ORIGINAL ARTICLE

Nummular Eczema: A Bibliographical Review

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ABSTRACT

Nummular eczema is a dermatosis that does not always receive the attention and recognition it deserves. It is often considered as part of atopic dermatitis, as a result of not doing in depth research among these patients, who frequently present a chronic and desperate evolution.

For this reason, we have been prompted to carry out extensive bibliographic research that will allow us to better understand this disease, and adequately manage it.

INTRODUCTION

Nummular eczema (NE) is a diagnosis that comes up very frequently on a dermatology consultation. Moreover, it is commonly observed that unspecific cases of round lesions of eczema are easily labeled and prescribed without having made a proper diagnosis. Especially when there are desperate patients on the waiting room.

NE is still unclear regarding its classification. Some physicians describe NE as an independent entity, while others place it as part of other processes or associate it to atopic dermatitis.

It is why there has been a strong interest to do an extensive bibliographical research on the matter, including conclusions in regards to historical aspects, classification, pathogenia, clinical forms, associations, research procedures. As a result, physicians are able to choose the most appropriate treatments based on an extensive study of the condition.

Throughout the development, some report cases that illustrate the review of this diagnosis are presented.

ETIMOLOGY

The term nummular comes from the latin *nummulus*, which means "coin-shaped,"[1] as illustrated on Fig. 1 (extracted from an article of *Revista Chilena de Dermatología*).[2]

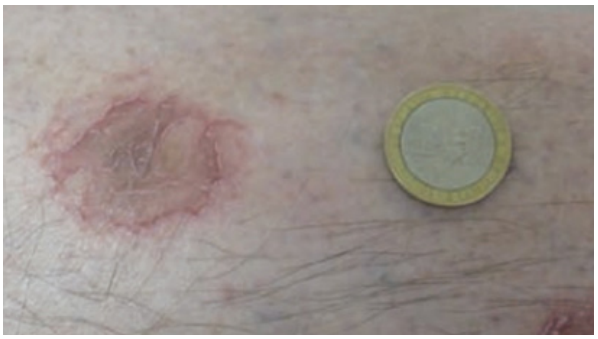

Figure 1: Illustration of shape similarities between NE and a coin (taken from Avayú et al.[2]).

SYNONYMS

NE is also known as:

- Discoid eczema
- Nummular dermatitis
- Microbial eczema

- Microbial dermatitis
- Sulzberger-Garbe disease
- Some associate this condition to NE.
- However, the disease, described by these authors in 1937, is an independent entity with very few cases reported within the global medical literature. It presents unique features, such as a predilection for middle-age males, especially Jewish, and lesions that evolve from exudative and discoid to lichenoid and vice-verse, round or oval, and commonly located on the genitals, showing a tendency toward spontaneous regression.
- Nonetheless, in some cases, such as the one presented herein,[3] it is difficult to differentiate between NE and the aforementioned picture. As a result, several publications present them as synonyms.

HISTORY

This condition was first clinically described in 1845 by Pierre Francois Rayer, (Fig. 2) and its name, as it is currently acknowledged, was defined in 1857 by French dermatologist Marie-Guillaume-Alphonse Devergie[4] (Fig. 3) who in his work stated having observed these lesions for the first time on a postal employee 8 years before, and afterwards observed a lot of cases each year, acknowledging the condition as nummular eczema because of its round lesions' similarities in size with a 5 franc coin.[5]

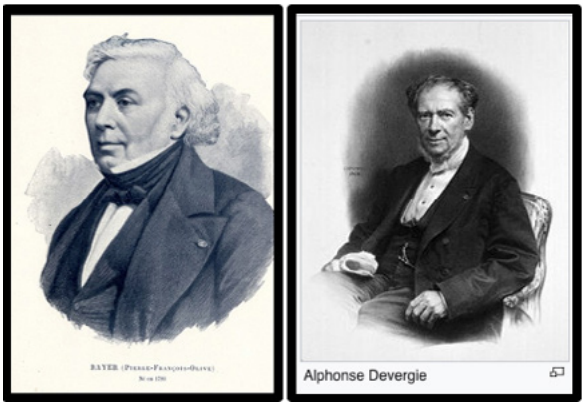

Figure 2 and 3: Respective portraits of Pierre Francois Rayer and Marie- Guillaume-Alphonse Devergie, fathers of the disease. Pictures taken from Wikipedia.

DEFINITION

NE or discoid eczema is a chronic inflammatory, cutaneous disease characterized by the presence of scarce or multiple eczematous coin-shaped lesions, commonly accompanied by pruritus. Preferential location: extremities, trunk (less frequently) on xerotic skin (Fig. 4).

NE is acknowledged within the general classification of eczemas as a subtype of idiopathic endogenous eczema.[4-6]

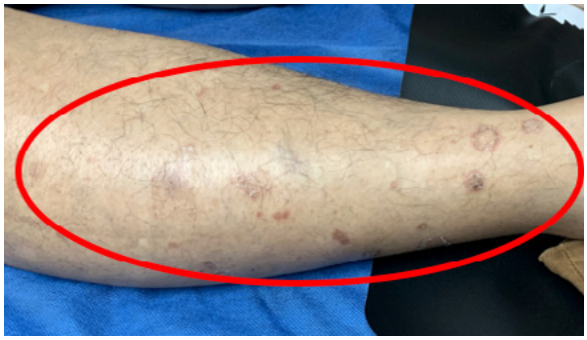

Figure 4: Round lesions on lower limb.

ECZEMA CLASSIFICATION

General classification of eczemas is always difficult to define. There is an ongoing discussion about the topic. However, it is based on causal and clinical factors.

For learning purposes, eczema is divided into two groups:

- Eczemas of exogenous origin, such as contact dermatitis.
- Endogenous or constitutional eczemas, such as AD.

In his work,7 Ferrándiz categorizes NE within endogenous eczemas (Table 1)

While, in his work, R. Arenas specifically classifies NE as:

- True nummular eczema, due to stasis, dyshidrosis, autoeczematization, recurrent chronic pustular eruption in palms and plants, etc.
- Infantile nummular dermatitis

Table 1: Adapted from Ferrándiz's work: Dermatología Clínica.[7]

CLASSIFICATION OF THE MAIN TYPES OF ECZEMA	
EXOGENOUS ECZEMAS	Irritant contact dermatitis
	Allergic contact dermatitis
	Photoallergic contact dermatitis
	Aero-transported dermatitis
	Eczema-like polymorphic light eruption
	Autolytic or autosensitization eczema
	Id reaction in dermatophytosis
ENDOGENOUS ECZEMAS	Atopic eczema
	Nummular eczema
	Seborrheic eczema
	Asteatotic eczema
	Infantile plantar dermatitis
	Pityriasis alba
	Hand eczema
	Neurodermatitis or lichen simplex chronicus of Vidal.
	Gravitational or stasis dermatitis

EPIDEMIOLOGY

The estimated prevalence of the disease is 2 cases per 1000 individuals. It is more common among men than women. Moreover, men present with NE towards the end of their lives, while women manifest this condition at a younger age. However, among pediatric patients, girls suffer from NE more commonly than boys.

