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ORIGINAL ARTICLE

Xeroderma Pigmentosum: Clinicopathological Review of the Multiple Oculocutaneous Malignancies and Complications

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Abstract Multiple oculo-cutaneous malignancies are a common manifestation on sun-exposed facial areas in patients with Xeroderma pigmentosum (XP). Commonly seen are the basal cell carcinoma and the squamous cell carcinomas which manifest in the early first decade in contrast to fifth and sixth decade in the general population. XP manifests as photosensitivity, hyperpigmentation, premature skin aging and malignant changes like squamous cell carcinoma, basal cell carcinoma, fibrosarcoma and rarely malignant melanoma as well as internal malignancies. We report 11 cases of Xeroderma pigmentosa managed in our institute which included sex males and five females. All had photosensitivity, hyperpigmentation and consanguinity with facial malignant lesions like SCC and BCC. Ocular signs of photophobia and excessive lacrimation was seen in all the cases while blurring of vision due to corneal clouding, corneal injection, pterygium and limbal SCC were seen in 5 cases. SCC of the lids were seen in 7 cases while BCC seen in 8 cases and limbal and conjunctival SCC seen in one case. All were managed with excision while one case of melanoma with neck secondaries needed radical neck dissection while the other orbital exenteration. Oculo-cutaneous malignancies occur in the sun exposed areas so patients are advised regular follow up with speciality care. Awareness about the rare condition and importance of early detection and prevention of UV rays induced skin damage should be propagated. The disease is ultimately fatal, life can be prolonged by simple preventive measures to minimize sun exposure and early detection of the skin lesions and management.

Keywords Squamous cell carcinoma · Basal cell carcinoma · Photosensitivity · UV radiation

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Introduction

Multiple oculo-cutaneous malignancies are a common manifestation on sun-exposed facial areas in patients with Xeroderma pigmentosum (XP) [1]. Commonly seen are the basal cell carcinoma and the squamous cell carcinomas which manifest in the early first decade in contrast to fifth and sixth decade in the general population [1]. XP manifests as photosensitivity, hyperpigmentation, premature skin aging and malignant changes like squamous cell carcinoma, basal cell carcinoma, fibrosarcoma and rarely malignant melanoma as well as internal malignancies [2, 3].

The incidence in India is lesser compared to the west and other Asian nations [2, 3]. Cutaneous DNA damage due to UV radiation cannot be repaired in these patients as the nucleotide excision repair (NER) is defective. [2, 3] The defective or damaged DNA leads to heritable chromosomal mutation and cell death, which possibly cause neoplastic and atrophic clinical abnormalities with 1000fold risk of malignancies below 20 year of age [4–6]. Only 40 % of the patients enter the third decade while the milder variant of the disease are reported surviving past the fifties [7, 8]. The disease is fatal in the third decade but reducing sun exposure and earlier management of oculocutaneous malignancies improves survival [7, 8]. Early detection of these malignancies is necessary because they are fast growing, metastasize early and lead to death [7–9].

Methodology

We report a case series analysis study of 11 cases of XP managed in our institute over a period of 5 year. There were 6 males and 5 females in our study. The average age of presentation of skin pigmentation and photosensitivity in males was 2.5 year and in females 2 year and on an average 2.2 year. (Table 1)

The incidence of photosensitivity, hyperpigmentation and consanguinity was 100 %. Nearly all the patients had facial lesions of BCC and SCC around 8–9 year of age melanoma in 2 cases. By the age of 12, 9 of the patients were operated 2–3 times for excision of the lesions in other institutes. Ocular signs of photophobia and excessive lacrimation was seen in all the cases while blurring of vision due to corneal clouding, corneal injection, pterygium and limbal SCC were seen in 5 cases (Figs. 1 and 2). SCC of the lids were seen in 7 cases while BCC seen in 8 cases and limbal and conjunctival SCC seen in one case. Fissuring and hyperpigmentation the lips were seen in 2 cases while whitening was seen in 2 cases. Subnormal intelligence was seen in 2 cases while no neurological deficits or microcephaly were seen in any of the cases.

The patient with limbal SCC was operated at 55 year with a milder variant of XP and is doing well after orbital exenteration (Figs. 3 and 4). He had only hyperpigmentation on the face and the sun exposed areas with no other cutaneous malignancies. 2 patients had along with SCC and BCC had malignant melanoma of the scalp with neck metastasis so radical neck dissection with multiple excisions of the lesions were done. 2 patients had huge SCC of the nose, with multiple BCC were widely excised with nasolabial flaps reconstruction. Healing of these lesions was excellent after excision.

