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Ophthalmic Manifestations and Histopathology of Xeroderma Pigmentosum: Two Clinicopathological Cases and a Review of the Literature

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Abstract

Xeroderma pigmentosum is a rare, autosomal recessive disease caused by a defect in DNA repair. Patients with xeroderma pigmentosum often have cutaneous and ocular sun sensitivity, freckle-like skin pigmentation, multiple skin and eye cancers, and, in some patients, progressive neurodegeneration. Xeroderma pigmentosum predominantly affects the UV exposed ocular surface, resulting in eyelid atrophy and cancers, corneal dryness, exposure keratopathy, and conjunctival tumors. We report the clinical history and ocular pathology of two Caucasian women who had xeroderma pigmentosum with neurological degeneration: Case 1, who died at age 44 and Case 2, who died at age 45. Case 1 with mutations in the *XPA* gene, had more than 180 basal cell carcinomas of her skin and eyelids and died from complications of neurodegeneration. Case 2, with mutations in the *XPD* gene, was sun protected and had 3 skin cancers. She died from complications of neurodegeneration and pneumonia. Both patients had bilateral pinguecula, corneal pannus and exposure keratopathy. Case 1 had bilateral optic atrophy, while Case 2 had bilateral peripheral retinal pigmentary degeneration. Both patients developed retinal gliosis. The ophthalmic manifestations and pathology of xeroderma pigmentosum are discussed and reviewed with respect to this report and other cases in the literature. These cases illustrate the role of DNA repair in protection of the eyes from UV damage and neurodegeneration of the retina.

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Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Keywords

ciliary body hamartoma; ocular pathology; optic atrophy xeroderma pigmentosum; pigmentary retinal degeneration

Introduction

Xeroderma pigmentosum (XP), first described by Hebra and Kaposi in 1874 presents in early childhood with photophobia, photosensitivity, cutaneous pigmentary changes, and a predisposition for malignancy in sun-exposed mucocutaneous areas and ocular structures.[36] XP patients have a defect in DNA repair related to the nucleotide excision repair pathway[15,17,20,75] or a bypass polymerase pathway.[9] Mutations in *XPA* or *XPC* are present in approximately 50% of patients.[55] The disease is extremely rare in North America and Europe (frequency 1/1,000,000),[47] but is more common in areas of the world with increased consanguinity, including Japan (frequency 1/22,000),[38] the Middle East, North Africa, and India.[47,66]

XP often presents with cutaneous manifestations within the first two years of life.[73] Patients are predisposed to malignant skin neoplasms in the face, neck and upper trunk, the tip of the tongue, and the anterior eye surfaces. Ocular disease is evident in at least 40% of XP patients and often causes visual impairment.[49] Clinically apparent ocular disease includes eyelid atrophy and tumors, corneal sicca and opacification, exposure keratitis, pterygium, and chronic conjunctival injection.[24,31] Here, we report the pathology of autopsied eyes from two XP patients, in which we found classic findings of this disease and retinal degeneration.

Case Reports

CASE 1 (XP12BE)

Clinical History—This 44 year-old Caucasian woman with a mutation in the *XPA* DNA repair gene[75,76] was followed at the NIH Clinical Center since age 4 years. From 1976 to 1992, she had 166 histologically documented basal cell carcinomas, most of which were on her face (cheeks, lips, nose, eyelids, eyebrows, and canthus). She had no squamous cell carcinomas or melanomas (Fig. 1A). During treatment with oral 13-cis-retinoic acid, from 1984 to 1986 the frequency of new basal cell carcinomas was dramatically reduced, but increased after treatment was discontinued. Treatment was resumed in 1987 and continued to 2000. Over time, the frequency of new cancers decreased and, from 1993 to her death in 2009, she had only 17 additional basal cell carcinomas.[50] She had progressive neurological degeneration beginning as absent deep tendon reflexes and progressing to loss of hearing, inability to walk, and eventually difficulty swallowing, necessitating G-tube placement (Fig. 1B). She had global cerebral atrophy on imaging. In July, 2009, she became progressively unresponsive and expired when supportive measures were withdrawn; autopsy was performed at the NIH.

Ocular History—At age 4, the patient had a normal eye exam except for slight elevations of the nasal conjunctiva. At age 17, her visual acuity was 20/20 in both eyes with a myopic correction, and she had an early nasal corneal pannus in the right eye and two biopsy-proven eyelid basal cell carcinomas. She had reactive pupils, full ductions, and normal pattern reversal visual evoked responses. At age 19, there were no further lid tumors, but bilateral pinpoint cortical opacities; mild, unilateral, peripheral corneal scarring; an early, unilateral pterygium and unilateral segmental iris atrophy had developed. She had 8 basal cell carcinomas removed by age 27 from her lower eyelids, bilateral inner canthi, and eyebrows.

At age 41, she complained of extreme photophobia and had scarring of the eyelids, retraction of both lower eyelids, and a 4–6 mm lagophthalmos bilaterally without lash loss (Fig. 1B). Both eyes exhibited conjunctival injection, exposure keratopathy and pannus formation threatening the visual axis, with a score of 9.0 on the Oxford scale[8], indicating corneal surface irregularity. She had an intermittent left exotropia. Pupils were 4 mm and minimally to nonreactive to light. Dilated fundus examination revealed mild optic disk pallor in both eyes and otherwise normal fundi. Soon after instillaltion of 1% tropicamide, she became less responsive and required medical attention. She returned to baseline within an hour, and her mental status change was attributed to an adverse reaction to the dilating drops. Three months later, the corneal pannus was stable, and meibomitis was observed bilaterally. The patient expired 2 years after her last eye examination. In summary, the XP-associated clinical ocular findings in case 1 were chronic conjunctival injection, pterygia, basal cell carcinomas of the eyelids and canthi, corneal pannus, exposure keratopathy, minimally reactive pupils, and optic nerve pallor.

Pathological Findings—Macroscopically, inferior corneal neovascularization and scarring were visible (Fig. 2A). Microscopically, the central corneal epithelium was irregularly thin with early keratinization and small focal bullous separations between the basal corneal epithelial cells and Bowman's layer, consistent with bullous keratopathy. The limbal epithelium had mild focal parakeratosis and flattening. A layer of fibrovascular tissue interrupted the peripheral corneal epithelium and an irregular Bowman's layer (Fig. 3). Neovascularization and inflammatory cellular infiltration (CD68+ (macrophages) cells > CD3+ (T lymphocytes) cells) were found superficially and in the stroma of the peripheral cornea and limbus. Focal thickening of Descemet's membrane, corneal guttata, prominence of Schwalbe's ring, and corneal endothelial cell loss were also noted. Corneal findings were similar in both eyes. The anterior chamber angle, iris, lens, and sclera were unremarkable.

The ciliary body had mild hyalinization in both eyes. In the right eye, a cluster of pigmented epithelial cells was arranged in multiple layers in the temporal ciliary body (Fig. 4A and 4B). This lesion had a positive Fontana-Masson stain for melanin, a positive keratin stain (indicating epithelial keratin filaments) (Fig. 4C), and a negative S100 stain (A positive S100 would suggest melanoma.). This staining pattern is consistent with a ciliary pigmented epithelial hamartoma. A small retinal tuft composed of retinal and glial tissues was found in the peripheral retina of the left eye. There were scattered macrophages (CD68+) in the retina. In both eyes, the optic nerves had moderate to marked axonal loss with vacuolization and thickened septae, indicative of mild to moderate optic nerve atrophy (Fig. 5A). Moderate thickening of the optic artery vessel wall, indicative of optic artery sclerosis, was present in the right eye. The macula shows strong positive glial fibrillary acidic protein (GFAP) immunoreactivity indicating retinal gliosis and mild edematous change with separation of Henle's fibers in the outer plexiform layer in the right eye (Fig. 6). In summary, ophthalmic pathology due to UV damage included corneal neovascularization, chronic keratitis, and pannus. Ocular lesions secondary to neurodegeneration include optic nerve atrophy, retinal degeneration, and possibly mild macular edema.

