Review Article

Noneczematous Contact Dermatitis

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Irritant or allergic contact dermatitis usually presents as an eczematous process, clinically characterized by erythematous-vesicular lesions with intense itching in the acute phase. Such manifestations become erythematous-scaly as the condition progresses to the subacute phase and papular-hyperkeratotic in the chronic phase. Not infrequently, however, contact dermatitis presents with noneczematous features. The reasons underlying this clinical polymorphism lie in the different noxae and contact modalities, as well as in the individual susceptibility and the various targeted cutaneous structures. The most represented forms of noneczematous contact dermatitis include the erythema multiforme-like, the purpuric, the lichenoid, and the pigmented kinds. These clinical entities must obviously be discerned from the corresponding “pure” dermatitis, which are not associated with contact with exogenous agents.

1. Introduction

Allergic contact dermatitis (ACD) is a common cutaneous eczematous disorder caused by contact (either direct or aeromediated) with a range of environmental substances. Pathogenetically, ACD results from an immune reaction involving both innate and adaptive immunologic mechanisms. In particular, hyperreactive response to small chemicals (haptens) penetrating the skin depends on a series of events, such as hapten capability to activate and mobilize cutaneous dendritic cells (cDC), generation of hapten-epitopes for T-cell recognition, and hapten−cDC complex ability to prime effector T cells with skin homing proprieties [1–3]. In sensitized individuals, skin or systemic challenge with the specific sensitizer determines rapid recruitment of effector T cells, along with natural killer lymphocytes, which mediate tissue damage through release of proinflammatory cytokines and through hapten-loaded keratinocytes killing.

Clinics of ACD are generally polymorphic. Besides the classic eczematous form, in fact, different noneczematous clinical variants are possible [1, 4–6]. The causes for such variability in ACD clinical aspects are many (Table 1). According to our data (unpublished), considering >30,000 patch tested individuals for contact dermatitis, noneczematous forms are slightly more common (52%) than the classic eczematous one (48%). Various clinical patterns of noneczematous ACD have been described: some are linked to topical use of specific haptens and others more often dependent on allergens systemic administration (Table 2). The most represented forms are described as follows.

2. Erythema Multiforme-Like Contact Dermatitis

Of all noneczematous clinical variants, the erythema multiforme-like (or “contact erythema multiforme”) is the most common. It can be elicited by different substances, particularly exotic woods, medicaments, and ethylenediamine (Table 3).

2.1. Causes

Woods and plants. Among exotic woods, Brazilian rosewood (Dalbergia nigra), pao ferro (Machaerium scleroxylon), and Eucalyptus saligna are relevant as occupational causes of erythema multiforme-like eruption in carpenters, foresters, and
Table 1: Factors determining the peculiar polymorphic clinical features of allergic contact dermatitis.

| Factor                                                                 | Description                                                                 |
|------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Eruptive polymorphism                                                  |                                                                             |
| Evolutive polymorphism                                                 |                                                                             |
| Causative agent                                                        |                                                                             |
| Patient sensitizing level                                              |                                                                             |
| Way of exposition (cutaneous, systemic)                                |                                                                             |
| Means of exposition (cutaneous direct, cutaneous aeromediated)         |                                                                             |
| Tissue structures targeted by the causative agent                      |                                                                             |
| Anatomophysiology of the cutaneous region involved                     |                                                                             |
| Causative agent possible concomitant irritant action                   |                                                                             |
| Environmental factors (UV, temperature, humidity)                      |                                                                             |
| Itching intensity variability                                           |                                                                             |
| Preexisting dermatitis underlying the overlapping contact allergy      |                                                                             |

Table 2: Different types of noneczematous contact eruptions.

| Type                                                                 | Description                                                                 |
|----------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Erythema multiforme-like contact dermatitis                          |                                                                             |
| Purpuric contact dermatitis                                           |                                                                             |
| Lichenoid contact dermatitis                                          |                                                                             |
| Lymphomatoid contact dermatitis                                       |                                                                             |
| Pigmented contact dermatitis                                          |                                                                             |
| Pustular contact dermatitis                                           |                                                                             |
| Dyshidrosiform contact dermatitis                                     |                                                                             |

cabinet makers. Antigens in pao ferro and Brazilian rosewood are crossreacting quinones, respectively, R-3, 4-di-methoxy-dalbergione, and R-4-methoxy-dalbergione [7, 8]. Literature also lists extraoccupational cases from wooden bracelet [9] and pendants [10] made of D. nigra. M. scleroxylon has been described to cause a similar eruption in hobbyists who handled this type of wood to build boxes [11].

Other reported causes of erythema multiforme-like reactions include Artemisia vulgaris [12, 13], poison ivy [14, 15], Hypericum erectum [16], and terpenes [17]. Tincture of capsicum caused an analogous reaction in a woman who used the concoction to treat her knee arthritis [18]. Inula helenium, contained in a mixture to treat back pain, has also induced erythema multiforme-like eruption, with positive patch tests to sesquiterpene lactone mix and alantolactone [19]. Notably, Primula obconica can also induce comparable eruptions [20–23]. We observed an erythema multiforme-like reaction in a plant nursery worker, who had handled plants of P. obconica. The dermatitis involved hands, forearms, and face. Patch tests were positive to primin (0.01% in pet), leaves and flower. Histology showed foci of hyperkeratotic orthokeratosis, mild spongiosis, eczocytes, and few isolated necrotic keratinocytes; at the superficial and mid dermis, a largely peri-vascular lymphocytic infiltrate was present [24].

