

Dermatologic and Allergic Conditions of the Eyelid

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The skin, the largest organ of the body [1], is composed of three layers: the epidermis, dermis, and subcutaneous. The outermost layer (the epidermis) is composed of keratinocytes (squamous cells), melanocytes (pigment cells), and the immunologically active dendritic cells (antigen-presenting cells). The thickness of the epidermis varies, with increased thickness in areas exposed to friction, such as the palms and soles, and a thin epidermal layer, such as that found in the eyelids [2], to allow for easier movement and flexibility. The second layer of the skin (the dermis) is composed of blood vessels, nerves, glands (eccrine and sebaceous), and other accessory structures such as hair follicles of the eyelashes and eyelids. In addition, the dermis of the eyelid is rich in arteriovenous anastomoses. The innermost layer is the subcutaneous layer. The eyelid contains loose areolar tissue and little subcutaneous fat, important characteristics that allow easy mobility of the first two layers over the underlying muscle. The loose tissue, however, has great potential for accumulation of fluid, leading to periorbital edema.

Clinical diagnosis of lesions on the skin is primarily based on proper description of the lesions and their categorization according to appearance and evolution. Primary lesions are caused by the disease stimulus, whereas secondary lesions are later changes that occur due to evolution of the primary lesions [3]. Primary lesions include macules, papules, vesicles, bullae, pustules, wheals, plaques, and nodules. Secondary lesions consist of

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scales, erosions, excoriations, ulcers, and lichenification. Primary and secondary lesions can occur together, in various combinations, and with evolving patterns that assist in the diagnosis of the disorder. Disease may be categorized according to the presenting primary lesions, but one should remember that diseases have “lives” and may evolve from one primary lesion to another and become associated with a variety of secondary lesions.

Seborrheic dermatitis

Seborrheic dermatitis (SD) is a common macular condition of skin that is commonly chronic and recurrent and characterized by symmetric erythematous inflammation with scaling that is often greasy and sometimes with crusting. When SD involves periocular tissue (the eyebrows and eyelids), it is known as seborrheic blepharitis. Other areas of predilection include the scalp, ears, sides of the nose, chest, axilla, and inguinal area. *Malassezia* (previously *Pityrosporum*) yeasts have been associated with the development of SD [4–6] through an altered immune response or as the result of hyperproliferation [4,5].

SD is common in the newborn (cradle cap) due to activation of sebaceous glands by maternal androgen stimulation. Endogenous androgens induce seborrhea in adolescence. Ocular complications of chronic seborrhea of the eyelids include hordeola (styes) and inflammation of the meibomian glands (meibomianitis) with secondary conjunctivitis (blepharoconjunctivitis). Uncontrolled severe SD has been observed in HIV patients and may be the initial presentation prompting workup for HIV infection [7].

Treatment

SD is easily controlled with steroid creams, but this treatment does not cure the dermatitis, which recurs. On the eyelids, which are very thin, a mild steroid may be used sparingly, but due to the possibility of side effects from steroids, only short courses or steroid-sparing remedies have been used for safety. Calcineurin inhibitors (eg, Elidel, Protopic) are effective, but their safety in children younger than 2 years is controversial [8]. Saline compresses and baby shampoo wiped gently on the affected areas are safe and mild remedies used to help alleviate the scaling and crusting of blepharitis. Topical antifungal creams, shampoos, and lotions containing selenium sulfide and zinc pyrithione have been used, with some improvement [5].

Vitiligo

These depigmented macules or patches occur due to loss of pigment on the skin; no secondary changes are evident (no scale, crusts, or erosions). Vitiligo is considered to be a multifactorial disorder; hypotheses on its development include neural, biochemical, and autoimmune mechanisms [9]. The association with autoimmune conditions such as autoimmune thyroiditis,

pernicious anemia, diabetes, rheumatoid arthritis, and alopecia areata supports the likely autoimmune etiopathogenesis of vitiligo [9,10]. The association between vitiligo and autoimmune thyroid disease has been suggested due to the presence of thyroid antibodies (antithyroglobulin and anti-thyroid peroxidase antibodies) and abnormalities in thyroid function [11,12]. In a retrospective study of 1436 patients who had vitiligo, atopic/nummular eczema was seen in 20 (1.4%) patients, bronchial asthma in 10 (0.7%), diabetes mellitus in 8 (0.6%) [13], thyroid disease in 7 (0.5%), and alopecia in 6 (0.4%) [14]. These findings stress the importance of a thorough assessment for autoimmune diseases in selected patients who have vitiligo. Vitiligo has also been associated with endocrinopathies (autoimmune polyglandular syndromes) [12], different skin diseases (psoriasis Ref. [15], lichen planus Ref. [16]), and rare syndromes (Vogt-Koyanagi-Harada syndrome Ref. [11]) [9].

Common areas affected are those around orifices (perioral, periorbital) and on areas of frequent trauma. Despite its benign nature, it has devastating implications due to the cosmetic problems it causes, and patients often seek camouflaging agents to conceal the defects. Differential diagnoses for flat hypopigmented lesions are postinflammatory hypopigmentation noted after various inflammatory cutaneous disorders (infections and drug-related eosinophilic and scaling skin syndromes); tinea versicolor that has fine scaling treated with antifungal agents; and pityriasis alba that also may have fine scales and is common in atopic dermatitis.

Heliotrope rash

Dermatomyositis may manifest with a violaceous discoloration of the eyelids, upper cheeks, forehead, and temples called a heliotrope cutaneous eruption, named after the color of the heliotrope flower. The cutaneous eruption can evolve to include underlying edema of the eyelids before, during, or after the development of muscle weakness; however, a subset may lack any evidence of myopathy. Diagnosis is through a skin biopsy to differentiate it from chronic eyelid dermatitis such as contact dermatitis. Pathology may show nonspecific inflammatory changes indistinguishable from lupus erythematosus [17]. There is epidermal atrophy, basement membrane degeneration, vacuolar alteration of basilar keratinocytes, a sparse lymphocytic inflammatory infiltrate around blood vessels, and interstitial mucin deposition [18].

Port-wine stains

Vascular malformations include port-wine stains, salmon patches, and malformations associated with syndromes (Sturge-Weber, Cobb, and Klippel-Trénaunay). Port-wine stains (nevus flammeus) are unilateral and commonly affect the face and other areas. They are present at birth up to 0.3% and range in size from a few millimeters to very large, covering the whole face or limb [19]. They are flat, erythematous to violaceous patches with

irregular well-delineated borders and are initially smooth but may become popular, nodular, or cobblestoned. They differ from hemangiomas in that they increase in size proportionate to child growth, then remain stable throughout life but may darken. Port-wine stains over the eyelid in the distribution of the trigeminal nerve (V1) has a risk of being associated with Sturge-Weber syndrome, which is associated with central nervous system findings (angioma of the meninges, hemiparesis contralateral to the skin lesions, epilepsy), mental retardation, renal angioma, coarctation of the aorta, visual impairment, high arched palate, and abnormally developed ears.

Xanthelasma and plane xanthomas

Xanthelasma affecting the eyelids, called xanthelasma palpebrum, are a variant of xanthomas, which are bilateral symmetric flat-topped yellowish papules or plaques located typically on the inner or outer canthus of the upper eyelid, rarely involving the lower eyelid or obstructing vision. Female sex and increasing age are predisposing factors. Xanthelasma may be associated with familial hypercholesterolemia but approximately 50% of patients have normal cholesterol levels [20]. Pathology of these lesions shows the presence of xanthoma cells—foamy, lipid-laden histiocytes—in the superficial dermis in perivascular and periadnexal areas [21]. When they appear before the age of 40 years, they may have a higher likelihood of being associated with familial hypercholesterolemia [22]. There may be an associated risk of atherosclerosis and pancreatitis in lesions found to be associated with lipid abnormalities. Hence, it is valuable to screen for lipid abnormalities in these patients. They have also been found to occur more often in diabetics [23].