CASE 2 (XP18BE)

Clinical History—Case 2 was a 45-year-old Caucasian woman with mutations in the *XPD* gene (Fig. 1C). She was diagnosed with developmental delay by age 7 and started special needs classes. The NIH Clinical Center began following her intermittently since age 12. By this time, she had photosensitivity with blistering, 3 skin tumors, and resection of several benign skin lesions. In contrast to Case 1, she had extensive early sun protection and did not have many skin cancers during her life; however, her neurologic deficits were significant. At age 31, neurologic examination revealed hearing loss, areflexia, and ataxia with a broad-

based gait. She was wheelchair-bound by age 36. At age 40, she complained of decreased vision with diplopia. In April 2010, respiratory arrest in the context of multiple organ failure led to her death.

Ocular History—During her adolescence, the patient had a normal ophthalmic exam except for mild myopia for which she did not regularly wear glasses. At age 35, she developed exotropia, which progressed over the next 5 years. She complained of diplopia and severe photophobia, and on occasion would reach for things in the wrong places. At age 40, her vision was 20/200 OD and 20/60 OS. She a comitant exotropia at distance and near with full ductions and no gross pupillary abnormalities. Slit-lamp examination showed healthy anterior segments, lids, and conjunctiva. The corneas did not stain with fluorescein, and the tear films appeared normal. Dilated fundus exam was normal. Five years elapsed between her last eye examination and her death.

Pathological Findings—Macroscopic examination revealed an inferior opacity, scar, and neovascularization 1.0 mm from the margin of the cornea, measuring 10.5 mm × 10 mm in both eyes (Fig. 2B). In the peripheral fundus, patchy, clumped, pigmentary spicules were deposited in both eyes (Fig. 7). Otherwise, the anterior and posterior segments were grossly unremarkable. Microscopic examination of the cornea revealed thinning of the corneal epithelium, epithelial bullae and basement membrane abnormalities, absence of Bowman's layer, and a superficial scar in both eyes inferiorly. Mild neovascularization and inflammatory cell infiltration was present in the superficial stroma of the peripheral cornea.

The iris had a mild lymphocytic infiltration. In the temporal mid-peripheral retina near the equator, several small retinal cysts spanned the ganglion cell layer to the inner nuclear layer, indicative of cystoid degeneration (Fig. 8A). Small focal chorioretinal adhesions with and without small drusen were present in both eyes. Mild focal lymphocytic infiltration was seen in choroid (Fig. 8B). RPE (retinal pigment epithelium) alterations with pigmentary degeneration and pigment clumps were noted in several areas in both peripheral retinas (Fig. 8B and 8C). The choroidal vessels were congested. The optic nerve had some corpora amylacea in both eyes, but no signs of optic atrophy (Fig. 5B). In the left eye, there was a small subconjunctival hemorrhage with mild conjunctival inflammatory cell infiltration and mild amorphous basophilic elastoid degeneration. Mild cataracts were also found in both eyes. In summary, ophthalmic pathology related to UV damage included conjunctival pinguecula, corneal scar, inflammation and neovascularization. Ophthalmic pathology related to neurodegeneration was peripheral retinal pigmentary degeneration. A comparison of the clinical and pathologic feature of Case 1 and 2 is presented in Table 1.

Literature Review and Discussion

SYSTEMIC FEATURES AND GENETICS OF XP

XP is an autosomal recessive disease of defective DNA repair that affects males and females equally and is frequently symptomatic in childhood.[15,24,49] Defects in nucleotide excision repair can lead to three diseases: XP, Cockayne syndrome, and trichothiodystrophy. XP and Cockayne syndrome both present with photosensitivity and progressive neurological degeneration.[67] XP has a greatly increased risk of sun-induced cancers, and Cockayne patients have normal cancer risk. Retinitis pigmentosa retinopathy is well recognized in Cockayne syndrome, while retinal abnormalities are not common in XP patients.[70] Cockayne syndrome patients may have poor vision with pupillary unresponsiveness, hypermetropia, nystagmus, hypoplastic irides, cataract, vitreous floaters, optic atrophy, and global progressive pigmentary retinal degeneration.[20,70] While Cockayne syndrome also presents with photosensitivity and neurologic dysfunction, patients tend to have a "bird-like" face, microcephaly, premature aging, dwarfism, cachexia, sunken eyes, and usually die

before age 30.[10,54] Though the genetic defects are closely related, these diseases have a different systemic and ocular manifestations.[20]

Genetic defects in XP are heterogeneous, resulting from defects in 8 different genes (complementation groups).[9,15,18,49] 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.[56] The prevalence of the complementation groups differs across the world, and complementation groups A, C, D, and variant are the most common in the United States and Europe.[49] Patients with differing complementation groups have varied abilities to repair UV exposure- induced DNA damage, but overlapping clinical phenotypes.[1] The two cases we presented have defects in different complementation groups, and case 1 XP12BE (group A) had many more cancers and a different ocular phenotype than case 2 XP18BE (group D).

Defects in nucleotide excision repair lead to premature sunlight-induced damage including hyperpigmentation, hypopigmentation, lentigos, telangectasias, actinic keratoses, and atrophy.[48,49,52,53,75] Cutaneous symptoms usually present before 2 years of age, and the median age of first skin neoplasm is under 10 years.[36,49] 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.[7,49,51,75]

Progressive neurologic symptoms are present in about 25% of affected patients.[49,55,76] XP complementation groups A, B, D, and G develop more central and peripheral nervous system abnormalities.[32] Neurologic abnormalities include cognitive impairment, acquired microcephaly, abnormal motor activity, areflexia, sensorineural hearing loss, and abnormal speech.[41,49,55,76] Studies suggest that neuronal degeneration in XP is a primary process, possibly caused by the inability to repair DNA that has been damaged by oxidative damage from endogenous metabolites.[77]

The majority of neoplasms in patients with XP occur in areas that are exposed to UV-radiation, including skin, anterior surfaces of the eye, and tip of the tongue.[13,39,45,49,60] There is an increased frequency of central nervous system tumors.[48,51] Internal neoplasms may be related to environmental carcinogen exposure that causes DNA damage, which, like UV-damage, is poorly repaired in XP patients.[48] Overall, XP patients have a 70% probability of survival to 40 years of age, which is 28 years less than expected in the United States.[49]

CLINICAL OCULAR MANIFESTATIONS OF XP

Ocular disease is evident in at least 40% of XP patients, and blepharospasm and photophobia are common symptoms.[24,49,78] Eyelid skin changes reflect local skin changes, including usually erythema, pigmentation, atrophy, and malignant change.[25,33,73] Telangectasias, loss of lashes, and chronic blepharitis are also seen.[23,25,45] Atrophic scarred skin may cause ectropion of the lower eyelid and symblepharon.[24,31,73] Lower lid loss may result in exposure keratitis, edema, and even corneal ulceration and perforation.[6,88] Corneal opacification, neovascularization, pterygia, and band keratopathy are common, and band-shaped nodular dystrophy and squamous cell carcinomas have also been reported.[24,26,28,29,30,34,41,43,44,49,92] Conjunctival involvement usually includes conjunctivitis, pinguecula, symblepharon, melanosis, and tumors developing from the interpalpebral zone of the limbus.[3,14,21,23,25,37,39,43,45,62,69,79,86,93] Limbal tumors, especially pterygia, are common, and squamous cell carcinomas, malignant melanomas and limbal stem cell deficiency have been reported.[24,27,31,44,64,86,87] The iris can be affected by iritis, stromal atrophy, pigment abnormalities, and, rarely, melanoma.[40,41] Orbital tumors include basal cell carcinomas, squamous cell carcinomas, and melanomas.[5,12,24,62,74,92] As

the posterior segment is protected from UV damage by the cornea and lens, fundus abnormalities are not common; however, choroidal melanoma rarely develops.[46,93,94] Unlike Cockayne syndrome, which is clinically associated with pigmentary retinal degeneration including retinitis pigmentosa, retinal abnormalities have not previously been reported in XP patients. Subclinical,histopathological retinal changes were found in these two patients (Table 1). Common clinical ocular manifestations of XP are summarized in Fig. 9.

