



Allergic Contact Dermatitis of the Face: a Review of the Common Agents Involved and Differential Diagnosis

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Abstract

Purpose of review Allergic contact dermatitis is a common form of type IV hypersensitivity reaction in response to exogenous agents directly or indirectly applied to the skin. Although any part of the body may be affected, the face's frequent exposition to environment, and consumer products, makes it one of the most commonly affected sites by the disease.

Recent findings As the consumer products are increasing worldwide, the list of potential allergens that may induce an allergic contact dermatitis of the face continues to grow. A correct diagnosis, and identification of the involved allergens, requires a careful interpretation of the clinical manifestations and patch test results (clinical relevance). It is therefore very important for the clinician to recognize the most common clinical manifestations and involved allergens of allergic contact dermatitis of the face to allow a correct diagnosis.

Summary In this chapter, we review the main current allergens, clinical presentations, and differential diagnosis of allergic contact dermatitis affecting the face.

Introduction

The face is one of the most frequently affected sites by allergic contact dermatitis, especially in women. Its frequent exposition to environment, low epidermal thickness, and presence of folds and wrinkles increase allergen exposure, predisposing to sensitization and development of allergic contact dermatitis.

Allergens can reach the face not only by direct exposure but also by airborne or indirectly, such as by scalp-applied products or by contact with the hands.

Allergic contact dermatitis is usually manifested by pruritic erythematous plaques with varying degrees of

vesiculation and lichenification, symptoms that can also be present in other cutaneous processes that frequently affect the face. Subtle clinical clues can help the clinician in the differential diagnosis.

In this chapter, we will review the main allergens, clinical presentations, and differential diagnosis of allergic contact dermatitis affecting the face. In addition, allergic contact dermatitis of the eyelids will be discussed with more detail.

Allergens and clinical presentation of allergic contact dermatitis of the face

The list of potential allergens that may produce an allergic contact dermatitis of the face is extensive and is summarized in Table 1.

According to the type of exposure, allergens can reach the face by three main mechanisms: direct, indirect, and via airborne. The type of exposure may correlate with the clinical presentation [1••].

Allergic contact dermatitis of the face induced by direct mechanisms

Allergens directly applied are the most common cause of allergic contact dermatitis of the face. The main sources of these allergens are present in cosmetics followed by topical drugs and herbal medicines and some objects [2–5].

Cosmetics are the most common cause of allergic contact dermatitis of the face, being their preservatives followed by their fragrances the most common culprits [6, 7]. The preservative Kathon CG seems to be the most frequently involved in all series [3, 8–10]. Kathon CG is 3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone and is present in numerous cosmetics such as make-up, moisturizers, soaps, and shampoos. Since its release in the 1980s, the prevalence of allergic contact dermatitis to Kathon CG has been increasing with a current prevalence around 2% [11]. In order to reduce Kathon CG incidence of allergic contact dermatitis, a “safer” methylisothiazolinone as a stand-alone preservative was introduced in 2004; however, after multiple cases of allergic contact dermatitis, methylisothiazolinone was found not as safe as it was thought [12]. Other preservatives commonly involved include Euxyl K-400, formaldehyde, and formaldehyde releasers such as quaternium 15, 2-bromo-2-nitropropano-1,3-diol (bronopol), diazolidinyl urea (Germal II), imidazolidinyl urea (Germal 115), and diaminodiphenylmethane hydantoin (DMDM hydantoin) [7, 13, 14]. Regarding fragrances, some of the most common allergens include balsam of Peru, cinnamic alcohol, cinnamic aldehyde, eugenol, hydroxycitronellal lyral (hydroxy-cyclohexene-carboxaldehyde), isoeugenol, geraniol, oak moss absolute, and alpha amyl cinnamic aldehyde [1••, 2].