Seborrheic keratosis

Seborrheic keratoses are very common benign cutaneous growths that may be skin-colored to hyperpigmented and occur anywhere on the body and commonly involve the eyelids. They are more common with increasing age and appear as well-circumscribed, thick, keratotic papules or plaques that have a smooth and flat surface or an irregular and rough surface. They can be brown, tan, or black and have a characteristic stuck-on appearance. Unlike actinic keratoses, they are not related to sun exposure and are benign. A genetic form is common in blacks and is termed dermatosis papulosa nigra. Even young and middle-aged blacks may develop these multiple brown-black, smooth, dome-shaped, or pedunculated 2- to 3-mm papules, usually on the face and neck.

Skin tags

Skin tags or acrochordon are frequently found on the eyelids but may also be found anywhere on the body, especially on the axilla, neck, and inguinal region. They may start as small brown or skin-colored growths

with a short stalk and may evolve to larger polyps with longer narrow stalks. There have been several reports suggesting that skin tags may be a marker for the presence of colonic polyps in symptomatic patients [24–26]. In a prospective study of 100 asymptomatic patients, no association was found between skin tags and colonic polyps [25]. A review of the literature and results of a meta-analysis show a significant association between skin tags and colonic polyps in 777 symptomatic patients, but no association in 268 asymptomatic patients [25]. Hence, the mere presence of acrochordons (skin tags) should not be used as an indication for screening colonoscopy.

Warts

Unlike the seborrheic keratoses and skin tags previously reviewed, warts are transient viral infections secondary to human papilloma virus (HPV). HPV infects the skin through breaks that easily occur on thin skin such as eyelids. Recent interest in warts has emerged due to their occurrence in immunocompromised individuals such as those who have HIV infection. Flat warts (*verruca plana*) are flat-topped and may be found on the face and eyelids and other areas of the body; common warts (*verruca vulgaris*) are less commonly seen on the face and more common on the extremities. There are many HPV types identified, with various types causing different clinical behavior and location preference [26]. Flat warts are often seen on the face and eyelids and may be present in large numbers as flat-topped papules that are skin-colored to tan to pinkish, whereas the more hyperkeratotic common warts do not normally occur on the eyelids.

Comedones

Comedones are commonly called blackheads when they are open comedones and white heads when they are closed comedones. These represent a stage in acne vulgaris and are caused by plugging of the hair follicle due to increased stickiness of keratinocytes. Comedones are common in adolescents on the face, nose, and chin. Senile comedones, which are larger, occur in the elderly around the eyes and temples and may be attributed to excessive sun exposure [27]. The sun damage causes the pilosebaceous duct to become distended and more easily filled with keratinocytes.

Syringoma

Syringomas are small, firm, flesh-colored, flat-topped or dome-shaped papules ranging from 1 to 5 mm commonly found on the lower eyelids and malar area but may also be present on the forehead, chest, and abdomen. They represent benign tumors of the sweat duct and have no malignant potential. They are found at any age but occur more commonly in the third and fourth decades and in women. They usually appear in crops. Palpebral

syringomas are a common cutaneous pathology in Down syndrome, more commonly in female patients [28].

Rosacea

Rosacea is often mistaken for acne, but the major difference is the lack of comedones. Rosacea may comprise erythema, edema, papules, pustules, or telangiectasias occurring on the cheeks, forehead, nose, and eyes. Patients look like they have a chronic blush. Rhinophyma is the involvement of the nose and is characterized by a bulbous appearance with chronic inflammation and hypertrophy. The actor W.C. Fields represents an example of rosacea involving the nose. The cause is unknown, but genetic, environmental, vascular, and inflammatory factors and microorganisms such as *Demodex folliculorum* and *Helicobacter pylori* have been considered [29]. The mite *Demodex folliculorum*, a normal resident fauna of hair follicles, has been found in increased numbers in patients who have rosacea [30]. Precipitating factors for this eruption include consumption of alcohol or hot beverages, spices, sun exposure, and stress.

Symptoms of ocular rosacea may range from mild to severe. Nonspecific symptoms may include conjunctivitis, blepharitis, soreness, lacrimation, and grittiness. Aside from involvement of the lid (blepharitis, chalazion), ocular rosacea can involve the conjunctiva (conjunctivitis, keratoconjunctivitis sicca), sclera (scleritis, episcleritis, scleral perforation), iris (iritis, iridocyclitis), and cornea (punctate keratopathy, scarring, corneal perforation, corneal neovascularization, ulceration, and blindness) [31]. Starr [32] examined the eyes of patients who had rosacea and found ocular complications in 58% and corneal involvement in 33%. Recent articles on the prevalence of ocular rosacea in patients who had acne rosacea suggest that between 6% and 18% of acne rosacea patients have signs or symptoms of ocular rosacea, but few cases are confirmed by an ophthalmologist [33]. Twenty percent of patients who have acne rosacea have ocular symptoms before the skin lesions [34]. Rosacea is found more often in female patients, but ocular rosacea occurs equally in both sexes. In patients who have acne rosacea and ocular complaints, a multidisciplinary approach is recommended, including evaluation by an ophthalmologist.

Lipoid proteinosis

Lipoid proteinosis is a rare genodermatosis characterized by protein infiltration of the skin, oral cavity, and larynx. The first clinical sign is hoarseness caused by infiltration of the vocal cords [35]. Patients are easily recognized due to their husky voice, inability to protrude the tongue and thickened eyelids [36]. The involvement of the eyelids with tiny papules produces the classic string of beads sign appearance [35,36]. Waxy, yellow papules and nodules on the skin or generalized skin thickening may also be seen.

Angioedema

Angioedema refers to the deeper swelling of the skin involving the subcutaneous layer. The overlying epidermis is normal, nonpruritic, and nonpitting. Any part of the body may be affected with angioedema, but the more common areas are the eyelids, lips, and genitalia. Possible causes of acute angioedema include an immunoglobulin (Ig)E-mediated allergic reaction to food or drugs. Although any food can provoke a reaction, relatively few foods are responsible for the most significant food-induced allergic reactions: milk, eggs, peanuts, tree nuts, fish, and shellfish [37]. In food-allergic patients who have atopic dermatitis, the ingestion of the food item can provoke the whole spectrum of IgE-mediated symptoms, from oral allergy syndrome to severe anaphylaxis [38]. Common drugs that cause angioedema are beta-lactam antibiotics (penicillins, penicillin derivatives, cephalosporins), sulfa-based antibiotics such as trimethoprim-sulfamethoxazole, insulin, extracts, heterologous antisera (equine antitoxins and antilymphocyte globulin), murine monoclonal antibodies, protamine, and heparin [39]. Local and systemic angioedema may be caused by hymenoptera stings or fire ant bites [40].

Bradykinin-induced angioedema is another cause of nonallergic angioedema that can be acquired or genetic. Examples are hereditary angioedema and angioedema secondary to use of angiotensin-converting enzyme (ACE) inhibitors. A well-known relationship exists between angioedema and ACE inhibitors (with angioedema occurring in 0.1%–6% of patients taking these drugs), which is thought to be due to defective degradation of bradykinin or substance P [41].

