The eye and skin disease

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INTRODUCTION

Ocular abnormalities associated with disease of the skin may involve any part of the eye or its adnexae. This review will discuss:

- Common skin conditions with ophthalmic manifestations
- Systemic conditions with both eye and skin manifestations
- Pigmented skin conditions.

COMMON SKIN CONDITIONS WITH OCULAR MANIFESTATIONS

Acne rosacea

This is a chronic disorder affecting the sebaceous glands of the face and neck. It is characterized by episodic flushing of affected areas, associated with consumption of alcohol, hot drinks or spicy food. Clinical findings include erythema, telangiectasia, papules, pustules and sebaceous gland hypertrophy. It is found in 10% of the population with a peak incidence between the fourth and seventh decade. Women are affected twice as often as men, although the ocular manifestations are usually more severe in men. The cause of the condition is unknown.

Ocular involvement occurs in more than 50% of patients and blepharoconjunctivitis is the commonest ophthalmic manifestation. The lid margin demonstrates capping and inspissation of the meibomian gland orifices along with telangiectasia of the lid margin. Excessive meibomian secretions may result in foamy tears. Changes to the conjunctiva include diffuse hyperaemia with papillary hypertrophy of the tarsal conjunctiva. Scleritis can also occur.

Corneal changes are less common, usually affecting the inferior quadrant. The findings may range from mild punctate epithelial keratitis to vascularization, infiltration, ulceration and perforation. Decreased visual acuity may result from scarring and any surface irregularity (Browning and Proia, 1986).

Both the ophthalmic and dermatological aspects of rosacea respond well to oral tetracycline therapy (Salomon, 1985). Aggressive lid hygiene helps to manage the blepharitis. Topical steroids are used with caution to treat the corneal infiltrates and in the rare circumstance of corneal perforation, glueing or a lamellar graft may be necessary.

Atopy

The term atopy describes the ability of an individual to produce a hypersensitivity reaction against a common environmental allergen. This response is mediated by immunoglobulin (Ig) E, and serum levels of IgE are elevated in these patients. Common expressions of this type of disease are eczema, asthma, hay fever and allergic conjunctivitis.

Skin manifestations vary with age. In infants, the lesions are exudative, vesicular and crusted. The affected areas are most commonly the facial skin and extensor surfaces of the extremities. In later childhood, the lesions are confined to the flexor surfaces, particularly in the popliteal region, and the skin becomes lichenified and pigmented.

In adolescents and adults, dry, thickened and lichenified lesions affect mainly the flexor surfaces. Vitiligo or hyperpigmentation of the skin may be seen in association with chronic atopic dermatitis.

The ophthalmic manifestations are wide-ranging affecting the eyelids, conjunctiva and cornea. An eczematous reaction to the eyelids gives rise to itching, with symptomatic relief by eye-rubbing. Allergic conjunctivitis is the main ocular manifestation of atopy and there are four main categories (Donshick, 1988): seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC).

SAC and PAC are the mildest expressions of the disease and are non-sight threatening. The symptoms of itching and burning may be intense and, particularly in PAC, the associated signs may be minimal. The lids are often swollen and the conjunctiva is diffusely injected. Small or medium-sized papillae may be visible below the upper lid together with conjunctival chemosis. Treatment involves attempts to reduce allergen exposure, and antihistamine drops in combination with a topical vasoconstrictor and topical mast cell stabilizers. These changes are non-sight threatening and topical steroids should not be used.

VKC is a severe inflammatory condition often associated with complicating corneal disease and therefore is potentially sight threatening. The majority of patients are male, under 20 years of age and the condition is more marked in the spring and summer. It is characterized by symptoms of itching, stringy discharge, conjunctival injection, tearing and photophobia. Large cobblestone papillae are seen particularly under the upper lid (*Figure 1*). White dots are seen at the limbus, referred to as Tranta's dots, which are cysts filled with eosinophils and epithelial cells. Corneal epithelial changes can occur with the formation of characteristic 'shield' ulcers. Secondary changes include corneal vascularization and opacities. The condition tends to regress spontaneously after puberty (Buckley, 1998).

AKC develops in older patients who are severely atopic and is sight threatening. The criterion for diagnosis is chronic conjunctivitis and keratitis associated with atopic dermatitis. The symptoms are similar to VKC but without any seasonal variation. The cornea can be severely involved by ulceration, scarring and neovascular-

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ization. Lid thickening and chronic infection complicate the picture as may herpes simplex infection of the cornea which can be bilateral (Tuft et al, 1991).