Clinical management of XP includes avoidance of sunlight, minimizing UV and cigarette smoke exposure, early excision of skin lesions, and genetic counseling.[55] Oral 13-cis retinoic acid has been shown to reduce the incidence of new cancers in XP patients.[50] Ophthalmic management includes UV-absorbing sunglasses with side shields, artificial tears, intermittent topical steroids, surveillance for ocular neoplasms, and management of complications.[11] A summary of the reported ocular malignancies in XP patients and current management is presented (Table 2). Eyelid and conjunctival cancers are the most commonly reported (Fig. 10). Current management of eyelid tumors is complete resection using Mohs' micrographic surgery, with or without reconstruction, or other tissue sparing techniques.[16,90] Malignant conjunctival tumors that can be excised should be removed and treated with adjuvant cryotherapy/irradiation/topical chemotherapy.[42,63,80,81,82,85] Some malignant limbal tumors can be removed by iridocyclectomy, while others may require enucleation.[81] Corneal tumors have been managed with keratoplasty and topical chemotherapy.[68] Iris tumors may be managed with local excision, plaque radiotherapy, or enucleation.[83] Choroidal melanomas are commonly managed with plaque radiotherapy, but this has not been specifically studied in XP patients.[84] If a tumor involves the orbit, imaging is required, and surgical excision with adjunctive radiation can be therapeutic.[58] Despite their extreme sensitivity to UV light, XP patients can be treated with standard doses of radiation for treatment of neoplasms.[19] Large or invasive ocular or orbital tumors may require enucleation and/or orbital exenteration.

OPHTHALMIC PATHOLOGY OF XP

In case 1, the patient had chronic conjunctival injection with an irregular surface that grew onto the corneal pannus, bilateral early nasal pterygia, and conjunctival melanosis. In case 2, there was a small subconjunctival hemorrhage, mild inflammation, and pingueculae. Conjunctival pathology in XP patients includes telangiectasia, xerosis, chronic congestion, pigmentation, and pingueculea.[78] Keratoacanthoma of the conjunctiva[14] and malignant melanoma of the conjunctiva have also been reported.[3,21,62] In XP patients, conjunctival cells have also been shown to have defective repair of DNA damage.[65]

In both cases, corneal pathology included exposure keratopathy, bullous keratopathy, pannus formation, keratitis, neovascularization and scar. Corneal pathology, occurring in 17–40% of XP cases, includes dryness, exposure keratitis, hazyness, band-like nodular keratopathy, scarring, ulceration, occasional perforation, and corneal opacity with vascularization.[78,91] Squamous cell carcinoma of the cornea, though rare, has been reported.[24,30,92] Corneal neovascularization is often present, and keratoplasty has variable success in XP.[6,29] In an animal model of XP, corneal neovascularization has been shown to be caused by DNA damage from chronic UV radiation-induced pyrimidine dimer formation.[4]

In case 1, basal cell carcinomas of bilateral eyelids, canthi, and eyebrows were resected, leading to ectropion and lagophthalmos. Only three skin tumors not involving the lids were observed in case 2. Eyelid pathology, reported in 16% of XP cases, is similar that of the skin.[49,78] Atrophic, scarred and retracted eyelids, coupled with a DNA damage repair defect, predispose XP patients to UV-damage and associated ocular surface tumors, both benign

(pinguecula and pterygia) and malignant (squamous cell carcinomas, basal cell carcinomas, and melanomas).

In the right ciliary body of case 1, a glandular pattern of ciliary pigmented epithelial cells (keratin+, melanin+, S100−) clustered and formed a hamartoma (Fig. 4). Ciliary body hamartomas are reported in patients with tuberous sclerosis complex, and choroidal melanomas are reported in XP.[22,93,94] This benign ciliary pigment epithelial hamartoma, which may be incidental, has not been previously reported in an XP patient. In contrast, ocular melanomas, present in 1% of XP patients, and cutaneous malignant melanomas, present in 36% of 106 XP patients seen at the NIH,[7] are more widely reported.[49,89]

As in other XP patients with defects in *XPA* and *XPD*, our two patients had severe, progressive neurologic disease.[66,76] Case 1 had global cerebral atrophy, minimally to non-reactive pupils, and optic disk pallor. Optic atrophy with loss of neuronal elements, vacuolization in the nerve bundles, and thickening of septae were visible histologically, as was mild ophthalmic artery sclerosis. These findings were not seen in case 2, who also had significant neurologic disease. Optic atrophy was previously described neuropathologically in a XP/Cockayne syndrome patient with severe neurologic degeneration.[59] While clinical findings of systemic neurologic impairment have been widely documented, optic atrophy has not been reported pathologically in XP patients.[20,49,71,76] In case 1, the optic atrophy may be related to the relatively advanced age (44) of the patient with a neurodegenerative disease, primary neurodegeneration, or secondary descending neurodegeneration. For unclear reasons, the patient with the *XPA* mutation had optic atrophy, while the patient with the *XPD* mutation did not. The neuropathophysiology of XP is still being elucidated, and increased oxidative stress is one possible mechanism for progressive neurodegeneration.[35,61,72]

The retinal findings in our cases are new associations for XP. Mild macular edema, seen in case 1 with prominent gliosis and loss of retinal neuronal cells, was previously reported as a secondary finding in an XP patient with a iris melanoma.[40] Case 1 had no other known causes for macular edema,[2] and it is also possible that the mild macular edema was post-mortem artifact. Case 2 had XP with peripheral pigmentary retinal degeneration, focal chorioretinal adhesions, cystoid degeneration of the retina near the equator, and retinal gliosis. The significance of the chorioretinal adhesions is unclear, and cystoid degeneration of the retina is an innocuous common finding in autopsy eyes.[67] The pigment deposition seen in inner retinal layers of the peripheral retina, however, was in a pattern similar to that found in Cockayne syndrome.[57] Investigation of the neurodegenerative process in this disease is warranted and hopefully will lead to the development of neuroprotective strategies for XP patients. Both UV protection and neuroprotection may become important in management.

Methods of Literature Search

The literature selection for this review included a Medline database search from 1965 to June 2010 of publications in the English language. Searches were conducted with the headings *xeroderma pigmentosum, ocular pathology, ocular tumor, melanoma, carcinoma, eyelid, ciliary body, cornea, iris, conjunctiva*, and *treatment*. Articles populated under ‘Related citations’ from these articles were reviewed. Additional articles and textbooks were selected from the bibliographies of the references.