Table 1. List of potential allergens that may produce an allergic contact dermatitis of the face

Product	Allergens	Clinical manifestation
Shampoos and conditioners	3-Aminophenol	Hairline, forehead, retroauricular region and neck
	p-Aminophenol	Sometimes eye edema (especially with paraphenylenediamine)
	Paraphenylenediamine	
	Toluene-2,5-diamine sulfate	
	Glyceryl thioglycolate	
	Ammonium persulfate	
	Phenoxyethanol	Wash off/rinse-off pattern
	Methylisothiazolinone	Eyelid dermatitis
	Methylisothiazolinone+ methylchlorisothiazolinone	
	Formaldehyde	
	Quaternium 15	
	Amerchol/lanolin	
	Propylene glycol	
Objects	Nickel	Localized dermatitis
Cosmetic creams and hygiene products	Formaldehyde	Patchy dermatitis
	Formaldehyde releases:	Eyelid dermatitis
	• Quaternium 15	
	• Imidazolidinyl urea	
	• Diazolidinyl urea	
	• DMDM hydantoin	
	• Bronopol	
	Parabens	
	Euxyl K-400 (phenoxyethanol/methyldibromo glutaronitrile)	
	Methylisothiazolinone	
	Methylisothiazolinone + methylchlorisothiazolinone	
	Iodopropynyl butylcarbamate	
	Thimerosal	
	Fragrance mix (cinnamyl alcohol, cinnamal, hydroxycitronellal, amyl cinnamal, geraniol, eugenol isoeugenol, oakmoss absolute)	
	Fragrance mix II (hexyl cinnamic aldehyde, hydroxyisohexyl 3-cyclohexene carboxaldehyde, farnesol, coumarin, citral citronellol)	
	Peru balsam	
	Propylene glycol	
	Cocamidopropyl betaine	
Lip products	Gallate	Cheilitis

Table 1. (Continued)

Product	Allergens	Clinical manifestation
Sunscreens	Benzophenone Octocrylene	Photoallergic contact dermatitis
Pastes and glues	Epoxy resin	Airborne contact dermatitis
Drugs	Ketoprofen Etofenamate	Photoallergic contact dermatitis
Plants (Compositae)	Sesquiterpene lactones	Airborne

Paraphenylenediamine usually induces an allergic contact dermatitis by an indirect mechanism, as it will be explained later on. However, in male patients, paraphenylenediamine, used in beard and mustache dyes, should induce an allergic contact dermatitis by direct mechanism [15].

Clinically allergic contact dermatitis of the face caused by cosmetics usually manifests with bilateral eczematous plaques with a characteristic patchy distribution [1••]. Although the cosmetic is usually applied evenly across the face, the dermatitis does not present homogeneously (Fig. 1). Some particular clinical presentations mimicking seborrheic and atopic dermatitis and lupus have also been described [16, 17].

Topical drugs and herbal remedies used to treat different diseases such as conjunctivitis, acne, rosacea, seborrheic and atopic dermatitis, and psoriasis are also frequent causes of allergic contact dermatitis of the face [2, 18, 19•]. In topical drugs, the most frequent allergens include antibiotics, antihistamines, anesthetics, corticosteroids, and non-categorized drugs such as minoxidil [20, 21, 22]. Moreover, in herbal remedies, balsam of Peru, terpenes, sesquiterpene lactones and essential oils seems to be the most frequent [19•].

Clinical manifestations of topically applied drugs and herbal remedies are usually varied and bizarre, so suspicion must be high as the clinical presentation



Fig. 1. Patchy dermatitis. Note the presence of eczematous plaques in a patchy distribution (affected and unaffected areas)

may mimic the patients own's dermatitis [18]. The lack of response to treatment and worsening or change in the patient's dermatitis should suggest the diagnosis.

A characteristic clinical pattern is the photoallergic. Photoallergic contact dermatitis induced by some topical drugs and herbal medicines is rare, but typically affect the face. Lesions characteristically present as pruritic eczematous plaques affecting the bridge of the nose, chins, and forehead and sparing the upper eyelids and retroauricular and submental areas. Involvement of the upper chest and dorsum of the hands is also characteristic. However, a secondary spread to sun-protected areas is notably common. Ketoprofen and etofenamate present in topical antiinflammatory drugs and octocrylene and benzophenone-3 present in sunscreens are the most frequently photoallergens involved. Other allergens to consider include halogenated phenolic compounds, cinnamates, dibenzoylmethanes, and fragrances such as musk ambrette and 6-methylcoumarin [23•, 24].