Contact urticaria

Contact urticaria is characterized by urticaria that develops due to contact with certain substances. The eruption commonly appears within 30 minutes to an hour after contact and results in erythema, pruritus, burning, and urticaria. A severe manifestation of contact urticaria of the conjunctiva manifesting with bulging chemotic conjunctiva is commonly seen in severe allergic conjunctivitis, which is typically bilateral. When contact urticaria affects only one eye, it is more commonly caused by the patient bringing the allergen to the eye by way of the fingers due to eye rubbing.

Erysipelas

Erysipelas is a deep infection of the dermis and subcutaneous tissue commonly caused by *Streptococcus pyogenes*. The eyelids may be involved, and erysipelas is characteristically found on one eye with associated erythema, tense edema, and tenderness. Patients may experience high fever, headache, and vomiting. This infection should be differentiated from allergic manifestations that are more commonly painless.

Trichinosis

Pyrexia, eyelid, or facial edema and myalgia represent the principal syndrome of the acute stage of trichinosis [42]. Other systemic symptoms include nausea, diarrhea, and muscle pain. Trichinosis can be complicated by myocarditis, thromboembolic disease, and encephalitis. Diagnosis is through the identification of *Trichinella* on muscle biopsy or by identification of larvae in the blood.

Chalazion

A chalazion is a slow-growing, often recurrent painless nodule on the eyelid caused by blockage of the meibomian gland, which is located on the tarsal plate of the lid about 3 to 4 mm from the margin. The skin over the nodule is freely movable but adherent to the tarsal plate. It may occasionally be associated with irritation of the conjunctiva. If it ruptures into the tarsal plate, granulation could result. More than half of chalazia resolve spontaneously.

Hordeolum

A hordeolum (stye) is an acute, suppurative, painful, localized inflammation of the eyelid margin involving the follicles of the eyelashes, the meibomian glands (sebaceous glands that empty out into the eyelashes), or the glands of Zeis (sebaceous glands that do not empty out into the eyelashes). *Staphylococcus aureus* is found in most cases. Exudation of purulent material may be seen from the hair follicle or on the conjunctiva.

Nevi

Nevi may erupt on the eyelids. In a retrospective analysis of 80 patients who had benign eyelid and conjunctival tumors (86 tumors), the most frequent tumor was intradermal nevus (44.6%), seborrheic keratosis (16.1%), and compound nevus (10.7%) in eyelid tumors, and compound nevus (29.2%) and intradermal nevus (25.0%) in conjunctival tumors.

Sarcoid

Cutaneous involvement in sarcoid occurs in 20% to 35% of patients [43]. Various specific cutaneous lesions occur in sarcoid, including maculopapules, plaques, nodules, lupus pernio, scar infiltration, alopecia, ulcerative lesions, and hypopigmentation. Erythema nodosum is the most common nonspecific dermatologic manifestation of sarcoid. Lesions may occur on the eyelid as nodules, swelling, scars, or lupus pernio. Lupus pernio appears as violaceous, infiltrated nodules that may be found on the eyelids and lid margin and on the external nares, ears, or along the vermilion border of the lips. Histologic analysis of specific lesions shows noncaseating granulomas consistent with

sarcoid. Sarcoid is also commonly associated with uveitis and must be differentiated from chronic conjunctivitis by signs and symptoms such as increased photosensitivity, pain, and unilateral involvement.

Hemangioma

Hemangiomas and malformations are congenital vascular lesions. Hemangiomas are classified as strawberry hemangiomas, which occur at birth or during the first year of life and affect more girls than boys. Most of these lesions are small and harmless, proliferating for 8 to 18 months, then regressing over the next 5 to 8 years. They appear as bright red, well-circumscribed masses that may start out flat and telangiectatic and become nodular, protuberant, and compressible. They are benign but may cause difficulty if they compress vital organs or interfere with normal function. Cavernous hemangiomas are similar to strawberry hemangiomas but are collections of dilated vessels deeper in the dermis and subcutaneous tissue. They may appear as skin-colored, pink, red, or blue masses. Hemangiomas may involve the eyelids, and when there is a possibility of encroachment of the orbit, early management is sought. Approximately 30% of hemangiomas resolve by the fourth birthday, 50% by the fifth birthday, and 75% by the seventh birthday, with 95% undergoing complete or partially complete regression [44].

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common malignancy affecting the periorbital area. It presents more commonly on the lower eyelid and medial canthus [45]. The age-adjusted incidence rates per 100,000 population per year for BCC of the eyelid are 16.9 for men and 12.4 for women [46]. It is slow growing and locally invasive but rarely metastasizes. The most common presentation of BCC is a shiny, waxy, pearly nodule with rolled borders and small visible telangiectasias on the surface. It is painless and immobile. Variants of the nodular type include the nodular-ulcerative form (also called rodent ulcer wherein the nodule ulcerates centrally) and the morpheaform or sclerosing type (characterized by a pale indurated plaque). Effacement of the meibomian gland orifices with loss of adnexal structures provides a further clue to the typical nodular appearance. Lesions may bleed on manipulation due to increased friability.

Squamous cell carcinoma

Squamous cell carcinomas (SCC) are less common, representing about 5% of eyelid cancers. When they occur on the eyelids, they tend to be seen more often on the upper eyelid. Unlike BCC, they metastasize more often. Risk factors include chronic sun exposure, increasing age, and type

I skin types. Other predisposing factors are immunosuppression and exposure to radiation, arsenic, and coal tar. SCC may arise de novo or from premalignant lesions such as actinic keratosis. The typical presentation of SCC is a shallow ulcer that is often crusted over a reddish base with a surrounding ridgelike border. Associated loss of eyelashes and destruction of the surrounding eyelid structure are additional clues. SCC must be differentiated from a keratoacanthoma, which is benign but grows rapidly and has a horny horn arising from a central crater. Due to the higher rate of metastasis (up to 10%) in SCC, a more aggressive approach is optimal.

Sebaceous carcinoma

Sebaceous carcinoma is a rare cancer involving the eyelid (1%–5.5% of all malignancies of the eyelid), but when present, it is an aggressive and threatening condition with a high tendency for recurrence, invasion, and local or distant metastasis. It arises from the sebaceous glands, of which about 75% are located in the periorbital area. In this region, the appearance is variable and may mimic other benign conditions such as a wart, chronic blepharitis, or a chalazion that is recurrent. When in doubt, a biopsy is suggested. There is a rare association with Muir-Torre syndrome, which should be evaluated in a patient who has sebaceous carcinoma [47].

Malignant melanoma

Malignant melanoma involving the eyelid is less common, developing in about 1% of eyelid tumors [48]. About half are of the nodular variant and approximately 40% are the superficially spreading type. When evaluating pigmented lesions that are suspicious, one needs to examine the lesion for ABCDs: asymmetry, irrregular border, variegate color (pigmentation), and rapidly increasing diameter. Malignant melanomas metastasize, so early detection, excision, and evaluation for metastatic disease are of vital importance. Tumor thickness is an important predictor of prognosis. Margin control by mapped serial excision or modified Mohs' micrographic surgery is a useful technique to ensure complete excision and minimization of local recurrence [49].

Eyelid dermatitis

Pruritic, erythematous, weeping, scaly, inflamed eyelids are caused by many etiologies. The more common causes include atopic dermatitis, contact dermatitis, contact urticaria, rosacea, seborrhea, and psoriasis [50].

A number of studies have been conducted to determine the frequency of various skin disorders causing eyelid dermatitis. Atopic dermatitis as a cause of eyelid dermatitis was reported in 39% [51], 23% [52], and 14% [53]. Allergic contact dermatitis was the etiology of eyelid dermatitis in 65%

[53] and 46% [52]. Irritant contact dermatitis was the cause of eyelid dermatitis in 24% [51], 16% [53] and 15% [52].