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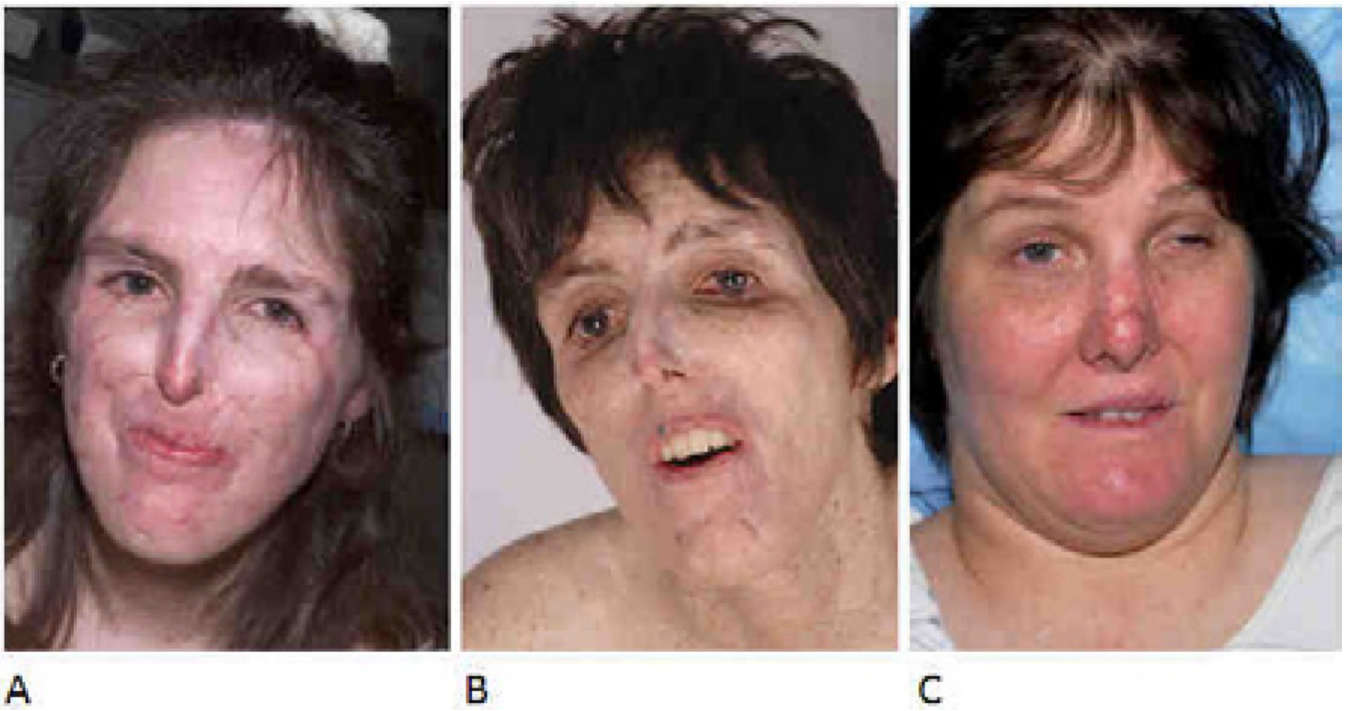

Fig. 1.

Clinical images. A and B) Case 1, patient XP12BE, disease progression. A) At age 35 yrs, her face is thin with loss of subcutaneous tissue and scars from more than 100 surgical procedures for removal of skin cancers. Her eyes show mild conjunctival injection bilaterally. Her lips have cheilitis. B) At age 41 yrs, she had progressive loss of subcutaneous tissue with deep set eyes. Scarring of the eyelids, retraction of both lower eyelids, and a 4–6 mm lagophthalmos was present bilaterally without lash loss. C) Case 2, patient XP18BE, at age 40 yrs. Her face shows diffuse erythema and a surgical scar on her nose. There is mild conjunctival injection and ptosis of the left eyelid. Her lips have cheilitis. [The patients and their families provided permission to use these images.]

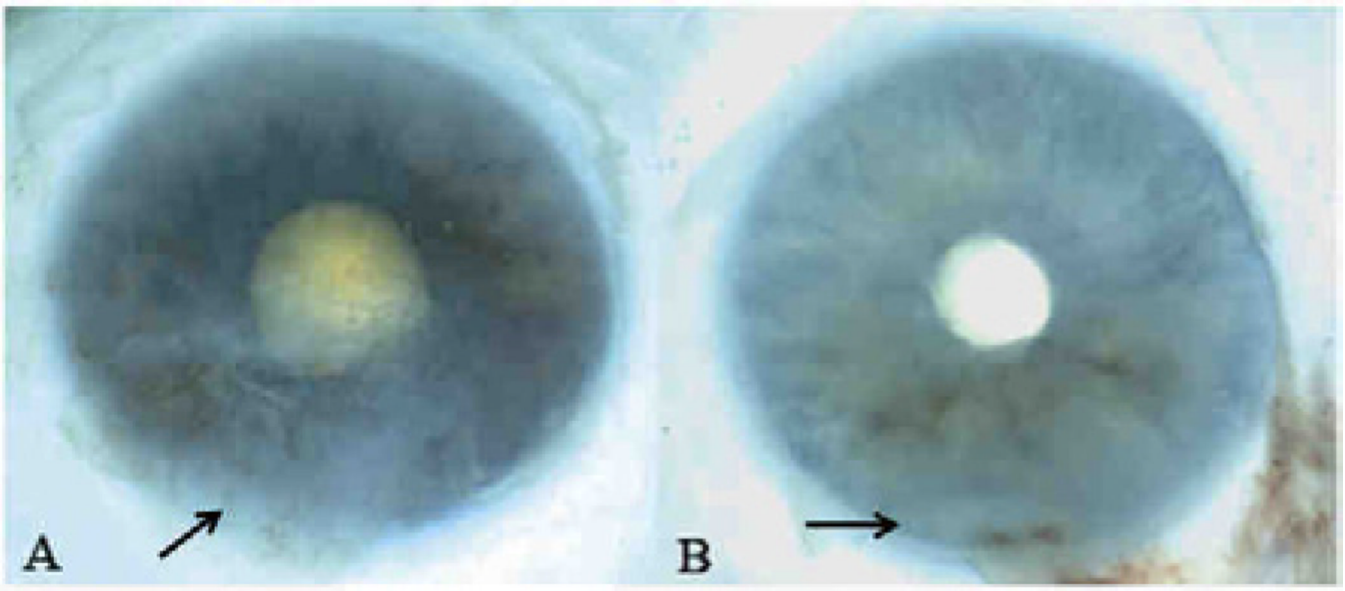

Fig. 2.

Macroscopic images of autopsy eyes of the XP patients. Both images show an inferior opacity (arrows), scar and neovascularization with pannus formation in the cornea that begins 2.0 mm from the center of cornea and measures 10.5 × 10.0mm. A) Case 1, XP12BE, right eye; B) Case 2, XP18BE, left eye