The treatment of VKC and AKC is similar with a long-term mast cell stabilizer supplemented with topical steroids when inflammation is severe and uncontrolled. T cells and eosinophils are involved in the pathogenesis of these chronic disorders and topical cyclosporin has been used successfully to control these conditions (Hingorani and Lightman, 1995).

Cataracts have been described as a complication of atopic dermatitis and occur in the chronic forms especially in young adults. Classically the cataracts have a shield-like configuration affecting the anterior cortex of the lens.

Psoriasis

This disorder of keratinocyte turnover leads to hyperproliferation of the skin and plaque formation. In particular, erythematous, silvery-scaled plaques commonly occur on extensor surfaces, in the scalp, lumbosacral and retroauricular regions.

The condition is lifelong with remissions that are unpredictable in terms of frequency and duration.

Ocular manifestations occur in 10% of cases with skin findings almost always occurring first. The skin of the eyelid and lid margin are commonly affected. Psoriatic plaques can be severe enough to cause trichiasis, cicatricial ectropion with subsequent corneal exposure together with blepharitis. A chronic non-specific conjunctivitis can be present which in time can lead to dry eyes. Nodular episcleritis and anterior uveitis are also associated with the condition, usually in patients with psoriatic arthropathy.

Ocular lubrication and punctal occlusion are used to treat the dry eyes. Surgical correction of the ectropion may be necessary. Topical corticosteroids are used to treat anterior uveitis (Steiner and Arffa, 1997).

Figure 1. Giant papillae in vernal keratoconjunctivitis.

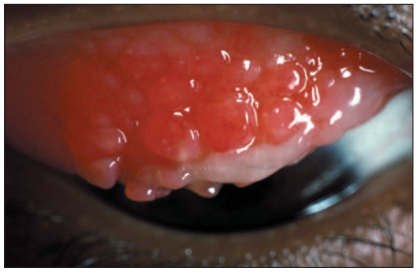
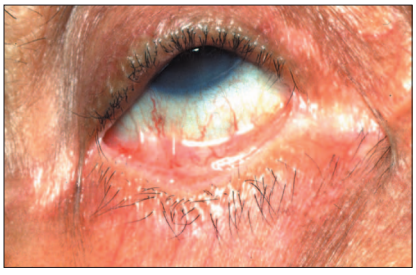


Figure 2. Fibrosis causing shortening of the fornices in ocular cicatricial pemphigoid.



BULLOUS SKIN CONDITIONS WITH OCULAR MANIFESTATIONS

Ocular cicatricial pemphigoid

Ocular cicatricial pemphigoid (OCP) is an autoimmune blistering condition of the skin and mucous membranes with a tendency towards scarring. It is a disease of the elderly, most commonly occurring in the seventh decade, and it affects women more than men. OCP is believed to be predominantly a type II hypersensitivity reaction characterized by the deposition of IgA or IgG and components of the complement system along the epithelial basement membrane.

The typical skin lesions are vesicobullous eruptions overlying an erythematous plaque. The characteristic ocular finding is progressive shrinkage of the conjunctiva. A chronic conjunctivitis with intermittent acute episodes of conjunctival inflammation gives rise to symblepharon formation and shortening of the conjunctival fornices (*Figure 2*). This results in cicatricial entropion of the eyelids and with lashes rubbing against the cornea (trichiasis). Also the conjunctival inflammation gives rise to strictures of the lacrimal ductules and loss of the conjunctival goblet cells, both of which contribute to dry eyes. This predisposes the cornea to infection and scarring. It is a bilateral condition, but may be markedly asymmetrical.

The natural course of OCP is variable, but in many cases the progression of conjunctival scarring is relentless. In the earliest stages of the condition, clinical observation is warranted to assess the rate of progression. Treatments are directed towards maintenance of ocular lubrication, eyelid hygiene and, where necessary, correcting the abnormal lid position.

Systemic treatment includes dapsone for mild to moderate inflammation and for those with severe conjunctival inflammation (Miserocchi et al, 2002). Cyclophosphamide may also be useful in controlling the condition (Elder et al, 1995).

Stevens–Johnson syndrome (erythema multiforme major)

This is a rare, acute disorder of the skin and mucous membranes with systemic toxicity. It is commonly categorized as a subcategory of erythema multiforme. It usually affects men more than women in a ratio of 2:1. The precise aetiology is not known, but evaluation of affected skin shows an immune complex vasculitis in the wall of the papillary dermis vessels. There are clear inciting agents linked with the syndrome:

- Drugs, e.g. sulphonamides, anticonvulsants, aminopenicillins
- Infectious agents, e.g. *Mycoplasma pneumoniae*, herpes simplex virus, adenovirus
- Radiotherapy
- Malignancy.

