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# Xeroderma pigmentosum and its relation to ophthalmic neoplasm.

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Report Submitted to fulfill the requirements for Scientific Research Activity

Date of Submission:.8.../…3…/ 2020

## Abstract

Xeroderma pigmentosum is a rare, autosomal recessive disease caused by defect in DNA repair. Patients with xeroderma pigmentosum often have cutaneous and ocular sun sensitivity, pigmented freckles, multiple skin and eye cancers. XP predominatly affects the UV  exposed ocular surface, resulting in eyelid atrophy, corneal dryness, and conjunctival tumors. In this study, we experienced the tumors involving the ocular surface from XP patient. Histo-pathological evaluation and immunohistochemistry was preformed using antibodies against the most common mutated genes in XP (XPA, XPC, and XPD). Sudanese male presented with neoplasms involving the ocular surface: squamous cell carcinoma(SCC), conjunctival abnormalities, including recurrent melanoma and nodular basal cell carcinoma(BCC) of the eyelid.

## Introduction

Xeroderma pigmentosum (XP) is a rare genetic disorder characterized by sever hypersensitivity to ultraviolet (UV) light due to mutations in genes responsible for DNA repair, that are involved in nucleotide excision repair (NER). XP is caused by autosomal recessive mutations. In XP repair of UV-associated damage is impaired, UV leads to dipyrimidine nucleotide products, which are recognized by the NER pathways[1]. Unrepaired products in XP during replication lead to errors resulting in the incorporation of a wrong nucleotide, resulting in characteristic C-to-T or CC-to-TT mutations of UV damage[1,4]. Alterations in eight different genes have been associated with XP; XPA, XPC, and XPD are the most common. XP disorder lead to complete protein loss, and that the mutations may occur in many sites of different genes, so the immunohistochemistry represents an attractive technique to identify the possible aberrant gene in tissues from the patient.

Overall the clinical manifestations of XP are commonly seen in sun-exposed areas such as skin, mucous membranes, and eyes, including the ones seen after a few minutes after a sun exposure (blisters), pigmented freckles, ocular abnormalities, and well known significant increased risk of developing neoplasia in these areas[2]. Ocular manifestations in patients with XP include photophopia, conjunctivitis, ectropion, and neoplasia[5]. The spectrum of neoplasia affecting the ocular surface of patients with XP has not been studied as cutaneous manifestations, but includes squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and malignant melanoma (MM).

Ocular tumors are rare enough that many general ophthalmologists will see only one to a handful during a career. Ocular tumors encompass a wide spectrum of disorders[3]. To clarify the spectrum of neoplasia affecting the ocular structures in XP patients, we present our experience with pathological, and immunohistochemical features of neoplasms involving the ocular surface in this report.

## Methods and Materials

Clinical records from our patient with XP and neoplasms involving the eye with pathologic material were studied. All histologic sections from tumors involving the ocular surface and stained with H&E were reviewed. Immunohistochemical studies were performed using antibodies against the most common proteins affected by XP mutations XPA, XPC, and XPD. In brief, slides were deparaffinized and antigen retrieval was performed with sodium citrate. Slides were incubated with the primary antibody overnight at room temperature, washed, and incubated for 1h with a biotinylated secondary antibody. Later, complete protein loss was seen in multiple samples and both neoplastic and non-neoplastic tissues was interpreted as suggestive of a germline mutation, while protein loss in neoplastic tissues would only be interpreted as suggestive of somatic protein dysfunction.