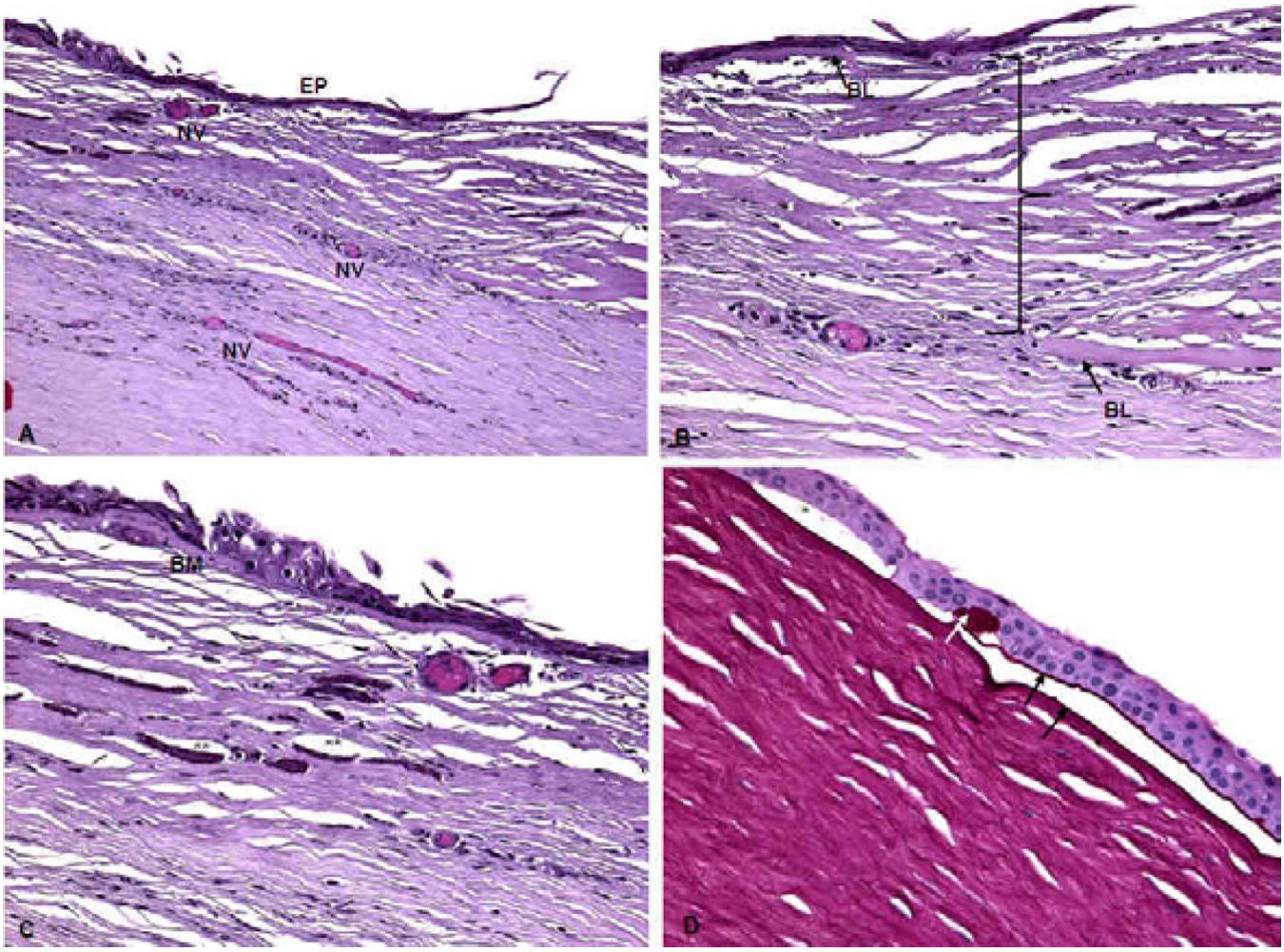

Fig. 3.

Microscopic images of the right cornea of Case 1, XP12BE. A) The central corneal epithelium (EP) is irregularly thin. There is early keratinization. Corneal neovascularization is present in the anterior stroma (NV). B) There is fibrovascular scar tissue between the peripheral corneal epithelium and Bowman's layer extending into the mid corneal stroma (bracket). There is a break in Bowman's layer (BL, two arrows). C) The epithelial basement membrane (BM) shows focal irregularities (*), is thickened and thinned in different locations, and has multiple layers. Calcifications (**) are noted. D) Bullous keratopathy is seen with focal small separations (*) between the basal corneal epithelial cells and Bowman's layer, where a small amount of serous material is visible. Reduplication of the basement membrane (black arrows) and clumping of the basement membrane (white arrow) are evident. (A–C: Hematoxylin & Eosin, D: Periodic acid-Schiff; original magnifications, A ×100, B–D × 200)

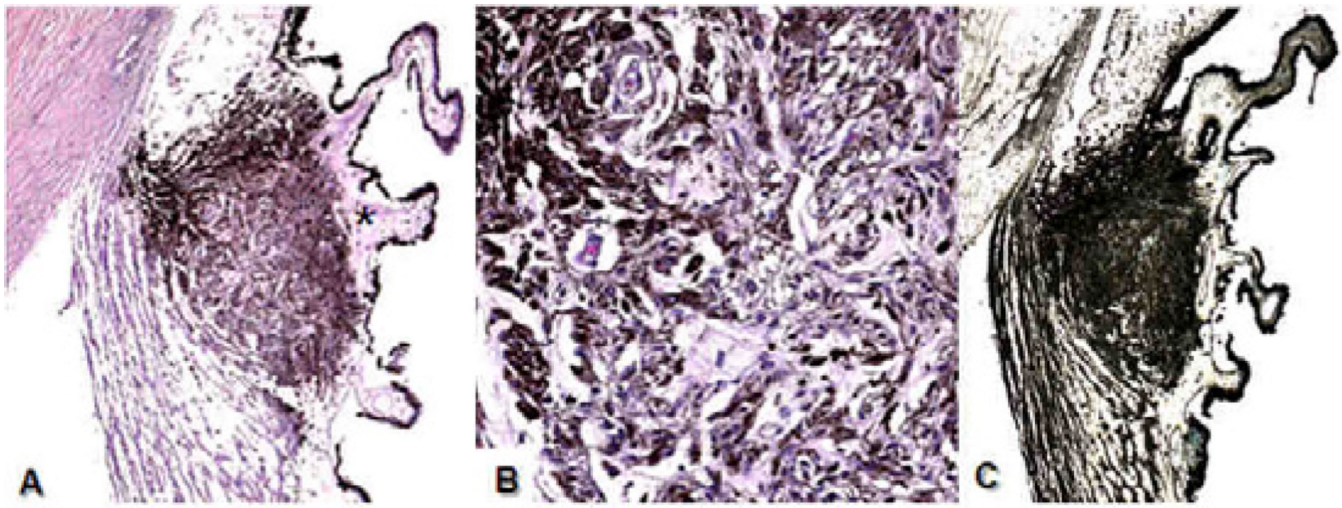

Fig. 4.

Microscopic image of the right ciliary body, Case 1, XP12BE. A) There is one cluster of pigmented granular cells in the temporal side of the ciliary body (arrow). Mild hyalinization (*) is also evident. B) The well-differentiated pigment epithelial cells are arranged in a linear glandular pattern. C) The hamartoma shows positive immunoreactivity against keratin (A and B: Hematoxylin & Eosin, C: avidin-biotin-complex immunochemistry with anti-keratin antibody; original magnifications, A and C: × 50, B × 200)

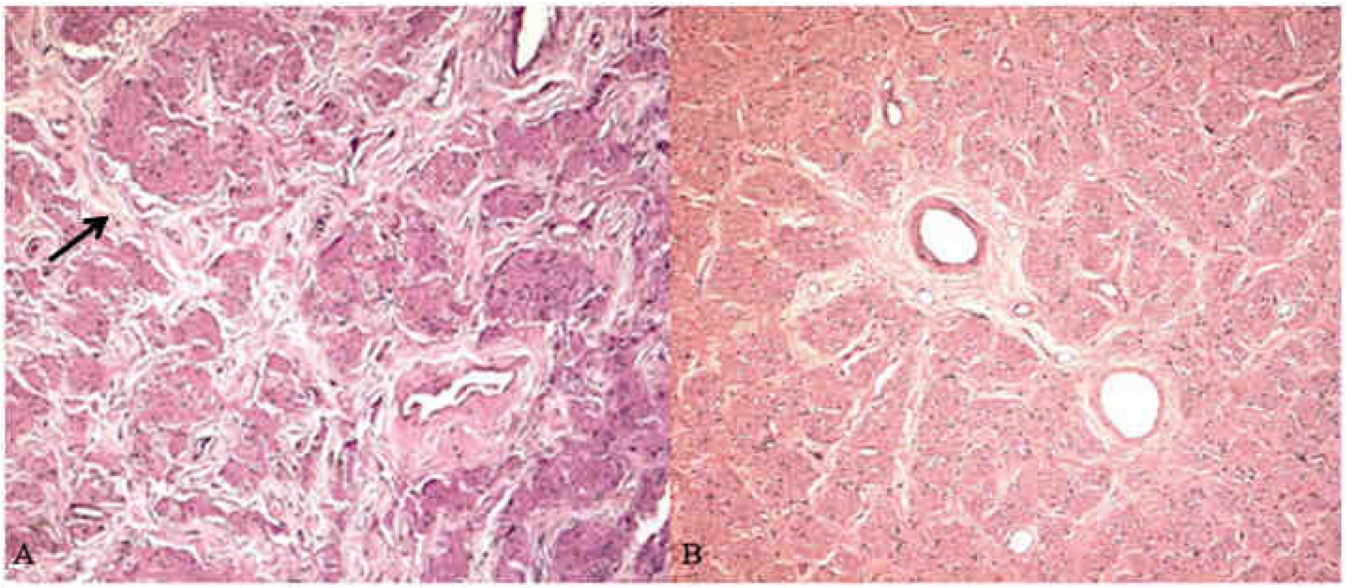

Fig. 5.