The vast majority are patients older than 50 (between the 5th and 7th decade of life). Furthermore, there are fewer cases on patients in the second and third decade of life (this group is associated with AD). Cases in the first decade of life are rare. Nonetheless, individuals of any age may be affected.[6-9]

There are authors who consider that NE is an underdiagnosed disease, which is frequent among children in their first five years of life.[10]

In their article, Magaña and collaborators report 40 clinically-diagnosed pediatric cases, with the same sex rate. They equally affirm that the condition is more frequent in patients aged 5 or under, with no associations to other diseases, such as AD or bacterial infections (an affirmation somewhat contradictory to what is usually stated).[11]

PATHOGENESIS

The pathogenesis of NE is still unclear. A great amount of factors have been acknowledged as causal:

Cutaneous barrier alterations

- Xerosis and a decreased level of skin lipids Xerosis on NE is produced because the skin surface does not receive enough water from the subjacent epidermis. This is because a well-conserved cutaneous barrier of the stratum corneum impedes it. This is different from what occurs in AD, where there are lower levels of hydration due to a greater loss of water provoked by an alteration of the stratum corneum barrier. Xerosis on NE causes the surface of the skin to crack and fissure, as well as to suffer from pruritus, constant scratching, which harms the skin and makes it permeable towards various environmental allergens.[12-13]
- Filaggrin deficiency and its natural moisturizing factors (NMF); Recent studies suggest that the lack of the protein filaggrin (FLG) and its natural moisturizing factors (NMF) contribute greatly to the condition because of its highly hydrogenous composition and nutritional supplementation during NE.[14] This protein's deficiency greatly affects the epidermal barrier, causing anomalies within the extracellular lipid matrix, as well as altering skin barrier function, causing xerosis in the skin surface, increase in staphylococcus' adhesion and proliferation, along with higher exposition to allergens and, last but not least, epithelial proinflammatory mediators liberation.[15]
- Seasonal variations; these variations affect patients, especially during cold winter seasons, when hydration levels are low. As a consequence,

the stratum corneum becomes drier than normal. Temperate and humid summer weather may also worsen lesions, especially on male patients (16).

Infectious causes

- Colonization by S aureus; A study of 40 patients with NE and 40 healthy control subjects living with those patients aimed to obtain samples extracted by swabs from lesional and non-lesional skin, as well as the anterior nostril and 2nd subungual space.
- S. aureus and methicillin-resistant s. aureus were found at a much higher percentage on NE patients than healthy control subjects, which is attributed to skin barrier alterations, leading for bacterial receptors, such as fibronectin and fibrinogen, to increase adhesion of pathogens and facilitate colonization by S. aureus.
- The vast majority was found on the lesional skin, followed by the anterior nostril. A lesser quantity was found on the subungual space.[17]

Other infectious causes (odontogenic - H. pylori); there are reports of diverse infectious pathologies that have been associated to cases of recalcitrant NE.

- Tanaka et al.[17] report 13 moderate to severe NE cases in patients who underwent dental panoramic examination. Among the findings were odontogenic infections, which were treated, and showed partial or total improvement. Consequently, such authors suggest that latent odontogenic infections may be aggravating factors on treatment-resistant NE.[18]
- This work corroborates what was reported in 1960 by Hans Krogh,[19] who examined 72 patients with NE, discovering infectious foci in several locations of 50 patients. Moreover, 33 of them manifested odontogenic infections. Finally, it was concluded that this treatment cured the vast majority of cases.
- Concurrently, Satoh et al.[20] report the case of a patient who presented with recalcitrant lesions of chronic nodular prurigo on NE patches. This patient showed bleeding of gums at the level of the 5th lower left tooth. X-rays revealed a notable loss of bone surrounding the tooth, indicating a severe periodontitis. The extraction of the tooth caused a transitory outbreak of per nodular erythema, accompanied by intense pruritus. Moreover, after a few weeks, there was notable improvement of the eczema.
- A publication by Lugovic et al. reveals a study on patients with NE and healthy control subjects. When a comparison was made, H. pylori showed significantly higher prevalence, while urogenital infections were found to represent 11.4%, especially E. coli (5.69%), as well as genital infections caused by ureaplasma and streptococci.

Sensitivity to aeroallergens such as C. albicans, domestic mites and other environmental allergens.

- Sensitivity to environmental aeroallergens, such as Cándida albicans or house dust mites, weeds, animal epithelia, fungi, has been identified as a triggering exogenous factor in AD, NE, rhinitis, etc.[6-22] In 1999, Aoyama et al. report cases of NE in senior patients, caused by aeroallergens, specially Cándida albicans, which penetrate the skin through provoked fissures due to itchy xerotic skin, inducing eczematous changes within elderly patients with adequate delayed-type hypersensitivity maintained in spite of their advanced age.

Contact dermatitis triggered by metal and other substances

- Rattan et al. consider that certain endogenous eczemas, such as NE (endogenous eczema variant), tend to complicate due to exogenous factors, such as contact and environmental allergens. Consequently, patch tests were done to 40 patients. 21 tested positive for nickel, fragrance, formaldehyde allergy, so it was concluded that NE patients may also develop allergic contact dermatitis because of xerosis.[23]

Different substances have been reported as causal,

- Contact with substances containing aloe.[24]
- Hair removal creams containing potassium thioglycollate, which provoke NE outbreak on lower limbs within 24 hours after application.
- Patients with NE caused by mercury in dental amalgams. It is known that ingestion of appreciable quantities of metals and dental metal alloys may

provoke a variety of dermatoses, such as oral and cutaneous lichen planus, palmoplantar pustulosis, dyshidrosis and in this particular case, NE.[26]

- Several studies have outlined nickel exposure as a common allergen for NE. A study made by Indrastuti et al. in 2019 confirmed this criteria, concluding that nickel allergic contact dermatitis is the most significant inducing factor within NE. Consequently, they recommend the performance of patch testing in recurrent and persistent cases.[27]
- Bonamonte et al. did a study in which they performed patch tests to 29323 patients with eczematous dermatitis of different kinds; 1022 suffered from NE. This group encountered 332 patients that tested positive for more than 1 allergen; being nickel the most frequent causal agent, followed by potassium dichromate, cobalt hydrochloride, p-phenylenediamine, ethylenediamine, etc.[28]

Medications

There are several reports that associate diverse medicamentous therapies to the manifestation of NE.

- Medications that cause cutaneous xerosis, such as isotretinoin: In regards to this subject, Bettoli y Tosti[29] reveal a study involving 21 patients suffering from acne, who were treated with isotretinoin. Eight presented with NE lesions one or 2 months after treatment was initiated, but these were easily resolved within a 20-day time frame due to a small dose reduction.
- Meanwhile, hepatitis C patients, treated with interferon alpha-2b and ribavirin, were diagnosed with NE, among other collateral cutaneous effects produced by this combination. One of the most significant reports is one conducted by Manjon et al.,[30] involving 210 hepatitis C patients treated with these 2 products. 14 patients were diagnosed with eczematous localized lesions and 2 with generalized. However, there are multiple reports of patients who developed both focal and generalized nummular eczemas[31-32-33] accompanied by intense pruritus, disappearing after the discontinuation of such combined therapy (2 drugs).
- Another product that has been mentioned is guselkumab, employed in the treatment of patients with palmoplantar psoriasis, causing NE after 3 months of use,[34] suggesting that the balance between Th1 and Th2 cytokines plays a significant role in the pathogenesis of some cases.[6] Although eczematous reactions in patients treated with biologics are commonly reported in medical literature, guselkuzumab is only mentioned in just a few NE reports. However, there are reports which reveal the presence of generalized eczema provoked by this medication. Such is the case reported by Reyn et al.[35] in a patient with psoriasis vulgaris. From 2005, there are reports outlining several cutaneous complications in patients with rheumatoid arthritis that were treated with TNF inhibitors. 19 of these patients were diagnosed with eczema, one of them reporting to manifest NE. Treatment was suspended among all patients, which resulted in the resolution of all lesions. One of the patients reinitiated adalimumab treatment, and, as a consequence, eczematous lesions reappeared.[36]
- Surprisingly, in 2015, Iwahira et al.[37] initiated an examination of 1662 patients who had gotten breast reconstruction surgery. There were 48 positive cases for NE manifesting in the reconstruction area. 22 patients presented with NE after the insertion of tissue expanders, 12 after the silicone replacement and 14 after reconstruction of the nipple-areolar complex. Histopathological examination was carried out in all patients. Authors conclude that NE may represent a complication caused by the use of artificial materials during breast reconstruction surgery. Another report[38] sheds light into an augmentation mammoplasty involving 365 implants, in which, two months after, the patient presented with NE on periareolar areas. Lesions did not resolve in spite of treatment. Consequently, the implants were removed and the clinical picture resolved after a month of therapy. In 2020, Yamamoto[39] reports 7 NE cases manifesting in locations involving surgical scars and 3 of them presented with lesions in distant areas; the author speculates that this

may be the result of an isomorphic response of Koebner and suggests that this falls within the 4 forms of classification of such reaction, specifically the fourth one (trauma-induced processes), and concludes that NE manifests in these cases, as the affected skin shows as not normal, and is susceptible to developing other lesions, associating this criteria to previous cases of the Iwahira study.[37]

Emotional factors

- These have been considered as aggravating factors or causals of NE. There are several studies that associate mental health and eczema. However, only few present with NE. An old study dated from 1971[40] has arisen some interest: patients suffering from various types of eczema are evaluated; among them, NE. Patients are divided into two groups, the first one receives dermatologic treatment and the second one receives dermatologic treatment plus psychiatric therapy for a short period of 4 months. On the follow-up, it was determined that psychiatric treatment greatly improves the resolution of eczema, and opposite results occur when patients are only treated dermatologically. Consequently, there is an inclination to think about some conclusive psychological influence.

