xeroderma pigmentosum: the star’s sons. case report and review of the literature.

**XERODERMA PIGMENTOSO: I FIGLI DELLE STELLE. CASO CLINICO E REVISIONE DELLA LETTERATURA.**

Miraglia E¹, Curatolo P¹, Rotunno R¹, Visconti B¹, Persechino F¹, Calvieri S¹, Giustini S¹

¹ Department of Internal Medicine and Medical Specialties, "Sapienza" University of Rome, Italy


**Key words:** Xeroderma Pigmentosum, photosensitivity, De Sanctis-Cacchione Syndrome

**Parole chiave:** Xeroderma Pigmentosum, fotosensibilità, Sindrome di De Sanctis-Cacchione

**Abstract**

Xeroderma pigmentosum (XP) is a rare condition inherited as an autosomal recessive trait and it is characterized by photosensitivity, pigmented changes, premature skin ageing and malignant tumors development resulting from the defect in DNA repair.

The skin cancers, that include squamous and basal cell carcinomas and melanomas, are predominantly caused by exposure to ultraviolet B (UVB) radiation, although UVA cannot be excluded. The mean age of onset of the neoplasms is 8 years of age in XP patients, in contrast of 60 years of age in the general population.

In addition to cutaneous findings, patients often have ocular abnormalities including ectropion, corneal opacities, neoplasms and neurologic abnormalities as ataxia, loss of reflexes, sensorineural hearing loss, dysphagia, and decreasing cognition.

The maximal form of neurological involvement has been defined the De Sanctis-Cacchione Syndrome that is characterized by retarded growth, spasticity and serious intelligence debility. Segmental demyelinisation, microcephaly, inner ear deafness and epilepsy may also be additional neurological signs of xeroderma pigmentosum patients.
XP was described in Vienna by a Hungarian professor of dermatology Moriz Kaposi in 1870 and in 1874 it was first called "xeroderma or parchment skin" while in 1882, the term "pigmentosum" was added to emphasize the striking pigmentary abnormality. Estimated incidences vary from 1 in 20,000 in Japan to 1 in 250,000 in the USA. It affects males and females equally and it is frequently symptomatic in childhood.

Xeroderma pigmentosum must be distinguished from other so-called DNA-Repair Deficiency Syndromes as the Cockayne Syndrome (CS) and trichothiodystrophy (TTD) and other rare disease characterized by pigmentation changes as Erythropoietic Protoporphyria, LEOPARD syndrome, Carney complex and Peutz-Jeghers syndrome. The prognosis of patients with XP includes a high morbidity and early mortality. Although there is no cure for XP, the skin effects can be minimized by rigorous protection from sunlight and early removal of pre-cancerous lesions. Oral 13-cis retinoic acid has shown to reduce the incidence of epithelial new cancers in XP patients because of retinoids modulate keratinocyte differentiation.

We present the case of a 30-year-old man who was diagnosed with XP at age 9. The first skin lesions had appeared five years, and over time had increased. Other clinical signs included photophobia and loss of eyelashes. Eye examination revealed bilateral corneal opacities and conjunctival chemosis.

We underline the importance of a multidisciplinary approach for the management of patients with XP to prevent the serious complications that this disease can determine.

Abstract

Lo Xeroderma Pigmentoso (XP) è una rara patologia ereditaria a trasmissione autosomica recessiva dovuta a un deficit di riparazione del DNA, caratterizzata da fotosensibilità, alterazioni della pigmentazione cutanea, invecchiamento precoce della cute e insorgenza di tumori cutanei maligni. Questi tumori, che includono carcinomi squamocellulari, carcinomi basocellulari e melanomi, sono prevalentemente causati da esposizione ai raggi ultravioletti B (UVB), anche se gli UVA non possono essere esclusi. L'età media di insorgenza delle neoplasie è di 8 anni di età, a differenza della popolazione generale dove è di 60 anni. Oltre alle alterazioni cutanee, i pazienti presentano spesso anomalie oculare quali ectropion ed opacità corneali ed alterazioni neurologiche, come atassia, iporeflexia, ipoacusia neurosensoriale, disfagia ed alterazioni cognitive. La forma massima di coinvolgimento neurologico è stata definita come sindrome di De Sanctis-Cacchione che è caratterizzata da ritardo di crescita, spasticità e seri deficit cognitivi. Demielinizzazione segmentale, microcefalia, sordità ed epilessia possono essere altri segni neurologici presenti in questi pazienti.

Lo Xeroderma Pigmentoso è stato descritto per la prima volta nel 1870 a Vienna da Moriz Kaposi, un professore ungherese di dermatologia e nel 1874 è stato chiamato per la prima volta"Xeroderma o pelle a pergamena", mentre nel 1882, il termine"pigmentosum" è stato aggiunto per sottolineare la sorprendente anomalia della pigmentazione. L'incidenza stimata varia da 1 su 20000 in Giappone a 1 su 250000 negli Stati Uniti. Questa malattia interessa maschi e femmine con la stessa frequenza, e risulta essere spesso sintomatica nella prima infanzia.