Microscopic images of the optic nerve A) Case 1, XP12BE. Mild-moderate optic atrophy with thickened septae (arrow), loss of neuronal elements, and vacuolization in the nerve bundles; B) Case 2 XP18BE. Normal optic nerve (A–B: Hematoxylin & Eosin, original magnifications × 100)

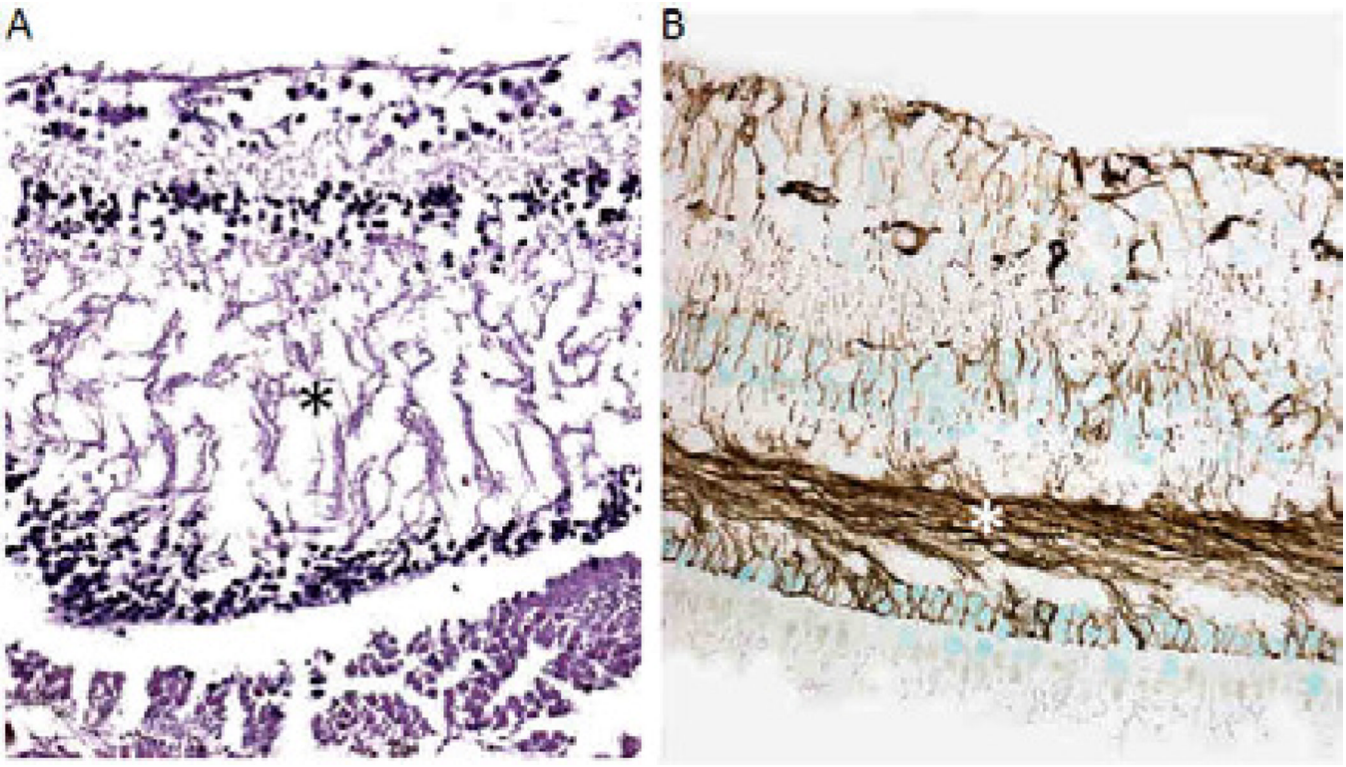

Fig. 6.

Microscopic images of the retina. A) Case 1, XP12BE. There is a loss of retinal neuronal cells and mild macular edema, visible by separation of Henle's fibers (*) in the outerplexiform layer. B) Case 2, XP18BE. GFAP is strong positive in the retina, particularly the Henle's fibers (*) (A: Hematoxylin & Eosin, B: avidin biotine peroxidase with GFAP as the primary antibody; original magnifications × 200)

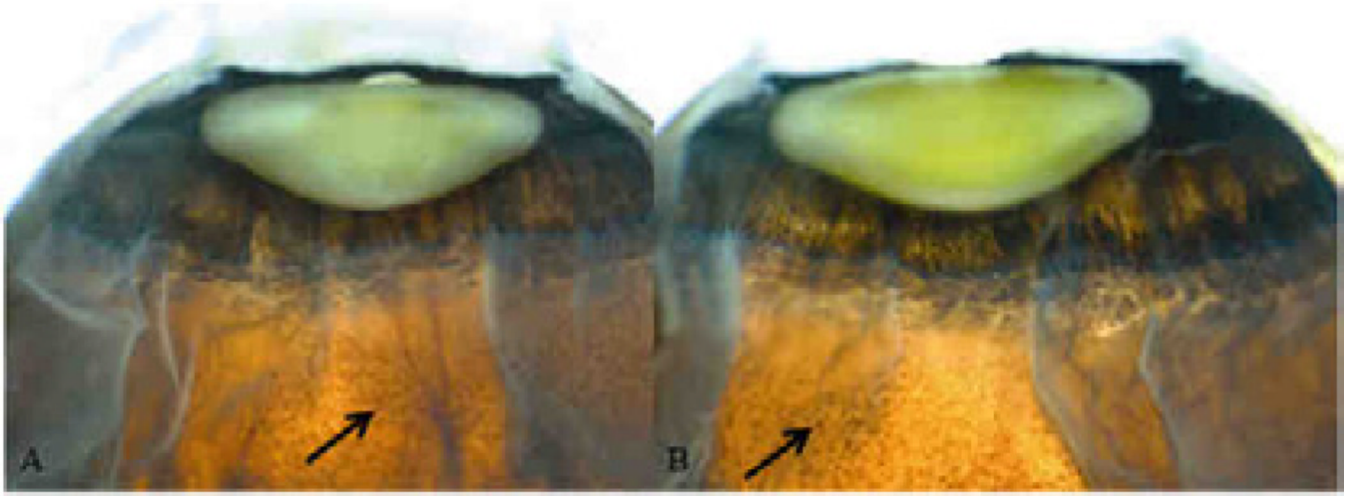

Fig. 7.
Macroscopic images of the retina, Case 2 XP18BE. Patchy pigmentary retinal degeneration (arrows) is visible in A) the right eye and B) the left eye

