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SKIN CANCER IN CHILDREN WITH XERODERMA PIGMENTOSUM

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ABSTRACT
Introduction: Xeroderma pigmentosum) is a rare disease, inherited in an autosomal recessive manner with disturbances in the repair of deoxyribonucleic acid (DNA) which often occur in malignancy. Irreversible DNA lesions and mutations also occur in the genes which regulate skin cancer development in Xeroderma Pigmentosum. Purpose: To explain the signs, symptoms, and management of skin cancer Xeroderma Pigmentosum. Case Report : A 6 year old girl with basal cell carcinoma arising from Xeroderma pigmentosum. The histopathological picture of the left nasolabial biopsy preparation was found to show basal cell carcinoma (BCC). The patient was treated with 5FU administration and were followed after 6 week In the second patient, a 3 year old boy, squamous cell carcinoma in the oocipital area. From the histopathological picture, moderately differentiated squamous cell carcinoma on the left frontalis occipital dextra and corresponds to mottled hypermegrance on the parietal dextra. In this patient, a wide excision of the occipital lump was performed and the defect was closed with a full-thickness skin graft. Provided education to the parents of both patients for direct prevention of sun exposure by using sunscreen/hats. Discussion and Conclusion: Xeroderma Pigmentosum patients who are Xeroderma Pigmentosum to ultraviolet radiation (UV) can result in the development of highly cancerous lesions consisting of squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and malignant melanoma (MM). Clinical management of Xeroderma Pigmentosum includes sun avoidance, minimizing UV eXeroderma Pigmentosumosure, early detection, skin lesions, and genetic counseling. Topical application of 5-fluorouracil or imiquimod is used for premalignant lesions, and surgical excision is performed for malignant neoplasms of the skin, tongue, eyelids, conjunctiva, and cornea.

INTRODUCTION

Xeroderma pigmentosum was first described in 1874 by Moritz Kohn Kaposi, a Hungarian professor of dermatology, who reported two patients with emaciated, dry skin, skin contractions, pigmentation, dilation of skin blood vessels, and the development of multiple skin tumors at a young age (Leung, Barankin, Lam, Leong, & Hon, 2022). Kaposi coined the term 'xeroderma pigmentosum' to denote the characteristic 'dry' and pigmented skin' (Al Wayli, 2015). Xeroderma pigmentosum is an inherited disease of autosomal recessive genodermatosis due to mutations in genes involved in DNA repair machinery, causing deficient repair of DNA damaged by ultraviolet radiation (UVR). This condition can manifest as photosensitivity and increased susceptibility to skin cancer (Moriwaki et al., 2017). Certain types of Xeroderma pigmentosum are more prone to eye disease and progressive

neurodegeneration, depending on the cause of the mutase Sun exposure is responsible for several adverse consequences ranging from early clinical signs such as sunburn reactions to long-term effects such as photoaging and skin carcinoma. Sunlight radiation plays a major role in the etiology of such cancers, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) that develop from epidermal keratinocytes (Liu-Smith, Jia, & Zheng, 2017). UVB directly introduces DNA damage to the bipyrimidine sequence, it is most frequent and abundant among which is the pyrimidine cyclobutene (Budden & Bowden, 2013). Both DNA lesions are mutagenic and must be repaired to maintain their genomic integrity and avoid tumorigenesis. Nucleotide excision repair (NER) is a versatile repair mechanism induced by UV-B DNA lesions (1) (Tian et al., 2015). NER proceeds through six successive enzymatic steps: recognition of DNA distortions introduced by lesions, DNA decomposition around lesions, stabilization of multiproteic complexes, single strand double incisions 39 and 59 of lesions, replication of filling gaps using the remaining strands as templates and ligation of newly synthesized DNA strands2.

Early recognition of Xeroderma Pigmentosum is important so that prevention and protection from UVR can begin early, minimizing complications arising from the harmful effects of UV (Naik et al., 2013).

BCC cases with Xeroderma Pigmentosum are very rare so it needs accuracy in diagnosing and it is hoped that this case report will be able to provide discourse on various clinical manifestations and management of BCC management with Xeroderma Pigmentosum.

RESEARCH METHODS

This research uses qualitative methods with a literature review approach. Literature review is a systematic, explicit and reproducible method for identifying, evaluating and synthesizing research works and thoughts that have been produced by researchers and practitioners. The step in writing this review literature begins with the selection of topics. Search libraries or sources to gather relevant information from Google Scholar, CINAHL, Proquest, Ebsco, or National Library databases. Determine keywords or keywords for journal searches. After the data is collected, it is processed, analyzed and conclusions drawn.