It was noted that elderly patients had a higher tendency for contact dermatitis to be allergic rather than irritant in nature. Women were affected more commonly [54]. Ocular rosacea was noted in 3% to 58% of patients who had cutaneous rosacea, and when there was ocular involvement, the peak age of onset was in the fifth decade [55]. Contact urticaria is less commonly diagnosed. Other dermatitis conditions of the eyelids include SD, psoriasis, dry eyes, dermatomyositis, and overlapping connective tissue disease.

A retrospective study [54] analyzing 1215 patients patch tested over 10 years showed that of the 105 patients who had eyelid dermatitis, 43.8% had allergic contact dermatitis, 36.2% had SD, 11.4% had other dermatitis/dermatosis, 7.6% had irritant contact dermatitis, 3.8% had psoriasis, and 2.9% had atopic dermatitis. With isolated eyelid dermatitis, SD was the most frequent diagnosis (46.3%), followed by allergic contact dermatitis (35.2%).

Guin [56] demonstrated in 2004 that over a 2.5-year study period, 215 patients presented with eyelid dermatitis for the first time. Women were predominantly affected (173 versus 42). Of the 215 patients, 165 had allergic contact dermatitis; another 9 had protein contact dermatitis without relevant positive patch tests; 37 (12%) had atopic dermatitis; 35 (16%) had SD, psoriasis, or both; 5 had rosacea or periorbital dermatitis; 2 had dermatomyositis; and others had infections [56].

Ayala and colleagues [57] studied 447 patients who had eyelid dermatitis and found that 50.2% were diagnosed with allergic contact dermatitis, 20.9% were found to have irritant contact dermatitis, 13.5% were affected by atopic dermatitis, 6.3% had SD, 6.5% were affected by nonspecific xerotic dermatitis, and 2.3% had psoriasis. These investigators noted that the main risk factor for allergic contact dermatitis was four-eyelid involvement, the main risk factor for irritant contact dermatitis was onset of symptoms between 2 to 6 months, and the main risk factor for atopic dermatitis was the onset of symptoms after 6 months along with personal history of atopy [57].

Atopic dermatitis

Atopic dermatitis occurs in patients who have an atopic background, that is, a personal or family history of asthma, allergic rhinitis, or eczema. Criteria for the diagnosis of atopic dermatitis include major and minor criteria [58]. Major criteria include severe pruritus, family/personal history of atopy, and areas of predilection of the rash (cheeks and extensors in infants, antecubital and popliteal areas for older children and adults). Numerous minor criteria include cataracts, cheilitis, conjunctivitis, perifollicular accentuation, facial pallor/erythema, food intolerance, hand dermatitis, ichthyosis, elevated IgE, cutaneous infections, Dennie-Morgan fold, itching when sweating, keratoconus, keratosis pilaris, nipple dermatitis, orbital

darkening, palmar hyperlinearity, pityriasis alba, white dermatographism, wool intolerance, and xerosis. There is a genetic predisposition for the development of T_H2 inflammatory response and elevated IgE in response to allergens. Hence, atopics usually have high levels of total IgE [59]. Patients who have atopic dermatitis have “twitchy skin,” whereby their skin is hyper-reactive or hyperesthetic. Wahlgren and colleagues [60] described this phenomenon as *allokinesis*, which refers to the sensation of itch in atopics in response to stimuli that would not cause itch in nonatopics. The major problem is pruritus, which occurs with or without visible eczema. Thus, there is a vicious cycle of itch causing the eczema, which is made worse by further itching.

The eyelids are commonly involved in atopic dermatitis because they are thin, exposed to irritants, and more easily traumatized by scratching. Constant rubbing leads to chronic changes and inflammation of the eyelid. Eyelid dermatitis was due to atopy in 14% of cases as reported by Valsecchi and colleagues [53], in 23% by Nethercott and colleagues [52], and in 39% as reported by Svennson and Moller [51]. The common presentation of atopic dermatitis of the eyelids consists of symmetric, scaly, erythematous, mildly lichenified plaques on the upper eyelids with or without concomitant involvement of the lower eyelids. The more chronic the eruption, the darker and more lichenified the lesions become. Atopics are also more prone to acquiring other types of eyelid dermatitis such as contact dermatitis. The appearance of the typical rash in areas of predilection and other major and minor criteria are helpful to differentiate atopic dermatitis from other eyelid dermatitis. If the possibility of contact dermatitis is considered, patch testing may be performed.

Many eye changes occur in association with atopic dermatitis. Conjunctivitis and keratoconjunctivitis may commonly occur in conjunction with allergic rhinitis and allergic conjunctivitis. “Allergic shiners” are dark circles around the eyes secondary to venous congestion. In addition, there may be loss of eyelashes, lid edema, itching, burning, tearing, chemosis, and mucoid discharge. The presence of an extra fold under the lower eyelids called the Dennie-Morgan fold is a clue to the presence of atopy. Cataracts can develop secondary to chronic severe atopic dermatitis. Keratoconus is a rare manifestation of atopic dermatitis characterized by a conical eyeball. A very rare complication is retinal detachment.

Many triggering factors contributing to the itch are sweat and heat, irritants such as wool clothing, exposure to cigarette smoke, and aeroallergens such as dust mites. Specific allergens may cause flare-ups of the dermatitis and may occur by way of contact, inhalation, ingestion, or injection [61]. Due to defects in innate and acquired immune responses in patients who have atopic dermatitis, patients have an increased susceptibility to bacterial, fungal, and viral infections [62]. Atopics are prone to staphylococcal colonization, which may lead to chronic anterior blepharitis when the colonization occurs on the eyelid. A subset of atopics may be sensitive to allergens

expressed by the yeast *Malassezia furfur* [62]. In addition, atotics are more commonly affected by contact dermatitis [63].

Contact dermatitis

Acute, subacute, and chronic

Contact dermatitis is the most common cutaneous eruption of the eyelids. The eyelid is prone to contact dermatitis because it is thin, pliable, and soft [64]. Contact dermatitis is also categorized according to its evolution into acute, subacute, and chronic forms. Acute contact dermatitis of the eyelid is characterized by itchy, erythematous, vesicular or papular inflammation. The subacute forms are [65] less vesicular and red and start to become more thickened and scaly. Chronic contact dermatitis is dry, thick, lichenified, more scaly, and usually less pruritic.

Epidemiology

Allergic contact dermatitis has been considered the most common of the many dermatologic conditions found with eyelid dermatitis [63]. In a retrospective study of 203 patients who had persistent or recurrent eyelid dermatitis, 74% were found to have relevant contact dermatitis. In a study of 1781 patients diagnosed with contact dermatitis over a 6-year period, 4.2% had allergy to cosmetic products.

Another retrospective analysis studied 1554 patients diagnosed as having conjunctivitis with or without dermatitis on the eyelids. Fifty-six percent [66] had a positive reaction to at least one of the contact allergens tested. The main sources were topical pharmaceutical products (antibiotics, corticosteroids), cosmetics (fragrance components, preservatives, emulsifiers, hair care and nail products), metals (nickel), rubber derivatives, resins (eg, epoxy resin), and plants [67].

In the 2003–2004 data of the North American Contact Dermatitis Group (NACDG) [68], 268 patients were found to have a final diagnosis of allergic contact dermatitis of the eyelids alone. Gold was the most frequently encountered etiology (12.5%).