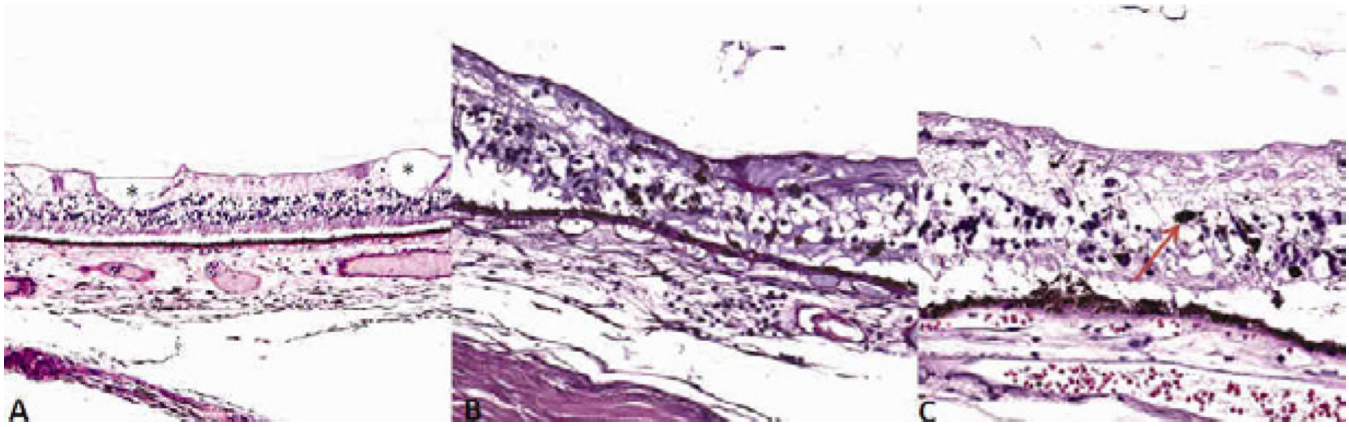

Fig. 8.

Microscopic images of the retina, Case 2 XP18BE. A) Typical peripheral cystoid degeneration of the retina (*). B–C) pigment migration to the inner retina (arrow) (Hematoxylin & Eosin, original magnifications, A × 100, B–C: × 200)

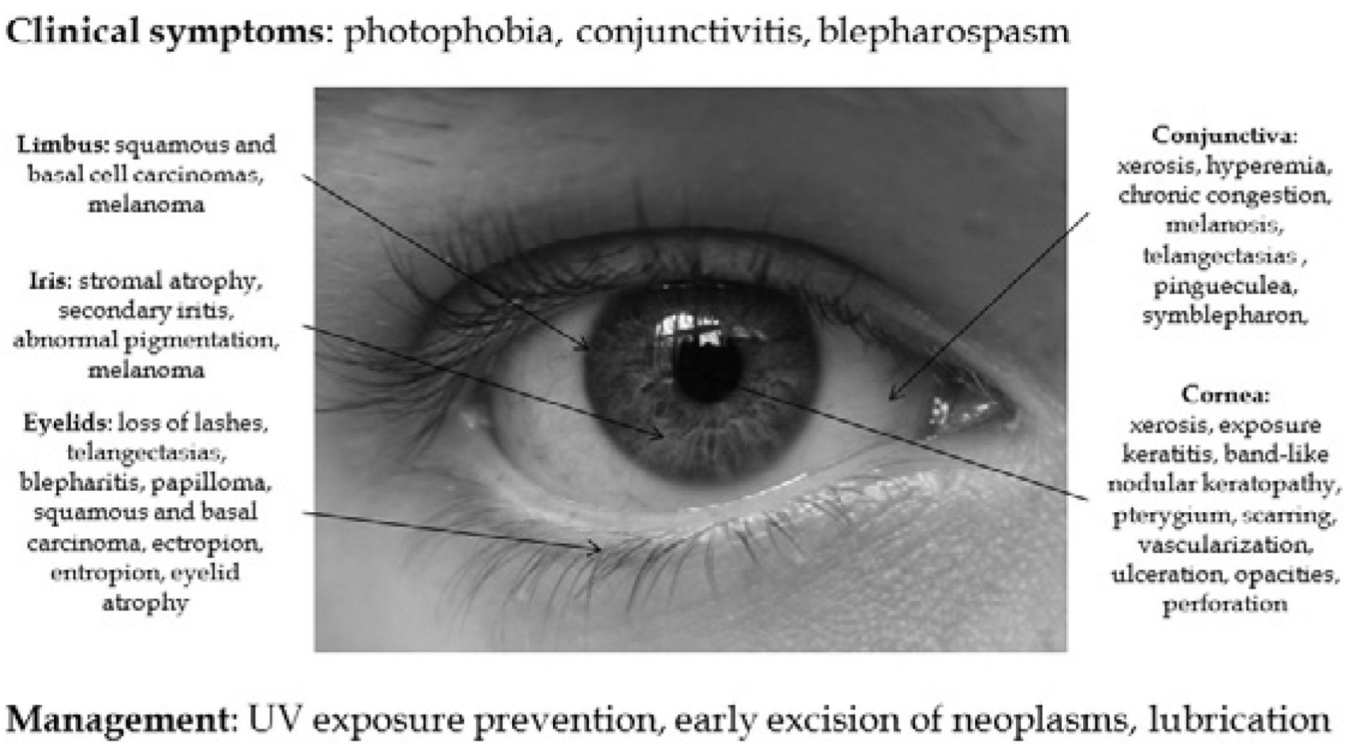

Fig. 9.
A summary of clinical ocular findings in XP.

