ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 08, pp.72686-72690, August, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

REVIEW ARTICLE

XERODERMA PIGMENTOSUM: A RARE GENODERMATOSIS

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ARTICLE INFO

Article History:
Received 29th May, 2018
Received in revised form
11th June, 2018
Accepted 27th July, 2018
Published online 30th August, 2018

Key Words:
Genodermatoses,
Xeroderma Pigmentosum,
Oral Manifestations.

ABSTRACT

Genodermatoses are an inherited skin disorder often grouped into three categories: chromosomal, single gene, and polygenetic. Several of these disorders are isolated and also have an oral phenomenon, called Oral Genodermatoses. Between this Xeroderma pigmentosum is a rare genodermatosis as well as rare autosomal recessive disease in which excessive ultraviolet radiation causes skin, ocular, neurological, and oral lesions along with the development of cutaneous and internal malignancies at an early age. There is no definitive cure for the disease. Avoidance of ultraviolet radiation, use of protective clothing, sunscreens, oral retinoid, and 5-fluorouracil and regular consultations with dermatologists, ophthalmologists, neurologists and dentists forms an important part of the treatment protocol. This paper aims to throw light on the etiopathogenesis, clinical features and treatment modalities of this life-threatening disease. There is also a special mention of the oral manifestations and dental health considerations of the rare disorder.

Citation: ***Supriya Sharma, Shaleen Chandra, Shalini Gupta and Surya Kant.*** **2018.** "Xeroderma pigmentosum: a rare genodermatosis", *International Journal of Current Research*, 10, (08), 72686-72690.

INTRODUCTION

There are various dermatologic disorders that have an inherited etiology or a genetic predisposition. Such genetically resolved skin disorders are subtitle as "Genodermatoses" (gene: genetic + dermatoses: skin lesions) (Rimoin et al., 1996). Genodermatosis ascribe to inborn genetic skin disorder contemporary with multisystem entanglement (Babu et al., 2015). A Genodermatoses can be entitled as "a cutaneous phenotype precipitate by a single mutation, which may be a chromosomal aberration, point mutation, or deletion (Kumar et al., 1996). " Numerous of these disorders is isolated and also has an oral phenomenon, called oral Genodermatoses. The amelodentinal (the enamel and dentine) fundamental of the teeth and epidermis of the skin are derived from a general embryologic neural source of the ectoderm.

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As a consequence, there survive many primary cutaneous diseases which find their indication in the mouth influencing the oral mucosa and dentition (Kumar et al., 2016). Therefore, it is of greatest importance for a dental surgeon to identify that not only a few dermatoses exhibit associated lesions of the oral mucous membranes but also demonstrations of some diseases may be preceded by oral lesions.

Classification of Genodermatoses (Sofaer, 1981; Bergendal et al., 1998; Aswegan et al., 1997)

Autosomal Dominant Disorder

- White sponge Nevus
- Pachyonychia congenita
- Hereditary Benign Intraepithelial Dyskeratosis
- Darier's disease
- Peutz-Jeghers syndrome
- Ehlers-Danlos syndrome
- Xeroderma pigmentosum

- Neurofibromatosis
- Tuberous sclerosis
- Ichthyosis Vulgaris
- Darier's disease
- Ehlers-Danlos syndrome
- Hailey-Hailey disease
- Peutz-Jeghers syndrome
- Hereditary hemorrhagic telangiectasia

Autosomal recessive disorders

- Lamellar ichthyosis
- Dystrophic Epidermolysis bullosa
- Pseudoxanthoma elasticum (PXE)

X-Linked Disorders

- Ectodermal dysplasia
- Fabry's disease
- Incontinent pigmenti

X-linked dominant disorders

- Incontinentia pigmenti
- Focal dermal hypoplasia
- Incontinentia pigmenti

X-linked recessive disorders

- Dyskeratosis congenita

Disorders with malignant potential and keratinization

- Basal cell nevus syndrome
- Palmoplantar keratodermas
- Ichthyosiform dermatoses

Xeroderma pigmentosum: Xeroderma Pigmentosum is a rare genodermatosis with autosomal recessive inheritance that result due to an inadequacy in normal repair of DNA of different cell types injured by exposure to ultraviolet radiation and is distinguished by the development of pigment abnormalities and multiple skin cancers in body areas exposed to the sun (Jain et al., 2018).

Epidemiology: The disease prevalence of XP varies geographically with 1 in 1,000,000 affected in the United States, 2.3 in 1,000,000 affected in Western Europe, and 45 in 1,000,000 affected in Japan (Goddard et al., 2018).

