Ocular manifestations in patient with congenital erythropoietic porphyria

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We present the case of a 52-year-old woman referred to our service because of extreme ocular surface dryness. The patient showed corneal, conjunctival, and eyelid manifestations of ocular congenital erythropoietic porphyria (CEP). We started treatment with autologous serum, topical steroids, and cyclosporine twice a day, topical retinoids, and intense corneal lubrication. The patient referred significant improvement of ocular bothering and less discomfort since treatment was initiated. We describe the management of the herewith presented case of ocular CEP.

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Porphyrias are a rare metabolic disorder characterized by the deficiency of any of the enzymes required for the biosynthesis of the heme group, which leads to a collection of photosensitive toxic heme intermediates, called porphyrins, in various tissues of the body. Patients with this metabolic disorder may present either neurological or cutaneous symptoms. Congenital erythropoietic porphyria (CEP) is characterized with photosensitive skin lesions at areas exposed to sunlight. There are few case reports illustrating porphyria-related complications like cicatricial ectropion, pterygium, punctual stenosis, scleral and corneal thinning, and corneal perforation.[1,2] However, sight-threatening complications, like keratolysis, leading to total corneal melt in the presence of other risk factors have rarely been reported.[3-5] We report a case of a woman diagnosed with CEP, presenting a serious variant of ocular disease.

Case Report

A 52-year-old Caucasian woman diagnosed with CEP [based on raised red blood cell coproporphyrin (12.8 μg/100 mL) (normal

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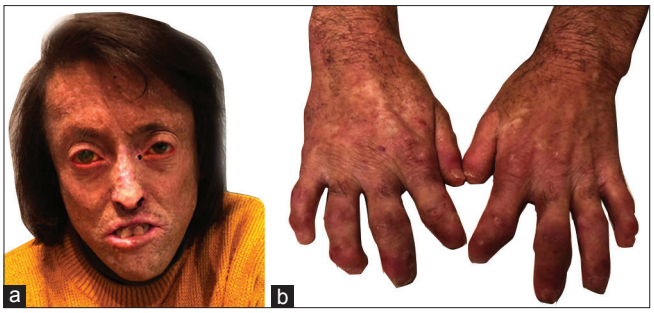

Figure 1: Intense dermatological lesions on face (a) and extremities. Systemic features suggestive of resorption of distal phalanges noted in both upper extremities (b)

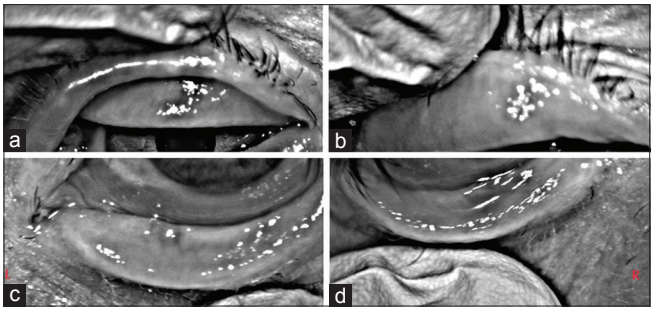

Figure 3: Meibography of both eyes where we can see complete atrophy of Meibomian glands. Right eye; upper eyelid (a) and lower eyelid (c). Left eye; upper eyelid (b) and lower eyelid (d)

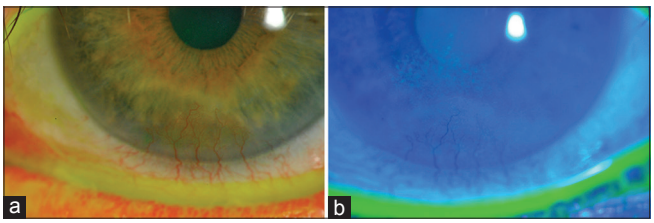

Figure 5: Left eye follow-up. Without staining (a) and with fluorescein (b), where mild superficial keratitis can be seen

