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Xeroderma Pigmentosum with Malignant Cutaneous Tumors in Two Siblings

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ABSTRACT

Xeroderma pigmentosum is an autosomal recessive genetic disease that accompanied by abnormalities in deletion and repair of DNA due to enzymatic damage by ultraviolet radiation. It is described by photo hypersensitivity of areas exposed to sun radiation, changes in the skin pigmentation, cutaneous premature aging and increased risk of developing cutaneous and ocular malignant tumors early in life. Most common types of malignant cutaneous tumors detected are basal cell and squamous cell carcinoma and less commonly malignant melanoma. It is very frequent in certain areas of the world, most markedly Middle East, like Egypt and North Africa with positive consanguinity. In patients with Xeroderma pigmentosum prior to the age of 20 years, the risk of developing skin cancer is several thousand times greater. In patients with XP for non-melanoma skin cancers, the median age of onset is eight years relative to the non-XP population with a median age of onset of sixty years. This research study presents two siblings; 18-years-old sister and 16-years-old brother; from relative parents that had xeroderma pigmentosum with development of different malignant skin tumors. Treatment protocol was surgical excision of the malignant tumor with adequate safety margin and removal of enlarged lymph nodes. Reconstruction options were directed mainly to flap surgery. Postoperative follow up revealed no recurrence.

Key Words: *Xeroderma – Pigmentosum – Skin – Malignant.*

INTRODUCTION

Xeroderma pigmentosum (XP) is an autosomal recessive genetic disease that is accompanied by abnormalities in deletion and repair of DNA due to enzymatic damage by ultraviolet radiation. The condition was first described by Kaposi and Hebra in 1874 and there have been a number of reports in the literature, describing the course of this disease **[1]**.

The incidence of XP is thought to be 1 in 250,000 individuals in Europe and United States and to be higher in Japan at 1 in 20,000 individuals **[2]**. It is very frequent in certain areas of the world, most markedly Middle East and North Africa with positive consanguinity. Consanguinity between the parents of affected children has been found in 30% of cases. The reason for the high prevalence in these regions is unknown, however possible heterozygosity have been suggested **[3,4]**.

Photosensitivity of areas exposed to sun radiation, changes in skin pigmentation, premature aging of the skinand an increased risk of developing malignant cutaneous and ocular tumors early in life are identified. In patients with XP prior to the age of 20 years, the risk of developing skin cancer is several thousand times greater. The median age of onset of malignant cutaneous tumors is eight years in patients with XP, while in the non-XP patients the median age of onset of malignant cutaneous tumors is sixty years **[5]**.

The most common types of malignant skin tumor found in patients with XP included basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) and less commonly malignant melanoma (MM). They occur primarily in the scalp, eyes, face and neck. It is mandatory to detect these malignancies early because they are increasing rapidly, metastasizing early and leading to death. Metastatic melanoma and SCC are two critical causes of mortality **[6]**.

This study describes two siblings (sister and brother) that had xeroderma pigmentosum with development of malignant skin tumors in young age. Their parents are relatives. Informed consent and written releases from patients were signed for their photos. The study was approved by the Institutional Review Board (IRB) for human researches in our faculty.

CASES PRESENTATION

Case (1):

The first case was 18-years-old sister that presented to our department with large ulcerated mass at left cheek. The lesion appeared six months earlier as a small mass that enlarged, became pedunculated and ulcerated with frequent bleeding. She had a history of freckling pigmentations in regions exposed

to sunlight (face and both hands) since she was 6 years old. When she was 12 years old, two pigmented brown to black lesions appeared at her cheek.

On clinical examination, there was a large pedicled ulcerating mass in the left cheek (preauricular region) measured about 6 x 7cm in diameter. The mass was infiltrating skin and soft tissues with involvement of part of the left ear lobe but not fixed to the underlying bone (Fig. 1 A). There were also two pigmented skin lesions (right infraorbital and left nasolabial areas) detected, (Fig. 1B). Neck examination revealed enlarged three left submandibular lymph nodes.

Ophthalmologic consultation revealed that she had photophobia, cataract with diminished visual acuity in the right eye and irregular lateral aspect of lower lid margin, symblepharon and limitation of ocular motility especially in the lateral gaze in the left eye. Ophthalmologic advice was to break adhesions from ocular surface in the left eye and reconstruction of the defect by amniotic membrane graft. Neurological examination revealed no manifestations.

Computed tomographic imaging (CT) confirmed the extent of the tumor and the lymph node involvement. Provisional clinical diagnosis suggested squamous cell carcinoma. Operation was done under general anesthesia. The following tissues were excised intraoperatively: The ulcerating tumor mass with adequate safety margin (2cm), the left parotid gland with scarification of the left facial nerve trunk and part of the left ear. This accompanied by modified radical neck dissection on left side (from level I to V) and the resultant defect was about 8 x 12cm on left side of the face and neck (Fig. 1C).