Etiology: It is an autosomal recessive disorganization with 100% penetrance and can consequences from mutations in any one of eight genes. The consequences of seven of these genes (XP-A along G) are included in the repair of ultraviolet-induced photoproducts in DNA by the procedure of nucleotide excision repair (NER) (Goddard et al., 2018).

Pathogenesis: Many XP patients with tumors show mutations in the p53 gene, indicating that p53 mutations are characteristic of UV exposure. Exposure to UV radiation contributes to DNA alterations between adjacent pyrimidine nucleotides including cyclobutane-pyrimidine dimers (CPDs) and 6-4 photoproducts (6-4PPs). Under normal circumstances, CPDs and 6-4 PPs are mechanism involving over 30 proteins. The roles of the seven proteins incriminated in the pathogenesis of XP subtypes related with the NER pathway are as follows. XPE and XPC recognize damaged DNA, triggering global genome repair. Then, a protein complex incorporating XPB and XPD mediates unwinding of the DNA helix. XPA activity allows endonucleases XPF and XPG to cleave the damaged DNA segment. Finally, DNA polymerase replaces the segment with complementary nucleotides sealed by DNA Ligase. The final XP subtype is due to a mutation in DNA polymerase η, a DNA polymerase that performs DNA replication involving a damaged template in a process known as translation synthesis. The accumulation of CBDs and 6-4 PPs has significant consequences ranging from the obstruction of DNA replication and transcription to mutations transmitted to all cellular lineage (Goddard et al., 2018). The resultant clinical manifestations are discussed below.

Clinical manifestations: During the first few years of life, patients affected by XP show a markedly increased tendency to sunburn. In sun-exposed regions, Lentigines (freckle-like pigmentation) are noticed in remaining 40% XP patients as early as two years of age. These pigmented areas are observed on the nose, zygoma, and forehead and followed by the sides of the neck, sparing the area under the chin (Figure 1and2).

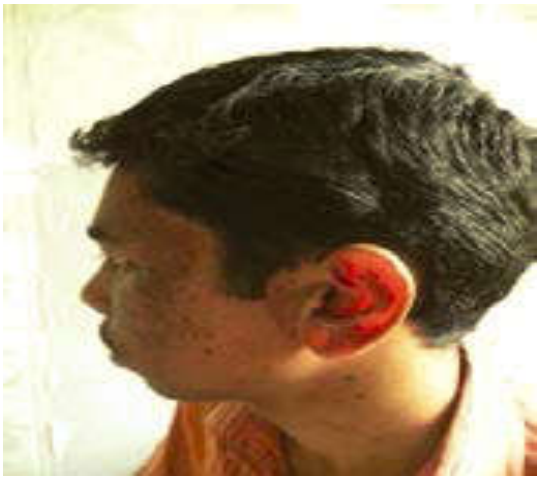

Fig.1. Shows Hyper pigmented macules disperse with patchy hypo pigmentation over ear

Figure 2. Shows Hyper pigmented macules disperse with patchy hypo pigmentation over eyes & forehead

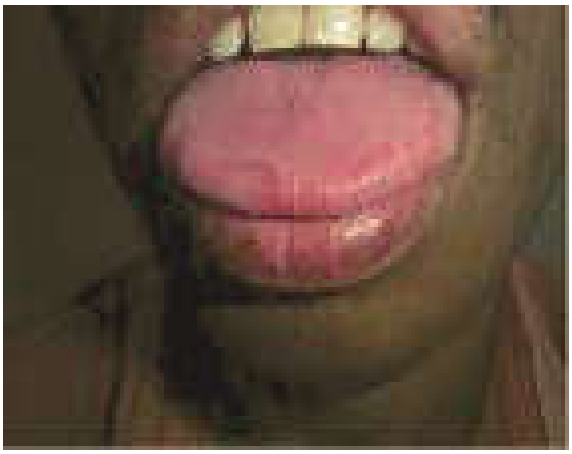

Fig.3. Shows Depapillated areas with whitish circinate borders, suggestive of geographic tongue

In early childhood, actinic keratosis begin developing, a process that normally does not take place before 40 years of age. These lesions quickly progress to squamous cell carcinoma, with basal cell carcinoma also appearing; consequently, in most patients, a nonmelanoma skin cancer develops during the first decade of life. Melanoma develops in about 5% of patients with XP, but it evolves at a slightly later time. As a consequence of sun exposure, the head and neck region is the site most frequently affected by these cutaneous malignancies. Ocular complications influencing the UV-exposed structures of the anterior eye are apparent in nearly 40% of patients with XP. Patients often illustrate keratosis and photophobia that contributes to neovascularization, opacification of cornea and malignancy with repeated UV insult. Neurologic exhibitions involve subnormal intelligence in 80% of patients with XP (Goncalves-Maia, 2017; Kraemer, 2016; Lehmann et al., 2015; Hasan, 2015; Kraemer et al., 1987).

