Cutaneous Malignancies in Xeroderma Pigmentosum: Earlier Management Improves Survival

Sudhir M. Naik · Ashok M. Shenoy · A. Nanjundappa · Rajshekar Halkud ·
Purshottam Chavan · K. Sidappa · Sumit Gupta

Received: 31 August 2012 / Accepted: 20 December 2012 / Published online: 5 January 2013
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Abstract Xeroderma pigmentosum (XP) is a rare autosomal recessive disease, characterized by hypersensitivity of the skin to ultraviolet (UV) radiation leading to high incidence of skin cancer and progressive neurological complications. It results in premature development of neoplasias due to an exacerbated hypersensitivity to UV radiation causing premalignant and malignant lesions leading to death in early adulthood. Two cases of clinical features of xeroderma pigmentosa with skin lesions were managed in our department. One had multiple clusters of basal and squamous cell carcinomas and the other had malignant melanomas and right neck nodes. Both were treated with multiple wide excisions and the neck node were surgically managed with radical neck dissections. Skin malignancies were common in the sun exposed areas and patients were advised regular 3 months follow up. The disease is ultimately fatal, life can be prolonged by simple preventive measures to minimize sun exposure. Comprehensive multimodality management includes patient education and counselling for the psychosomatic disorder and genetic counseling remains the most important preventive measure.

Keywords Xeroderma pigmentosum ·
Nucleotide excision repair · Skin malignancies ·
UV radiation

Introduction

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease, seen in all races worldwide with equal sex incidence [1]. A failure to properly repair UV-induced DNA damage by the nucleotide excision repair (NER) mechanism is seen [1]. This is characterized by hypersensitivity of the skin to ultraviolet (UV) radiation leading to high incidence of skin cancer and progressive neurological complications [2]. It results in premature development of neoplasias due to an exacerbated hypersensitivity to UV radiation causing premalignant and malignant lesions leading to death in early adulthood [2].

Hebra and Kaposi in 1874 first described it and later in 1882, Kaposi coined the term XP [3, 4]. An estimated incidence of 1: 250,000 is seen in United states and 1:40,000 in Japan, but its incidence is not significant in India [3–6]. It is characterized by photosensitivity, pigmentary changes, premature skin aging and malignant tumour development which commonly include squamous cell carcinoma, basal cell carcinoma and rarely fibrosarcoma [1]. Malignant melanoma arises in only about 3 % of patients with XP [1]. The lesions occur chiefly in areas of skin exposed to sunlight leading to excessive solar damage at an early age [1]. Patients in the second decade have exponential increase in non-melanoma skin cancer and melanomas with the mean age being 8 years while in healthy population is 60 years [5]. The overall survival can be prolonged by minimizing sun exposure and have regular follow-up for detecting early malignancies that may occur [5]. Less than half of the patients diagnosed survive till the third decade while milder variants of the disease marginally fair well [5]. Dwarfism, mental retardation or delayed development are also seen in some variants while a prognostically better variant called XP-V are seen where a

S. M. Naik (✉) · A. M. Shenoy · A. Nanjundappa ·
R. Halkud · P. Chavan · K. Sidappa · S. Gupta
Department of Head and Neck Oncosurgery, KMIO,
Bangalore, India
e-mail: sud223@gmail.com

normal ability to repair UV-induced DNA damage is seen [5].

Here we report 2 cases one in second and third decades presenting with different cutaneous malignancies manifested with poor quality of life.

Case Report

Case 1

A 24 year old male reported with chief complaints of hyperpigmented macules all over the body as well as photo-sensitivity and swelling in the right side of the neck since 3 months. The patient was examined with skin lesions over the face which later involved the whole body. The skin pigmentation was progressive and more so after exposure to sunlight. He presented with progressive increase in the size of the lesion on the face. There was no history of consanguinity and the parents and the other siblings were normal. Complete haemogram and serum biochemistry was within normal limits. Chest radiography and ultrasonography of the abdomen were normal but neck sonography revealed lymph nodes enlargement at level II, III, IV on the right side (Figs. 1, 2).