Patients with acquired immunodeficiency syndrome are more prone to developing Stevens–Johnson syndrome, particularly when taking sulphur-based drugs.

Stevens–Johnson syndrome presents with a prodromal fever and malaise. The skin changes consist of target lesions, i.e. maculopapules with a red centre and a white surround on an erythematous base. The mucosae most frequently involved are the oral and conjunctival surfaces. The frequency of stomatitis approaches 100%. Ocular involvement occurs in around 90% of cases (Wright and Collin, 1983) and the acute phase is marked by a mucopurulent and pseudomembranous con-

junctivitis. A small percentage of patients develop the chronic phase, which results from the interruption of smooth conjunctival surface. From the pseudomembranes may come membranes that heal with scarring, resulting in symblepharon and ankyloblepharon where the lid fornices become obliterated. Aberrant lashes located in the meibomian gland orifices give rise to trichiasis. Scarring of the conjunctiva decreases the number of goblet cells and may obstruct lacrimal gland ducts producing a dry eye. The limbal epithelial stem cell population can be disrupted further jeopardizing corneal integrity.

Treatment in the acute phase includes lubrication with artificial tears and peeling of the pseudomembrane. In the chronic phase, symptomatic management to deal with in-growing lashes, dryness and infection with long-term follow up is the best way to reduce morbidity (Faraj and Hoang-Xuan, 2001).

SYSTEMIC DISEASE WITH SKIN AND EYE MANIFESTATIONS

Sarcoidosis

This granulomatous disease of unknown aetiology may involve any organ system. The lungs are most commonly affected followed by the lymph nodes, eyes and skin.

Cutaneous lesions occur in up to 35% of patients. Erythema nodosum is the most common skin lesion and consists of elevated, tender nodules typically affecting the pre-tibial surfaces. Other skin changes include violaceous plaques and nodules involving the skin of the nose and cheeks (lupus pernio), maculopapular and nodular infiltrated plaques.

Sarcoid can affect any structure of the eye and 20% of patients present with ocular signs (Jabs and Johns, 1986). These include granulomas to the eyelids, conjunctiva, episclera and infiltration of the lacrimal gland, which leads to dry eyes. Intra-ocular inflammation is a common feature giving rise to anterior, posterior or panuveitis associated with mutton-fat precipitates and iris nodules (*Figure 3*). In the retina, peripheral retinal periphlebitis may be seen, and retinal vasculitis can be complicated by a branch retinal vein occlusion and retinal neovascularization. In the late stage, multiple small atrophic chorioretinal scars can be seen indicating previous active chorioretinal granulomas (*Figure 4*).

Systemic lupus erythematosus

This chronic autoimmune connective tissue disorder primarily affects women of child-bearing age. It has a diverse spectrum of clinical manifestations ranging from relatively mild cutaneous and joint conditions to lethal kidney, heart and brain involvement. It is believed to result from dysfunction in immunoregulation, triggered by an environmental agent such as a microbe, drug or other chemical.

Skin lesions develop in up to 80% of systemic lupus erythematosus patients at some point during their lives. The pathognomonic malar or butterfly rash occurs in approximately 30% of sufferers. This consists of a flat or raised erythematous rash across the nose and cheek. Discoid lesions with adherent keratotic scaling can occur. Also patients may demonstrate marked photosensitivity. Other skin changes include livedo reticularis and alopecia.

Figure 3. Large iris nodule in sarcoidosis.

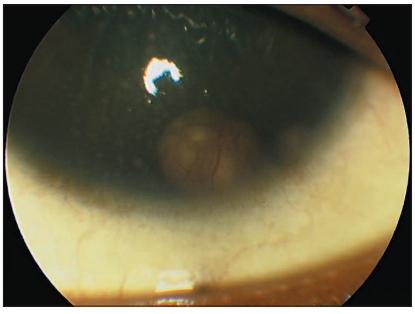
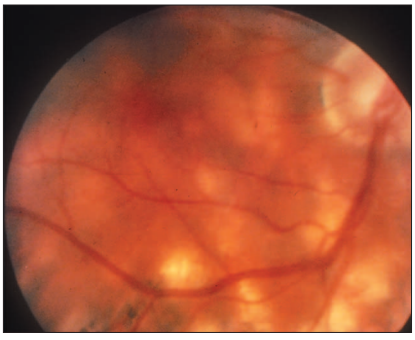


Figure 4. Chorioretinal scars in sarcoidosis.