Lo Xeroderma pigmentoso deve essere distinto da altre sindromi caratterizzate da deficit di riparazione del DNA come la sindrome di Cockayne (CS) e la tricotiodistrofia (TTD) e da altre malattie rare caratterizzate da alterazioni della pigmentazione come la Protoporfiria eritropoietica, la sindrome di LEOPARD, il complesso di Carney e la sindrome di Peutz-Jeghers. La prognosi dei pazienti con XP è caratterizzata da un'alta morbilità e da una mortalità precoce. Sebbene non vi sia alcuna terapia per lo XP, le gravi alterazioni della cute possono essere limitedate da una protezione solare rigorsa e dalla rimozione precoce di lesioni precancerose. L'acido retinoico 13-cis ha dimostrato di ridurre l'incidenza di tumori epiteliali in pazienti con XP grazie alla sua azione sulla modulazione della differenziazione dei keratinociti. Presentiamo il caso di una ragazza di 30 anni a cui è stata fatta diagnosi di XP all'età di 9 anni. Le prime lesioni cutanee erano comparse all'età di cinque anni ed erano aumentate nel corso degli anni. Altri segni clinici erano rappresentati da fotofobia e da perdita delle ciglia. Esame degli occhi rivelava opacità corneali bilaterali e chemosi congiuntivali.
Sottolineiamo l’importanza di un approccio multidisciplinare per la gestione dei pazienti con XP per prevenire le gravi complicanze che questa malattia può determinare.

Background
Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by clinical and cellular sensitivity to ultraviolet (UV) radiation, pigmentary changes, premature skin ageing and neoplasm development (1). It is the archetype of an expanding family of nucleotide-excision repair (NER) diseases that includes XP itself, the XP variant (XP-V), Cockayne syndrome (CS), cerebro-oculofacial skeletal syndrome (COFS), a mild ultraviolet (UV)-light-sensitive syndrome, trichothiodystrophy (TTD) and some diseases with combined symptoms of XP/CS and XP/TTD (2,3). XP was described in Vienna by a Hungarian professor of dermatology Moriz Kaposi in 1870 (4) and in 1874 it was first called “xeroderma or parchment skin” while in 1882, the term “pigmentosum” was added to emphasize the striking pigmentary abnormality (5). Estimated incidences vary from 1 in 20,000 in Japan to 1 in 250,000 in the USA, and approximately 2.3 per million live births in Western Europe. It affects males and females equally and it is frequently symptomatic in childhood (6).

Genetic defects in XP are heterogeneous, resulting from defects in 8 different genes. Seven of the complementation groups (XP complementation groups A through G) are deficient in nucleotide excision repair, and one group (XP variant) has defective post-replication repair.

The incidence of the complementation groups varies geographically. In general, the most frequent complementation group is A, followed by XP-V and XP-C. All three account for about 90% of cases (7).

We report the case of a 30-year-old man with Xeroderma pigmentosum.

Case report
We present the case of a 30-year-old man who was diagnosed with XP at age 9. He presented with multiple brownish to blackish macules and papules on the face and upper limbs (fig. 1).

Fig. 1 - Multiple brownish macules of the face
This abnormal pigmentation initially appeared at 5 years of age and became more severe over time; moreover the patient referred a worse clinical during prolonged exposure to sunlight.

Other clinical signs included photophobia, keratitis and loss of eyelashes.

Eye examination revealed bilateral corneal opacities and conjunctival chemosis; fundus examination was normal. Routine blood, urine, and stool examination were within normal limits.

He had 2 normal siblings, and there was no family history or other past medical history of note. The mother denied any consanguinity in the patient's recent lineage.

Thereafter, he underwent regular dermatology examinations and various skin biopsies. Pathologic evaluation led to the diagnosis of various cutaneous malignancies including 8 basal cell carcinomas, 1 cutaneous melanomas, 2 squamous cell carcinomas, and one melanoacanthoma (fig. 2).

Fig. 2 - Melanoacanthoma at 10 years of age

Annual neurological and ophthalmological examinations were performed and no abnormalities were identified. Currently, the patient performs a dermatological examination every 3 months while an ophthalmology examination and a neurological is carried out every year.

Discussion and Conclusions

Xeroderma pigmentosum is characterized clinically by erythema with scaling and diffuse hyperpigmentation or freckle-like lesions, especially in sun-exposed areas and usually onsets very early in life. Approximately half of XP patients present severe acute sunburn reactions after short sun exposure. Freckling of sun-exposed areas of the skin in children less than 2 years of age is unusual and it is indicated as a diagnostic marker for XP.

Continued sun exposure of skin causes the appearance of poikiloderma, hypo- and hyper-pigmentation, atrophy and telangiectasia (1).

Clinically XP can be classified into 3 subgroups that include: 1) mild form with light brown freckles on the face alone; 2) moderate form with dark brown freckles with burning on the face, neck, ears, chest, hands, photophobia but without other associated skin and ocular changes and 3) severe form with extensive, dark brown freckles all over the body with cutaneous changes such as ulcers, keratoconjunctivitis, ectropion and skin malignancies.