Wide excisions of the lesions of the scalp were done along with radical neck dissections of the right side of the neck. The lesions on the scalp were positive for malignant melanoma and the nodes were positive for the same. The patient was later discharged on the fifth postoperative day. The postoperative and 10 months follow-up are uneventful with no crops of lesions arising afresh.

Case 2

A 13 year old boy came with history of multiple warty facial lesions on the face, scalp and the sun exposed part of the anterior neck. The lesions were seen on the lateral to the outer canthus, two lesions on the left nasolabial fold, two in the supraciliary region, two in the forehead, one in the dorsal nose and other in the lower left conjunctiva. Many similar smaller lesions were spread out on the face and the anterior neck and dorsal aspect of the left leg. The boy was having hyperpigmentation at the age of four, but at the age of eight he developed multiple warty lesions for which he underwent multiple excisions which turned out to be basal cell carcinoma with sebaceous differentiation. He was advised sun protection and sunscreens. At the age of ten he developed similar lesions for which he underwent excisions on the forehead and the lesion on the nose was excised and reconstructed using right nasolabial flap. Later after 7 months he developed similar lesions on the face for which similar multiple excisions were done (Figs. 2, 3, 4).

Now at the age of thirteen he has presented with similar lesions and was planned for multiple excisions. His blood parameters, liver and renal function tests, serum electrolytes, blood glucose, chest x-ray, ultrasound abdomen was normal. So under general anaesthesia multiple excisions were done and the post operative period was uneventful and discharged on the third day. The appearance improved after the surgery and the patient was advised sun protection. He had similar lesions 53 months back and had multiple excisions of the lesions of the face done in an hospital outside and was referred to our institute.

Fig. 1 Scalp lesions of malignant melanoma with neck metastasis underwent right radical neck dissection

Fig. 2 Normal chest x-rays in both cases

Fig. 3 Young boy underwent multiple excisions of the facial lesions

Discussion

Xeroderma pigmentosum is a rare pigmentary atrophic disease that begins in childhood and progresses to early development of senile changes in sun exposed skin [7]. The basic defect is a NER defect leading to defective repair of DNA damaged by UV radiation [5]. NER involves removal and the replacement of damaged DNA with new DNA. The two types of NER are global genome NER (GG-NER) and transcription coupled NER (TC-NER) [8]. These patients in the first two decades of age have more than thousand times of risk of skin cancers. [6, 9] Most commonest cancers developing are basal cell carcinoma and squamous cell carcinoma occurring in the sun exposed face, head and neck region [6]. Melanomas occur in one-fourth of these

cases and one-third of these cases occur in head and neck [6].

Half of the patients below 2 years experience acute sunburn on minimal exposure to UV radiation and tend to develop neurological abnormalities [10]. Clinical cutaneous manifestations appear below 2 years and nearly 60 % of the cases develop skin cancers with multiple primary lesions [11–13]. Skin cancers usually arise at the age of 8 nearly 50 years younger than the general population [11]. There is no difference in incidence of skin cancers in dark and light-skinned people with the disease and hence nullifying the photo protective role of melanin in these individuals [5]. Melanin provides protection against UV-induced DNA damage and is responsible for the difference in the incidence of premalignant and malignant

Fig. 4 Lesions in the sun exposed areas

skin lesions in light skinned and dark skinned people [14]. In normal individuals where NER mechanisms are intact, the levels of UV-induced molecular damage in pigment protected dark skin can be effectively repaired so that cellular transformation and malignant transformation do not occur [14].

On the converse in XP where the NER mechanisms are defective and dysfunctional, the same amount of UV penetration of the pigmented skin produces the same quantum of UV-induced molecular damage, but beyond the repair capabilities of the defective NER [14].

In light skinned individuals where greater penetration of the UV in the absence of a heavy pigment layer, can bring about molecular damage of an extent that even an intact and fully functioning NER system cannot cope and cellular transformation [14]. Three stages of the disease are defined depending on the skin lesions [1]. The first stage usually starts when the child is 1–2 years old, with slight diffuse erythema which is associated with scaling and small areas of hyper-pigmentation resembling freckles at the sun exposed areas [1]. In the second stage, atrophy of the skin, mottled pigmentation and telangiectasias appear with the skin appearance similar to chronic radio-dermatitis [1]. Third stage usually seen in adolescence with varying types of skin malignancies often leading to death [1]. Malignancies include squamous cell carcinoma, basal cell carcinoma, fibrosarcoma and rarely malignant melanoma (3 %) [1].