Systemic lupus erythematosus gives rise to a recurrent conjunctivitis producing subepithelial fibrosis and forniceal shortening. Episcleritis, scleritis and keratoconjunctivitis sicca are associated with the condition. The latter results from chronic lymphocytic infiltration of the lacrimal glands. Posterior segment findings range from small vessel vasculitis with periarteriolar exudates to large vessel occlusive disease and associated retinal haemorrhage. In severe cases, retinal ischaemia results from non-proliferation which the possibility of new vessel formation. Features of hypertensive retinopathy may be caused by the systemic hypertension (Bouchard and Melton, 1996).

Progressive systemic sclerosis

This condition of unknown cause is characterized by inflammation, fibrosis and degenerative changes of many systems. Skin features include thickening and tightness of the skin, particularly of the face, producing the characteristic pursed mouth and pinched nose appearance. Ocular features are associated with generalized progressive systemic sclerosis and include stiffness or tightness of the eyelids, conjunctival shortening and keratoconjunctivitis sicca. Choroidal vascular abnormalities can occur, including areas of choroidal non-perfusion (Foster, 1997).

Pseudoxanthoma elasticum

This is a rare, inherited disorder of elastic tissue. The pathogenesis is unknown. Skin changes include yellowish papules producing a plucked chicken or peau d'orange appearance, particularly over flexural surfaces and at the sides of the neck. There is also reduced elastic recoil of the skin on stretching.

Angioid streaks (*Figure 5*) are seen on the retina which have a slate grey appearance in contrast to the orange fundus and usually radiate from the optic nerve head (Grand et al, 1987). They represent breaks in Bruch's membrane which contains elastin and collagen and separates the choroid from the retinal pigment epithelium. Vascular complexes from the choroid can grow beneath the retina, which tend to bleed

producing a scar. If this occurs at the fovea, then vision is severely affected.

PIGMENTARY CHANGES TO THE SKIN

Albinism

This is a congenital, hereditary disorder of pigment production. Various forms exist:

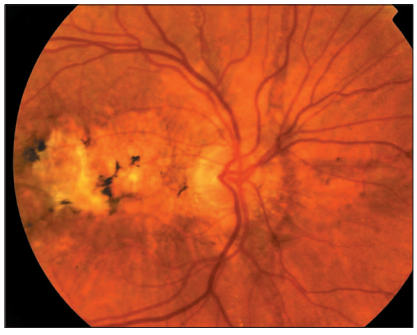
- Oculocutaneous albinism is usually inherited as an autosomal recessive trait and is associated with hypopigmentation of the hair and skin and specific developmental abnormalities of the eye and visual tract
- Ocular albinism which is limited to the eye and is usually X-linked.

The cutaneous features of oculocutaneous albinism are the result of absent or decreased skin melanin production and the resulting solar damage to unprotected skin. These patients are prone to develop both squamous cell and basal cell carcinomas.

Ocular features include hypopigmentation of the iris giving rise to translucency. The fundus typically appears depigmented and the underlying choroidal vessels are visible. Developmental abnormalities of the eye can include dysgenesis of the anterior segment, foveal hypoplasia and increased decussation of the nerve fibres at the optic chiasm. Associated with these are reduced vision, photophobia, nystagmus and reduced binocular function (Kinnear et al, 1985). Strabismus and high refractive errors are commonly encountered.

Treatment includes correction of refractive errors, tinted lenses to reduce the photophobia and strabismus correction.

Figure 5. Retinal angioid streaks with macular scar from choroidal neovascular membrane.



Vogt–Koyanagi–Harada syndrome

This condition affects the eye, skin, meninges and ear. The cutaneous manifestations of Vogt–Koyanagi–Harada syndrome consist of skin and hair depigmentation along with alopecia areata. These usually occur late in the disease.

Vogt–Koyanagi–Harada syndrome often presents with ocular features, notably a bilateral granulomatous uveitis. Anterior uveitis may be marked by keratic precipitates and iris nodules. Posterior segment inflammation changes include choroidal infiltrates, exudative retinal detachment and intense congestion of the optic disc. As the inflammation subsides, there is generalized pigmentary disturbance throughout the retina (Flores-Guevara et al, 1996). Depigmentation of the lashes may occur, known as poliosis (*Figure 6*).