The lesions have a high risk of progression to cancers; the most frequent skin tumors in XP patients are basal cell carcinoma, squamous cell carcinoma and lentigo maligna melanoma. Keratoacanthomas and sarcomas (fibrosarcomas and angiosarcomas) have also been described.8
The mean age of onset of the neoplasms is 8 years of age in XP patients, in contrast of 60 years of age in the general population. The frequency of non-melanoma skin cancer is increased 10,000-fold and melanoma is increased 2,000-fold in XP patients under age 20 years compared to the general US population. 2/3 of xeroderma pigmentosum patients die before reaching adulthood because of tumoral progression (9, 10, 11).

About 20-30% of patients with XP develop severe progressive neurologic deterioration characterized by ataxia, loss of reflexes, sensorineural hearing loss, dysphagia and decreased cognition (12).

The maximal form of neurological involvement has been defined the De Sanctis-Cacchione Syndrome. These children are characterized by retarded growth, spasticity and serious intelligence debility. Segmental demyelination, microcephaly, inner ear deafness and epilepsy may also be additional neurological signs of xeroderma pigmentosum patients (13). The incidence for central nervous system tumours (CNS) is also ten times higher than in the normal population. Astrocytomas, medulloblastomas, glioblastomas and malignant schwannoma are among the CNS tumors (12).

About 40 % of xeroderma pigmentosum patients present same ophthalmological symptoms. Usually the light-exposed lids and the anterior sections of the eye are affected. Conjunctival inflammation, blepharitis, keratoconjunctivitis, ectropion, symblepharon, vascular pterygia, fibrovascular pannus formation and corneal ulcerations are some of the clinical findings which have been described in xeroderma pigmentosum with severe visus decline (14).

The incidence for tumors of the oral mucosa and internal organs is also elevated; more frequent occurrence of leukaemia is also characteristic of xeroderma pigmentosum patients.

The initial clinical diagnosis can be made on the basis of either the extreme sensitivity to UV or in the early appearance of lentiginosis on the face. The diagnosis can be confirmed definitively by employing robust cellular tests for defective DNA repair available in many countries (15).

Xeroderma pigmentosum must be distinguished from other so-called DNA-Repair Deficiency Syndromes as the Cockayne Syndrome (CS) and trichothiodystrophy (TTD)² and other rare disease characterized by pigmentation changes as Erythropoietic Protoporphyria, (16) LEOPARD syndrome, (17) Carney complex (18) and Peutz-Jeghers syndrome (19).

Cockayne Syndrome is characterized by neurological symptoms (ataxia, mental retardation, inner-ear deafness), distinct facies (large, deepset eyes, prominent nose), progressive weight loss (cachexia), myopathy, microcephalus, dwarfism, calcifications of the basal ganglia, retinal pigment degeneration optic nerve atrophy and cataracts.

Trichothiodystrophy is characterized by limited intelligence, reduced fertility and by short and brittle hair due to sulphur deficient hairs (deficit of cystein-rich proteins in keratines).

Erythropoietic Protoporphyrina is easily screened through the finding of normal porphyrins and not every exposed skin site is affected in polymorphic light eruption.

The pigmented lesions of Carney complex and LEOPARD syndrome are not related to sun exposure and in Peutz-Jeghers syndrome the cutaneous pigmentation are perioral and acral.

A family history should also exclude these autosomal dominant lentiginoses.

In limited number of cases, however, diagnosis can be less clear because of pigmentation changes not appearing until adolescence. Solar urticaria can be excluded by the fact that the rash resolves within an hour of going indoors.

The prognosis of patients with XP includes a high morbidity and early mortality. Usually, two-thirds of XP patients die before reaching 30–40 years of age because of metastases, generally related to multiple SCCs with lymphatic and visceral expansion and less frequently, malignant melanoma (2).

Early diagnosis has an important role in the management of disease that includes avoidance of sunlight, minimizing UV and cigarette smoke exposure, early excision of skin lesions and genetic counseling.

Oral 13-cis retinoic acid has shown to reduce the incidence of epithelial new cancers in XP patients because of retinoids modulate keratinocyte differentiation (20).

Ophthalmic management includes UV-absorbing sunglasses with side shields, artificial tears, intermittent topical steroids, surveillance for ocular neoplasms, and management of complications. Eyelid and conjunctival cancers are the most commonly reported.

We underline the importance of a multidisciplinary approach for the management of patients with XP to prevent the serious complications that this disease can determine. Increased awareness and crucially early diagnosis, followed by rigorous protection from daylight and careful patient management, can dramatically improve the quality of life and life expectancy of affected individuals.
References

Corresponding Author: Emanuele Miraglia
Department of Internal Medicine and Medical Specialties, “Sapienza” University of Rome, Italy
e-mail: info@preventionandresearch.com

Autore di riferimento: Emanuele Miraglia
Dipartimento di Medicina Interna e Specialità Mediche, “Sapienza” Università di Roma
e-mail: info@preventionandresearch.com