Atopic dermatitis

The relationship between NE and atopic dermatitis is very controversial, given that there are people who consider NE as a form of AD.[41] Nonetheless, there are studies which negate an association between the two clinical pictures, based on the fact that NE does not have as high levels of serum IgE as AD;[42] although, posteriorly, two subtypes of AD who share the same clinical data have been recognized: an extrinsic form (allergic IgE) and an intrinsic form (allergic non-IgE).[43] Moreover, Hellgren and Mobacken.[44] published a study involving 131 hospitalized patients with NE. 13 of them had some family medical history that included asthma, bronchitis, allergic rhinitis, urticaria or AD, which coincided with 10% of the general population who suffered from atopy. It is common knowledge that within the atypical forms of AD is atopic NE,[22] which generates confusion, especially when there are AD cases with nummular pattern. Although AD manifests early in childhood, there is a form of AD which commences at a later or adult stage. This may present with clinical variations. In many cases, the classical flexural pattern is absent, which makes diagnosis more difficult. AD may reappear in adulthood with specific clinical features.[46] Among them, a nummular form. Consequently, in 2000, Bannister y Freeman,[47] introduced the term adult AD after they conducted a study in which they found out a considerable percentage of AD patients manifested the condition at 20 years old, proving that AD may manifest nummular lesions both in children and adults. NE, in this case, is a phenotypical variant of AD,[46-49] with an incidence of 9% and 12% respectively. Furthermore, there are studies that indicate that nummular lesions represent the most common atypical morphological variant of AD in children and adults. Even so, it is not rare to observe, in infants, the presence of nummular lesions that coexist with typical lesions of AD in folds. Additionally, nummular lesions in adults represent, according to some, 37.3% of atypical morphological variants of AD.[50] As a conclusion, it is stated that NE is a fairly significant presentation pattern of AD, without taking in consideration the IgE total, specific IgE, or family medical history involving atopy.

CLINICAL MANIFESTATIONS OF NE AND ITS VARIANTS

The process starts with small papules and vesicles that grow and gradually fuse to form eczematous, scaly, coin-shaped, slightly edematous, well-rounded and delimited plaques accompanied by intense nocturnal pruritus, especially with new lesions. Commonly, lesions are 1 to 10cm in diameter.[6-51] (Fig.5).

Lesions evolve in two phases. The first one is acute, exudative, with scabs and predominance of papules and vesicles on a muted red background (Fig 6). The second phase is chronic, mainly scabby and desquamative. As time passes by, lesions become dry, squamous, and annular and occasionally present with central clearing giving an annular appearance.[6] (Fig. 7)

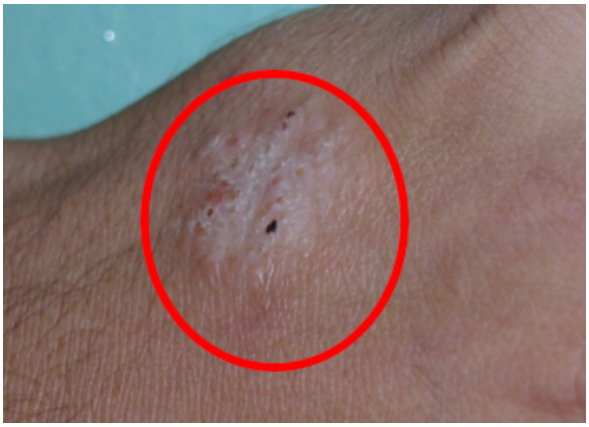

Figure 5: Lesion on dorsum of hand, characteristic of NE with papules and vesicles forming a rounded scaly plaque.

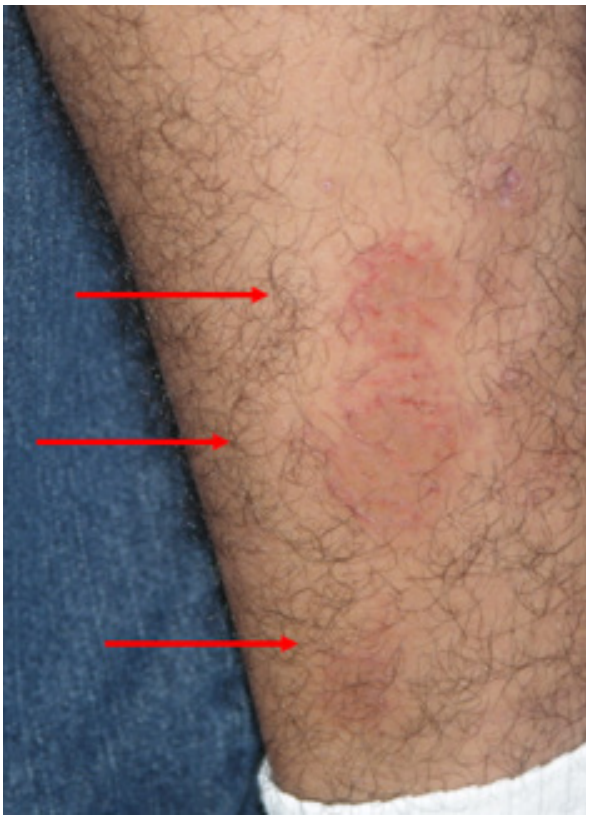

Figure 6: Acute phase with rounded and exudative lesions.

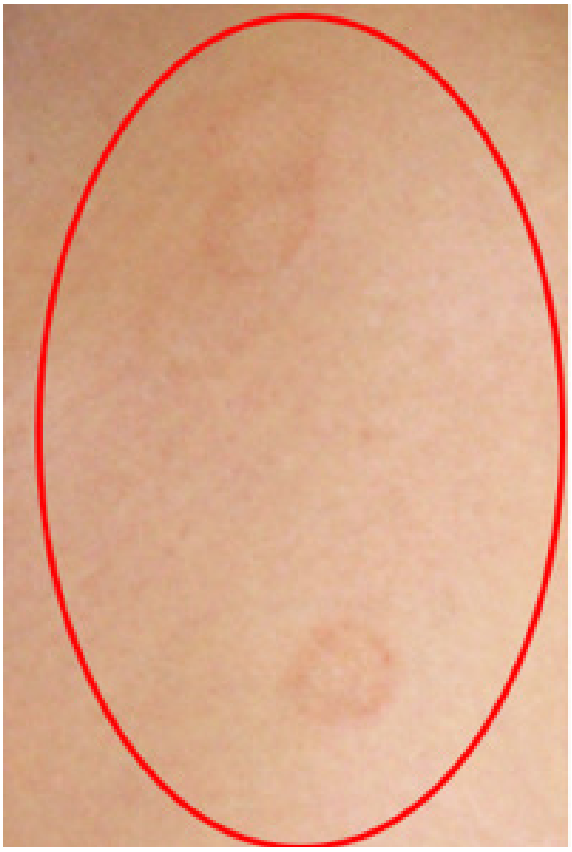

Figure 7: Chronic phase with lesions of annular appearance due to central clearing.