The occurrence of all these three malignancies together is very rare and two occurring two is uncommon [15]. These malignancies are very aggressive and spread faster and so early management is necessary to avoid metastasis and death [15]. These patients usually don't enter the fourth decade of life as the metastasis with melanoma and squamous cell carcinoma are very high [15]. These cutaneous malignancies can be prevented with UV radiation

protection and premalignant lesions treated with cryosurgery or topical antimitotic agents [16]. Early removal of these lesions done with either excision, chemosurgery or intralesional IFN- α , oral isotretinoin drastically reduce mortality of these lesions [17]. Recent studies have shown that topical application of T4 endonuclease V, significantly reduces the onset of basal cell carcinoma and actinic keratoses [15].

Primary prevention includes genetic counselling, while secondary prevention not only includes early detection and treatment but also counselling for, psychosomatic and socioeconomic problems [15]. The patients with XP should avoid exposure to UV-radiation by use of protective clothing, sunscreen and UV-blocking film [18]. Ophthalmic complications are seen in 40–80 % of cases with photophobia, conjunctivitis, keratitis leading to corneal opacification, hyperpigmentation of the eyelids, loss of eyelashes, and malignancies including squamous cell carcinoma, basal cell carcinoma and melanoma [11, 13, 14]. Apart from ocular-cutaneous malignancies, malignancies in the brain, bone marrow, stomach, testis, lungs and pancreas are also reported [19]. Neurological abnormalities may be mild to moderate including loss of fine motor control, ataxia, spasticity, rigidity, loss of hearing and progressive mental retardation seen in 20–30 % of cases [10, 20, 21]. Accumulation of endogenous genotoxic damaged DNA lead to apoptosis and neuron loss giving rise to neurological symptoms [22].

Premalignant and malignant lesions of the lips and tongue like leukoplakia, erythroplakia actinic cheilitis and squamous cell carcinoma are seen in patients with XP [4, 5, 23]. Normally the tobacco and alcohol induced squamous cell carcinomas affects posterolateral and ventral surfaces of the tongue and floor of the mouth of elderly users running an aggressive course [4, 5, 23]. But in XP patients SCC

affects the tip of the tongue of persons younger than 20 years of age and runs a slowly progressive course [4, 5, 23].

The basic pathology is in the NER leading to deficient repair of DNA damaged by UV radiation [1]. There are ten genetic complementation groups, while one group exhibits defective, post replication repair (XP variant), nine are deficient in excision repair (XP group A-I) [1]. The DNA loses its ability to repair, becoming defective and damaged leading to heritable chromosomal mutation and cell death, which possibly cause neoplastic and atrophic clinical abnormalities [24]. Seven XP repair genes, XPA -G have been identified [1]. UVB radiation also has immuno-suppressive effect which acts concurrently with defects in gene repair [3–5]. XP is a multiorgan and multi-system disease and malignant tumors usually develop around the third and fourth decade [25, 26]. Early diagnosis and immediate implementation of rigorous sun-protection measures delay the onset of skin malignancies [25, 26]. About 70 % of unmanaged subjects die before the age of 20 years but lesser than 10 years in tropical areas where sunlight exposure is high and limited access to oncological services [25, 26].