Finally, several objects may be responsible of allergic contact dermatitis by direct contact. Allergic contact dermatitis in these cases usually presents as localized erythematous plaques confined to the area of contact with the allergen. Although the allergens can be very varied, nickel present in jewelry, cell phones, and eyewear seems to be one of the most common culprits (Fig. 2).

Allergic contact dermatitis of the face induced by indirect mechanisms

Allergic contact dermatitis of the face can occur by allergens that are not applied directly to the face, but to other regions, such as the scalp, with secondary contact of the face, or those that are unintentionally transfer by the hands.

Ingredients present in hair dyes are the most common allergens inducing allergic contact dermatitis by this mechanism. Although the product is applied to the head, the clinical manifestations are mainly located on the face. Patients present with varying degrees eczema usually affecting the airline, forehead, retro auricular region, and neck. Involvement of the eyelids, sometimes with prominent edema, is also frequent.



Fig. 2. Dermatitis of the dorsum of the nose due to allergic contact dermatitis to nickel present in sunglasses

Paraphenylenediamine, toluene-2,5-diamine, p-aminophenol, and glyceryl monothioglycolate are well known scalp-applied contact allergens, being paraphenylenediamine, the most commonly implicated agent in most of the series [25, 26]. Paraphenylenediamine not only is mainly present in dark dyes but can also be found at lower concentrations in blonde hair dyes [27]. It is considered a very strong sensitizer inducing sometimes severe acute eczematous reactions affecting the face and neck with prominent eyelid involvement [1••].

Other allergens that may induce allergic contact dermatitis of the face by an indirect contact mechanism are those present in shampoos and hair conditioners. Allergic contact dermatitis to these products is uncommon, as allergens are usually quickly rinsed off. The most frequent allergens are fragrances such as cocamidopropyl betaine and preservatives such as quaternium 15 and methylchloroisothiazolinone and methylisothiazolinone [28]. Clinically, this allergic contact dermatitis is typically manifested by subacute eczematous plaques affecting the sides of the face (preauricular and mandibular regions) and the neck. The clinical pattern has been referred as the washing or wash or rinse-off pattern as the lesions are produced by the allergen running along the side of the face when the product is being rinsed [28].

A central facial dermatitis involving the forehead, nose, chin, and cheeks has been described in patients allergic to gold sodium thiosulfate. Gold sodium thiosulfate is usually present in rings and transferred by the hands to the face, whereas after contact with cosmetic products such as titanium dioxide, this releases ions that induce sensitization [29–32].

Allergic contact dermatitis of the face induced via airborne

This particular pattern of allergic contact dermatitis usually presents in an occupational setting, being drugs, plants, and resins the most common culprits [33, 34•, 35••]. Other less frequent occupational sources include rubber, preservatives, and metals. Airborne allergic contact dermatitis from drugs mainly affect employees of pharmaceutical industries involved in the production of the drugs and healthcare workers crushing the tablets for disable patients. The list of involved drugs is extensive and differs in the different countries reflecting the prescribing habits. Some of the most commonly reported include antibiotics such as beta-lactams, macrolides, and nitrofurazone; corticosteroids and immunosuppressive drugs such as budesonide, azathioprine, and methotrexate; inhibitors of gastric secretion such as omeprazole and ranitidine; and analgesics such as paracetamol and 3-(aminomethyl)-pyridyl salicylate among others [34•, 36].

The sesquiterpene lactones present in plants of the Compositae (Asteraceae) family are the most common plant allergen worldwide. The allergen is usually present in outdoor powdered dry plants that are disseminated by the wind mainly affecting middle-aged men, working outdoors [37–39]. However, non-occupational cases of airborne allergic contact dermatitis to edible Compositae plants, such as vapor from chamomile tea, have also been described [40]. In the USA, plants from *Toxicodendron* genus such as poison ivy, poison oak, and poison sumac, which usually induce allergic contact dermatitis by direct contact, has also been reported as a cause of airborne contact dermatitis by accidental burning of the plants. The urushiol found in stems, roots, leaves, and fruits is the responsible allergen [38].