Discussion

Oculocutaneous malignancies in XP mainly comprise of basal cell carcinomas (BCC) which are slow growing and rarely metastatize while squamous cell carcinomas(SCC) are fast growing, invasive and often metastatize. [10] These malignancies are seen in 50 % of the patients in the first decade and SCC have double(4 %) metastatic potential compared to the normal population(2 %) [11]. Ocular malignancies are common in the lids, conjunctiva, and cornea as they are exposed as much as the facial skin whereas the deeper structures the eyelids, cornea and lens being shielded are lesser affected [12–14]. Photophobia is the earliest ocular symptom reported in 21 % and more marked in the younger than the adults [12–14]. Photophobia may be seen with keratitis or even with clear cornea. [12–14]

The eyelid skin like other part of the facial skin shows pigmentation, atrophy, loss of lashes, ectropion and loss of lids due to malignant growth erosion [12–14]. Lids are involved in 80–100 % of the cases [12–14]. Pathologically altered melanocytes due to mutations accumulate and form cutaneous freckles and hyperpigmented spots [12–14]. The lesions in the lower eyelid are lesser compared to the upper as the upper lids form a shade to the lower [12–14]. Interpalpabral fissures being the sun exposed part of the conjunctiva shows telangiectasia, xerosis, chronic congestion and pigmentation in 18 % of cases [12–14]. Corneal dryness exposure keratitis, hazyness, band-like nodular keratopathy, scarring, ulceration and even perforation resulting in corneal opacities and vascularisation are seen in 17–40 % of the cases [12–14].

Corneal opacification and neovascularisation are suggested to be due to the accumulation of the pyrimidine dimers seen due to UV exposure [15]. So corneal transplants are not indicated as corneal vascularisation, xerosis and inadequate lid coverage are seen in many of them [12, 15]. Pterygium formation is seen in most of the cases in both the eyes [16]. SCC is the most frequent ocular surface neoplasm followed by BCC and melanoma, commonly seen in the limbal area. [12, 15] These epibulbar neoplasms are reported in 11–20 % of the cases with variable extension to the cornea and conjunctiva [14, 15]. No conservative methods can be contemplated and exenteration is indicated in most of the cases [12, 13].

Iris is spared as the corneal opacification shields it from UV damage but late changes like inferior half stomal atrophy, pigment alteration, iritis and iris melanoma are reported [17, 18]. The retina with its macular area rarely show any changes as the crystalline lens prevents any UV passing through [14]. So blindness is usually caused by corneal opacities, pterygium, tumour invasion from the limbus and corneal vascularisation [12, 14]. Visual acuity of less than 6/36 is reported in 12–50 % of the cases [12, 14]. Protection from UV radiation by sunglasses and UV absorbing soft contact lenses are helpful, while artificial tears, steroid drops, bland ointment at night and eye drops containing quinoline derivatives reduce photophobia and ocular irritation [12, 14]. Oral retinoic acid is also helpful in preventing corneal damage [12, 14].

Goyal et al. described similar sun sensitivity in porphyrias and aminoaciduria but skin neoplasms are not seen [12, 14]. They reported skin malignancies ranging from 45 to 60 % under 20 year of age [12, 16]. Kraemer et al., reported carcinoma of the tip of the tongue upto 6 % of cases while Goyal et al. reported in 2 out of the 10 cases reported [12, 13]. Incidence of internal malignancies like intracranial, bone marrow, stomach, testis, lungs and pancreas upto 10–20 fold higher than the normal population are reported [17, 19]. Initially the skin shows slight diffuse erythema which is associated with scaling and small areas of hyperpigmentation resembling freckles seen as early as 1–2 year old, later skin atrophies with mottled pigmentation and telangiectasias mimicking chronic radio-dermatitis. Malignancies appear in adolescence proving fatal in the third decade [8, 9].

Table 1 Summary of patients with Xeroderma pigmentosa

		1	2	3	4	5	6	7	8	9	10	11
general	Age of onset	4	2	3	2	2	3	2	2	2	3	2
	Sex	M	M	M	F	F	M	F	M	F	M	F
	consanguinity	+	+	+	+	+	+	+	+	+	+	+
	Family history	no	no	no	no	no	no	no	no	no	no	no
	Stunted growth	−	−	−	−	−	−	−	−	−	−	−
skin	Photosensitivity	+	+	+	+	+	+	+	+	+	+	+
	Hyperpigmentation	+	+	+	+	+	+	+	+	+	+	+
	Scaling	+	−	−	+	+	+	−	+	+	−	+
	erythema	−	−	−	−	+	+	−	−	−	−	−
Skin cancers	SCC	+	+	+	+	+	+	+	−	+	+	+
	BCC	+	+	+	+	+	+	+	−	+	+	+
	Melanoma	+	−	−	−	−	+	−	−	−	−	−
ocular	Photophobia	+	+	+	+	+	+	+	+	+	+	+
	Excessive lacrimation	+	+	+	+	+	+	+	+	+	+	+
	Blurring of vision	−	−	+	+	−	−	+	+	−	−	+
	Corneal injection	−	−	+	−	−	−	−	+	−	−	−
	Corneal clouding	−	−	−	+	−	−	+	+	−	−	+
Ocular cancers	Lid SCC	+	−	+	+	+	−	+	−	+	−	+
	Lid BCC	+	+		+	+	−	+	−	+	+	+
	Limbal SCC	−	−	+	−	−	−	−	+	−	−	−
	Conjunctrival SCC	−	−	−	−	−	−	−	+	−	−	−
Oral	Fissuring of lips	+	−	−	−	−	−	+	−	−	−	−
	Hyperpigmentation of lips	+	−	−	−	−	−	+	−	−	−	−
	Whitening of lips	−	−	−	+	−	−	−	−	−	−	+
Neurological	Microcephaly	no	no	no	no	no	no	no	no	no	no	no
	Intelligence	N	N	N	SN	N	N	N	SN	N	N	N
	Neurological defects	no	no	no	no	no	no	no	no	no	no	no