Topical Medicaments. Numerous topical drugs are reported as cause of erythema multiforme-like contact dermatitis, the vast majority being antimicrobials. According to our observation, pyrrolnitrin can trigger this kind of eruption [25, 26]. Other causative drugs include sulfonamide [27, 28], promethazine [25], neomycin [25], mafenide acetate [29], ethylenediamine [25, 30], and mephenesin [31, 32]. Among nonsteroid anti-inflammatory drugs, phenylbutazone [33], bufexamac [34], and mofebutazone [35] have been reported. Among corticosteroids, budesonide [36] and triamcinolone acetonide [37] caused analogous reactions.

Miscellany. Erythema multiforme-like eruptions can be the expression of contact allergy to nickel [38–41] and cobalt [39]. 9-Bromofluorene induced a skin acute reaction in several chemistry students, who were exposed to the product during its synthesis [42, 43]. Finally, many other compounds have been associated to erythema multiforme-like reactions, although exceptionally [5, 6].

2.2. Clinical Features. Early lesions are eczematous in morphology and localized at the allergen contact site. After a 1 to 15 days delay, the erythema multiforme-like eruption follows, involving the area around the original lesions or rather extending to the whole cutaneous surface. The latter
Table 4: Differential diagnosis between true erythema multiforme (EM) and erythema multiforme-like contact dermatitis.

| Criteria               | EM                              | EM-like contact dermatitis          |
|------------------------|---------------------------------|-------------------------------------|
| Etiology               | Viruses, bacteria, systemic drugs| Various topical chemicals            |
| Clinical features      | Erythematodematous lesions with cockade appearance, sometimes bullous, with acral localization (face, hands, forearms, thighs) | Polymorphic lesions located peripherally to the contact site with the sensitizing agent |
| Fever                  | Often present                   | Absent                              |
| Mucosal involvement    | Frequent                        | Rare                                |
| Histology              | Epidermis: basal cells necrosis, subepidermal vesicobullae Dermis: edema, capillary vasodilation, vasculitis signs | Epidermis: spongiosis Dermis: edema, lymphohistiocytic infiltrate |
| Pathogenesis           | Immunocomplexes                  | Type IV hypersensitivity            |
| Patch tests            | Negative                         | Positive                             |
| Course                 | Self-limited in 3 weeks          | Favorable after allergen withdraw    |

occurrence generally ensues systemic exposition to drugs which the patient had previously been sensitized to topically. Target-like, erythematovesicular, or urticarial lesions are characteristic. Resolution is slow-paced; these manifestations persist usually much longer than the original eczematous lesions (or sometimes appearing after regression of the latter). Itching sensation is also typically present in polymorphic reactions [1]. Patch tests generally elicit eczematous positive reactions, with the exceptional vesico-bullous or urticarial lesions.

Differential diagnosis is set out with true erythema multiforme (Table 4), the latter showing almost all target-like lesions with typical acral distribution and crops-like onset.

2.3. Histopathology. The histology is generally aspecific. Epidermis shows spongiosis and exocytosis. Mild upper dermis edema and perivascular lymphohistiocytic infiltration are noticeable. Vacular degeneration of basal cells is rarely present, while epidermal necrosis is very mild or absent. When bullae are present, they are intraepidermal [1].

The histopathology of true erythema multiforme shows frank epidermal necrosis and vacuolar basal cells degeneration, while bullae are subepidermal [1].

3. Purpuric Contact Dermatitis

This particular form of noneczematous contact dermatitis is of unusual observation, and many cases remain undiagnosed. The eruption evolves in several weeks after the withdrawal of the offending agent and resolves with more or less persistent pigmentation. The purpuric aspects of contact dermatitis, and the respective patch test reactions can be secondary to irritant, or more frequently allergic, mechanisms [44].

3.1. Causes. The most frequent causative factors are listed in Table 5. Certain components of rubber and textile are recurrently reported in the literature.

Rubber. First reported cases date back to 1968: 9 women developed purpura from cloth elastic inserts; in every instance patch tests turned positive to N-isopropyl-N-phenyl-para-phenylenediamine (IPPD), a rubber antioxidant [45]. Other 2 cases, showing diffuse purpuric reactions with negative bloodwork, were associated to IPPD and specifically to the use of rubber boots [46]. Fisher reported 3 cases, respectively, from rubber diving suit, elasticized shorts, and rubberized support leg bandage; in all 3 patients patch tests turned positive to IPPD [47, 48]. The author therefore fashioned the “PPPP syndrome,” defined as an ACD characterized by pruritus, petechiae, and purpura, caused by IPPD. IPPD also prompted similar eruption in a woman in the pattern of her brassiere [49] and in a man at rubber boots contact sites [50]. PPPP syndrome has also been described following use of orthopedic elastic bandages [51] and rubber gloves [52]; in the latter case patch tests were positive not just to IPPD but to N-cyclohexyl-N′-phenyl-para-phenylenediamine and N,N′-diphenyl-para-phenylenediamine as well.

Textile. From 1969 to 1972, Osmundsen gathered 167 cases of purpuric reactions from an optical whitener contained in washing powders [53, 54]. The petechial and itchy dermatitis interested those areas which are typically subject to tighter contact with clothes (armpits, arms, upper limbs folds, neck and thighs). The offending agent was Tinopal CH 3566, a mixture of 2 noncrossreactive pyrazolines (monochlorobiphenyl-pyrazoline and dichloro diphenyl pyrazole). Tinopal CH 3566 was used to bleach nylon fibers and caused a similar epidemic outbreak in Spain, where 103 were collected [55]. From that time on, the product was discontinued with no more cases reported. As of today, risk-free stilbene-based optical whiteners are employed.