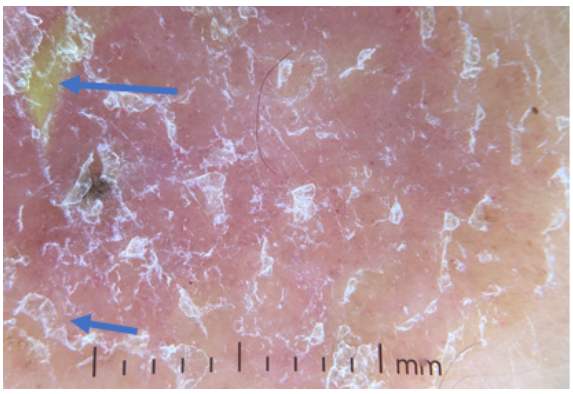

Figure 8: NE. Dermoscopy. Blue arrows signal the presence of meliceric scabs.

The disease course is usually chronic. Prevalence is probable, as lesions tend to reappear in the same areas.[51]

Superinfection may take place on all stages of the condition. Almost always involves the clinical manifestation of Staphylococcus aureus due to the presence of yellow, meliceric scabs.[52] (Fig. 8)

NUMMULAR ECZEMA ON INFANTS

Regarding this particular type, García Magaña confirms,[53] that NE is one of the ten most frequent cutaneous affections on infants. However, lack of knowledge regarding this is attributed to how little have been written about the subject.

In a study involving 40 patients, it was found a greater predominance during the first 5 years of life, along with a chronic curse. No association with AD or other illnesses was reported. NE is children is characterized by the presence of eczematous plaques on the skin of the trunk, upper and lower limbs, accompanied by marked pruritus.

Infiltrate lesions manifest in two ways: a damp or wet form, represented by erosive and humid lesions, and a dry form, characterized by intense desquamation.[54] It is acknowledged that AD has a non-usual nummular variant. The true difficulty lies in recognizing conjunct cases of DA and NE. In spite of identification difficulties, there are clear differences between them.[55] NE, in contrast to AD, rarely develops during the first years of an individual's life. It usually manifests at around five years of age.

Its natural curse does not present with cutaneous xerosis. And the condition does not develops further than at the puberty stage. NE lesions at a pediatric and adult stage are more exudative, unlike atopic lesions, which are generally more dry and desquamative. They are not as numerous, but asymmetric and irregular.

When they resolve, they leave hypochromic and hyperchromic spots, affecting mostly extensor areas. The face and flexural areas are less affected.

NUMMULAR ECZEMA ON THE NIPPLE

Eczema on the nipples can constitute a problem for the diagnosis and therapeutic procedure, due to its chronicity and tendency to reappear. Generally, it is classified as an allergic contact dermatitis.[56] Although sometimes this cannot be demonstrated through patch testing, which is why it is identified as a manifestation or lesser criteria for AD, which commonly manifests in female adolescents or during pregnancy, especially in the first or second trimester[57] and the lactation period.[58] There is a case report regarding unilateral nipple eczema on a male patient with asthma history.[59] Although, atopic NE tends to be bilateral. There are multiple studies which conclude that nipple eczema is not characteristic of AD. They demonstrate that the frequency of presentation of this type of eczema has no significant percentages that would qualify it as lesser criteria for AD.[58,60,61]

Arguments about NE development as a complication in patients who had been treated for breast reconstruction surgery have been previously discussed.[37]

Mario Magaña and collaborators consider that dermatitis or nipple eczema is, in many occasions, a form of NE. There is a report[11] that shows two cases with exclusive nipple involvement, qualifying them as NE cases with a peculiar location and indicating that these cases are subject to the same clinical morphology, histology, evolution and therapy response as NE.

Clinically, nipple eczema presents various manifestations, such as erythema, vesicles, fissures, erosions, scabs during the acute phase. During the chronic phase, there is lichenification and desquamation. It may manifest unilaterally (Fig. 10) or bilaterally (Fig. 11), settling on the nipple and areola or through a NE disseminated disposition (Fig. 12), accompanied by pruritus (variable intensity or burning sensation). This may be settled on the nipple area or extend to an area beyond the areola, evolving intermittently.

NE Anatomic location[6-16] (Fig. 13-15):

- Extensor areas, both on the legs and upper limbs, as well as the gluteus, are the most commonly affected areas.
- Dorsum of hands and feet are equally affected.
- Trunk involvement is less common. When it is present, the lower part is more involved than the upper one.
- NE generally does not manifest on the head and the face. If they do, alternative diagnoses must be considered.
- Disseminated forms, accompanied by profusion in lesions, mostly adjust to the described anatomical localization (Fig. 16). There is no causal factor which justifies this particular form. However, it has been associated to the use of medication for hepatitis C.[33]

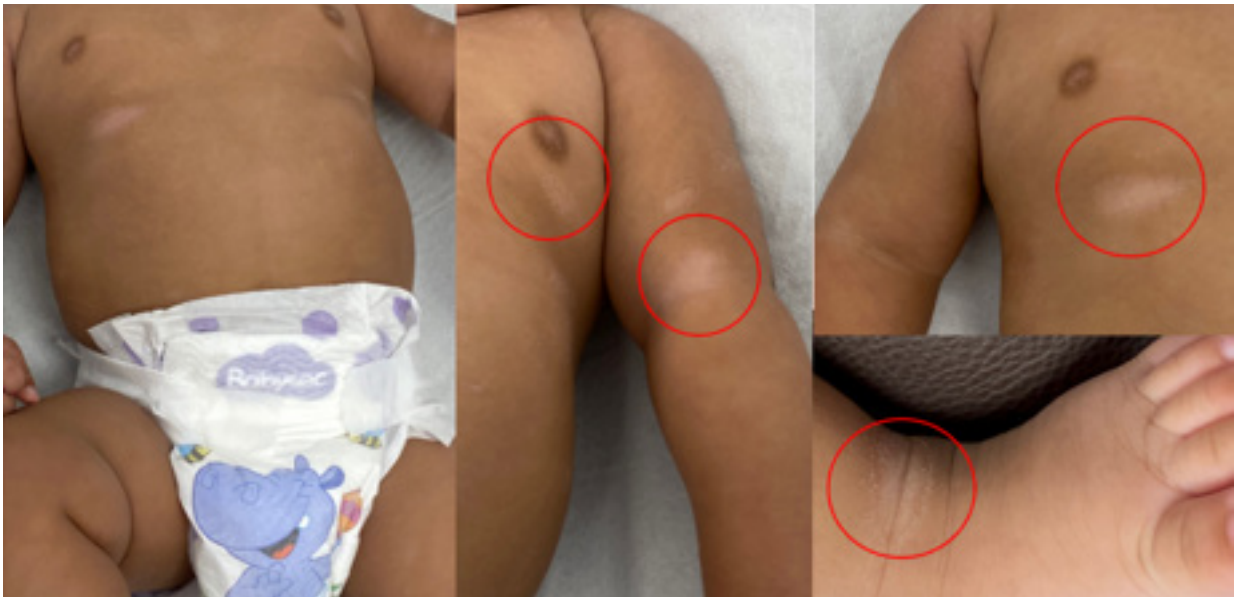

Figure 9: NE in children with eczematous and desquamative lesions leave hypochromic spots in the trunk and limbs. Annular lesion on the foot (instep area).