Resins, the intermediate compounds from which plastics are made, are found in a wide variety of substances. Most cases of allergic contact dermatitis

of the face by resins occur during their production or manipulation rather than with the final product, being epoxies the most common culprit [41–43].

In a non-occupational setting, the preservative methylisothiazolinone, alone or in combination with methylchloroisothiazolinone, is one of the most common causes of airborne contact dermatitis. Cases usually occur after exposure to fresh paint and may induce local and systemic reactions [12, 33, 44, 45].

Clinically, airborne contact dermatitis manifest with eczematous plaques that affect upper eyelids; nasolabial fold; and retroauricular, submental, and chest areas. Lesions characteristically spare the dorsum and tip of the nose, a sign that has been named, the beak sign [1••, 46] (Fig. 3). Involvement of the cheeks and forehead may mimic photoallergic contact dermatitis; however, the latter is usually more erythematous and does not affect photo-protected areas such as the upper eyelids and retroauricular area [1••].



Fig. 3. Airborne contact dermatitis. Eczematous plaques affecting front, eyelids, nasolabial folds, submental area, and neck. Note the absence of lesions on the dorsum and tip of the nose (beak sign) (courtesy of Dr. Juan Francisco Mir-Bonafé)

Allergic contact dermatitis of the eyelids

The eyelids are one of the most susceptible regions of the body to the development of allergic contact dermatitis. The frequent exposure and thin epidermis, along with the orbicularis muscle, which acts as a sphincter, catch antigens and make eyelids one of the most predispositional areas of sensitization. The clinical presentation is varied manifesting with edema, conjunctivitis, isolated pruritus, scaling, or acute and chronic eczema, making the differential diagnosis extensive [47–49].

Unlike the face, where lesions of allergic contact dermatitis usually occur on the area where the allergen has been applied, allergic contact dermatitis of the eyelids occurs more frequently after application of products in other areas, such as the cheeks or the scalp, hindering the diagnostic suspicion. In addition, primary application sites may not have symptoms making the diagnosis a real challenge.

Direct applied allergens are very similar to the ones already mentioned in the face; however, fragrances seem to be more frequent than preservatives [2, 3, 5, 50]. Special mention deserves nickel, which is reported as one of the most common allergens of eyelid dermatitis in some series [51]. Nickel is found in many face- and eyelid-applied cosmetics, such as eyeliner pencils, eye shadows, and mascaras. In addition, nickel seems to be a common contaminant of several cosmetics, either by its presence in the container or by manipulation during its manufacturing (Fig. 4) [52]. Metallic objects such as eyelashes or eyeglasses contain nickel and may be the source of an allergic contact dermatitis [53, 54].

Benzalkonium chloride, thiomersal, phenylmercuric acetate, beta-adrenergic agents, and antibiotics found in ophthalmic solutions are also a common cause of eyelid dermatitis [55•]. Patch test with ophthalmic ingredients is difficult, as false-negative results are common, due to the low concentration of allergens and thicker epidermis of the back compared with the eyelids [56]. Scratching or stripping of the skin's back or the previous use of surfactants such as sodium lauryl sulfate has been proposed to improve sensitivity [21]. Allergic contact dermatitis by ophthalmic solutions should be suspected when dermatitis predominantly affects the lower eyelids in a run-off or drip pattern, although sometimes, upper eyelids are also affected [1••] (Fig. 5).

Regarding allergens inducing allergic contact dermatitis of the eyelids by indirect mechanisms, the most commonly involved include gold sodium thiosulfate, nickel, preservatives, fragrances, and paraphenylenediamine [2, 52]. Gold sodium thiosulfate is considered by some series as one of the most common allergens inducing isolated eyelid allergic contact dermatitis.



Fig. 4. Eyelid contact dermatitis due nickel present in the container of eye shadow cream. The cream itself did not present nickel



Fig. 5. Run-off or drip pattern of eyelid contact dermatitis due to eyedrops. In this case, upper eyelids are also affected (courtesy of Dr. Juan Francisco Mir-Bonafé)

However, other authors have doubted its relevance as gold sodium thiosulfate is a common irritant, with patch test reactions being difficult to interpret [57].