A sailor developed generalized purpuric lesion with pigmentary outcomes at sites of contact with the military blue uniform. Patch tests evidenced positive reaction to Disperse Blue 85, while histology demonstrated Schamberg disease sign [56]. We directly observed a case of purpuric ACD to Disperse Yellow 27 (Serisol Fast Yellow 6DW), an azoic dye used in acetate and polyester fibers, a result of para-aminoacetanilide and paraphenylenphenol. The dye was part of a pair of trousers inner lining, and the dermatitis, while interesting
Table 5: Causative agents in purpuric contact dermatitis.

| Rubber compounds | Textile compounds | Plants | Miscellany |
|------------------|-------------------|--------|------------|
| N-isopropyl-N’-phenyl-paraphenylenediamine | Optical whiteners (Tinopal CH 3566) | *Agave americana L* | Paraphenylenediamine |
| Mercaptobenzothiazole | Azoic dyes | *Zea mais* | Fiberglass |
|                     | Rubber compounds | *Frullania* | Peru balsam |
|                     | Formaldehyde resins | d-Limonene | Epoxy resin |
|                     |                   |         | Oxynquinoline |
|                     |                   |         | Proflavine |
|                     |                   |         | Cobalt |
|                     |                   |         | Benzoyl peroxide |

the whole skin surface, started from and was particularly manifest at the thighs. Thin layer chromatography from textile extract demonstrated only one component, Disperse Yellow 27. Histology proved traditional aspects of ACD, with lymphocytic infiltrate and intense perivascular edema, associated to noticeable erythrocyte extravasation [57]. Purpuric eruptions have also been described in a black hats vendor from paraphenylenediamine [58], in British soldiers from formaldehyde resins contained in kaki wool shirts [59], and in a man assigned to mixed wool-synthetic residues harvesting [60].

Plants. *Frullania* induced a diffuse purpuric reaction; histology showed signs of leukocytoclastic vasculitis; however, circulating immune complex and complement deposition assays were also positive [61]. *Agave americana* L, of Agavaceae family, can determine purpuric contact dermatitis with histological features of leukocytoclastic vasculitis [62]. We also observed a similar case, secondary to plant latex contact [63]. *Zea mais* (corn) has been shown to induce irritant purpuric phytodermatitis some hours after contact to green leaves. Patch, photopatch, and scratch tests with alcoholic extracts of different plant parts (leaves, trunk, efflorescences) all resulted negative [64]. Two-hour experimental exposition to 98% d-limonene resulted in a severe and several week persistent purpuric reaction 6 hours after contact [65].

Miscellany. Fiberglass can induce direct or aerommediated contact dermatitis, with pruriginous, 0.1–0.5 mm diameter, mostly follicular purpuric papules. Exposed and nonexposed areas are both affected, since these fibers are able to pass through clothing [66, 67]. Clothes contaminated by being washed together with fiberglass curtains can also induce purpuric dermatitis [68].

Vasculitic purpuric eruptions to Peru balsam [25, 69], ethylenediamine [70, 71], benzoyl peroxide [72], and proflavine [73] have also been reported.

3.2. Patch Tests Purpuric Reactions. As is well known among those who practice dermatoaergology, petechial reactions to cobalt patch test, without edema, vesicles, and infiltration, can be observed. These are toxic in nature rather than allergic. Schmidt et al., in a 4-year time span, observed 123 cases (4.7%) of cobalt petechial reactions out of a total of 2594 patch-tested patients. Twenty-three patients were retested and developed new petechial responses in 60% of cases. Based on these authors data, the incidence of positive allergic reactions to cobalt was lower (2.9%) than the incidence of primary irritant reactions [74]. Judging on our practice, cases of petechial nonallergic reactions to cobalt and chrome are indeed rather numerous and frequently reproducible.

3.3. Clinical Features. Purpuric contact dermatitis can be either toxic or allergic in nature. From a clinical-morphological perspective, differential diagnosis is not straightforward: both present palpalpable purpuric elements, evolve slowly and are followed by variably intense and persistent pigmentation. At times, clinical extension represents a useful feature in differentiating the 2 forms, the irritant being strictly limited to contact sites. Moreover, lesional elements resolve more rapidly and are less infiltrated in the irritant form compared to the allergic one.

Diffuse contact irritation from fiberglass must be discerned from scabies, eczema (prurigo-like), animal and vegetal acariasis, and if persistent, from Hodgkin disease. The anamnestic data of epidemic bursts in industries or bureaus (fibers dispersed from defective air conditioners) greatly aid diagnosis [75].

The allergic form of purpuric contact dermatitis generally features diffuse and polymorphic manifestations: papulopurpuric and papulovesicular lesions parallel classic eczematous foci. The latter are limited to the original contact site with the offending noxa. Secondary distant lesions can also present polymorphic or vasculitic aspects, as we have directly observed. Purpuric patch tests reactions are obviously vesicular and infiltrated [44].

3.4. Pathogenesis and Histopathology. The pathogenetic mechanism of purpuric contact dermatitis is currently unknown. Hemostasis or complement system alterations are not generally described in reported cases nor are immune complexes commonly isolated. In every case we observed, among which 3 severe cases from Peru balsam with frankly vasculitic and bullous lesions and various cases from ethylenediamine (in which the rash had followed systemic administration of aminophylline), specific laboratory exams fell into normal range [25, 44].
Since endothelial cells degeneration is evident at electron microscopy, a selective effect on these cells has been hypothesized. In detail, specific toxic or allergic substances as well as certain mechanical stimuli (fiberglass) would exhibit an affinity for vessels endothelium [47, 57, 58]. Alternatively, a primary lymphocytic reaction in response to the antigen at the perivascular site would free toxic lymphokines, ultimately responsible of endothelial damage [72].

Histopathology has been described, with comparable results, in most reported cases. In the epidermis, spongiosis and lymphocytic exocytosis are constant features, along with possible bulla formation. In the upper dermis the signs of leukocytoclastic vasculitis (vessels fibrinoid degeneration, edematous endothelium, scarce perivascular lymphomonocytic and neutrophilic infiltrate, erythrocytes extravasation, and karyorrhexis) are visible. The same features are present when examining a patch test response lesion (Table 6) [47, 74].