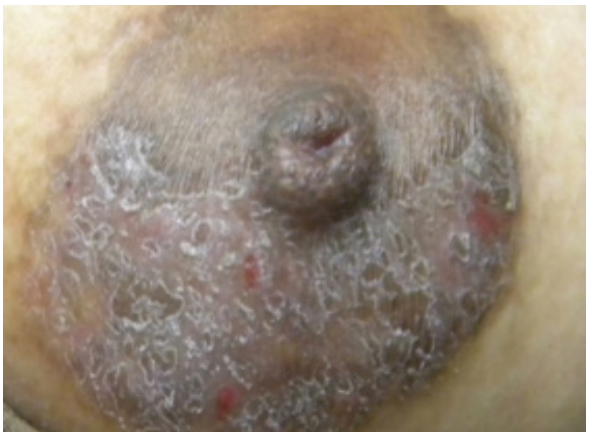

Figure 10: Unilateral NE. Erosions, desquamation and lichenification

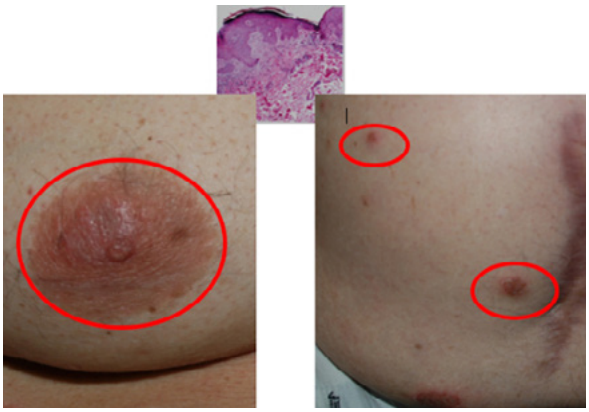

Figure 12: Nipple, areola NE and surrounding skin, accompanied by body lesions on male patient, clinical picture with clinical and histopathological correlation.

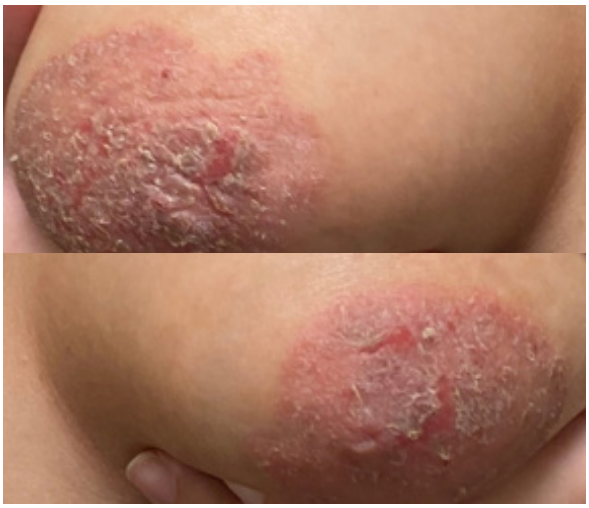

Figure 11: Bilateral NE. Erythema, erosions and desquamation, overgrowing the areola.

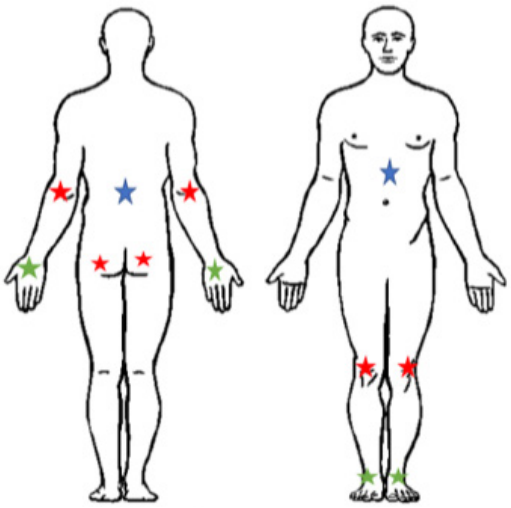

Figure 13: Most common affected areas in NE.

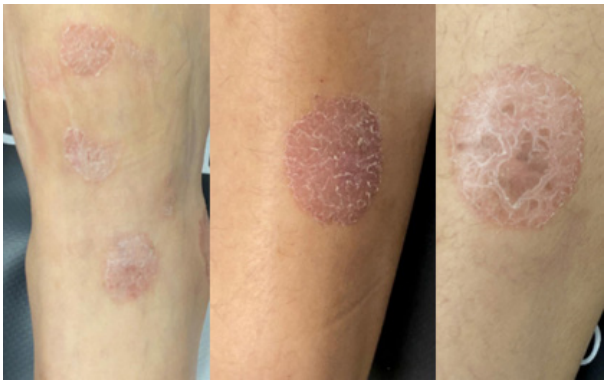

Figure 14: Lower limb NE

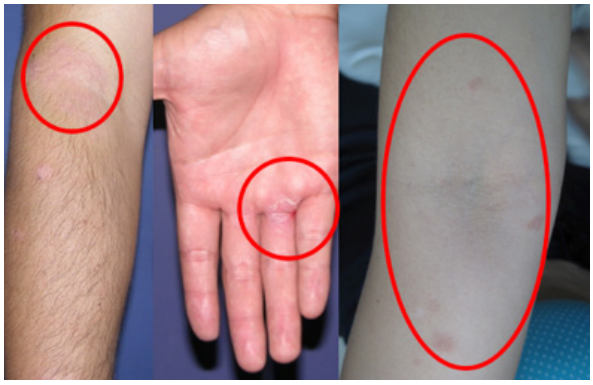

Figure 15: Atypically disposed upper limb NE in patients with no AD history.

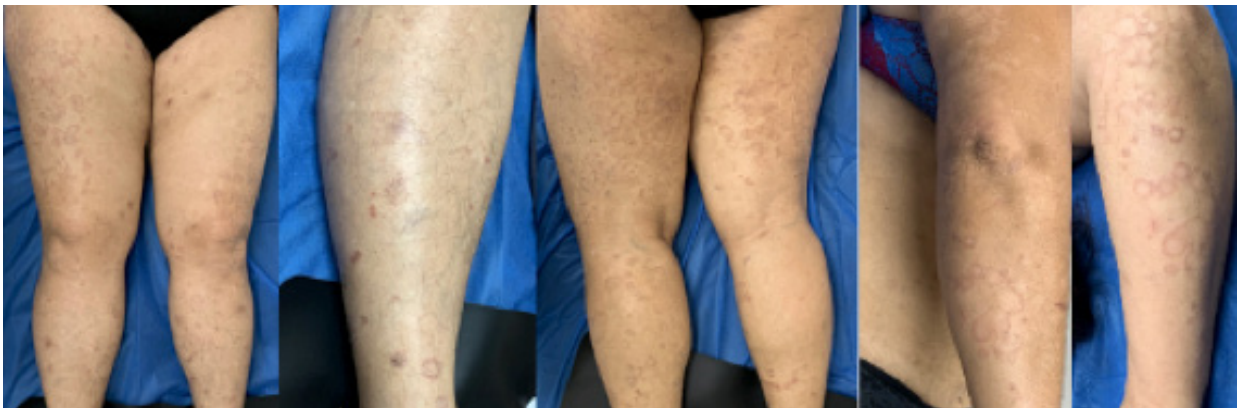

Figure 16: Disseminated NE. Most lesions adjust to anatomical location, process characteristics.

EVOLUTION

NE is an imminently chronic and recurring disease. Days or months after the clinical picture's apparent resolution, inactive-like lesions are reactivated. New lesions may as well manifest in adjacent areas.[6]

In a report about recurring factors in NE,[63] authors found that 3 out of 9 cases of this type of condition relapsed due to an infection caused by S aureus, 2 due to allergic contact, 3 due to xerosis and environmental humidity and, in one case, the triggering factor could not be identified.

NE PATHOLOGY

NE histopathology is considered as indistinguishable from other forms of eczema. The epidermis presents a typical subacute eczematous appearance with inflammatory exudative exoserosis and spongiotic vesicles.