Drugs and chemicals (Hasan, 2015): A number of DNA-damaging agents apart from UV radiation have been implicated to cause a hypersensitive response to XP cell (Table 1).

Drugs	Carcinogens
1.Psoralens plus long wavelength UV radiation (PUVA)	1. Plant toxin-Aflatoxin
2. Chlorpromazine	2. Alkylating agents-benzo (a) pyrene
3. Nitrofurantoin	3. Nitroquinilone oxide derivatives
4. Mitomycin C	4. Acetaminofluorene derivatives
5. Anthramycin	5. Phenanthrene derivatives

Oral manifestations: Few common oral manifestations related with XP are Erythroplakia, Actinic cheilitis Leukoplakia, Squamous cell carcinoma (SCC) of the tip of the tongue and lips. The precancerous and cancerous lesions of the tip of the tongue are sites that are seldom affected in the normal population and are likely to be induced by UV radiation. SCC of the tip of the tongue in XP patients usually occurs in individuals younger than 20 years of age and progresses slowly. Actinic cheilitis is a potentially malignant lesion that influences the lower lip of white patients who are frequently exposed to the sun. Several labial plasty results in areas of fibrosis. Stretching of these fibrosed areas causes pain when the patients open the mouth for eating, speaking, breathing, and oral hygiene procedures.

These patients usually have poor oral hygiene habits and a high rate of dental plaque, caries, and periodontal disease. Cases of fissured tongue, geographic tongue, chronic desquamative gingivitis and keratoacanthoma have also been reported (Figure 3) (Hasan, 2015).

Histologic features: The Histopathologic features of XP are comparatively nonspecific, in that the cutaneous premalignant lesions and malignancies that occur are microscopically indistinct from those noticed in unaffected patients (Neville et al., 2002).

Classification: The milieu of clinical manifestations a patient with XP will experience relies on the patient's XP subtype, which is differentiated by the protein implicated in disease pathogenesis. Subtype XPA, for instance, is associated with mutations in the NER protein XPA, while subtype XPB is associated with mutations in the NER protein XPB. The variant subtype, XPV, is an exception to this common rule and is caused by a mutation in the error-prone DNA polymerase η (Goddard et al., 2018).

Table 1. Generalized findings associated with each xp subtypes are provided

XP Subtype	UnitedStates Prevalence	Cutaneous Manifestation Severity	Mean Age of BCC	Neurologic Regression Severity
XPA	9%	Severe	9.7	Mild to Severe
XPB	1%	Moderate	-	None to Severe
XPC	43%	Moderate	14.0	Absent
XPD	28%	Moderate	38.0	None to Severe
XPE	3%	Mild	38.3	Absent
XPF	0%	Mild	43.7	None or Severe
XPG	3%	Moderate	32.0	None or Severe
XPV	7%	Mild	41.5	Absent

Diagnosis: XP is usually made when the patient is evaluated for the cutaneous lesions because it is highly unusual for a very young person to have skin cancer. Because XP is an autosomal recessive trait, a family history of the disorder is not likely to be present, but the possibility of a consanguineous relationship of the affected child's parents should be investigated. The initial clinical diagnosis can be made on the basis of either the extreme sensitivity to UV in those individuals who show this feature or in the appearance of lentiginosis on the face at an unusually early age.

The diagnosis can be confirmed absolutely by employing robust cellular tests for inadequate DNA repair that are available in various countries. The most commonly used test is the measurement of unscheduled DNA synthesis in cultured skin fibroblasts (Limsirichaikul et al., 2009). More recently, next-generation sequencing has simplified the diagnosis of XP. The sequence of DNA composing the eight causative XP proteins can be constructed from saliva samples or blood samples and compared to a human reference genome to detect mutations. This process can be performed rapidly, eliminates the necessity of skin biopsies, and has been readily employed to diagnose XP (Goddard et al., 2018).

Differential diagnosis: Acanthosis Nigricans, Basal cell nevus syndrome, Bloom Syndrome (Congenital Telangiectatic

Hartnup Disease, Erythropoietic protoporphyria, Dyschromatosis symmetrica hereditaria, Hydroa Vacciniforme, LEOPARD Syndrome, Lupus Erythematosus, Acute, Porphyria, Rothmund-Thomson Syndrome, Werner Syndrome (Goddard et al., 2018; Lehmann et al., 2011).