Irritant versus allergic

Contact dermatitis may be categorized as irritant or allergic. Irritant contact dermatitis is more common and develops secondary to the application of an irritating substance. Irritant contact dermatitis is a more diffuse, less well defined area of inflammation that develops depending on strength and concentration of the substance, duration of contact, condition of the eyelid before contact (eg, the presence of fissures or prior inflammation), and individual susceptibility. Allergic contact dermatitis is secondary to delayed hypersensitivity reaction to the substance that is T-cell mediated and

occurs after previous sensitization. Patients who develop allergic contact dermatitis are genetically predisposed with an atopic background. The appearance and distribution of the inflammation correspond to the area of contact (eg, cosmetics used on the eyelids) but may be more diffuse due to rubbing of the eyelids with the material (eg, nail polish) and occur more rapidly within 12 to 24 hours after a period of prior sensitization. Although irritant and allergic contact dermatitis have some characteristics that distinguish one from the other, they are not always readily distinguishable [66].

Etiologies

In general, rhus (poison ivy) and chrysanthemums are the most common causes of allergic contact dermatitis. For the eyelids, a common substance causing allergic contact dermatitis is nail polish coming in contact with the eyelid through scratching. Important sources of contact dermatitis include nickel (from glasses, jewelry, metal eyelash curlers), cosmetics, fragrances, contact lens solutions, and topical medications such as corticosteroids and neomycin, or preservatives such as formaldehyde resin and benzalkonium chloride [54,63]. There is also airborne contact dermatitis, caused by things such as pollen, dust mites, animal dander, and chemicals suspended in the air. The eyelids are particularly predisposed to airborne contact dermatitis because they are exposed and materials may lodge and get deposited on the upper eyelids.

One meta-analysis showed that nickel (14.7% of tested patients), thimerosal (5.0%), cobalt (4.8%), fragrance mix (3.4%), and balsam of Peru (3.0%) are the most prevalent allergens, whereas the five least prevalent allergens are paraben mix (0.5%), black rubber mix (0.6%), quaternium-15 (0.6%), quinoline mix (0.7%), and caine mix (0.7%). NACDG data, however, show that the five most prevalent allergens are nickel (14.3%), fragrance mix (14%), neomycin (11.6%), balsam of Peru (10.4%), and thimerosal (10.4%) [69].

Cosmetics

Cosmetic alteration of a patient's orbital skin is a common reason for professional consultation [70]. The NACDG conducted a study in 13,216 patients and found contact dermatitis related to cosmetics in 5%. These figures are believed to underestimate the total number of cases because most reactions thought to be trivial are not investigated [69].

The most common cause of contact dermatitis of the eyelids is cosmetics applied to the hair, face, or fingernails rather than to those applied to the actual eye area [66]. Hence, nail polish applied to nails and hair dye applied to the hair and scalp are common causes of eyelid contact dermatitis. Ectopic dermatitis occurs when the primary area of application causes the eruption in another area. Other cosmetics that come in contact with the

eyes and may cause eczema are facial creams, foundations, and blush. Eye makeup such as mascara, eye shadow, and eyeliner can cause burning and itch in predisposed individuals. Irritation may also develop from propylene glycol and soap emulsifiers or from volatile components such as mineral spirits, isoparaffins, and alcohol [66].

The common ingredients in cosmetics causing contact dermatitis of the eyelid include various pigments, fragrances, resins, additives, nickel, emulsifiers, preservatives, and vehicles. Examples include parabens, phenyl mercuric acetate, imidazolidinyl urea, quaternium-15, potassium sorbate, antioxidants, butylated hydroxyanisole, butylated hydroxytoluene di-tert-butylhydroquinone, colophony, bismuth oxychloride, emollients, lanolin, and propylene glycol [65,71].

p-Phenylenediamine (PPD) is the most frequent sensitizer in hair dyes and semipermanent henna tattooing. It can cause marked edema of the eyelids. Recent reports have shown PPD to cause contact dermatitis secondary to use in permanent eyeliners, or dye in eyelash and eyebrow creams [72,73]. Hair loss developed in one patient secondary to PPD in tinting mascara [74].

Parabens, phenyl mercuric acetate, imidazolidinyl urea, and quaternium-15 are preservatives used to decrease contamination of the cosmetics. Quaternium-15 and imidazolidinyl urea may induce hypersensitivity reactions by the released formaldehyde [75]. To decrease exposure to parabens, potassium sorbate has been used in formulations, but cases of sensitization to sorbic acid have also been reported [76]. Not all individuals who are sensitive to parabens have to avoid it altogether. Some are able to apply parabens-containing products if the underlying skin is intact and devoid of any abnormality or inflammation.

Tetrahydracurcumin derived from extracts of the root of the *Curcuma longa* plant, also known as turmeric, has been found in cosmetics used for skin lightening and protection against UV-B and in antiaging preparations [77]. Sunscreen agents and fragrances can also cause photoallergic dermatitis, in which exposure to the UV light is required for the development of contact dermatitis.

In general, cosmetics are manufactured such that potential irritants are usually weak, especially if they are to be placed in the eye area [66]. The cosmetics industry must ensure that it maintains standards to make products safe for topical application and accidental insertion into the eye [64].

Irritation due to mascara and eye cosmetic preservatives

Mascara is water based or waterproof. Water-based mascara contains emulsifiers such as sodium borate and ammonium stearate, which are irritating to the conjunctiva. Cases of allergic contact dermatitis to shellac in mascara have been reported [78].

Allergic contact dermatitis has been reported after exposure to resin (colophony) [79] and dihydroabietyl alcohol (Abitol) [80,81], which are contained in some mascara products.

In eye shadow makeup, allergies have been reported secondary to ditiarybutyl hydroquinone, which is an antioxidant; yellow D & C No. 11 dye [82]; and diisopropanolamine, which is used in cosmetic gloss formulas [66]. A special removal product for waterproof eye makeup containing surfactants such as cocamidopropyl betaine has caused allergic contact dermatitis [83]. In these patients, it is recommended that they avoid waterproof products [64].

Fragrance

As per the 2001–2002 report of the NACDG [83], fragrance mix is the fourth most frequent patch-test positive reaction (10.4%) compared with reactions to nickel (16.7%), neomycin (11.6%), balsam of Peru (11.6%), gold (10.2%), and quaternium-15 (9.3%).

Irritation due to conjunctival deposition

The conjunctivae could be irritated by inadvertent deposition of cosmetics such as eyeliner and mascara into the eye. The pigment could cause discoloration of the conjunctiva, discomfort, tearing, and itching or the patient may not be bothered by such deposition of cosmetics and any irritation may go away spontaneously.

Artificial eyelashes may cause irritation secondary to the natural or synthetic fibers or to the adhesive used to attach them to the lids. The adhesive is a mixture of rubber latex, cellulose gums, casein solubilized with alkali or other resins, and water. Although no reports have documented that the rubber latex in the adhesive has caused latex hypersensitivity, there have been reports of latex sensitivity to rubber used in older forms of eyelash curlers [66].

Nail polish

The main allergen responsible for nail polish contact dermatitis is toluene sulfonamide formaldehyde resin (TSFR) [84]. “Hypoallergenic” nail polish has been manufactured, whereby a polyester resin replaces the TSFR. There have been a few cases of contact dermatitis caused by phthalic anhydride/trimellitic anhydride/glycols copolymer, which is not available for patch testing, but contact dermatitis can be diagnosed using patch testing of the varnish itself [85]. One should note that the dermatitis from nail lacquer is not found on the nails and the surrounding nail fold, which are thicker, more resistant areas. Some reactions have occurred with artificial nails containing cyanoacrylate or methacrylates [86].