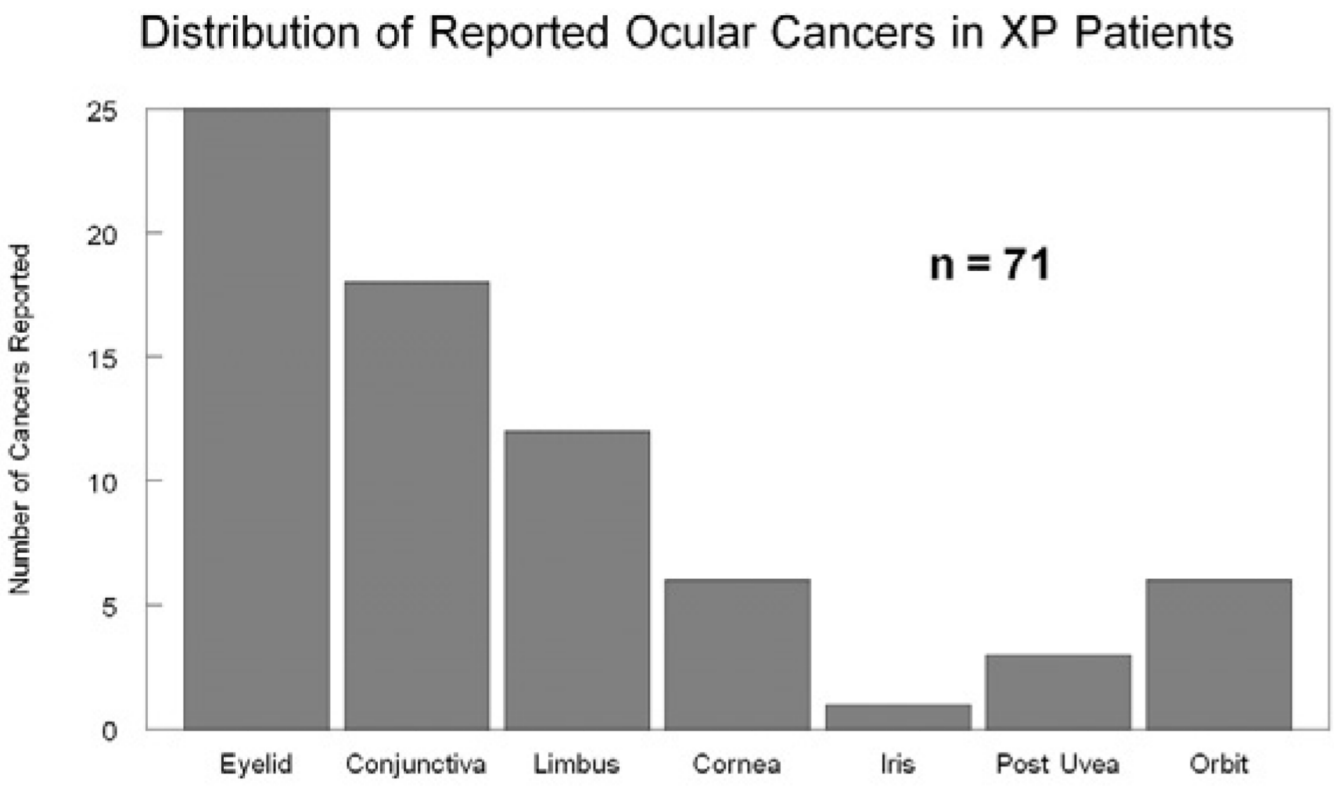

Fig. 10.
A summary of the reported ocular neoplasms in XP.

TABLE 1

A Comparison of Case 1 and Case 2

	Case 1 XP12BE	Case 2 XP18BE
Demographics		
Age at death	44	45
Sex	Female	Female
Clinical information		
Genetic mutation	*XPA*	*XPD*
Photosensitivity	++	++
Skin cancers	++++	+
Neurodegeneration	+++	++
Sensorineural hearing loss	+++	+++
Clinical ocular symptoms		
Photophobia	+++	+++
Conjunctivitis	+++	−
Blepharitis	++	−
Blepharospasm	−	−
Dry eye	++	−
Diplopia	−	++
Eye exam findings		
Ectropion	++	−
Lagophthalmos	++	−
Myopia	+	+
Exotropia	++	+++
Exposure keratopathy and corneal pannus	+++	+++
Pupil abnormality	++	−
Optic nerve pallor	++	−
Pinguecula/pterygia	+	+
Conjunctival injection	++	−
Pathologic ocular findings		
Conjunctiva		
Conjunctivitis	++	+
Pinguecula	+	+
Cornea		
Neovascularization	++	++
Epithelial irregularity	+++	++
Band keratopathy	+	−
Epithelial bulbi	++	+
Bowman’s layer break	+	+
Keratitis	++	+
Ptyerygium	+	−
Lens		

	Case 1 XP12BE	Case 2 XP18BE
Cataract	−	+
Uvea		
Ciliary body hamartoma	+	−
Iritis	−	+
Retina		
Macular edema	+	−
Pigmentary retinal degeneration with pigment migration	−	++
Cystoid degeneration	+	+
Drusen	−	+
Gliosis	+	−
Focal chorioretinal adhesions	−	+
Optic nerve		
Optic atrophy	++	−
Optic artery sclerosis	+	−

− = not present; + = mild; ++ = moderate; +++ = severe.

TABLE 2

A Summary of Reported Ocular Malignancies in Xeroderma Pigmentosum Cases

Location	No. Cases	Median[a] Age (years)	Clinical Exam	Clinical Pathology	Current Management	Author (Year)
Eyelid	16	8.3	Thick red lid with ulceration, crusting, lid eversion; elevated mass; local invasion and spread involving nose and face	Squamous cell carcinoma	Complete surgical resection[21] with modified Mohs micrographic surgery [12,16] and reconstructive therapy;[102] photodynamic therapy if surgery not appropriate[98]	El-Hefnawi and Mortada (1965)[25] El-Hefnawi and Rasheed (1966)[26] Hertle et al (1991)[40] Calugaru et al (1992)[11]
	2		Rapidly growing solitary nodule with central crater	Keratoacanthoma		Khatri et al (1992)[48] Khatri et al (1999)[49] Hadi et al (2000)[35] Khatri et al (1999)[49]
	6		Elevated mass with ulceration and clear margins	Basal cell carcinoma		El-Hefnawi and Mortada (1965)[25] Khatri et al (1992)[48] Khatri et al (1999)[49]
	1		Flat pigmented lesion with irregular borders	Melanoma		Gulati et al (1967)[34]
Conjunctiva	8	4		Squamous cell carcinoma	Early complete excision with adjuvant cryotherapy and/or irradiation, topical chemotherapy, and orbital exenteration for more invasive disease[46,68,86,87,89,92]	Siegelman and Sutow (1965)[93] Hertle et al (1991)[40] Jacyk (1999)[42] Chowdhury et al (2005)[14]
	1		Pale pink glistening swelling	Keratoacanthoma		El-Hefnawi and Mortada (1965)[25]
	2			Intraepithelial carcinoma		
	7	14.5	Pigmented conjunctival lesion	Melanoma		Jensen (1962)[43] El-Hefnawi and Mortada (1965)[25] Vivian et al (1993)[101] Aoyagi et al (1993)[3] Mackiewicz et al (1994)[64] Mehta et al (1996)[67]
Limbus	9	7	Non-nodular, elevated, vascular, diffuse, pigmented tumor	Squamous cell carcinoma	Local resection (iridocyclectomy), enucleation or modified exenteration[88]	Siegelman and Sutow (1965)[93] Sivasubramaniam and Hoole (1952)[94]
	2	15	Pigmented inner limbal tumor	Melanoma		Khatri et al (1992)[48] Goyal et al (1994)[32]
	1	20		Leiomyosarcoma		Zafar et al (1997)[104]
Cornea	6	17.5	Elevated pearly vascular proliferative mass	Squamous cell carcinoma	Local excision,[88] topical chemotherapy,[73] enucleation	Khatri et al (1999)[49] Nalgirkar et al (2000)[69] El-Hefnawi and Mortada (1965)[25]
Iris	1	31	Large pigmented mass arising from the iris with anterior chamber blood	Melanoma	Local excision if circumscribed; enucleation if more than half of the iris and TM involved or secondary glaucoma; plaque radiotherapy in some cases[90]	Saebo et al (1978)[83] Wolff-Rouendaal et al (1976)[103] Giller and Kaufmann (1959)[31] El-Hefnawi and Mortada (1965)[25] Varghese et al (1997)[100] Johnson et al (1989)[44]

Location	No. Cases	Median[a] Age (years)	Clinical Exam	Clinical Pathology	Current Management	Author (Year)
Posterior Uvea	3	24.5	B-scan with apparent ciliary body mass; Incidental finding after enucleation for other tumor	Choroidal melanoma	Plaque radiotherapy Small: laser/ TTT; Large: local resection, enucleation, rare orbital exenteration[91]	Wolff-Rouendaal et al (1976)[103] Kitagawa et al (1981)[50] Vivian et al (1993)[101]
Orbit	3	14	Proptosis with infiltration of the eyeball	Squamous cell carcinoma	CT/MRI; surgical excision: if negative margins possible: Mohs[62] or en face[21]; If orbital invasion: orbital exenteration with adjunct radiation[97]	Calugaru et al (1992)[11] Varghese et al (1997)[100]
	2	11	Large orbital mass; proptosis	Melanoma		El-Hefnawi and Mortada (1965)[25] Rizvi et al (2008)[79]
	1	6	Large fungating vascular mass	Angiosarcoma		Bellows et al (1974)[5]

CT = computed tomography; MRI = magnetic resonance imaging; TM = trabecular meshwork; TTT = transpupillary thermotherapy.

[a]Median age and sex distribution were calculated from cases that reported demographic data with pathology, not all cases.