Nickel is transported by the hands after contact with metallic objects such as keys or coins [58], and preservatives and fragrances are found in shampoos and hair conditioners, as has been already mention in the face section.

In airborne contact dermatitis, the upper eyelids are particularly susceptible being in some cases the only affected site. To the list of aeroallergens involved in the face section, it is important to consider resin p-toluenesulfonamide formaldehyde and acrylates found in nail varnishes and artificial nails, respectively. These allergens are also a cause of indirect allergic dermatitis by transfer of allergens from the hands [59, 60].

Table 2 summarizes allergens most commonly involved in eyelid allergic contact dermatitis, excluding those already mentioned in the section on the face.

Table 2. Allergens most commonly involved in eyelid allergic contact dermatitis

Product	Allergens
Eye drops	Benzalkonium chloride Antibiotics (neomycin, gentamicin, bacitracin) Corticoids (budesonide, tixocortol pivalate) Propylene glycol
Rubber	Thiuram mix
Objects	Nickel Cobalt
Jewelry	Gold
Nail lacquers	Toluene sulfonamide
Adhesive artificial nails/eyelashes	Acrylates

Differential diagnosis of allergic contact dermatitis of the face

Differential diagnosis of allergic contact dermatitis of the face is extensive and includes a wide range of inflammatory and sometimes infectious conditions that usually affect this region. In this review, we will discuss the most common entities. The different diseases can be classified into eczematous, non-eczematous, and infectious.

Eczematous diseases

Allergic contact dermatitis clinical hallmark is the presence of eczematous lesions, which are characterized by the presence of erythematovesicular lesions in acute and subacute stages and hyperkeratotic lesions in chronic stages. It is therefore not surprising that other eczematous conditions that usually affect the face such as irritant contact dermatitis, atopic dermatitis, and seborrheic dermatitis are the most common and challenging differential diagnosis to consider.

Irritant contact dermatitis

Irritant contact dermatitis is the most common cutaneous reaction occurring after contact with an external agent, representing up to 80% of all contact dermatitis. Irritant contact dermatitis occurs as a result of direct damage to the skin by an inflammatory non-immunologic reaction without prior sensitization [61]. Although the underlying mechanisms of allergic and irritant contact dermatitis are different, the physical and histopathological features are very similar. Clinical clues that suggest an allergic over an irritant contact dermatitis include the presence of pruritus rather than pain, eczema at other sites such as hands and eyelids, the presence of vesicles, and lesions outside the area of the skin that comes in contact with the allergen. However, it can be extremely difficult for the clinician to differentiate allergic from irritant contact dermatitis on the basis of the clinical history and examination alone, making patch test an essential tool for the diagnosis. The most common irritants implicated in irritant contact dermatitis of the face include eye cosmetics; mascaras based on volatile petroleum distillate; detergents; shampoos containing surfactants such as sodium lauryl sulfate and benzalkonium chloride; pesticides with chlorothalonil; and physical agents such as metal tools, wood, fiberglass, plants, paper, dust, and soil among others [61].

Atopic dermatitis

Differentiating atopic dermatitis from allergic contact dermatitis of the face, especially when affected the eyelids and present with chronic lesions, can be extremely difficult. In addition, patients with atopic dermatitis are predisposed to sensitization and may also have a superimposed allergic contact dermatitis [48]. A personal and/or family history of atopy (atopic dermatitis, hay fever, allergic asthma, and perennial allergic rhinitis) and the presence of symmetric eczematous lesions at other characteristic locations outside the face such as inner creases of the elbows and knees, hands, and neck may help in the diagnosis. Some clinical signs

such as pityriasis alba, keratosis pilaris, Hertoghe sign, Dennie-Morgan lines, and allergic shiners are also frequent and typically seen in patients with atopic dermatitis. Pityriasis alba are hypopigmented macules and patches usually located on the cheeks. Keratosis pilaris are perifollicular papules with central keratotic cores located on the cheeks and extensor surface of extremities. Hertoghe sign is the absence or thinning of the eyebrows. Dennie-Morgan lines are symmetric folds located at the lower eyelids, and allergic shiner is a blue-gray darkening of the skin around the eyelids. In case of doubt, patch test can help in the differential.