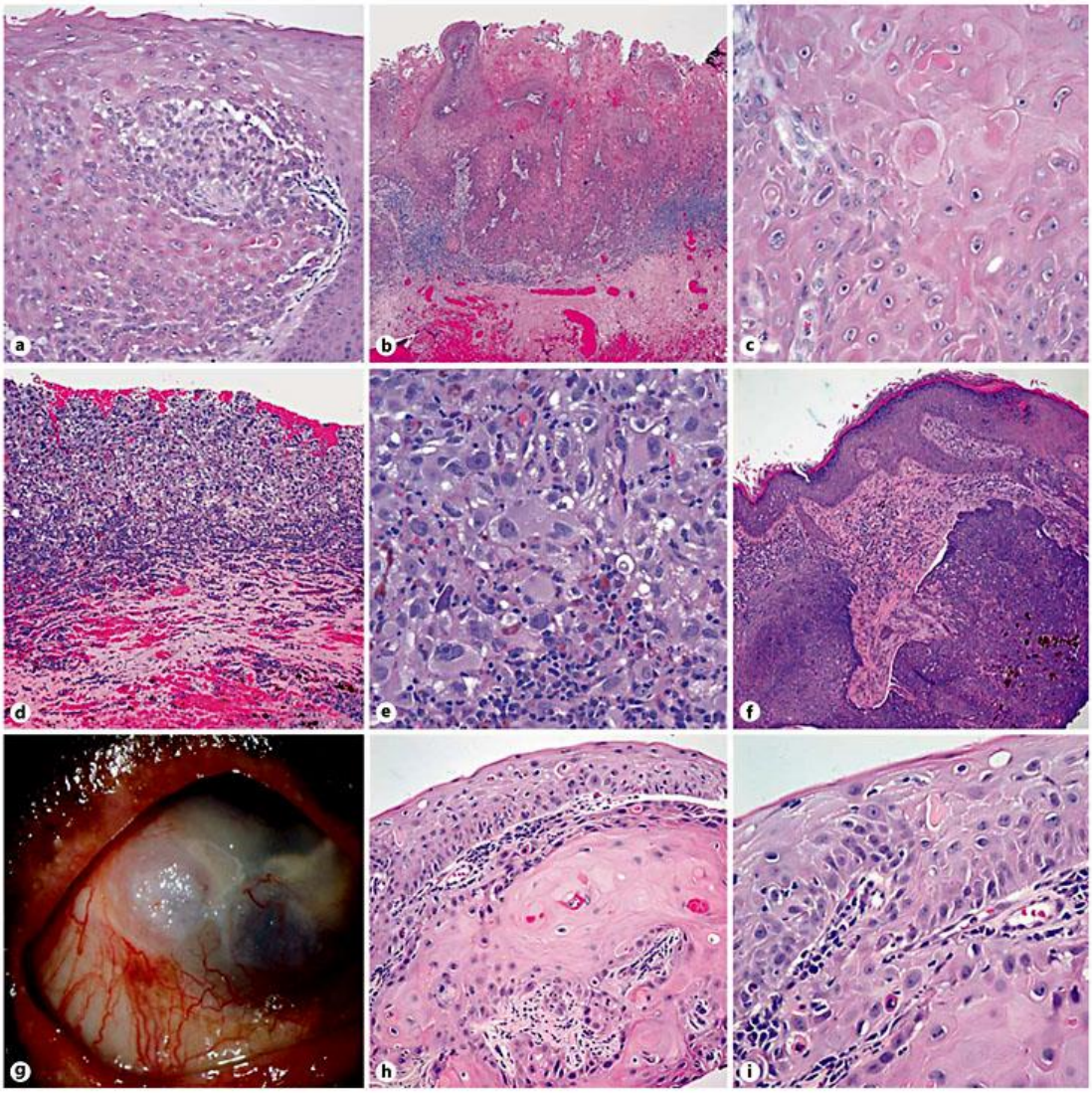
## Results

Immunohistological structure of this patient with XP associated proteins:

| | Pathology | XPA | XPC | XPD |
|---|---|---|---|---|
| Patient | Malignant melanoma<br>Recurrent melanoma<br>Nodular BCC on the lower eyelid<br>Well-differentiated SCC of the lower eyelid<br>Well-differentiated SCC of the conjunctiva | Negative<br>Weak/focal<br>Negative<br>Positive<br>Positive | Weak/focal<br>Weak/focal<br>Positive<br>Positive<br>Negative | Weak/focal<br>Weak/focal<br>Positive<br>Weak/focal<br>Positive |

**Fig. :**

Spectrum of neoplasms involving the eye and ocular surface in patient with XP. XP patients are predisposed to ocular surface squamous neoplasia including in (**a**) and frankly invasive SCCs of the conjunctiva (**b**, **c**). This patient developed the whole spectrum of XP-associated neoplasia, including recurrent melanoma (**d**, **e**), nodular BCC of the eyelid (**f**), and striking conjunctival, keratinized limbal and conjunctival lesions (**g**), which histologically demonstrated and superficially invasive SCCcomponents (**h**, **i**).



## Discussion

Xeroderma pigmentosum, which is known as XP, is an inherited condition characterized by an extreme sensitivity to ultraviolet (UV) rays from the sunlight. It mostly affects the eyes and the areas of skin exposed to the sun. XP is caused by mutations in gene that are involved in repairing the damaged DNA. Many of genes related to XP are part of DNA-repair process known as nucleotide excision repair (NER). Nucleotide excision repair (NER) is an important general process that cells use to correct many different types of damaged DNA, including UV radiation which produces thymine dimer . The NER uses a set of proteins called uvrA, uvrB, uvrC, and uvrD. These are responsible to correct the damaged DNA, in addition the DNA polymerase and DNA ligase are also used to complete the repair.