Metals

Nickel and mercury are well-recognized contact allergens. Nickel is the most common positive patch test. The exposure to nickel is common due to the use of fancy jewelry and accessories. Stainless steel products are recommended in susceptible individuals in whom nickel-plated eyelash curlers and tweezers may cause reactions [66]. Mercury is found in thimerosal,

a commonly used antiseptic or preservative in vaccines and topical medications. Mercury is also found in dental amalgam and in thermometers. Gold and palladium have been detected as contactants and have been included in patch-test screening trays. Cobalt is another possible etiologic agent. Cobalt and palladium allergy may be associated with nickel allergy [87].

Aeroallergens

There have been reported cases of contact dermatitis secondary to airborne contactants [66]. Dermatitis can occur from exposure to burning poison ivy. Other contact allergens that are airborne and cause eyelid dermatitis are insecticides, animal dander, and dust mites [63], household sprays, and occupational volatile chemicals. Other reported causes are household products such as oil of lemon peel and dyes of Florida orange skin, and phosphorous sesquisulfide in “strike anywhere” matches used to light wood fireplaces [88,89].

Medications/eyedrops/contact lens solution

Many topical medications have been reported to cause hypersensitivity of the eyelids and conjunctivae. Neomycin sulfate, which is used for treatment of conjunctivitis, is a common contactant [90]. Lack of resolution or worsening of the condition should raise the suspicion of contact dermatitis.

Allergens identified in topical ophthalmics include antibiotics, antivirals, β -blockers, mydriatics, anesthetics, and preservatives such as benzalkonium chloride, thimerosal, and phenylmercuric acetate [88]. Medicated eye drops and contact lens solutions may contain ingredients that have the potential for irritation or sensitization, leading to eyelid dermatitis, conjunctivitis, or both. Benzalkonium chloride and thimerosal (commonly used preservatives in ophthalmic solutions) may lead to dermatitis [91]. Contact allergy to sodium metabisulfite has been reported rarely so far, leading to the increasing use of this agent as a preservative by manufacturers of cosmetics and medications [92]. An alternative preservative is chlorobutanol, which is rarely sensitizing. Patients who are very sensitive could opt to use preservative-free solutions. Topical medications used for glaucoma have been documented to cause contact dermatitis. A prostaglandin F2 alpha analog called latanoprost used to lower intraocular pressure has been described to cause sensitization. It was reported to cause pruritus, erythema, swelling, and erosions of the eyelids, especially in the elderly, and symptoms can appear several months after therapy [93]. Propine, containing epinephrine hydrochloride, also used to treat glaucoma, has caused patch test-proven ocular hypersensitivity [94].

Paper

Perfume, formaldehyde, or benzalkonium chloride found on facial tissues has been found to produce dermatitis in sensitized individuals. In persons

sensitized to formaldehyde, dermatitis could be caused by contact with newsprint and carbon paper products [66].

Plants

Sensitizing plants in cosmetics are tea tree oil, arnica, chamomile, yarrow, citrus extracts, common ivy, aloe, lavender, peppermint, and others. The sensitizing potential of these plants varies [95]. Toxicodendron species include poison ivy, poison oak, and poison sumac and are a cause of contact dermatitis affecting millions of Americans each year [96]. When the eyelids are affected, it can produce marked swelling with minimum dermatitis of the face [66]. The dermatitis may also affect other parts of the body that come in contact with the plant.

Histology

Histologically, eczema is generally characterized by the presence of spongiosis. Spongiosis refers to the increased intercellular edema in the epidermis resulting in the pulling away of the keratinocytes from their surrounding desmosomes. Hence, spongiosis is a pathologic nonspecific finding in contact dermatitis.

Diagnosis

Diagnosis is through clinical suspicion. A compatible history and examination is fundamental in the diagnosis and can be supported by patch testing. Patch testing for poison ivy is not necessary because history and clinical appearance are usually diagnostic. When the diagnosis is in question or the causative substance is unknown, patch testing may be used. The thin-layer rapid epicutaneous patch test is a commercially available Food and Drug Administration (FDA)-approved patch test panel and the global standard [69]. It is an easy diagnostic tool, with 24 patches containing 42 unique allergens and four complex mixtures [97]. The patch is applied on noninflamed skin, removed after 48 hours, and read by an experienced practitioner after 48 and 96 hours. Positive results range from 1 to +2 and depend on the presence of erythema, vesiculation, and induration. Irritant reactions caused by a direct toxic effect that occur after 48 hours should disappear by the fifth day, whereas allergic responses worsen.

There are many limitations to routine patch-test panels. Many possible contactants are not found on the FDA-approved panels available in the United States [54]. These panels contain only approximately 1.4% of the more than 3700 known allergens [97]. Comparison with data from the NACDG suggests that clinically important allergens may be missed by the TRUE test [69]. Hence, due to the difficulty in determining the etiology of eyelid dermatitis with routine patch testing, open and closed patch testing can be performed “as is” with eye cosmetics if liquid cosmetics such as

mascara and certain eyeliners are allowed to dry before occlusion [64]. Furthermore, the fragrance mix detects only 70% of perfume-allergic patients and causes false-positive and false-negative reactions [98]. A big problem is the relative lack of information on some of the new ingredients that have been used in hundreds of marketed cosmetic formulations [99]. To assist the clinician in making a diagnosis, Cosmetic Industry On Call [100] provides information to assist in contacting manufacturers who may provide the ingredients necessary for patch testing. Reference information on the chemical concentrations and vehicles to use to test cosmetics ingredients is provided by de Groot and colleagues [101].

Herpes simplex

Herpes simplex is a viral infection caused by herpes simplex virus (HSV) 1 and 2. Herpes simplex may be primary or recurrent. The first or primary infection is usually more severe. On resolution of the primary infection, the virus remains in a latent or dormant phase in the sensory ganglia. For the eyelid, this is the trigeminal or superior cervical ganglion. Recurrent disease occurs with reactivation of the virus, which travels back to the skin from the nerve fiber. These recurrences may be triggered by stress, infections, immunosuppression, UV light, trauma, cold wind, or menstruation. Infection of the eye could involve the periorbital skin, the conjunctiva, or cornea. Typical lesions on the eyelid are grouped vesicles on an erythematous base (“dewdrops on a rose petal”) associated with itch and burning with or without ocular involvement. Lesions on the cornea or conjunctiva manifest as erosions or superficial ulcers. With recurrent disease, deeper erosions and stromal keratitis can develop. Untreated infection could lead to herpes simplex keratitis, which is regarded as the leading cause of infectious blindness in the United States [102].

A Tzanck test can be performed to make a quick diagnosis of herpes simplex. It entails scraping the floor of an intact vesicle and examining it under the microscope after staining with Wright’s or Giemsa stain. The presence of multinucleated giant cells is considered positive for herpes infection. A more accurate tool is the use of viral culture or testing for herpes simplex antibodies in serum.

Herpes lesions typically improve in 7 to 10 days, but recurrences are common. In immunosuppressed individuals, lesions are more severe, more frequent, harder to treat, and may become disseminated.

Herpes zoster

Herpes zoster, also known as shingles, is caused by varicella-zoster virus. It commonly presents initially as pain followed by a unilateral rash in a dermatomal distribution. The rash begins as erythematous papules that become vesicular and sometimes pustular over an erythematous patch. In

immune-competent patients, the eruptions last between 2 and 4 weeks; however, postherpetic neuralgia is a common problem, especially in the elderly. Trigeminal neuralgia, which may occur with ophthalmic zoster, can recur months to years after the resolution of the active lesions and can range in intensity from mild to severe and disabling. Atypical lesions, more severe eruption, and bilateral involvement may occur in immunocompromised individuals.

Vesicles found on the tip or side of the nose, called the Hutchinson's sign, is a clue that the eyes will be affected [103]. These early skin lesions should alert the physician to treat aggressively to prevent potential vision loss. In herpes zoster involving the eyes, or herpes zoster ophthalmicus, about half of the patients have ocular involvement such as conjunctivitis or keratitis.