Bloodwork, histologic and patch test examinations are valid to differentiate the condition from vascular, hemostatic, and idiopathic purpuric affections.

### 4. Lichenoid Contact Dermatitis

A particularly uncommon form of noneczematous contact dermatitis presents with clinical features resembling those of lichen planus. It affects both skin and mucosal membranes.

#### 4.1. Causes.

Color developers, substances derived from paraphenylenediamine, are the most common cause of allergic contact lichenoid eruption. Among these compounds, Kodak CD2 (4-N, N-diethyl-2 methylphenylenediamine), Kodak CD3 (4-N-ethyl-N-2-methanesulfonylaminoethyl-2-methylphenylenediamine sesquisulfate monohydrate), Kodak CD4 (2-amino-5-N-ethyl-N-(hydroxyethyl)-aminoaniline sulfate), Ilford MI 210 (N-ethyl-N (5-hydroxy-amyl) paraphenylenediamine hydrogen sulphate), and Agfa TSS (4-amino-N-diethylaniline sulfate) [75].

Other cases of lichenoid contact dermatitis have been reported by Mandel, in 9 out of 11 workers with contact allergy to a color developer [76], and by Fry in 7 out of 20 patients with analogous sensitization [77]. High speed, black-and-white film processing implies the use of similar chemicals, which can induce lichenoid reactions [78]. As a general rule, the eruption from color developers spares the oral mucosa [79]. Cases from paraphenylenediamine in hair dyes [80], P. obconica [81], nickel [82], epoxy resins [83], aminoglycoside antibiotics [84], and methacrylic acid esters for industrial use [85] have also been described. Oral mucosa involving forms are due to copper [86], zinc [87], and mercury [88] contained in dental restorations.

#### 4.2. Clinical Features.

Eczematous lesions evolve or associate with papulous lesions with peculiar lilac-red gradation. The eruption mostly involves contact sites, later widely spreading with mucosal sparing. Course is prolonged and leaves variably intense pigmentary changes lasting up to some months. Lichenoid contact dermatitis has to be differentiated from lichen planus, with its characteristic papulous polygonal lilac lesions. The onset of lichenoid contact dermatitis is almost invariably acute and the eruption spreads rapidly. Frankly eczematous lesions at the primitive site are noticeable in many cases.

Positive reactions to patch tests are eczematous in nature, but might turn lichenoid.

#### 4.3. Pathogenesis and Histopathology.

Pathogenesis of contact lichenoid dermatitis is unclear. Systemic absorption of offending agents can elicit skin lesions far from the original site of contact. In 5 cases we observed (3 from color film developers and 2 from paraphenylenediamine), histology displayed lack of hypergranulosis, foci of moderate spongiosis, and focal basal stratum vacuolization. A patchy mononuclear infiltrate was evident in the upper dermis [86]. Basal cell vacuolization is the cause of incontinenta pigmenti, which could explain skin lesions peculiar color, a blend of red from flogosis with blue from dermal melanin. Table 7 compares the different histopathological characteristic of lichenoid contact dermatitis and lichen planus.

### 5. Lymphomatoid Contact Dermatitis

This uncommon dermatitis manifests with the clinical features of plaque parapsoriasis or an early stage mycosis fungoides [1, 70]. There are no specific causing hapten [89–95], the most frequently reported being paraphenylenediamine, para-tert-butyl phenol resin, gold, ethylenediamine, and nickel. Patch test reaction to these is eczematous in nature.
Table 8: Histopathological characteristics of lymphomatoid contact dermatitis (LCD) and mycosis fungoides (MF).

| Criteria                              | LCD  | MF   |
|---------------------------------------|------|------|
| Spongiosis                            | +++  | +    |
| Exocytosis                            | −/+  | +++  |
| Inflammatory cells                    |      | Atypical lymphoid cells (microabscesses) |
| Lymphocytic infiltrate                | Perivascular | Band-type |
| Lymphocytes with cerebriform nuclei   | −/+  | +++  |

and can persist for several days. Lymphomatoid contact dermatitis and mycosis fungoides alike present with infiltrative patches; the former, however, demonstrates a bright erythematous color and undefined margins.

Histology is crucial in differentiating the above two conditions. Spongiosis is much clearer, and exocytosis is typically lymphocytic in contact dermatitis. Mycosis fungoides instead shows atypical lymphocytes in focal abscess-like aggregations (i.e., the pathognomonic Pautrier’s microabscesses) and a band-like subepidermal infiltration of large lymphoid cells with cerebriform nuclei (Table 8).

6. Pigmented Contact Dermatitis

Described by Osmundsen in 1970, it is a melanic primitive hyperpigmentation, usually observed in dark phototypes and mostly occupational [96]. The author observed an intense and bizarre skin hyperpigmentation due to contact with an optical whitener (Tinopal CH 3566) used in washing powders and made by a combination of two pyrazolone derivatives, as of now discontinued.

Clinically, involved sites were those of textile contact dermatitis, with brown-blue to grayish hyperchromia. The same occurred at patch test application sites. Histology evidenced melanin deposits inside and out melanophages in the upper dermis.

Pigmented contact dermatitis can also be prompted by azoic dyes. An epidemic outburst from contact to naphthol AS has been reported in a textile business [97]. Hyperpigmentation was noticeable in dark skinned individuals, while fair skinned ones showed the signs of classical eczema. Sudan I, Vacanceine Red [98], and Brilliant Lake Red R [99] are other offending colorants which have been reported. Isolated occupational cases from insoluble cutting oils [100], paraphenylenediamine [101], and other substances are also described (Table 9) [102]. Riehl’s melanosis is nowadays also considered a pigmented contact dermatitis, mostly from cosmetic sensitizing fragrances and chemicals [103].