Seborrheic dermatitis

Seborrheic dermatitis is a chronic and relapsing disease characterized by eczematous lesions affecting facial areas rich on sebaceous glands such as scalp, eyelids, forehead, eyebrows, glabella, nasolabial folds, and retroauricular area.

Diagnosis of facial seborrheic dermatitis is usually straightforward as lesions of allergic contact dermatitis usually do not occur at oily skin areas, as the increase sebaceous gland concentration prevents penetration of allergens and the development of allergic contact dermatitis. However, isolated eyelid involvement can be challenging as the clinical manifestations may overlap. In cases with recalcitrant seborrheic dermatitis of the eyelids, patch testing is recommended to rule out an allergic contact dermatitis [62].

Exceptionally, some cases of facial allergic contact dermatitis mimicking seborrheic dermatitis by propylene glycol, dodecyl gallate, and methylchloroisothiazolinone and methylisothiazolinone have been described [63, 64]. In such cases, a high clinical suspicion and performance of patch test allow a correct diagnosis.

Non-eczematous diseases

Various non-eczematous diseases may enter in the differential diagnosis of allergic contact dermatitis of the face. The most commonly involved will be reviewed.

Rosacea

Rosacea is a common and chronic condition that typically affects the face. Patients may present with varying degrees of erythema that in some cases may mimic allergic contact dermatitis. In addition, the characteristic rosacea epidermal barrier impairment makes it very susceptible to the development of irritant contact dermatitis. A history of recurrent transient erythema (flushing) and exacerbations by sun exposure, stress, exercise, alcohol, and spicy foods along with the presence of telangiectasias, papules, and pustules usually allows the correct diagnosis.

Immune-mediated diseases

Immune-mediated diseases such as polymorphous light eruption, lupus erythematosus, and dermatomyositis usually affect the sun exposed areas of the face such as the bridge of the nose, chins, and forehead with a clinical pattern that resembles photoallergic contact dermatitis. In addition, although rare, some cases of lupus-like allergic contact dermatitis to acrylates, methylchloroisothiazolinone, and methylisothiazolinone have been described [65, 66].

Polymorphous light eruption can be recognized by the typical seasonal variation and the "hardening" phenomenon. Lupus and dermatomyositis usually do not present with eczematous pruritic lesions and present with other systemic

symptoms such as asthenia, arthritis, photosensitivity, and weakness that will guide in the diagnosis. Diagnosis may be further established by skin biopsy and photo patch testing.

Infectious diseases

Regarding infectious diseases, superficial mycosis, especially tinea, has to be considered in the differential diagnosis. Tinea is one of the most common differential diagnosis of allergic contact dermatitis of the hands, and although tinea affecting the face is less frequent, lesions can also be confused with eczematous lesions of allergic contact dermatitis. Clinically, facial tinea typically presents with unilateral annular lesions with an elevated border and a central clearance. Superficial papules and pustules can also be present. Unlike lesions of allergic contact dermatitis that usually respond well to corticosteroids, lesions of tinea characteristically get worse with topical corticosteroid treatment suggesting the diagnosis in unsuspected cases. In case of doubt, examination of skin scraping on potassium hydroxide 20% and mycologic culture confirms the diagnosis. Other infection that may be considered is erysipelas/cellulitis. Erysipelas/cellulitis may present with erythema and edema of the face that may be confused with an acute allergic contact dermatitis. The presence of systemic symptoms such as malaise and fever, which are very unusual in allergic contact dermatitis, usually allows a correct diagnosis.

Conclusions

Allergic contact dermatitis of the face is a common condition that may produce an important impact on the patient's quality of life. The wide range of clinical manifestations together with the multiple possible etiologies makes its diagnosis a real challenge. It is therefore essential for clinicians to adequately recognize the most important agents involved, main clinical presentations, and differential diagnosis to properly establish a definitive diagnosis and develop an appropriate treatment.

Compliance with Ethical Standards

Conflict of Interest

Eduardo Rozas-Muñoz declares that he has no conflict of interest. Denise Game declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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