The defect was reconstructed, by pedicled latissimus dorsi myocutaneous flap with skin paddle 8 x 10cm (Fig. 1D). Histopathological examination revealed that the ulcerating mass was moderately differentiated squamous cell carcinoma with keratinization and free safety margin in the specimen. She was satisfied with the results postoperatively (Fig. 1E). The patient was advised to avoid exposure to sun radiation, to use sunscreens and protective eye glasses. She was referred to oncology department for further screening and treatment. Follow-up period maintained only for 2 months and showed no recurrence (Fig. 1F). She died after 3 months postoperatively.

Case (2):

The second case was a younger brother in the same family. He presented with multiple skin tumors that appeared in different periods during his life. He had a history of freckling pigmentations in regions exposed to sunlight (face and both hands) since he was 5 years old. When he was 16 years old; he presented to our clinic with superficial ulcer (actinic cheilitis) 1 x 1cm in diameter at the vermilion of lower lip, (Fig. 2A) that healed with topical application of 5-fluorouracil cream. Ocular manifestations included: No perception of light, enophthalmos, and atrophic globe with opaque microcornea in the right eye.

One and half years later, he presented with small ulcerated nodule at the right cheek that was diagnosed clinically as basal cell carcinoma (Fig. 2B). Excision with safety margin (5mm) then reconstruction by rhomboid flap was performed. Histopathological examination revealed nodular type basal cell carcinoma.

When he was 20 years old, he presented to our outpatient clinic with large ulcerated mass at the right cheek. The lesion started five months earlier as a small raised mass that increased in size and ulcerated. On clinical examination there was a large ulcer (5 x 6) cm on his right cheek (sub orbital region) and infiltrating skin and soft tissues but it was freely mobile (not fixed to the underlying bone), (Fig. 3A,3B).

Neck examination revealed one small enlarged submandibular lymph nodes on the right side. Ophthalmic consultation of the right eye revealed irregular lateral aspect of the lower lid margin by the mass, limitation of ocular motility especially in the right gaze. Neurological examination revealed no manifestations. Computed tomographic imaging (CT) confirmed the extent of the tumor and lymph node involvement.

Provisional clinical diagnosis suggested squamous cell carcinoma. Under general anesthesia, excision of the ulcer with safety margin (2cm) and enlarged lymph nodes were performed. The defect size was 5 x 6cm in diameter (Fig. 3C) and reconstructed with transverse forehead flap, (Fig. 3D). Histopathological examination report revealed well differentiated squamous cell carcinoma. Postoperatively, he was satisfied from the result (Fig. 3E). The patient was advised to avoid exposure to sun radiation, to use sunscreens and protective eye glasses. He was referred to oncology department for further screening and treatment. Follow-up after 6 months showed no recurrence. Later on, some hair growth developed in the flap (Fig. 3F) and planned for removal by laser therapy.

Fig. (1): Case No. (1) A 18-years-old female with xeroderma pigmentosum:

(A): Lateral view shows large ulcerated and pedunculated mass in the preauricular area. (B): Anterior view shows two pigmented skin lesions with eye manifestations. (C): The defect size after excision with safety margin. (D): Harvesting the latissimus dorsi myocutaneous flap. (E): Postoperative photo after ten days. (F): Two-months postoperative photo.

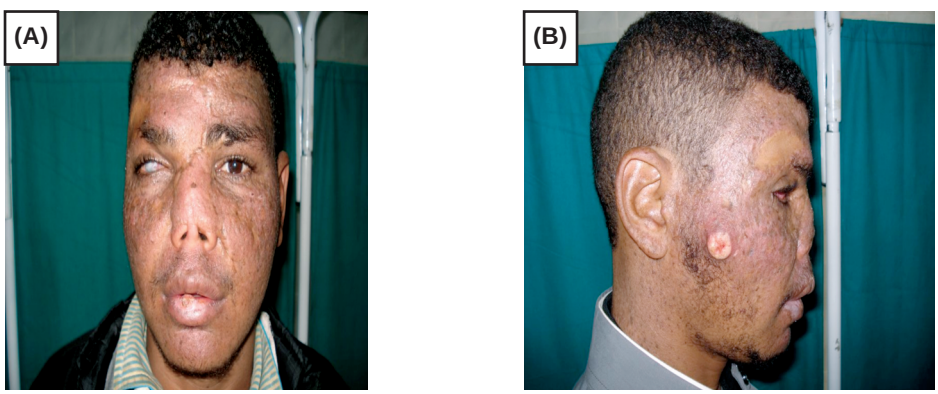

Fig. (2): Case No. (2) A 16-years old male with xeroderma pigmentosum:

(A): Shows actinic cheilitis in vermilion of lower lip and eye manifestations. (B): A small ulcerated nodule at right cheek (basal cell carcinoma).