Table 9: Causative agents in pigmented contact dermatitis.

| Optical whiteners                  | Tinopal CH 3566 |
|------------------------------------|-----------------|
| Optical whitener:                  | Naphthol AS     |
| Dyes                               | Sudan I         |
| Dyes                               | Brilliant Lake Red |
| Solvent orange 8                   | Vacanceine Red  |
| Cosmetics                          | Solvent orange 2 |
| Pigments:                          | Solvent orange 8 |
| Dyes                               | Naphthol AS     |
| Dyes                               | Sudan I         |
| Dyes                               | Brilliant Lake Red |
| Solvent orange 8                   | Vacanceine Red  |
| Pigments:                          | Solvent orange 2 |
| Cosmetics                          | Solvent orange 8 |
| Fragrances                         | Jasmine         |
| Antiseptics                        | Hydroxycitronellal |
| Antiseptics                        | Ylang-ylang     |
| Antiseptics                        | Patchouli       |
| Antiseptics                        | Cananga         |
| Antiseptics                        | Formaldehyde    |
| Antiseptics                        | Nickel          |
| Antiseptics                        | Rubber          |
| Antiseptics                        | Primula obconica |
| Antiseptics                        | Musk ambrette   |

7. Pustular Contact Dermatitis

Pustules are usually associated with irritant reactions. Nevertheless, allergic pustular reactions are known from nitrofurazone [104], black rubber [105], and minoxidil [106]. The latter has been described in a woman who developed a vesicopustular eruption on the forehead after applying 2% minoxidil solution. Histology showed perifollicular lymphocytes, histiocytes, and eosinophils. Patch test response was erythematovesicopustular. Patch test was strongly eczematous in another case of pustular allergic contact dermatitis from isiconazole nitrate [107].

The implication of such rare pustular reactions remains uncertain. Pustules are sterile and transient and can displace subcorneally, as observed in a case from trichloroethylene [108].

7.1. Pustular Patch Test Reactions. Pustular reactions to contactants are frequently observed in patch test reading. Hjorth stated that atopics are predisposed to such reactions [109]. Metal salts, particularly nickel, copper, arsenic, and mercury represent the most common causes of these reactions, which are irritant in nature [110, 111]. As a matter of fact, pustular responses to nickel patch test are widely observed when testing atopics on lesional skin, with follicular papules, erythema, or lichenification [112]. This further supports the irritant nature of the phenomenon.

In subjects affected by atopic dermatitis, we often observed such pustular follicular reactions when patch testing with nickel but also with potassium bichromate. Pustules are always sterile, dry promptly, and resolve rapidly. Erythema is mild and the reaction is not pruriginous. Histology, documented in various cases, has always evidenced intraepidermal aggregations of neutrophils, without signs of lymphomonocytic exocytosis or spongiosis. We have always considered these reactions we directly observed irritant in nature [113, 114].
8. Dyshidrosiform Contact Dermatitis

Certain authors include this condition among noneczematous allergic contact forms [6]. In our opinion, this dermatitis retains frankly clinicohistologic eczematous aspects, and a proper differential diagnosis would have to be made with the endogenous eczema pompholyx. As per our observations, dyshidrosiform allergic contact dermatitis can be primitive or secondary [70, 115, 116]. The latter is defined as a contact sensitivity which complicates a preexisting primitive palmoplantar pompholyx. The latter tends to a chronic recurrent course, thus constituting a predisposing factor to occupational and extraoccupational contact allergy [117, 118]. From studies we carried out on 354 subjects with pompholyx genuine lesions, observed during a 5-year period, incidence of relevant positive patch tests reactions was 29.6%. Topical medicaments (used to treat the original pompholyx) and other substances among which paraphenylenediamine (31.5% positive reactions), chrome (25%), cobalt (10.2%), mercaptobenzothiazole (9.3%), nickel (6.5%), and para-tert-butylphenol formaldehyde resin (2.7%) were the most often implicated haptens. Patch tests relevance was related to specific occupational activities, use of peculiar gloves rather than shoes [115]. More recently, we conducted on 45 individuals affected by palmoplantar pompholyx confirmed an ACD incidence of 31% [116].

Primitive dyshidrosiform ACD is instead an expression of systemic contact allergy, of common observation in nickel sensitized patients. Oral challenge test with nickel reproduces the dyshidrosiform eruption in these subjects [119–122], although this phenomenon has not been widely confirmed [123, 124].

Table 10 designates differential diagnosis between dyshidrosiform ACD and pompholyx. Intense erythema and constant hand dorsum involvement in the former represent useful discerning characteristics. Histologically, spongiosis and exocytosis are much more marked in ACD than in pompholyx.

Table 10: Differential diagnosis between dyshidrosiform ACD and pompholyx.

| Characteristics      | Dyshidrosiform ACD | Pompholyx |
|----------------------|--------------------|-----------|
| Palms/soles          | +++                | +++       |
| Hands/foot dorsum    | +++                | +         |
| Erythema             | +++                | +         |
| Hemorrhagic vesicles | +                  | –         |
| Bullae               | +/++               | +/+++     |
| ACD primary locus    | Present            | Absent    |
| Spongiosis           | +++                | +         |
| Exocytosis           | +++                | +         |
| Vesicles             | Minute             | Large from coalescing |

References

[1] D. Bonamonte, A. Cavani, and G. Angelini, "Allergic contact dermatitis," in *Textbook of Dermatology & Sexually Transmitted Diseases*, A. Giannetti and C. Del Forno, Eds., vol. 2, pp. 933–961, Piccin, Padova, Italy, 2013.

[2] A. Cavani, O. De Pità, and G. Girolomoni, “New aspects of the molecular basis of contact allergy,” *Current Opinion in Allergy and Clinical Immunology*, vol. 7, no. 5, pp. 404–408, 2007.