RESULTS AND DISCUSSION

Xeroderma pigmentosum is a rare inherited disorder, almost 100% an autosomal recessive disorder, with a characteristic defect in the enzyme when the DNA pathway is repairing, namely nucleotide excision repair (NER) (Weon & Glass, 2019). The incidence rate depends on geographic distribution (2.3/1000,000) in births in Western Europe and among no differences in cases between women and men (Pallasmaa, 2014). For Asia region (Japan 1: 20,000 and India and Africa 1:10,000-30,000 1-5 Patients with Xeroderma pigmentosum will show symptoms sensitive to sunlight, there is burning on the skin, the skin will feel dry (xerosis) and spots on the skin (pigmentosum). Different levels of skin damage and may increase the incidence of face/neck/head1,2,3

In Xeroderma pigmentosum patients there are 7 variants (Xeroderma Pigmentosuma-Xeroderma PigmentosuMG), along with the Xeroderma Pigmentosum variant has a NER function (nucleotide excision repairing) with DNA polymerase interference involved in DNA replication. Each gene involved in this NER process, will show symptoms and severity that varies.1,4,5,The gene that has the most damage is Xeroderma Pigmentosuma which has damage at locus 9q22.33 reaches 30%, and the lowest damage to the Xeroderma Pigmentosumb gene at locus 2q14.3 reaches 0.5%.1 In the epidermal layer of DNA, especially in keratinocytes and in Langerhans cells dendritic antigen cells are found that absorb UV-B and undergo changes Structural interchanges between adjacent pyrimidine bases (thymine and cytosine) include the formation of ciklobutane and 6, 4-photoproducts. These structural changes are potentially mutagenic and are found in most BCCs and SCCs. They can be fixed by cellular mechanisms that result in their recognition and excision and restoration of normal base sequences1-4 (Pope, 2019).

Some oculocutaneous malignancies are common manifestations on sun-exposed areas of the face in patients with Xeroderma Pigmentosum (Halkud et al., 2014). BCC and SCC are commonly seen in the first decade of fifth and sixth age in the general population,1,3,5.

Xeroderma pigmentosum patients are most likely to experience skin malignancies(3). Age 3-5 years have a risk of skin cancer in the case of Xeroderma Pigmentosum is 10,000 times greater than normal children to experience non-melanoma type skin cancer, namely basal cell carcinoma and squamous cell carcinoma. This non-melanoma skin cancer originates from the keratinocyte layer of the basal cell layer of the epidermis (Fusi et al., 2014). The frequency of non-melanoma skin cancer in the case of Xeroderma Pigmentosum reaches 50% experienced by patients less than 10 years (Garbutcheon-Singh & Veness, 2019). Basal cell carcinoma can continue to grow and rarely metastasize when compared to squamous cell carcinoma which can develop into invasive and can metastasize (Burton, Ashack, & Khachemoune, 2016). For malignant melanoma cancer there can be abnormalities in melanocytes and can occur 15-20% atypical (Raghavan et al., 2020).

Histopathological features of the first phase of Xeroderma Pigmentosum do not show a typical picture, only limited to hyperkeratosis, increased melanin, atrophy of the epidermal varies and focal basal hypermelanosis with several elongated rete ridges and some rete redge is only atrophied. In addition, in the first phase of the histopathological picture an atonic keratosis picture is obtained. The second phase is hyperkeratosis, pigment changes and sometimes telengectasis and sometimes also does not show typical signs due to changes leading to changes in cancer cells namely changes to basal cell carcinoma and squmous cell carcinoma 3,8

Xeroderma Pigmentosum is an incurable disease, the management of this case can be through several ways can be through prevention and palliative therapy to prevent becoming a skin cancer. However, therapeutic strategies in the case of Xeroderma Pigmentosum cannot repair the damage that repaired nucleotide DNA is the main cause in this case of Xeroderma Pigmentosum. Some treatments that can be given to Xeroderma Pigmentosum Patients1. Direct prevention of sun exposure by using sunscreen/caps etc., ablation/dermabrasion, chemical peels on tumors, laser and photodynamic therapy (PDT), retinoids, Salap 5-fluorocil, T4 endonuclease, Imiquimol, antioxidant photoliase, and alpha interferon. There are several therapies that are considered as future therapy in the case of Xeroderma Pigmentosum are oral vismodegib, immunotherapy, nicotinamid, Acetohexamide or glimepiride and diet supervisors6. Surgical excision is a modality used for the treatment of skin neoplasms. However, lesions on some sides may not be possible, this is due to aesthetic deformities 1-4.

Several classes of anti-cancer drugs have been considered for the treatment of Xeroderma Pigmentosum patients as an alternative to surgical resection of skin tumors. Among these, topical applications of 5-Fluorouracil (5-FU) or Imiquimod have been shown to be the most efficient. In particular, 5-FU has been shown to exert its function through inhibition of deoxythymidine mono-phosphate (dTMP), a key component in the replication and transcription of DNA1.