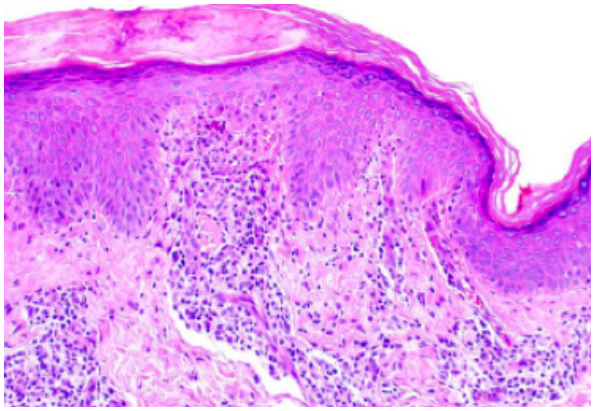

Fig 17. – Biopsy compatible with NE. Presence of acanthosis and focal parakeratosis. Diffuse moderate spongiosis. Perivascular lymphocytic superficial dermal infiltrate.

Presence of edema and inflammatory infiltrate, especially the perivascular type, in the superficial dermis, and epidermal psoriasiform thickness (acanthosis, parakeratosis and intermittent hyperkeratosis), all compatible with NE.[6-10] (Fig 17).

DIAGNOSIS

It tend to be clinical. It is stated that a biopsy may not be necessary.[6] Nonetheless, in many cases, a diagnosis is required due to these aforementioned clinical characteristics, which paint a confusing picture because of its similarities with other cutaneous illnesses. As consequence, the picture's clinical history, physical examination, lesional identification, distribution and evolution manage to justify biopsies with no specific characteristics. In most cases, the histopathological clinical picture is classified as compatible with NE.

Skin and rhinopharyngeal bacterial cultures must be conducted in patients whose lesions are exudative or scabby. For example, when there is a suspicion of infection involving unusual organisms or therapy-resistant lesions. The causal relationship between staphylococci and its endotoxins has been frequently cited in regards to these eczemas.[17-43]

Patch testing may be useful in unmanageable clinical pictures or contact allergic dermatitis. It is essential to discover the triggering agent, especially if we consider NE patients with an altered barrier function contributing to the severity and chronicity of such dermatitis.[64]

Most involved agents in contact allergy are nickel, rubber, fragrances, gold, formaldehyde, neomycin, and chrome respectively.[16]

Several reports[16] outline the possibility of urogenital infections as causal factors, especially E coli, as well as genital infections, mainly caused by Ureaplasma and Streptococci.

Others consider it is essential to research about H pylori because of its excellent response to treatment and a study showing 30.9% of NE patients testing positive for H pylori against a 13.33% of healthy control subjects.[21]

DIFFERENTIAL DIAGNOSIS

Its history and clinical presentation may indicate similarities with multiples dermatological conditions, such as (Fig. 18):

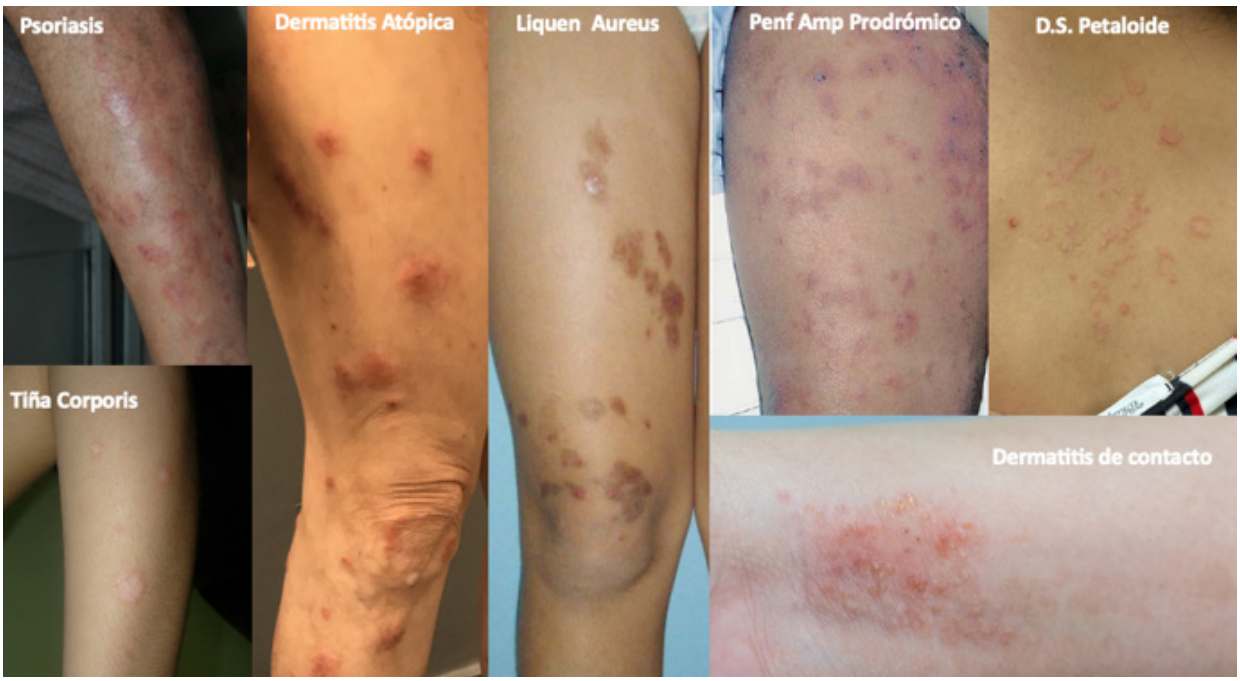

Fig 18. Some processes that must be considered in differentials. The picture concerning the blistering pemphigoid is extracted from the article cited in reference # 67.

Atopic dermatitis, when this disease is presented as a classical type, its history, lesional type, and location facilitate diagnosis.

Early stages of AD in adulthood present with complications in the diagnosis due to its atypical presentation. Although Kanwar and Narang[65] believe the criteria of Hannofin and Rajka for the diagnosis of AD may be employed in adults, in reality, these criteria may vary or get lost as the patient ages. This is important because, in their study involving 36 cases, they have established that the percentage of patients suffering from AD at its early stages correspondingly manifest NE at a rate of 16.7%.

Equally, Katsarou et al.[43] confirm that nummular lesions constitute an atypical and fairly frequent morphological variant in atopic adults and establish that early stage AD in childhood compared to early stage AD in adulthood shows some variations. On the second one, distribution on the head and neck is more frequent. There is a real difficulty in defining AD with nummular lesions and AD associated to NE.

Allergic contact dermatitis is rarely confused with NE, unless this were to be fairly localized. In this case, patch testing would be useful to identify allergens.

Multiple early lesions of tinea corporis may simulate NE, but the centrifugal evolution and the clinical findings of this mycosis define the picture, a KOH will help clear out any doubts. Correspondingly, seborrheic dermatitis may be differentiated in the basis of clinical picture and lesional location. The petaloid form may bring the most doubts.

Confusion with stasis dermatitis comes from the fact that these patients present with frequent eczematous nummular lesions, especially on lower limbs, result of probably autoeczematization from pruritus, which was proved by a study conducted by Bendl JB[66] in 1979, who included 113 patients with NE lesions. These were gathered during a period of 8 years. 33 were excluded for presenting distinct clinical entities. In 82 individuals, the presence of edema and several varicose veins on the lower limbs were identified. Conclusively, nummular lesions were the result of autoeczematization. This autoeczematization commences with a stasis NE lesion, which originates on a plaque of varicose eczema. Furthermore, it is believed that this eczematous lesions may extend to other parts of the body if irritated.

Psoriasis' well-known classic characteristics facilitate differentiation. Factitious dermatitis may simulate any illness and must be suspected on the basis of each patient's characteristics.

Lichen aureus is a variant of pigmented purpuric dermatosis and may be confused with NE due to its presentation in the form of macules, papules and plaques on lower limbs, with a lesional pattern that is very similar to NE.

In the search for differentiation, authors[67] performed a dermoscopy and found positive manifestations that are not observed on NE, such as a diffuse coppery-orange background, as well rounded or oval red blood cells, grey spots and a network of interconnected lines. Moreover, there was an absence of serous and hemorrhagic scabs, which are observed on NE.

The prodromal blistering pemphigoid may manifest as unspecific pruriginous eczematous lesions for a long period of time, before the actual manifestation of the classic form of illness.