[3] S. F. Martin and T. Jakob, “From innate to adaptive immune responses in contact hypersensitivity,” *Current Opinion in Allergy and Clinical Immunology*, vol. 8, no. 4, pp. 289–293, 2008.

[4] G. Angelini and G. A. Vena, “Dermatite allergica da contatto,” in *Dermatologia Professionale e Ambientale*, G. Angelini and G. A. Vena, Eds., vol. 2, pp. 483–512, ISED, Brescia, Italy, 1999.

[5] C. L. Goh, “Non-eczematous contact reactions,” in *Textbook of Contact Dermatitis*, R. J. G. Rycroft, T. Menné, P. J. Frosh, and J.-P. Lepoittevin, Eds., pp. 413–431, Springer, Berlin, Germany, 3rd edition, 2001.

[6] R. L. Rietschel and J. F. Fowler, “Noneczematous contact dermatitis,” in *Fisher’s Contact Dermatitis*. 6. Hamilton, R. L. Rietschel and J. F. Fowler, Eds., pp. 88–109, BC Decker, 2008.

[7] R. Holst, J. Kirby, and B. Magnnusson, “Sensitization to tropical woods giving erythema multiforme like eruptions,” *Contact Dermatitis*, vol. 2, no. 5, pp. 295–296, 1976.

[8] P. Martin, H. Bergoend, and F. Piette, “Erythema multiforme-like eruption from Brazilian rosewood,” in *Proceedings of the 5th International Symposium on Contact Dermatitis*, Barcelona, Spain, March 1980.

[9] A. A. Fisher, “Erythema multiforme-like eruptions due to exotic woods and ordinary plants: part I,” *Cutis*, vol. 37, no. 2, pp. 101–104, 1986.

[10] A. A. Fisher and J. Bikowski Jr., “Allergic contact dermatitis due to a wooden cross made of Dalbergia nigra,” *Contact Dermatitis*, vol. 7, no. 1, pp. 45–46, 1981.

[11] C. Irvine, A. Reynolds, and A. Y. Finlay, “Erythema multiforme-like reaction to ‘rosewood’,” *Contact Dermatitis*, vol. 19, no. 3, pp. 224–225, 1988.

[12] G. Kurz and M. J. Rapaport, “External/internal allergy to plants (Artemesia),” *Contact Dermatitis*, vol. 5, no. 6, pp. 407–408, 1979.

[13] S. L. Moschella, “Erythema multiforme,” in *Dermatology*, vol. 1, WB Saunders, Philadelphia, Pa, USA, 1975.

[14] S. B. Mallory, O. F. Miller III, and W. B. Tyler, “Toxicodendron radicans dermatitis with black lacquer deposit on the skin,” *Journal of the American Academy of Dermatology*, vol. 6, no. 3, pp. 363–368, 1982.

[15] R. S. Schwartz and T. F. Downham II, “Erythema multiforme associated with Rhus contact dermatitis,” *Cutis*, vol. 27, no. 1, pp. 85–86, 1981.

[16] W. Torinuki, “Generalized erythema-multiforme-like eruption following allergic contact dermatitis,” *Contact Dermatitis*, vol. 23, no. 3, pp. 202–203, 1990.

[17] J. D. Kirby and C. R. Darley, “Erythema multiforme associated with a contact dermatitis to terpenes,” *Contact Dermatitis*, vol. 4, no. 4, p. 238, 1978.

[18] A. A. Raccagni, F. Bardazzi, U. Baldari, and M. G. Righini, “Erythema-multiforme-like contact dermatitis due to capsoicum,” *Contact Dermatitis*, vol. 33, no. 5, pp. 353–354, 1995.

[19] M. P. G. Mateo, M. Velasco, F. J. Miquel, and J. de la Cuadra, “Erythema-multiforme-like eruption following allergic contact dermatitis from sesquiterpene lactones in herbal medicine,” *Contact Dermatitis*, vol. 33, no. 6, pp. 449–450, 1995.

[20] N. Hjorth, “Primula dermatitis,” *Transactions of the St. John’s Hospital Dermatological Society*, vol. 52, pp. 207–219, 1966.
[21] A. Virgili and M. Corazza, “Unusual primin dermatitis,” *Contact Dermatitis*, vol. 24, no. 1, pp. 63–64, 1991.

[22] F. Lengrand, A. S. Tellart, M. Segard, Y. Dejobert, and P. Thomas, “Erythema multiforme-like eruption: an unusual presentation of primula contact allergy,” *Contact Dermatitis*, vol. 44, no. 1, p. 35, 2001.

[23] R. Gallo, S. Sorbana, and F. Rongioletti, “Contact erythema multiforme from Primula obconica,” *Contact Dermatitis*, vol. 53, no. 6, pp. 351–352, 2005.

[24] D. Bonamonte, R. Filotico, V. Mastrandrea, C. Foti, and G. Angelini, “Erythema multiforme-like contact dermatitis from primin,” *Contact Dermatitis*, vol. 59, no. 3, pp. 174–176, 2008.

[25] C. L. Meneghini and G. Angelini, “Secondary polymorphic eruptions in allergic contact dermatitis,” *Dermatologica*, vol. 163, no. 1, pp. 63–70, 1981.

[26] C. L. Meneghini and G. Angelini, “Contact dermatitis from pyrrolnitrin,” *Contact Dermatitis*, vol. 8, no. 1, pp. 55–58, 1982.

[27] H. R. Gottschalk and O. J. Stone, “Stevens Johnson syndrome from ophthalmic sulfonamide,” *Archives of Dermatology*, vol. 112, no. 4, pp. 513–514, 1976.

[28] Z. Rubin, “Ophthalmic sulfonamide induced Stevens Johnson syndrome,” *Archives of Dermatology*, vol. 113, no. 2, pp. 235–236, 1977.