Table 1: Review of the literature about systemic manifestations of the disease

Systemic manifestations
Scarring and mutilation of sun-exposed structures, particularly nose, ears, fingers, and scalp[11,12]
Higher risk of developing secondary bacterial infections[12-14]
Facial hypertrichosis, madarosis, scarring alopecia, and scleritis and corneal ulceration leading to blindness[12-14]
Erythrodontia (red-brown staining of teeth that fluoresce pink under Wood's light), bone changes (osteodystrophia, osteolysis, and osteoporosis), and bone marrow hyperplasia[13]
Hemolytic anemia and splenomegaly and profound hemolytic anemia that may result in hydrops fetalis[12]
Nonmelanomatous skin cancer[15]

range 0–1 μg/100 mL), raised urinary uroporphyrin (9000 μg/L), and raised fecal coproporphyrin (201 μg/g dry weight and relied on homozygous mutation in the uroporphyrinogen III

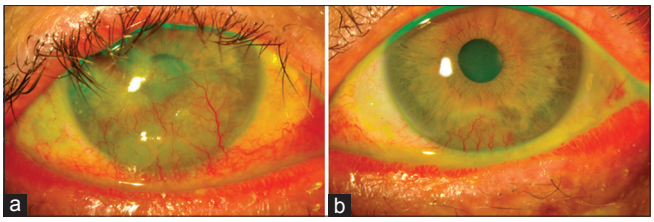

Figure 2: Central pannus in OD (a) and severe conjunctivalization in OS (b)

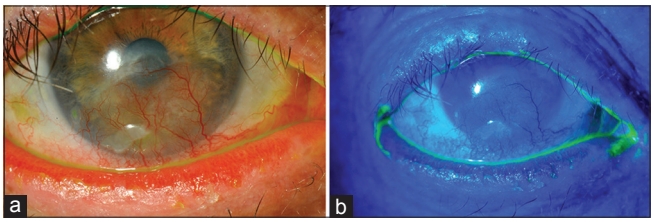

Figure 4: Right eye follow-up. The only remaining signs of conjunctival hyperemia and corneal conjunctivalization in both eyes. Without staining (a) and with fluorescein (b), where no fluorescein-positive staining is seen

consynthase gene], epilepsy, hypertension, hyperuricemia, and glaucoma on antiglaucoma medication (Timolol 2/day) was referred to our service to assess the performance of a keratoplasty. As systemic symptoms, she showed intense dermatological lesions on the face and extremities [Fig. 1]. The patient is double homozygous for CEP. She had been followed in another center because of central corneal conjunctivalization of the right eye (OD) and the onset of inferior conjunctivalization of the left eye (OS). She complained of foreign body sensation, burning, and dryness, accompanied by progressive visual acuity loss in both eyes (OU). She had only been treated with artificial tears and lubricant ointments and eyelid hygiene.

Exploration revealed a visual acuity of 0.16 OD and 0.4 OS. Intraocular pressure in OU was 1 6mm Hg. On slit-lamp examination, the patient presented tear break-up time (TBUT) inferior to 1 second, central corneal pannus in OD, and lower epithelial irregularity with less severe conjunctivalization in OS [Fig. 2]; associated with scales and keratinization of the eyelid margin and complete atrophy of Meibomian glands [Fig. 3]. Schirmer test value without topical anesthesia was 3 mm in OD and 15 mm in OS. Fluorescein staining was positive with moderate affectation (grade III) in the Oxford Squeme.

We suggested adding medical treatment with autologous serum 6 times a day or more as needed, cyclosporine 0.05% twice a day, topical steroids, and an ointment with vitamin A without preservatives and with anti-ultraviolet A radiation filter. After 4 months of treatment, the patient reported less eye discomfort and bothering with the only remaining signs being conjunctival hyperemia and corneal conjunctivalization [Figs. 4 and 5]. Foreign body sensation and ocular discomfort have decreased and the progress of ocular involvement seems to have slowed down, TBUT persists up to 3 seconds, and fluorescein staining has decreased to minimal (grade I) in the Oxford Squeme.