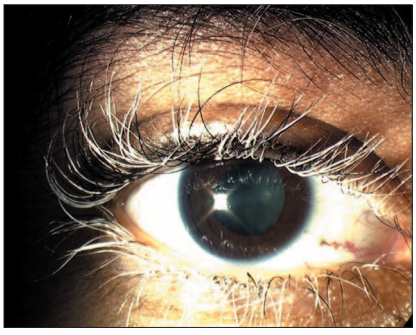
Incontinentia pigmenti

This an X-linked dominantly inherited ectodermal disorder. It usually affects only females, being lethal to male embryos. The diagnosis is made in infancy with skin manifestations.

Changes to the skin include an erythematous vesicobullous eruption, followed by a verrucous one. Later changes consist of streaky brown or grey hyperpigmentation distributed irregularly on the torso. Resolution of the hyperpigmentation occurs in early adulthood, giving rise to hypopigmented lesions (Landy and Donnai, 1993).

A third of cases have ophthalmic abnormalities, with the developing retinal vessels and underlying pigment cells most commonly affected. Areas of retinal ischaemia promote neovascularization, with subsequent bleeding fibrosis can lead to a tractional retinal detachment (Goldberg and Custis, 1993). In most cases these changes arrest spontaneously at an early stage, and normal vision is retained. Children with this diagnosis should be screened for retinal abnormalities, since treatment of the affected areas with laser photocoagulation can prevent visual loss. Other ophthalmic associations include cataracts, corneal changes, microphthalmos and optic atrophy. HM

Figure 6. Poliosis occurring with Vogt–Koyanagi–Harada syndrome.



Bouchard CS, Melton JL (1996) Lupus erythematosus. In: Mannis M, Macsai M, Huntley A, eds. *Eye and Skin Disease.* Lippincott-Raven Publishing, Philadelphia: 177–84

Browning BJ, Proia AD (1986) Ocular rosacea. *Surv Ophthalmol* **31:** 145–58

Buckley RJ (1998) Allergic eye disease – a clinical challenge. *Clin Exp Allergy* **28**(suppl 6): 39–43

Donshick PC (1988) Allergic conjunctivitis. *Int Ophthalmol Clin* **28:** 294–302

Elder MJ, Lightman S, Dart JK (1995) Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol* **79:** 264–6

Faraj HG, Hoang-Xuan T (2001) Chronic cicatrizing conjunctivitis. *Curr Opin Ophthalmol* **12:** 250–7

Flores-Guevara JA, Tessler HH, Solomon N (1996) Vogt-Koyanangi-Harada syndrome. In: Mannis M, Macsai M, Huntley A, eds. *Eye and Skin Disease.* Lippincott-Raven Publishing, Philadelphia: 303–9

Foster CS (1997) Systemic lupus erythematosus, discoid lupus erythematosus, and progressive systemic sclerosis. *Int Ophthalmol Clin* **37:** 93–110

Grand MG, Isserman MJ, Miller CW (1987) Angioid streaks associated with pseudoxanthoma elasticum. *Ophthalmology* **94:** 197–200

Goldberg MF, Custis PH (1993) Retinal and other manifestations of incontinentia pigmenti. *Ophthalmology* **100:** 1645–54

Hingorani M, Lightman S (1995) Therapeutic options in ocular surface disease. *Drugs* **50**(2): 208–21

Jabs DA, Johns CJ (1986) Ocular invovement in chronic sarcoidosis. *Am J Ophthalmol* **102:** 297–301

Kinnear PE, Jay B, Witkop CJ (1985) Albinism. *Surv Ophthalmology* **38:** 1–24

Landy SJ, Donnai D (1993) Incontinentia pigmenti. *J Med Genet* **30:** 53–9

Miserocchi E, Baltatzis S, Roque MR, Ahmed AR, Foster CS (2002) The effect of treatment and its related side effects in patients with severe ocular cicatricial pemphigoid. *Ophthalmology* **109:** 111–18

Salomon SM (1985) Tetracyclines in ophthalmology. *Surv Ophthalmology* **29:** 265–75

Steiner G, Arffa RC (1997) Psoriasis. In: Smolin G ed. *Ocular Manifestations of Dermatological Disorders.* Lippincott-Raven Publishing, Philadelphia: 41–5

Tuft SJ, Kemeny DM, Dart J, Buckley RJ (1991) Clinical features of atopic keratoconjunctivitis. *Ophthalmology* **98**(2): 150–7

Wright P, Collin JRO (1983) The ocular manifestations of erythema multiforme and their management. *Trans Ophthalmol Soc UK* **103:** 338–41