregular and hairpin vessels along the periphery and a central yellow crust (Figure 2). A punch biopsy was performed under the presumption of keratoacanthoma or squamous cell carcinoma; however, pathological examination revealed malignant melanoma (MM) (Figure 3). Subsequent excision and sentinel lymph node examination confirmed nodular MM with a Breslow thickness of 3.4 mm (pT3b) and sentinel lymph node involvement. No distant metastases were identified.

Genetic consultation and whole-exome analysis revealed a homozygous c.491-6T>G mutation in the *POLH* gene, confirming the patient's XPV diagnosis at the age of 33.

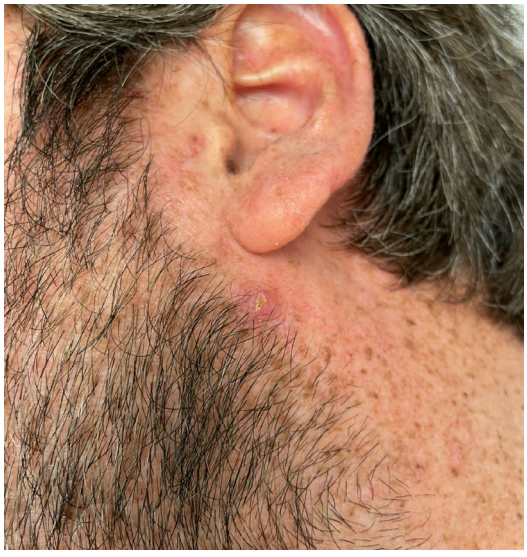

Figure 1. Clinical presentation of subauricular nodular lesion

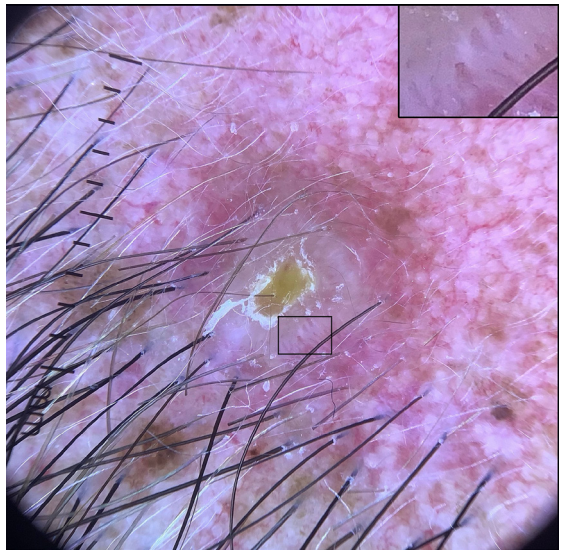

Figure 2. Dermoscopy of the lesion, showing a non-pigmented nodule with linear-irregular and hairpin vessels (square, enlarged)

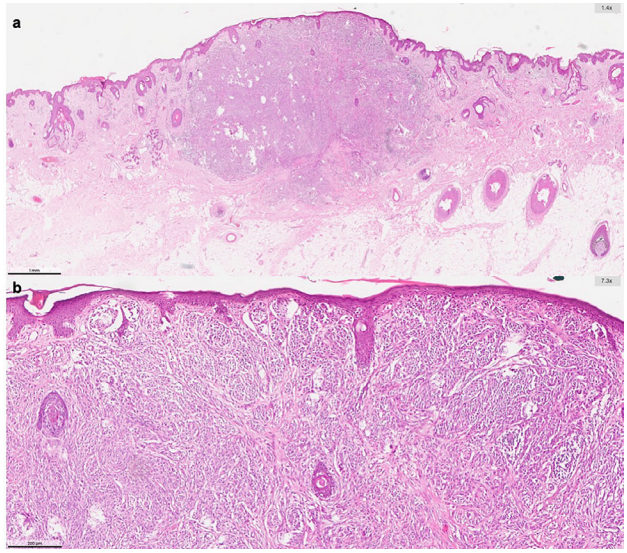

Figure 3. Histopathological features of the malignant melanoma lesion. A spindle cell tumor occupying the entire dermis and presenting with an ulcerated surface is observed. **(a)** Hematoxylin and eosin, x2; **(b)** Hematoxylin and eosin, x10

Discussion

XP subtypes A-G result from defects in the nucleotide excision repair (NER) pathway, rendering the removal of UV-induced photoproducts defective. XPV is characterized by a deficiency in post-replication repair rather than NER, primarily due to the *POLH* gene defect. This gene is involved in DNA synthesis after damage (translesion synthesis process), and POLH mutations in XPV patients result in a decreased ability of postreplication repair of damaged DNA following UV exposure, leading to the mutagenic effects of UV and subsequent skin cancers[2]. Unlike other groups, genetic complementation tests are not used for XPV diagnosis; instead, *POLH* gene examination is performed[3].