Clinical diagnosis is usually adequate if a typical eruption is discovered. A Tzanck test showing multinucleated giant cells assists in the diagnosis. Serum antibody testing for herpes zoster antibodies or viral culture differentiates it from herpes simplex.

Treatment considerations for the eyelids

Eyelid dermatitis

Whenever appropriate, finding and eliminating an identifiable cause is the main goal of therapy. Prevention is key. For example, for contact dermatitis, avoidance of the contactant is essential. For cases in which cosmetics play a role in the eyelid dermatitis, Draelos [64] recommended that cosmetics for patients who have eyelid dermatitis be formulated with a paucity of ingredients, an absence of sensitizers, a minimum number of irritants, and no cutaneous sensory or vasodilatory stimulants.

Saline compresses and baby shampoo wiped gently on the affected areas are safe and mild remedies used to help alleviate the scaling and crusting of blepharitis. For SD lesions, topical antifungal creams, shampoos, and lotions are used with much improvement [5]. Antidandruff shampoos that have fungistatic ingredients such as selenium sulfide and zinc pyrithione are advised for regular use on active lesions and two to three times a week to prevent eruptions. Systemic antifungals and antibiotics (erythromycin or tetracycline) are reserved for severe infections, superinfection, or persistent inflammation.

Management of eyelid dermatitis (contact dermatitis, atopic dermatitis, SD) includes improvement of inflammation using corticosteroids. This treatment should be used with caution because the eyelids are very thin and become more prone to side effects of topical steroids such as thinning of the skin, visible blood vessels, and more serious ocular side effects such as glaucoma and cataracts with chronic use, especially with high potency. Most inflammatory conditions respond to topical corticosteroids. Possible

side effects of steroids used on the eyelids include atrophy, telangiectasias, glaucoma, cataract formation, and risk of infection [104]. The mildest and nonfluorinated steroids should be used and only for a brief period of time [105,106]. The potential for side effects increases with the longer use of higher potency steroids. For severe cases, oral steroids may be warranted.

In light of the side effects of steroids, more physicians now prescribe the newer topical calcineurin inhibitors (TCIs)—pimecrolimus (Elidel) or tacrolimus (Protopic). TCIs cause minimal systemic absorption [107,108] and have a low incidence of side effects such as local burning, stinging, and itching [109,110]. They can be used for longer periods of time. TCIs help decrease the inflammatory features of dermatitis and decrease the need for steroids, which have many side effects when applied chronically and on thin skin such as the eyelids [111,112]. The safety of the TCIs in children younger than 2 years is controversial [8].

Measures to avoid itching are of utmost value to prevent the itch–scratch cycle associated with atopic dermatitis. Cold compresses alleviate the sensation of itch. Because histamine is not the cause of the inflammation or itch, antihistamines are not recommended, apart from the use of sedating antihistamines to help the patient fall asleep. When identified, triggering factors such as irritants, tobacco smoke, and exposure to aeroallergens should be avoided.

Infections

Infections of the eyelids are treated according to the etiology. A culture or eye swab is recommended to confirm the diagnosis. Use topical (eg, mupirocin, polysporin) or oral antibiotics for bacterial infections such as pyoderma. Use antivirals (oral acyclovir, valacyclovir) for viral infections such as herpes simplex and herpes zoster.

Treatment for herpes simplex should be started early, within the first 2 days of the infection. The treatment of choice is systemic antivirals such as acyclovir or valacyclovir. Topical acyclovir (Zovirax) can be used for herpes keratitis, in which the infection is confined to the epithelium [113]. Topical acyclovir, trifluridine, or vidarabine has been found to result in greater proportion of healing within 1 week of treatment compared with idoxuridine [102]. Corticosteroids can be added for herpetic stromal disease and iritis. Ocular HSV disease can be treated with 12 months of acyclovir to reduce the recurrence of ocular and orofacial HSV. This long-term prophylaxis for patients who have a history of HSV stromal keratitis is important to prevent recurrences and visual loss [113].

Herpes zoster is treated with antivirals. Acyclovir should be started as early as possible, preferably within the first 72 hours (164,165). Starting treatment early has been shown to decrease the duration of the illness and decrease the risk of ocular and systemic complications [113]. Giving an oral steroid early in addition to antivirals is an option to improve the early

quality of life in herpes zoster patients. Additional measures include symptomatic treatment of pain and prevention of secondary infection. The varicella-zoster virus vaccine is used for prevention of herpes zoster [114].

Warts may be transient infections but may spread, recur, and become difficult to treat. With this in mind, various treatment options have been tried with variable success [115]. Surgical measures include electrodesiccation, laser, and excision. Destructive modalities include cryotherapy, photodynamic therapy, salicylic acid, and trichloroacetic acid. These modalities have good results in destroying lesions. Other modalities include antiproliferative agents such as 5-fluorouracil, intralesional bleomycin, and podophyllin. Therapies targeting the immune system include interferons, imiquimod, and duct tape occlusion therapy [116].

Molluscum contagiosum may resolve spontaneously and may be left alone, especially in young children. Lesions may last 2 to 4 months, with autoinoculation causing more lesions to erupt. Most lesions resolve by 6 to 9 months, but others persist for longer periods up to few years. Conventional therapy relies on tissue destruction using modalities such as curettage, cryotherapy, carbon dioxide laser, electrodesiccation, trichloroacetic acid, and cantharidin. More recently, topical immune modulators have been used with some success [117,118].

Inflammation

Acne is treated with keratolytics such as tretinoin to loosen up the impacted keratinocytes. Alternatively, acne surgery using comedone extractors is a quick remedy to extract the contents of the follicle.

Treatment for rosacea was evaluated in a recent meta-analysis; however, the quality of the studies was generally poor [119,120]. There is evidence for the use of topical metronidazole and azelaic acid and some evidence for the use of oral metronidazole and tetracycline. Tetracycline or erythromycin is the primary treatment option for rosacea. The lesions that are thought to respond to this treatment include blepharitis, keratitis, and inflammatory papules and pustules. The efficacies of doxycycline and tetracycline, including treatment effect, optimal dose, duration of therapy, and side effects when used for ocular rosacea, have not been established [121]. Minocycline or doxycycline (100–200 mg/d) may be tried to decrease the blushing. Metronidazole (200 mg two times a day) is another option. Response is hard to predict. Some lesions clear in 2 to 4 weeks, whereas others require chronic suppression. Isotretinoin has been effective in severe refractory cases of rosacea. A newer treatment modality for rosacea is low-dose (40 mg) doxycycline monohydrate (Oracea), which is used as an anti-inflammatory agent, not as an antibiotic. The low dose allows for maintenance, with less chance for development of resistance [122]. It may be used alone or in combination with topical metronidazole [123]. Topical therapy may be used for mild rosacea or for maintenance. Topical metronidazole (Metrogel) 0.75% or

1% is commonly used [124]. It may exert its effect by inhibiting the neutrophil-induced oxidative injury. Clindamycin is another option for topical application, especially for pustular lesions. Use of 15% azelaic acid showed a clear improvement, as rated by physicians and patients [123]. Sulfur/sulfacetamide lotion also controls pustules. These topical creams may be used alone for milder disease or in combination with oral antibiotics. Lack of response to antibiotics may be due to demodex infestation or tinea, which can be confirmed using potassium hydroxide smear and be treated with crotamiton, lindane, sulfur/salicylic acid lotions.