A case report[68] reveals typical lesions of NE that turn into classic blisters of blistering pemphigoid, that which is confirmed by immunohistopathology.

Fig. 17 exposes some examples of NE differentials through some cases. Nevertheless, prodromal blistering pemphigoid does not present any cases, which is why a picture of the article is placed.

TREATMENT

Regarding NE treatment, we may schematize it in the following manner.[6]

1. Detailed clinical history
2. Try to identify and avoid triggering or exacerbating factors, such as allergens, inadequate clothing, irritative or itchy chemical products. This is not always easy though, especially in elderly patients

who don't always bathe properly or they are constantly exposed to aggravating factors.

3. Rule out unjustified food restrictions.
4. General measures:
    a. Wearing fresh cotton clothing.
    b. Washing clothing with detergents comprising non-ionic surfactants and/or double-rinsing.
    c. Taking daily relaxing warm baths, while avoiding the use of soup on lesions. It is preferable to use syndet soups and engage in oatmeal baths to alleviate pruritus. Some individuals might find bath oils useful.
    d. Applying moisturizing cream containing BID ceramides immediately after bath. These creams create an effective barrier to prevent water loss and additional dryness.
    e. Reduce xerosis cutis.
    f. Avoiding the exposure to irritants.
    g. Using a humidifier for the bedroom and house.
    h. Treatment of skin inflammation
5. Treatment of NE must reestablish the lipid layer and protect the epidermis by isolating it from the environment and bacteria while avoiding water loss, as well diminishing inflammatory reactions. Furthermore, treatment for secondary infections must be addressed as well.[54]

Lebwohl,[69] in his study, divides therapy specifically into three groups:

1. First line treatment

Calming and repair creams that contain products, such as glycerin, panthenol, water, etc., which alleviate symptoms once frequently applied on the skin.

High potency topical corticosteroids are considered as a first line treatment both used alone or combined with antibiotics. When therapy is discontinued, especially after a long time, one must consider secondary effects, tachyphylaxis production, or an upsurge of the condition. A study conducted by Gupta M.[70] in 50 patients aged 6 months-18 years, who had been treated with topical corticosteroids for a long period of time, whether they were automedicated or used longer than advised by the dermatologist, revealed they were employed due to the presence of eczema (32%). The most common corticosteroid was identified as mometasone, followed by clobetazol and betametazone, which were applied for 3 days, and up to a year. Most common secondary effects were tinea incognito (6%), steroid acne (4%), depigmentation (2%), hypertrichosis (2%) and stretch marks (2%).

The advised application period corresponds to once or twice a day for 2 or 4 weeks or until the resolution of the lesions. Some authors recommend the application of humid compresses prior to the use of cream or occlusive bandages to increase penetration.[6]

Calcineurin inhibitors with limited benefits. Initially, both tacrolimus and pimecrolimus surpassed expectations as a second topical therapeutic option for different inflammatory cutaneous diseases, such as AD. This treatment is based on active T lymphocyte calcineurin inhibition to avoid the synthesis of diverse involved cytokines, such as IL 2-3-4 and α.[71] It is believed that therapeutic potency of tacrolimus equals the one from a potent topical corticosteroid. There is an unguent in doses of 0.1% for adults and 0.03% for children. There are certain limitations regarding its use. It must not be applied on irritated or erosive skin as to avoid greater irritation. The application on occlusive bandages is not recommended either.[72] It is considered as a continuous maintenance therapy option to avoid prolonged corticosteroid treatment and a potential inflammation relapse.[73]

Oral antibiotics are required if there is an infection. Regarding this subject, Jiamtom S. reports a study about diverse infections among NE's aggravating factors and the usage of various antibiotics for treatment.[16]

Oral antihistamines (sedating, moderate sedation, non-sedating) are used to alleviate pruritus, which is associated with diverse cytokines and an abnormal distribution of C nerve fibers that cause an itchy sensation. This occurs as well with substance P and nerve peptides, such as the nerve growth factor and histamine.[72-74] The inhibiting effects of antihistamines about pruritus vary according to the clinical characteristics of each individual. Consequently, it is essential to conduct a pre-

vious evaluation of the patient so that when antihistamines are administered (one-type or combined), they can be adequately associated with other topical and systemic therapies and work conjunctly on the causal factors of NE, especially for severe and therapy resistant cases.[75]

In patients with moderate but recalcitrant illness, a 4% to 6% coal tar-zinc paste formula may be employed. This old preparation must be covered with light bandages. In spite of the discomfort, this type of treatment achieves remarkable results.[76]

2. Second line treatment, especially for severe or refractory illnesses:

Phototherapy

Indicated for patients who present with severe, prolonged and therapy-resistant illness. In these cases, phototherapy is an excellent therapeutic option.

- Narrowband UVB phototherapy is mainly indicated for vitiligo, psoriasis and AD. However, it is also indicated for severe NE. 10 to 30 sessions, administered twice or three times a week, are required before one can expect results. Once all lesions are resolved, the frequency is reduced to once a week for one month, then every two weeks for two months, if required and tolerated, making it an excellent alternative instead of the prolonged use of steroids,[6-77] and, in the case of elderly patients who sometimes cannot receive this type of medication on unmanageable cases, this type of therapy may be convenient thanks to its mechanism (resolving or diminish the lesions and pruritus, which is common and the first indication of the need for phototherapy).[78] The nervous system of skin has nerve endings which are free of cutaneous sensory nerve fibers, reaching the epidermis. Stimulation of prurireceptors within this group of sensory nerve fibers generates a neuronal signs which are transmitted to the brain. This is recognized as pruritus. UV lights may directly affect epidermal cutaneous sensory nerve fibers by decreasing their number, or, through the liberation of skin cell mediators, by indirectly modulating their function, as well as the transmission of itchy sensations to the central nervous system. As a consequence, an antipruritic effect is generated, which is the aim of this phototherapy treatment.[79-80]
- If phototherapy treatment is not possible to conduct, patients can opt for natural lighting. They ought to expose themselves to the sunlight for ten minutes between 10 am and 2 pm, and increase the time several minutes (up to 30 minutes) each day. Patients with slightly pigmented skin and/or redheaded or blondes may commence with 5 minutes of sun exposure and limit exposure time to a maximum of 20 minutes.[6]

Systemic therapy

Corticosteroids, in case of a lack of response to aforementioned established treatments or non-existence of phototherapy under the following schemes.[6]

- Oral prednisone starting with 40 mg QD, and reducing it to a dose of 10 mg every 5 days, followed by discontinuation.
- Intramuscular triamcinolone in doses of 40 mg, up to one dose every 3 months.
- In isolated recalcitrant lesions, intramuscular triamcinolone is a treatment option, 0,5 to 1 ml (4 to 5 mg/ml) per lesion.

Methotrexate (MTX)

- Although, there is a moderate quantity of information about the usage of MTX in NE, the results are quite positive both for children and adults and the collateral effects regarding the usage of this product are scarce.
- A study conducted involving 28 children with severe chronic NE,[81] who had previously received systemic corticosteroids, azathioprine and cyclosporine with no results, were treated with systemic MTX (0,2-0,5 mg/kg per week).
- Six months after treatment, the following results were registered: 3 patients with near resolution, 12 with notable improvement, 12 with slight improvement and a patient whose treatment did not work.
- After an average of 13.4 months, there were 10 patients who fully improved, 12 with notable improvement, 4 with slight improvement and 1 whose treatment did not work.