Fig. (3): The same patient in Fig. (2) after two and half years.

(A): Anterior view shows large ulcerated mass at right cheek with eye manifestation. (B): Lateral view shows large ulcerated mass in right cheek (infraorbital). (C): The defect size after excision with safety margin. (D): Harvesting the transverse forehead flap. (E): Early postoperative view after ten days. (F): Late postoperative view after 6 months.

DISCUSSION

Treatment of xerodermic patients with malignant cutaneous tumors is challenging. Meanwhile, the treatment of non-xerodermic patient with these malignant tumors can be a reasonably simple procedure with different therapeutic modalities. However, treatment options are becoming more difficult in patients with this genetic disorder who have various forms of skin malignancies and who continue to develop skin tumors at a high rate **[7]**.

Treatment algorithim for skin tumors in XP should be tailored according to type of the tumor, its behavior and extent. Choice of the donor site for coverage should be from non-sun exposed areas to avoid development of skin tuomrs. Every surgical resection should be tailored individually for each patient and the benefit/harm ratio should be taken into consideration **[8]**.

There is no specific management for patients with xeroderma pigmentosum. Management options

includes prevention against the exposure to ultraviolet radiation (UV), use of sunscreens, protective eyeglasses, prophylaxis with isotretinoin, chemical peeling, dermabrasion, surgical excision of premalignant and malignant skin tumors, skin grafts harvesting for resurfacing techniques and flap reconstruction surgery **[9,10]**.

In the present study, the sister had squamous cell carcinoma on her left cheek. Treatment protocol was surgical excision of the malignant tumor with adequate safety margin and removal of enlarged lymph nodes. A pedicled latissimus dorsi myocutaneous flap was performed for defect reconstruction. Postoperative clinical follow-up revealed no recurrence.

The brother had three different types of skin tumors in different periods during his life. He presented firstly with a superficial ulcer (actinic cheilitis) in vermilion of lower lip that healed by topical application of 5-fluorouracil cream. After one and half years, he had basal cell carcinoma that was surgically excised with adequate safety margin and reconstructed by local transposition (rhomboid) flap. After two and half years, he presented with large ulcerating squamous cell carcinoma on right cheek that was treated by surgical excision with adequate safety margin. The defect was reconstructed by a transverse forehead flap. Postoperative clinical follow-up revealed no recurrence.

Ideal facial skin reconstruction for soft-tissue defects achieved with the same form of tissue. The most practical and cosmetic results are produced by the preservation of identical skin texture, color and thickness. Primary wound closure and local tissue flaps such as bilobed, rhombic flaps are good choices simply because of their ability to incorporate similar types of tissue into the defect for small to moderate-sized skin defects **[11]**.

For small skin defects and skin resurfacing, either split-thickness or full-thickness skin grafts can however be applicable. Unfortunately, contour irregularity, color mismatch, and graft contracture are common disadvantages to the use of skin graft and when used on visible areas of the face, can be particularly catastrophic **[12]**.

Meanwhile, it will provide closure of slightly larger defects by harvesting larger local flaps such as the paramedian forehead, transverse forehead flap, cheek advancement flap and nasolabial. Skin incision lines may be well concealed in folds and rhytids in preparing acceptable flap designs. Furthermore, distant pedicled flaps such as pectoralis major and latissimus myocutaneous flaps will provide good coverage in areas of the head and neck for large defects **[12]**.

Xeroderma pigmentosum with malignant cutaneous tumors of the face in siblings had been reported in many studies with or without history of consanguineous marriage of the parents **[13-15]**.

In the present study, the parents of the two siblings were relatives but unaffected by the disease. In literature, studies revealed that both parents of XP patients are asymptomatic carriers of mutations in one of their genes. They are obligate heterozygotes with 1 mutated gene and 1 normal gene. There is a 1 in 4 chance that their offspring will have inherited a mutated gene from each parent and thus have symptomatic XP **[16]**.

Therefore, genetic counseling of affected families is important. Amniocentesis for prenatal diagnosis of XP and termination of pregnancy may be discussed with parents in areas where religion allows it. There is, however, the promising possibility of in vitro fertilization with implantation of unaffected embryos **[17]**.

Conclusion:

There is no definitive treatment available and it is difficult to fully cure xeroderma pigmentosum. The main treatment included strict sunshine protection and the application of appropriate sunscreen and it is generally supportive. Early excision of skin tumors is highly recommended. Routine regular examination is mandatory in order to early detect the cutaneous malignancies and once these tumors are identified, they should be adequately treated.

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