Primary prevention include avoiding exposure to sources of UV light including sunlight, fluorescent, halogen and mercury-vapour lights, and must wear protective clothing and UV-absorbing eye glasses, and must use high protection factor sunscreens [4, 5]. Cutaneous, ocular and oral lesions and disorders should be managed as in other patients [4, 5, 23]. Role of topical application of 5-fluorouracil or imiquimod in premalignant lesions are disputed [4, 5, 23]. Due to complete sun protection vitamin D supplementation to be done as deficiency can occur [5]. Challenges during anaesthesia include facial oropharyngeal changes causing difficult intubation, prolongation of neuromuscular effect, epiglottis subsidence during extubation and above all harmful effects of anesthetic drugs such as inhalation agents on NER [18, 27, 28]. Volatile inhalation anesthetics may worsen the symptoms of XP as reported that agents such as halothane deranged NER in cells [18, 27]. Total intravenous anesthesia (TIVA) is better than anesthesia with volatile agents as a method for general anesthesia for XP patients [18, 27]. They are sensitive to muscle relaxants due to the neuronal dysfunction and muscle so minimum use of muscle relaxants is recommended that too under the monitoring of neuromuscular blockade [18]. Regional anesthesia should be preferred over general anaesthesia [2]. As the patient needs frequent surgeries preanesthetic evaluation is necessary as the disease progresses limitations to daily activities also increases [2].

Only 40 % of patients survive beyond 20 years showing a poorer prognosis. Patients with milder variants of the

disease survive beyond middle age [5]. Simple preventive measures like prevention of sun exposure can prolong the life span even as the disease is ultimately fatal [1]. Early detection of any malignancies and regular follow up reduces the mortality increasing the overall survival [5]. The risk of UV exposure for these patients are present even indoors with the increased use of high intensity discharge light sources such as energy-saving fluorescent lamps which emit higher levels of UVR and blue light than do low-intensity incandescent light sources which emit light towards the yellow/red end of the spectrum [29, 30]. Prolonged exposure to high-intensity discharge light sources, in particular at short range may constitute a health risk not only to photosensitive-related skin conditions including XP and lupus erythematosus photosensitive people, but even to the general population [29, 30].

Conclusion

Skin malignancies were common in the sun exposed areas and patients were advised regular 3 months follow up. The disease is ultimately fatal, life can be prolonged by simple preventive measures to minimize sun exposure. Comprehensive multimodality management includes patient education and counselling for the psychosomatic disorder and genetic counseling remains the most important preventive measure.

References

1. Marwah N, Garg S, Chhabra S, Dayal S, Sen R (2011) Malignant melanoma in a case of xeroderma pigmentosum: Egyptian. *Dermatol Online J* 7(2):11
2. Gupta AK, Singh S, Khindria A, Ommid M, Divekar DS (2011) Anaesthetic implications in a case of indian patient of xeroderma pigmentosum: *Anesthesia Pediatrica e Neonatale* 9(1):Settembre–Ottobre 2011
3. Johnson BL, Yan AC (2009) Congenital diseases (genodermatoses). In: Elder DE, Elenitsas R, Elenitsas R, Johnson BL, Murphy GF, Xu X (eds) *Lever's histopathology of the skin*. Lippincott Williams & Wilkins, Philadelphia, p 141
4. Rao TN, Bhagyalaxmi A, Ahmed K (2009) A case of melanoma in xeroderma pigmentosum. *Indian J Pathol Microbiol* 52:524–526
5. Pradhan E, Padhye SB, Malla OK, Karki KJD (2003) Case of xeroderma pigmentosum with well differentiated squamous cell carcinoma in the eye. *Kathmandu Univ Med J* 4:278–283
6. Mohanty P, Mohanty I, Devi BP (2001) Multiple cutaneous malignancies in xeroderma pigmentosum. *Indian J Dermatol Venereol Leprol* 67:96–97
7. Kocabalkan O, Ozgur F, Erk Y, Gursu KG, gungen Y (1997) Malignant melanoma I xeroderma pigmentosum patients: report of five cases. *Eur J Surg Oncol* 23:43–47
8. Itin HP, Burgdorf WF, Happle R, Paller A, Konig A, Pierini A (2003) Genodermatoses. In: Schaner LA, Hansen RC (eds) *Pediatric dermatology*, 3rd edn. Elsevier Limited, Mosby, pp 328–332