[29] H. S. Affee and D. P. Dressler, “Topical application of mafenide acetate. Its association with erythema multiforme and cutaneous reactions,” *Archives of Dermatology*, vol. 100, no. 3, pp. 277–281, 1969.

[30] A. A. Fisher, “Erythema multiforme-like eruptions due to topical medications: part II,” *Cutis*, vol. 37, no. 3, pp. 158–161, 1986.

[31] H. Degreef, A. Bonamie, D. van Derheyden, and A. Dooms-Goossens, “Mephenesin contact dermatitis with erythema multiforme features,” *Contact Dermatitis*, vol. 10, no. 4, pp. 220–223, 1984.

[32] A. Schulze-Dirks and P. J. Frosch, “Contact allergy to Mephenesine,” *Hautarzt*, vol. 44, no. 6, pp. 403–406, 1993.

[33] S. Kerre, A. Busschots, and A. Dooms-Goossens, “Erythema-multiforme-like contact dermatitis due to phenylbutazone,” *Contact Dermatitis*, vol. 33, no. 3, pp. 213–214, 1995.

[34] P. Koch and F. A. Bahmer, “Erythema-multiforme-like, urticarial papular and plaque eruptions from bufexamac: report of 4 cases,” *Contact Dermatitis*, vol. 31, no. 2, pp. 97–101, 1994.

[35] M. Walchner, F. Rueff, and B. Przybilla, “Delayed-type hypersensitivity to mofebutazone underlying a severe drug reaction,” *Contact Dermatitis*, vol. 36, no. 1, pp. 54–55, 1997.

[36] L. Stingeni, S. Caraffini, D. Assalve, V. Lapomarda, and P. Lisi, “Erythema-multiforme-like contact dermatitis from budesonide,” *Contact Dermatitis*, vol. 34, no. 2, pp. 154–155, 1996.

[37] R. Valsecchi, A. Reseghetti, P. Legghissa, L. Cologni, and R. Cortinovis, “Erythema-multiforme-like lesions from trimacnilone acetoneid,” *Contact Dermatitis*, vol. 38, no. 6, pp. 362–363, 1998.

[38] C. D. Calnan, “Nickel dermatitis,” *British Journal of Dermatology*, vol. 68, pp. 229–232, 1956.

[39] L. J. Cook, “Associated nickel and cobalt contact dermatitis presenting as erythema multiforme,” *Contact Dermatitis*, vol. 8, no. 4, pp. 280–281, 1982.

[40] S. J. Friedman and H. O. Perry, “Erythema multiforme associated with contact dermatitis,” *Contact Dermatitis*, vol. 12, no. 1, pp. 21–23, 1985.

[41] A. A. Fisher, “Erythema multiforme-like eruptions due to topical miscellaneous compounds: part III,” *Cutis*, vol. 37, no. 4, pp. 262–264, 1986.

[42] E. W. Powell, “Skin reactions to 9-bromofluorene,” *British Journal of Dermatology*, vol. 80, no. 8, pp. 491–496, 1968.

[43] J. Roed-Petersen, “Erythema multiforme as an expression of contact dermatitis,” *Contact Dermatitis*, vol. 1, no. 4, pp. 270–271, 1975.

[44] D. Bonamonte and G. Angelini, “Dermatitis da contatto purpurica,” *Annali Italiani di Dermatologia Allergologica*, vol. 55, pp. 53–61, 2001.

[45] B. Batschvarov and D. M. Minkov, “Dermatitis and purpura from rubber in clothing,” *Transactions of the St. John’s Hospital Dermatological Society*, vol. 54, no. 2, pp. 178–182, 1968.

[46] C. D. Calnan and R. D. C. Peachey, “Allergic contact purpura,” *Clinical Allergy*, vol. 1, no. 3, pp. 287–290, 1971.

[47] A. A. Fisher, “Allergic petechial and purpuric rubber dermatitis: the PPPP syndrome,” *Cutis*, vol. 14, pp. 25–27, 1974.

[48] A. A. Fisher, “Purpuric contact dermatitis,” *Cutis*, vol. 33, no. 4, pp. 346–351, 1984.

[49] C. Romaguera and F. Grimalt, “PPPP syndrome,” *Contact Dermatitis*, vol. 3, no. 2, pp. 102–103, 1977.

[50] C. Romaguera, F. Grimalt, and J. Vilaplana, “Eczematous and purpuric allergic contact dermatitis from boots,” *Contact Dermatitis*, vol. 21, no. 4, p. 269, 1989.

[51] L. Carlsten, K. E. Andersen, and H. Egsgaard, “IPPD contact allergy from an orthopedic bandage,” *Contact Dermatitis*, vol. 17, no. 2, pp. 119–121, 1987.

[52] J. Roed-Petersen, O. J. Clemmensen, T. Menne, and E. Larsen, “Purpuric contact dermatitis from black rubber chemicals,” *Contact Dermatitis*, vol. 18, no. 3, pp. 166–168, 1988.

[53] P. E. Osmundsen, “Contact dermatitis due to an optical whitener in washing powders,” *British Journal of Dermatology*, vol. 81, no. 11, pp. 799–803, 1969.

[54] P. E. Osmundsen, “Contact dermatitis from an optical whitener in washing powders,” *Cutis*, vol. 10, pp. 59–66, 1972.

[55] J. P. A. Veer, F. Grimalt, C. Romaguera et al., “Dermatitis por blanqueadores opticos,” *Medicina Cutanea*, vol. 5, p. 249, 1971.

[56] J. P. Van der Veen, H. Neering, P. de Haan, and D. P. Bruynzeel, “Pigmented purpuric clothing dermatitis due to Disperse Blue 85,” *Contact Dermatitis*, vol. 19, no. 3, pp. 222–223, 1988.