Treatment of cutaneous manifestations: Treatment of XP is challenging because in most instances significant sun damage has already occurred by the time of diagnosis. Patients are advised to avoid sunlight and unfiltered fluorescent light and to wear appropriate protective clothing and sunscreens if they cannot avoid sun exposure. A dermatologist should evaluate the patient every 3 months to monitor the development of cutaneous lesions. Rigorous sun-protection is likely to result in vitamin D deficiency, so vitamin D supplements should be prescribed.

Intercession in patients with XP to manage precancerous or cancerous lesions are analogous to those for the universal population. Freezing with liquid nitrogen is an alternative to manage actinic keratosis (AKs), while curettage or surgical excisions and electrodesiccation are viable treatment methods for cutaneous malignancies. Anesthetic agents known to damage DNA including halothane should be avoided. Patients with XP are known to exhibit prolonged awakening from anesthesia (Goddard et al., 2018). Topical chemotherapeutic agents may be used to treat actinic keratoses. Surgical excision in patients with XP requires special consideration. Cryosurgery has also been implemented to treat facial Basal cell carcinoma (BCCs) in patients with XP. Nonmelanoma skin cancers should be excised conservatively, preferably with microscopically controlled excision to preserve as much normal tissue as possible. Patients should also receive genetic counseling because a high number of consanguineous marriages have been reported in some series (Jain et al., 2018).

Pharmacologic treatment of cutaneous manifestations: 5-fluorouracil (5-fu) and imiquimod are pharmacologic medications proven to manage precancerous and cancerous lesions in patients with XP. 5-fu is a thymidylate synthase inhibitor whose activity results in death of cell through apoptosis and is proven to manage AKs and superficial carcinomas.

Treatment of extracutaneous manifestations: The neurological complications associated with 20-30% of XP cases are poorly understood and presently cannot be prevented. Patients with XP should receive orderly audiometry investigations as well as gait and deep-tendon reflex evaluations to screen for neurologic involvement. Management of complications involves hearing aids in response to sensor neural hearing loss, speech therapy in response to dysarthria, physical therapy in response to ataxia, and occupational therapy in response to dysphagia. Additionally, special care should be taken in patients with XP to avoid carcinogen exposure. Patients are especially exposed to compounds generally eliminated by the NER pathway such as benzo[a]pyrene in cigarette smoke, photo activated psoralens, Aflatoxins and cis-platinum. Patients with XP who smoke cigarettes have been shown to develop early-onset lung cancers. A case report also demonstrates severe adverse events including multi-organ failure occurring in two patients with XP exposed to cisplatin. This set of adverse events should be explored due to the implications for chemotherapy (Goddard et al., 2018).

Dental considerations: Important dental health considerations in XP patients include:

Use of a uv light meter: The patient may be exposed to a variety of light sources in the dental office, including overhead lights, view boxes, dental lamps, fiber optic lights, computer screens and dental curing units. If the UV light meter shows a reading above 0 nm/cm2 for UV light, the use of that unit should be contraindicated. Although light-emitting diode curing lights emit a wavelength of only 450 nm, the degree of biological damage resulting from such exposure is not sufficiently understood. Restorative materials such as glass ionomers offer a good substitute to resin sealants and composite restorations for treating XP patients. Curing light filters may become inefficient or worn out as time progress, and permit transmission of wavelengths in the UVB range (290-320 nm), which are known to have considerable carcinogenic reaction on normal epithelium. A regular clinical examination is usually a must for timely detection of premalignant or malignant lesions.

Additionally, the establishment of protocols for prevention and topical fluoride application, along with the use of chlorhexidine digluconate 0.12%, focus at the homeostasis of the oral environment. Mouthwashes with high alcohol concentration are usually avoided as it is associated with an increased risk of oral cancer development in these patients Regular dental procedures, such as restoration, dental extraction and rehabilitation pose a challenge to the dentist due to difficulty in accessing the oral cavity. Periodic oral examinations are important and usually include complete inspection and palpation of soft tissues (lips, tongue and oral mucosa). Radiation therapy is used to treat the head and neck tumors and is known to cause radiation-induced caries and permanent damage to salivary glands. Meticulous oral hygiene procedures such as proper brushing, flossing and fluoride rinses are usually advised for XP patients, as these patients do not maintain routine dental appointments (Hasan et al., 2015).

Prognosis: Prognosis for patients except neurological deformities, who are diagnosed early and accomplish stringent protection measures as indicated above, the prognosis, is favorable. They can expect a comparatively normal lifespan but will require maintaining their protection throughout their lives. The neurological abnormalities are progressive, leading to progressive disabilities, which will vary in severity between patients and are likely to result in a shortened lifespan (Lehmann et al., 2011).

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