In the classic XP phenotype, freckling appears before the age of 2, and severe sunburns occur with minimal sun exposure. The median age for the first non-melanoma skin cancer is reported to be 9, and for melanoma, it is 22[4]. XPV typically presents with less severe clinical manifestations of UV sensitivity compared to other groups. Although abnormal pigmentation responses such as freckling and lentigines occur in these patients, they have normal minimal erythema dose values, and sunburn reactions are not as severe, with some even retaining the ability to tan[5,6]. Consequently, sun protection behaviors in XPV patients are not as early and stringent as in other groups, leading to higher skin cancer prevalence due to delayed diagnosis and increased sun exposure[7]. XPV patients generally do not exhibit neurodegeneration seen in other types, and long-term survival is better[4].

XPV accounts for approximately 25% of all XP cases. In Japan, 80% of XPV patients have a history of skin cancers, including BCC in 63%, squamous cell carcinoma in 30.4%, and MM in 23.9% of cases[7]. Skin cancers in this group appear at a later age compared to classic XP patients, with the first BCC occurring at an average age of 41.5[6]. Notably, MM is significantly more common in XPV patients than in other groups[7].

Identifying and clinically distinguishing skin tumors in XP patients, who have severe underlying actinic damage, is more challenging than in normal individuals. Dermoscopy remains an indispensable diagnostic tool, with the features sought in XP patients' skin tumors being similar to those in normal individuals. In XP patients, MM lesions most commonly present with asymmetry, multiple colors, prominent pigment networks, blue-gray areas, and atypical globules/dots[8,9].

The MM lesion in our patient lacked a pigment network; the vascular pattern within such lesions may aid in malignancy diagnosis. Although linear-irregular vessels suggestive of melanoma are observed, the presence of hairpin vessels with occasional peripheral halo and crusting in dermoscopy is a characteristic more commonly associated with keratinizing tumors. Nonetheless, the observation of this dermoscopic pattern in an XP patient strongly raises suspicion of a malignant lesion. This case highlights the frequency of delayed diagnosis in XPV patients and the challenges in diagnosing skin tumors in these patients. It also underscores the difficulty in diagnosing skin tumors, especially amelanotic melanoma lesions, even dermoscopically in actinically damaged skin. Due to the higher incidence of melanoma and overall increased frequency of skin tumors, dermatologists should consider the variant subtype of XP in patients with abnormal pigmentation changes but no rapid and severe sunburn history.

Ethics

Informed Consent: The patient in this manuscript has given written informed consent to the publication of their case details and images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.S., Ö.D., Y.A., C.D., S.Ş., Literature Search: G.S., Writing: G.S., Ö.D., S.Ş.

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References

1. Lehmann AR, McGibbon D, Stefanini M. Xeroderma pigmentosum. Orphanet J Rare Dis. 2011;6:70.
2. Gratchev A, Strein P, Utikal J, Sergij G. Molecular genetics of Xeroderma pigmentosum variant. Exp Dermatol. 2003;12:529-36.
3. Tanioka M, Masaki T, Ono R, et al.: Molecular analysis of DNA polymerase eta gene in Japanese patients diagnosed as xeroderma pigmentosum variant type. J Invest Dermatol. 2007;127:1745-51.
4. Black JO: Xeroderma Pigmentosum. Head Neck Pathol. 2016; 10: 139-44.
5. Leung AK, Barankin B, Lam JM, Leong KF, Hon KL: Xeroderma pigmentosum: an updated review. Drugs Context. 2022;11:2022-2-5.
6. Moriwaki S, Kanda F, Hayashi M, et al.: Xeroderma pigmentosum clinical practice guidelines. J Dermatol. 2017;44:1087-96.
7. Nishigori C, Nakano E, Masaki T, et al.: Characteristics of Xeroderma Pigmentosum in Japan: Lessons From Two Clinical Surveys and Measures for Patient Care. Photochem Photobiol. 2019;95:140-53.
8. Malvehy J, Puig S, Martí-Laborda RM: Dermoscopy of skin lesions in two patients with xeroderma pigmentosum. Br J Dermatol. 2005;152:271-8.
9. Faria Licarião Rocha LK, Ferreira P, Avancini J, et al.: Dermoscopic features of 61 skin lesions in xeroderma pigmentosum patients: A cross-sectional study. J Am Acad Dermatol. 2022;86:1361-2.