9. Patil MR, Vishwanath V, Arya M (2007) Pilomatrixoma in a case of familial xeroderma pigmentosum. *Indian J Dermatol Venereol Leprol* 73:198–199
10. Kraemer KH, Patronas NJ, Schiffmann R (2007) Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype-phenotype relationship. *Neuroscience* 145:1388–1396
11. Rünger TM, DiGiovanna JJ, Kraemer KH (2008) Hereditary disorders of genome instability and DNA repair. In: Wolff K, Goldsmith LA, Katz SI (eds) *Fitzpatrick's dermatology in general medicine*, 7th edn. McGraw Hill Co, New York, pp 1311–1325
12. Goyal JL, Rao VA, Srinivasan R et al (1994) Oculocutaneous manifestations in xeroderma pigmentosa. *Br J Ophthalmol* 78:295–297
13. Halpern J, Hopping B, Brostoff JM (2008) Photosensitivity, corneal scarring and developmental delay: Xeroderma pigmentosum in a tropical country. *Cases J* 1:254
14. Feller L, Wood NH, Motswaledi MH, Motswaledi MH, Khammissa RAG, Meyer M, Lemmer J (2010) Xeroderma pigmentosum: a case report and review of the literature. *J Prev Med Hyg* 51:87–91
15. Grampurohit US, Rao R, Dinesh US (2011) Multiple cutaneous malignancies in a patient with xeroderma pigmentosa. *J Cancer Res Ther* 7(2):205–207
16. Alymlahi E, Dafiri R (2005) Bilateral facial squamous cell carcinoma in an 18 month old girl with xeroderma pigmentosa. *J Postgrad Med* 51:128–130
17. DiGiovanna JJ (2001) Retinoid chemoprevention in patients at high risk for skin cancer. *Med Pediatr Oncol* 36:564–567
18. Soen M, Kagawa T, Uokawa R, Suzuki T (2006) Anesthetic management of a patient with xeroderma pigmentosum. *Masui* 55(2):215–217
19. Ramachandra I, Shenoj KR, Santosh Pai U (2002) Xeroderma pigmentosa in siblings: cystosarcoma phylloides in a case of xeroderma pigmentosa. *Indian J Dermatol Venereol Leprol* 68:168–170
20. Mahindra P, DiGiovanna JJ, Tamura D et al (2008) Skin cancers, blindness, and anterior tongue mass in African brothers. *J Am Acad Dermatol* 59:881–886
21. Khan SG, Oh KS, Emmert S et al (2009) XPC initiation codon mutation in xeroderma pigmentosum in patients with and without neurological symptoms. *DNA Repair* 8:114–125
22. Niedernhofer LJ (2008) Tissue-specific accelerated aging in nucleotide excision repair deficiency. *Mech Ageing Dev* 129:408–415
23. Arora R, Sharma A, Gupta R, Vijayraghavan M (2008) Cutaneous angiosarcoma in a patient with xeroderma pigmentosum. *Indian J Pathol Microbiol* 51:504–506
24. Pathy S, Naik KK, Bhasker S (2005) Squamous cell carcinoma of face with xeroderma pigmentosa—a case report. *Indian J Med Paediatr Oncol* 26:47–49
25. Neville BW, Damm DD, Allen CM (2009) Dermatologic diseases. In: Neville BW, Damm DD, Allen CM (eds) *Oral and maxillofacial pathology*, 3rd edn. Saunders Elsevier, St. Louis, pp 747–748
26. Champion RH, Burton JL, Burns DA (1998) Rook, Wilkenson, Ebling *Textbook of Dermatology*, 6th edn. Blackwell Science Ltd, Oxford, pp 357–436
27. Hasanoglu A, Gücüyener K, Tümer L (1996) Association of xeroderma pigmentosum with thrombasthenia. *Türk J Pediatr* 38:261–264
28. Masuda Y, Imaizumi H, Okanuma M, Narimatsu E, Asai Y, Namiki A (2002) Anesthesia for a patient with xeroderma pigmentosum. *Masui* 51(2):169–171
29. Zhu Y, Yang H, Chen Q et al (2008) Modulation of DNA damage/DNA repair capacity by XPC polymorphisms. *DNA Repair* 7:141–148
30. Gupta B, Anegundi R, Marya CM (2007) Xeroderma pigmentosa; Review and case report. *J Oral Health Community Dent* 1:43–45