[57] C. Foti, G. Elia, R. Filotico, and G. Angelini, “Purpuric clothing dermatitis due to Disperse Yellow 27,” *Contact Dermatitis*, vol. 39, no. 5, p. 273, 1998.

[58] E. Shmunes, “Purpuric allergic contact dermatitis to para-phenylenediamine,” *Contact Dermatitis*, vol. 4, no. 4, pp. 225–229, 1978.

[59] F. F. Hellier, “Dermatitis purpurica after contact with textiles,” *Der Hautarzt; Zeitschrift für Dermatologie, Venerologie, und verwandte Gebiete*, vol. 11, pp. 173–174, 1960.

[60] C. Romaguera, F. Grimalt, and M. Lecha, “Occupational purpuric textile dermatitis from formaldehyde resins,” *Contact Dermatitis*, vol. 7, no. 3, pp. 152–153, 1981.

[61] M. Faure, C. Dambuyant, G. Chabeau, P. Souteyrand, and J. Tguviket, “Immune complex vasculitis and contact dermatitis to Frullania,” *Contact Dermatitis*, vol. 7, no. 6, pp. 320–325, 1981.

[62] M. R. Ricks, P. S. Vogel, D. M. Elston, and C. Hivnor, “Pulpuric agave dermatitis,” *Journal of the American Academy of Dermatology*, vol. 40, no. 2, pp. 356–358, 1999.
[103] L. Wattanakrai, L. Miyamoto, and J. S. Taylor, “Occupational pigmented disorders,” in *Handbook of Occupational Dermatology*, L. Kanerva, P. Elsner, J. E. Wahlberg, and H. I. Maibach, Eds., pp. 280–294, Springer, Berlin, Germany, 2000.

[104] C. G. Burkhart, “Pustular allergic contact dermatitis: a distinct clinical and pathological entity,” *Cutis*, vol. 27, no. 6, pp. 630–638, 1981.

[105] V. J. Schoel and B. J. Froshch, “Allergisches Kontaktekzem durch Gumiin-haltstofte unter dem Bild einer Pustulosis palmaris,” *Dermatosen*, vol. 38, pp. 178–180, 1990.

[106] C. G. Burkhart, “Pustular allergic contact dermatitis: a distinct clinical and pathological entity,” *Cutis*, vol. 27, no. 6, pp. 630–638, 1981.

[107] A. Lazarov and A. Inger, “Pustular allergic contact dermatitis to isonazol nitrate,” *American Journal of Contact Dermatitis*, vol. 8, no. 4, pp. 229–230, 1997.

[108] A. Lazarov and A. Inger, “Pustular allergic contact dermatitis to isonazol nitrate,” *American Journal of Contact Dermatitis*, vol. 8, no. 4, pp. 229–230, 1997.

[109] L. Conde Salazar, D. Guimaraens, L. V. Romero, and E. Sanchez Yus, “Subcorneal pustular eruption and erythema from occupational exposure to trichloroethylene,” *Contact Dermatitis*, vol. 9, no. 3, pp. 235–237, 1983.

[110] N. Hjorth, “Diagnostic patch testing,” in *Dermatoxicology and Pharmacology*, F. Marzulli and H. I. Maibach, Eds., pp. 344–351, John Wiley & Sons, New York, NY, USA, 1977.

[111] A. A. Fisher, L. Chargin, R. Fleischmayer, and A. Hyman, “Pustular patch test reactions; with particular reference to those produced by ammonium fluoride,” *Archives of Dermatology*, vol. 80, pp. 742–752, 1959.

[112] J. E. Wahlberg and H. I. Maibach, “Sterile cutaneous pustules: a manifestation of primary irritancy? Identification of contact pustulogens,” *Journal of Investigative Dermatology*, vol. 76, no. 5, pp. 381–383, 1981.

[113] G. Angelini and M. Grandolfo, “Test diagnostici,” in *Dermatologia Allergologica e Professionale*, G. Angelini and G. A. Vena, Eds., vol. 2, pp. 572–592, ISED, Brescia, Italy, 1997.

[114] D. Bonamonte, C. Foti, A. Carpentieri, and G. Angelini, “Dermatite allergica da contatto in età pediatrica,” *Annali Italiani di Dermatologia Allergologica*, vol. 64, article 1, 2010.

[115] C. L. Meneghini and G. Angelini, “Contact and microbial allergy in pompholyx,” *Contact Dermatitis*, vol. 5, no. 1, pp. 46–50, 1979.

[116] G. A. Vena, S. Mazzoccoli, and G. Angelini, “Studio epidemiologico, clinico ed eziopatogenetico della disidrosi,” *Bollettino di Dermatologia Allergologica e Professionale*, vol. 7, pp. 259–273, 1992.

[117] M. Reichenberger, “Die Dyshidrosis als Schrittmancher für berufliche Dermatosen,” *Beruf Dermatosen*, vol. 29, pp. 127–130, 1975.

[118] T. Menne and N. Hjorth, “Pompholyx—dyshidrotic eczema,” *Seminars in Dermatology*, vol. 2, no. 1, pp. 75–80, 1983.

[119] O. B. Christensen and H. Moller, “Nickel allergy and hand eczema,” *Contact Dermatitis*, vol. 1, no. 3, pp. 129–135, 1975.

[120] O. B. Christensen and H. Moller, “External and internal exposure to the antigen in the hand eczema of nickel allergy,” *Contact Dermatitis*, vol. 1, no. 3, pp. 136–141, 1975.

[121] E. Cronin, A. D. Di Michiel, and S. S. Brows, “Oral challenge in nickel sensitive women with hand eczema,” in *Nickel Toxicology*, S. S. Brown and F. W. Sunderman Jr., Eds., pp. 149–152, Academic Press, New York, NY, USA, 1980.