- One must acknowledge that 15 cases saw a variable increase of the dose due to an insufficient response. There were no significant collateral symptoms. The response was good, especially regarding an imminently chronic clinical picture.
- Another report,[82] involving 25 pediatric patients with recalcitrant NE, outlined a treatment with MTX on doses of 5 to 10 mg per week; after an average of 10.5 months, 16 patients with NE had complete resolution of their lesions and other 3 fully improved their lesions. There were no collateral effects.
- Sepúlveda et al. reported similar results, concerning doses and obtained results, as well as scarce collateral effects,[83] in six children with severe NE, resistant to other therapies.
- In a study conducted in India involving 56 patients with dermatologic diseases (psoriasis and eczema) and treated with MTX, adverse effects were monitored. Some collateral effects were observed. These were dose-dependent. A slight reduction of such dose meant these effects were significant enough to require hospitalization.[84]

Cyclosporine

- Treatment commences with a dose of 3 to 5 mg/kg a day, which is maintained until the illness is under control; normally over a period of 2 to 6 weeks. Then, the dose is reduced to 100 mg a day for 1 to 2 months.[6]

L-hystidine

- Filaggrin is a protein located on the stratum corneum, which is fundamental for adequate skin barrier formation and function. Such protein's deficiency will highly affect the barrier as its hydrolipidic film and protection function would be altered. Consequently, there would be an increase of xerosis, transepidermal water loss and the entry of irritant substances and infectious agents who would aggravate dermatologic clinical pictures, such as AD and NE.[85]
- Filaggrin is formed by the rupture of profilaggrin, its precursor, which is insoluble and can be found in keratinocytes, precursor cells of corneocytes. These rupture to originate multiple copies of filaggrin. This is essential because filaggrin aggregates filaments between keratin fibers and ends up degrading to become the natural moisturizing factor (NMF), which maintains the skin moisturized and gives it elasticity. It also assists in the desquamation process and optimizes the conditions of the skin barrier.[86]
- L histidine is an essential aminoacid whose deficiency produces nitrogen negative balance, anemia, and histamine and carnosine production decrease.
- It makes up 8% of filaggrin's composition.
- Oral supplementation of L histidine increases filaggrin levels in keratinocytes, improving xerosis.
- A study involving adult patients with AD, who were treated with oral L histidine once a day, revealed a 34% reduction of the severity of the illness after 4 weeks of treatment. Its efficiency was equaled to the one obtained from medium potency topical corticosteroids.
- This group, treated with L histidine, was compared to another group, administered with placebos, which showed no results.
- No side effects were reported.[87]

Rothkopf[88] reports its use on a severe therapy-resistant NE case. An oral dose of 8mg a day was administered. Notable improvement was registered after 4 months of treatment. There was also a decrease in the number and size of lesions, and a great decrease of pruritus.
There are no collateral effects

3. Third-line therapies

Azathioprine and mycophenolate mophetil: Coulson Ian, co-author of Lebwohl's study, in the chapter about NE,[69] identifies azathioprine and mycophenolate mophetil as therapeutic possibilities for the treatment of NE without further detail. However, a survey about azathioprine's use in NE, conducted to 248 dermatologists in the UK in 1997, revealed they agree on the fact that this medication should be employed to treat the disease (no one had used it for this pathology before).[89]

Active immunotherapy: Treatment for patients suffering from recalcitrant NE with Specific Active Im-

munotherapy has been reported. This has been combined with a super transfer factor. Full resolution of lesions was obtained after a few months of therapy, identifying it as an alternative therapy for NE.[90]

Psychiatric treatment and hypnosis: Psychotherapy has been identified as a treatment for NE for a long period of time now. Hypnosis has been equally acknowledged as treatment for its usefulness, capacity to improve lesions and pruritus.

Regarding Infliximab, as per cited by Lebwohl.[69] in his study about NE treatment and most discovered studies, it is referred for its use in moderate to severe AD.[93-94] Nevertheless, multiple articles[95-97] have also mentioned that, paradoxically, this medication has provoked NE when used in other illnesses, such as ulcerative colitis or psoriasis.

Lastly, Dupilumab is the first monoclonal antibody that is approved for moderate to severe AD treatment.[98] This acts as inhibitor for IL 4 and IL-13 in the differentiation of T Th2 cells. In a study involving the use of Dupilumab in AD patients with the purpose of discovering about collateral effects and laboratory monitoring,[99] it was determined that there are in fact adverse effects (ocular, arthralgia, alopecia, among others), that are not significant enough to stop treatment. It has also been acknowledged that there is no need for laboratory monitoring (practiced with similar medications). It has been outlined as efficient in a series of 5-6 patients with NE without any AD history. The response, according to the report, was excellent.[100] These authors consider that this medications works because in NE there is a hyperactivation of the axis Th2, which is prone to be blocked by dupilumab. Another study involving 30 patients with NE revealed that after 16 weeks of treatment there was notable improvement, along with conjunctivitis as an adverse effect.[101] Nonetheless, other authors, such as Zirwas[6] have tried this medication with NE patients who had experienced failed phototherapy treatment and systemic immunosuppressors. The results obtained with this medication were disappointing. For that reason and its expensive value, the use of this medication is only recommended in cases where other possibilities fail.

Cascada de la filagrina hasta el Factor Natural de Hidratación

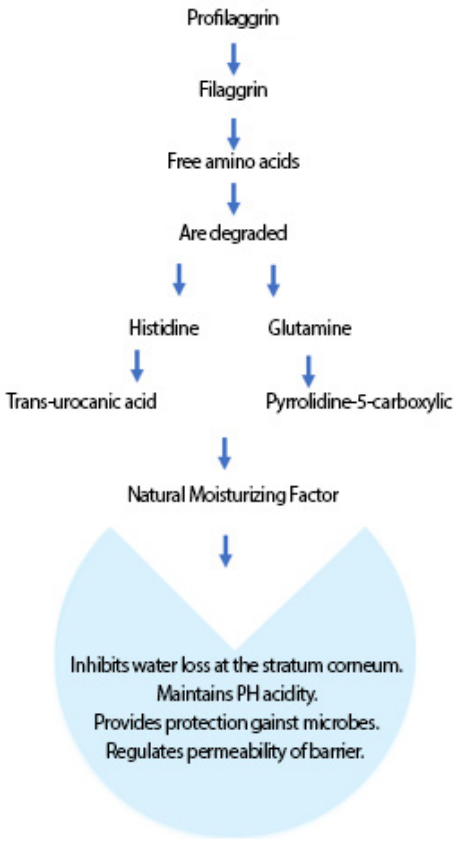

Figure 19: Clinical picture which schematizes the transformation of filaggrin into NMF.

CONCLUSIONS

Finally, one can define NE as a clinical picture which must not be taken lightly. Furthermore, the word eczema must no prompt individuals to obtain unjustified easy prescriptions. The following conclusions are established:

1. NE is a chronic inflammatory illnesses of unclear pathogenesis, characterized by multiple rounded eczematous lesions, which are nummular and fairly pruriginous. They vary in diameter from 1 to 10 cm, mostly targeting the limbs and the trunk.
2. It has been associated to diverse processes, such as xerosis, stasis dermatosis, infections, contact sensibilization, etc. But it is important to distinguish actual NE from AD with nummular morphology, which involves certain therapeutic differences.

3. Diagnosis is clinical. Patch testing may be useful in cases with patients suffering from recalcitrant illnesses or with contact allergic dermatitis history.
4. A histopathology study is no always necessary, as there are no specific characteristics. However, many cases required a biopsy because similarities with other diseases, such as pityriasis rosea, pityriasis lichenoides or other, interfere with diagnosis, and histopathology facilitates the ruling out of such differentials.
5. In regards to treatment, the most common possibilities have been considered. Sometimes, it is not simple to accept that extreme therapies are necessary to resolve NE. Nonetheless, the clinical picture's chronicity and its most severe presentation may justify them. This evolutive chronicity, accompanied by a constant relapse and years of evolution, may severely affect the mental state of these patients. Consequently, intense therapies are duly justified. One must not forget that it is not uncommon to easily prescribe corticosteroids and antipruritic agents when faced with this condition. One ignores the importance of research about the triggering factors of NE.
6. Conclusively, for any treatment used on NE cases, it is essential for the patient to acknowledge and accept that NE may extend for a period of weeks, months or even years. Moreover, when all seems ok, recurrences tend to emerge, unless etiological or contributing factors are eliminated or resolved

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