After considering the possibility of performing a keratoplasty, we decided to wait longer until a better state

Table 2: Congenital Erythropoietic Porphyria differences with other similar diseases

EPP	Bullae formation and lack of paraesthesia typically experienced in CEP upon sun exposure
HEP	Absence of isocoproporphyrin in urine or feces
PCT	Much more common and usually with onset in adulthood with an acquired defect in UROD associated with hepatitis C virus and HIV infection

EPP=Erythropoietic protoporphyria, HEP=Hepatoerythropoietic porphyria, HIV=Human immunodeficiency virus, PCT=Porphyria cutanea tarda, UROD=Uroporphryinogen decarboxylase

of the ocular surface is achieved. To get more guarantees of avoiding graft rejection, we have proposed treating before corneal neovascularization (with fine needle cauterization). When possible, we will try a deep anterior lamellar keratoplasty (DALK), covering with amniotic membrane and lateral permanent tarsorrhaphy.

Discussion

CEP usually presents with dermatological features including bullae, hyperpigmentation, scarring, pseudoscleroderma, and hypertrichosis in sun-exposed areas. Table 1 summarizes the systemic manifestations of the disease after the review of the literature. The differences with other diseases that can be confused with CEP are shown in Table 2. The most common ocular involvement is painless, non-inflammatory scleral lesions in the interpalpebral areas.[6] The diagnosis of CEP is genetic. The exact mechanism of scleral damage in porphyria is still unclear. Takamura *et al.* found that the levels of porphyrins were raised in teardrops of patients with porphyria, suggesting excretion of heme precursors in tears, and suggested that sunlight triggers inflammation by activating porphyrins present in tears.[7] Hence, a combination of accumulated toxic metabolites in scleral end vessels with increased tear porphyrin levels predisposes sclera to necrosis and melting. However, the cornea is spared as it receives its blood supply from the limbal arcade, which is not exposed to sunlight.[8] Very few cases of corneal involvement have been reported in literature.[3-5]

As described by Arya *et al.*,[9] the limitation of this case study was that we were not able to collect any direct histopathological or biochemical evidence of the presence of porphyria in either the eyes or the tear film because the patient did not consent for a scleral or a conjunctival biopsy and we did not have the facility to process the tear film. However, we took indirect evidence from the typical clinical presentations in previously reported cases and tear studies to establish our diagnosis.[3-5,8,10] Such atypical presentations of CEP can mimic other inflammatory causes of scleritis, thereby demanding careful history taking and examination. It must be understood that unlike conventional thinking, these patients may progress to corneal perforation, especially in the presence of other risk factors. Therefore, in the presence of the progression of the disease, other risk factors should be evaluated.

Management depends upon the stage of CEP presentation. If the patient is at an early stage of the disorder, it is better to instill copious lubricant along with general protective measures. Vitamin A used topically and orally has been reported to speed epithelial healing. Vitamin A exerts a moderate antioxidant activity; it plays an essential part in epithelial growth and limbal stem cell differentiation, promoting corneal wound healing. Studies suggest that vitamin A may modulate the expression of thrombospondin-1 in the corneas to accelerate the re-epithelialization of wounded corneas. Scleral patch graft is mandatory to restore globe integrity. Considering the poor fate of grafts, Boston keratoprosthesis has emerged as a viable option, though a long-term follow-up is required. What actually triggers these recurrences is yet to be explored. We suggest long-term genetic studies to better understand the long-term history of the disease. Further studies regarding the care of patients with porphyrias are required to treat these rare ophthalmic conditions more effectively.

In conclusion, corneal involvement in CEP is a rare ocular manifestation with very complex therapeutical management. Lubrication is the main treatment, but in severe cases, it must be completed with autologous serum or topical retinoid in order to improve corneal conjunctivalization.

We must inform these patients that treatment is only symptomatic as there is no cure for the base disease until further investigations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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