Cutaneous cancers i.e., BCC and SCC are the commonest cancers universally, occurs in old age while in teenage XP patients [19, 20]. BCC is currently the most common cutaneous cancer in humans [19, 20]. Incidence ratio of BCC to SCC is 1.5 worldwide while males are affected 1.8 times more than females [21, 22]. Multiplicity was seen in 15 % of BCC and 4 % in SCC, while SCC lesions were larger explained by their faster growth [21, 22]. Mostafa et al., found in their group of 25 patients found 13 having BCC and 12 having SCC with no sex predilection while similar were seen in studies by Saadia Nasheen et al. in 20 patients and Kharti et al. in 24 Libyan XP patients [21, 22]. The mean age of appearance of cutaneous cancers reported were 12 year by Mostafa et al., 8 year by Kramer et al., 10 year by Kharti et al., 8 year by Saadia Nasheen et al. [21, 22] Multiple cutaneous cancers were reported in 88 % in Mostafa which is similar to other studies [21, 22]. Mostafa et al. found cutaneous malignancies concentrated in the maximally sun exposed areas of the face i.e., the forehead, nose, ocular and the malar region in 93 % and similarly by Saadia et al. (80 %) and Kramer et al.(97 %) [21, 22].

Mostafa et al., analysed statistical difference between cutaneous malignancies arising in XP and non-XP patients [23]. Significant higher incidence of BCC compared to SCC were seen in non-XP patients while no significant difference were seen between BCC and SCC in XP patients [23]. The average age of appearance of BCC was 57.9 year in non XP compared to 13.6 year in XP patients, while SCC was 53.9 year in non XP compared to 12.8 year in XP patients [23]. A male predominance was seen in nonXP patients only while multiplicity of cutaneous cancers were seen upto 89 % in XP patients while only 1 % in XP patients [23, 24]. Nasal dorum was the commonest area for BCC in non XP patients while the cheek region was the commonest in XP patients [23, 24]. Also more significant lesions were seen in the sun exposed upper limb areas [23, 24]. Studies in Hawaii and southern Australia reported more incidence of BCC in the trunk and the limbs while worldwide statistics these lesion were common in the

Fig. 1 Oculocutaneous lesions seen in 11 year old boy

nose in 26 %, cheek 16 % and the peri-orbital region in 14 % [25, 26]. SCC in non XP patients involved the lower lip and the lower limbs more while nose and the cheeks were the commonest in XP patients [25, 26]. Similar results were reported with lower lip showing 36 % SCC incidence while lower extremities showing 34 % in non XP patients [26, 27].

Fig. 2 SCC of the nose with corneal clouding seen in 8 year old girl

Fig. 3 Limbal SCC in milder variant of XP

Lesions detected early in the pre malignant stages can be treated with excision, cryosurgery or topical antimitotic agents [28]. Oral isoretinoin and topical enzyme T4 endonuclease V application have significantly reduced the onset of these oculocutaneous malignancies [29].

Conclusion

Oculo-cutaneous malignancies occur in the sun exposed areas so patients are advised regular follow up with speciality care. Awareness about the rare condition and importance of early detection and prevention of UV rays induced skin damage should be propagated. The disease is ultimately fatal, life can be prolonged by simple preventive measures to minimize sun exposure and early detection of the skin lesions and management.

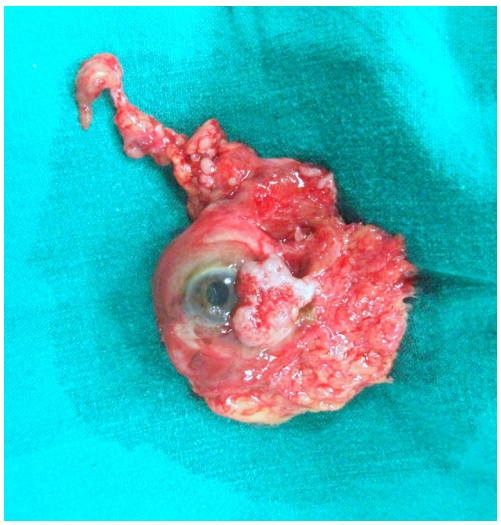

Fig. 4 Orbital exenteration done

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