Due to its involvement in fundamental cellular processes, 5-FU inhibits inducing P53-mediated apoptosis. Numerous studies have shown that administering topical 5-FU to Xeroderma Pigmentosum patients is useful to negatively control the malignant transformation of superficial skin cells and to control actinic keratoses Apart from its anti-cancer activity, 5-Fluorouracil is a non-specific drug that promotes side effects such as induced cell death from non-cancerous cells and pyroptosis, a recently described process involving apoptosis aggravated by Inflammation. After all, recent studies report that topical treatment with 5-FU fails in the destruction of prolonged skin cancer, also causing painful lesions.

The U.S. Food and Drug Administration states dosage recommendations for superficial KSB with application are done thinly 2 times daily for 3-6 weeks. This therapy can be applied up to 1-2 mm

around healthy skin and allowed to stand for 10- on-these patients are treated with topical administration of 5FU. Patients were followed up after 6 weeks with scar evaporation, the cancerous lesions became smaller. In addition, effective sun protection and early recognition of skin cancer play an important role in the management of Xeroderma Pigmentosum. 14 hours.15 The total area of skin that 5-FU can be given in one therapy is not more than 500 cm2 or 23 x 23 cm.12 Large areas can be treated alternately at a later time. In the sixth week, therapy evaluation is carried out through clinical appearance, if there is still residual tumor then therapy can be continued for a maximum of 12 weeks.15 Occlusion therapy will increase inflammatory reactions in the skin. Responses that can occur after topical application of 5-FU include erythema that will worsen to blackness or necrosis, then will heal. In addition, it can cause pain, bullae, and skin ulcers.

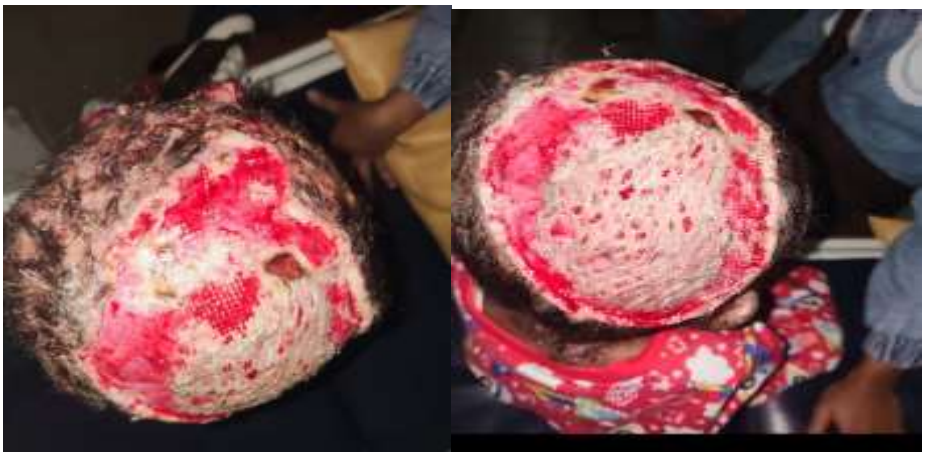
Figure 6a. Lesions ar nasolabialis sinistra before topical application 5 FU (First case)

Figure 6b. Lesions shrink after topical application of 5fu for 6 weeks (First Case)

In the second case, the choice of therapy in XP patients accompanied by other skin cancers is radical resection which is the standard management in non-melanoma skin cancers. Non-melanoma skin cancers require extensive excision with tumor-free boundaries accompanied by reconstruction but not in patients with Xeroderma pigmentosum. In XP patients, even small excision performed and prepared with good reconstruction still gives poor results due to lack of skin pliability4. So that patients in cases two and three only performed excision on lesions that disturbed the patient and

without boundary vc and closed the defect using a fullthickness graft from the abdomen, Both patients were grafted on day 5 and partially grafted intake.

Education is given to the parents of both patients for direct prevention of sun exposure by using sunscreen / hat / shirt and pants / skirt that can cover areas of the body that are directly exposed to sunlight.



6c. Re-control after 2 weeks (Second Patient)

CONCLUSION

Xeroderma Pigmentosum is a rare autosomal recessive disorder characterized by varied deficiency repair of UV-induced photo products, and skin phenotypes often manifest as dry skin that looks like skin that undergoes premature aging. They can also manifest as basal cell and squamous cell carcinoma (SCC) and melanoma in the first two decades of life. Patients with Xeroderma Pigmentosum should avoid exposure to UV light sources and should wear protective clothing and UV absorbent goggles. Topical application of 5-fluorouracil or imiquimod is used for pramalignant lesions, and surgical excision is performed for malignant neoplasms of the skin, tongue, eyelids, conjunctiva, and cornea. Eye drops containing methylcellulose or quinidine and ointments can be used for eye care9.

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