The process begins with the loading of protein trimer on the DNA double helix. This trimer consist of two uvrA molecules and one uvrB molecule. This trimer moves along the DNA scanning for damage as the thymine dimer. When the trimer finally reaches to the damaged site it stops, the uvrB remains at the damaged site while the uvrA proteins are released, uvrC then binds to the site and make two cuts on the damaged strands, both cuts are away from the damaged site. UvrD then comes and binds to the site and separate the segment damaged strand from the rest of the DNA molecule. UvrB, urvC, and uvrD are all then released from the damaged region. This leaves a gap that is then filled with proper nucleotides by DNA polymerase and then sealed by DNA ligase. The end result is now the damaged DNA has been replaced with correct bases.

However, its not a necessarily problem, but it can be a problem in this condition. Patients with XP when exposed to the UV light, the thymine dimer form and it cant be fixed because of lack of enzymes and the genes which are involved in repairing the damaged DNA. These genes are XPA, XPB, XPC, XPD, XPF, XPG, and XPV.

Ocular tumors are rare enough that many general ophthalmologists will see only one to a handful during a career. Ocular tumors encompass a wide spectrum of disorders. Between 40% and 80% of patients suffering from XP have ocular abnormalities caused by UV-induced alteration to epithelial cells of conjunctiva, cornea, and eyelid. They also have photophopia, conjunctivitis, keratitis that may lead to corneal opacification, hyperpigmentation of eyelid, loss of eyelashes, iris problems, and malignancies including squamous cell carcinoma(SCC) most frequent, basal cell carcinoma(BCC), and malignant melanoma(MM).

Conjunctival involvement which includes telangiectasia, xerosis, chronic conjunctival congestion, and pigmentation most prominently seen in sun exposed interpalpebral fissure.

The cornea may show dryness, exposure keratitis, hazyness, scarring, ulceration, and even perforation resulting in corneal opacities and vascularization.

Iris involvement in XP is uncommon. It includes stromal atrophy, especially of the inferior half, pigment ulceration, iritis, and iris melanoma.

A Sudanese male with a history of his parents and siblings with XP, developing eye pain, photophopia, irritation and blurry vision at age of 4, with subsequent bilateral corneal opacities and a history of multiple skin cancers. Then at age 20 he presented with discomfort in both eyes with associated photosensitivity for many years. His visual acuity in the right eye was 20/50. External examination revealed multiple patchy, hyperpigmented areas of the skin. Slitlamp examination was remarkable for scarred area and hyperemic upper and lower lid as well as for bilateral lower-lid ectropion. Both eyes presented corneal opacities and neovascularization, more in left than the right. At age 25, both lower lids became inflamed, scarred, and thickened. One year later, a hemorrhagic exudative right anterior orbital mass was noted. This was found to be malignant melanoma(MM) with positive margins that recurred 1 year later and for which he went further surgical excision. He later developed basal cell carcinoma(BCC) of the lips and eyelids and squamous cell carcinoma(SCC) of conjunctiva and cornea.

Clinical records from this patient was studied using histologic sections from tumors involving the ocular surface. Immunohistochemical studies were performed using antibodies against most common protein affected by XP mutations; XPA, XPC, and XPD. Slides were deparaffinized and antigen retrieval was performed with sodium citrate. Slides were incubated with primary antibody overnight at room temperature, then later it has been washed and incubated for 1 hour with a biotinylated secondary antibody. Finally, it shows complete protein loss in multiple samples.

Immunohistological structure of this patient with XP associated proteins:

Malignant melanoma(MM) results as: negative XPA, and weak/focal XPC, XPD.
Recurrent melanoma: XPA, XPC, and XPD are all weak/focal.
Nodular BCC on the lower eyelid: negative XPA and positive XPC, XPD.
Well-differentiated SCC of the lower eyelid: positive XPA, XPC and weak/focal XPD
Well-differentiated SCC of the conjunctiva: positive XPA, XPD and negative XPC.

## Conclusion

To conclude my discussion/report,  XP is related to ophthalmic neoplasm. This was proven through my case study in which a Sudanese patient had a history of parents and siblings with XP and he developed symptoms at age 4 and later developed pain in both eyes and photosensitivity.

## References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