For ocular rosacea, lid hygiene is important. Warm compresses and gentle massage of the tarsal plate help to decrease the lipid secretions from the meibomian glands. For dry eyes that may accompany ocular rosacea, artificial tears are effective. Bacterial overgrowth on the lids is treated with topical antibiotics. Inflammatory lesions respond to steroid applications used for short durations to avoid telangiectasias and other local effects of steroids.

Urticaria and angioedema

In the more acute forms in which an identifiable cause is known or suspected, avoidance is mainstay of treatment, followed by symptomatic relief of swelling with antihistamines and glucocorticoids. Therapy is more challenging when a cause is not found despite extensive workup. Empiric therapy that includes H_1 with or without H_2 blockers may be effective. If the eruption is more chronic, control is sought with use of regular daily H_1 antihistamines, followed by the addition of other classes of H_1 . Doxepin, a tricyclic antidepressant that has both H_1 and H_2 inhibition, has been a rewarding adjunctive therapy. Side effects of antihistamines such as somnolence in the sedating types should be taken into consideration. Corticosteroids and immune modulators may be tried in refractory and severe cases.

In the hereditary forms of angioedema, treatment is much different. Prophylactic treatment of the condition for long-term management and before surgical procedures includes the use of attenuated androgens (danazol) and antifibrinolytics (aminocaproic acid). Treatment with fresh frozen plasma and plasma-derived C1 inhibitor concentrate (available in Europe and in phase 3 trials in the United States) has been used for acute attacks. Newer treatment modalities that target specific elements of the complement or kinin pathways are being developed. Measures to replace C1 inhibitor with plasma-derived or recombinant C1 inhibitor and to inhibit bradykinin with a highly specific kallikrein inhibitor (ecallantide or DX-88) or a specific bradykinin-B2-receptor antagonist (Icatibant) are in development [125–128]. These treatments may prove effective in acute attacks and are being studied for their potential use as prophylaxis [129]. Rituximab has been tried for treatment of acquired angioedema associated with lymphoproliferative and autoimmune diseases [128].

Benign tumors and growths

Benign growths on the eyelids include milia, syringomas, chalazia, hordeola, moles, skin tags, and xanthelasmas. Milia are benign cysts that can be removed using a comedone extractor after being pricked with a blade tip or lancet. Application of mild pressure will allow extrusion of soft, white material. For those who do not want to undergo extraction, topical retinoids can be tried but have less success and should be used with caution around the eyelids because they are irritating. Patients seek treatment of syringomas for cosmetic purposes. Effective treatment methods include electrodesiccation and curettage or low-dose electrocoagulation [130]. More recently developed treatments consist of the use of lasers [131]. More than half of chalazia resolve spontaneously. Conservative management is through warm compresses. Some ophthalmologists inject steroids into the lesions that are not infected [42]. Drainage and excision (and cautery and curettage) may be done. These surgical procedures and injections have potential for hypopigmentation, atrophy, and disfigurement. Argon laser treatment is an interesting alternative technique, particularly in cases with cosmetic indications [132]. A hordeolum may be self-limiting and may drain spontaneously. Supportive measures include warm compresses or removal of an eyelash if the hordeolum is external. For more immediate relief of the infection, incision and drainage may be performed. If the infection spreads beyond the immediate area of the nodules, topical and systemic antibiotics are indicated.

Due to the benign nature of moles, no treatment is necessary. Patients seek removal for cosmetic reasons or because of irritation, interruption with normal function (eg, the mole may be in the line of vision), or suspicion that lesions are atypical or malignant. Surgical excision or lasers are used for removal of moles depending on the situation [43,133]. The use of Q-switched lasers has revolutionized the treatment of nevi of Ota [134–136]. Although good results may be achieved with laser ablation of these lesions, laser treatment modalities for congenital melanocytic nevi remains controversial because of the potential for malignancy [134].

Xanthelasmas may be removed with chemicals such as trichloroacetic acid or liquid nitrogen. They may be surgically excised or removed using lasers [21]. Despite successful treatment, lesions often recur.

Skin tags are benign growths commonly removed for cosmetic reasons or when function is impaired (such as lesions obstructing vision if occurring near the eyes). Simple surgical excision can be performed by way of curettage, cautery, snipping (when small or pedunculated), cryotherapy, or lasers. When lesions are atypical or the diagnosis is in doubt, histologic biopsy is recommended to rule out premalignant and malignant lesions such as melanoma.

Malignant tumors

A diagnostic biopsy assists in the proper evaluation. Surgical treatment of carcinomas may have good results. Smaller lesions may be treated with

electrodessication and curettage. Larger lesions can be surgically excised or treated with cryosurgery, chemical surgery, radiotherapy. For areas that need more aggressive management such as large areas, those found in difficult locations such as around the medial and lateral canthi, or recurrent lesions, referral to a skilled Mohs' surgeon is recommended.

Despite rare metastasis of BCC, the tendency for local invasion warrants early intervention and removal. The overall cure rate is approximately 95%; however, despite excision, lesions seen arising from the medial canthus have been found to have a high recurrence rate (~60%) [137].

SCC has a higher rate of metastasis (up to 10%) such that a more aggressive approach is optimal. Immediate histologic monitoring of surgical margins with frozen sections or Mohs' micrographic surgery also allows for smaller margins of excision in an area where tissue conservation is important [138]. Mohs' surgery is the treatment of choice to ensure complete removal, especially in difficult-to-manage areas.

As with other cancers of the eyelid, wide local excision or Mohs' surgery is necessary for sebaceous carcinomas [139]. Prognosis is poor, with mortality second only to malignant melanoma. A clinicopathologic study of sebaceous carcinoma revealed the occurrence of death in 9% and mutilating exenteration in 23% of the patients studied [140].

Malignant melanomas metastasize, so early detection, excision, and evaluation for metastatic disease are of vital importance. Tumor thickness is an important predictor of prognosis. Margin control by mapped serial excision or by modified Mohs' micrographic surgery is a useful technique to ensure complete excision and minimization of local recurrence [49].

"Cosmetic" lesions of the eyelids

Vascular lesions

Due to the natural course of hemangiomas, they are usually left alone. Treatment is available when the lesions present cosmetic problems, affect surrounding organs, or interfere with normal functions. When sought, treatment for hemangiomas includes oral steroids, intralesional steroids [141], ultrapotent topical steroids [142], and laser [45,143].

Port-wine stains are cosmetic problems. Treatment is with the use of lasers. Alternatively, camouflage techniques (DermaBlend, CoverMark) may be used to cover the defect.

Vitiligo

Vitiligo involving the eyelids is best treated with cover-up measures. Cosmetic camouflaging agents such as DermaBlend and Covermark are available and can be chosen to match the patient's natural skin color. For localized vitiligo, topical corticosteroids are the preferred drugs. Extensive lesions over the body may be treated with topical or oral psoralens with UV-A light exposure (PUVA). In a recent double-blind randomized control

trial, 56 patients who had nonsegmental vitiligo, narrow-band UV-B therapy was found to be superior to oral PUVA therapy [144,145]. Newer therapies include topical immunomodulators (tacrolimus, pimecrolimus), which display comparable effectiveness over steroids with fewer side effects; vitamin D analogs; surgical therapy or transplantation; laser therapy; L-phenylalanine therapy; and pseudocatalase [146].

Others

Dermatomyositis is hard to treat and is often resistant. The mainstay of treatment is corticosteroids that are tapered according to clinical response, creatine kinase levels, and side effect profile [147]. Inadequate response or need for steroid-sparing agents may prompt the use of hydroxychloroquine [148], dapsone [149], or immunomodulators such as methotrexate, azathioprine [150], cyclosporine [151], and mycophenolate mofetil [152].

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