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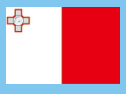

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WJD is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of dermatology. *WJD* covers fungal diseases, dermatitis and eczema, urticarial diseases, drug eruptions, pruritus, erythroderma desquamativum, connective tissue diseases, bullous skin diseases, vascular skin diseases, skin appendage diseases, pigmentary diseases, genetic diseases, nutritional and metabolic disorders, tumors, sexually transmitted diseases, AIDS, traditional medicine, integrated Chinese and Western medicine, evidence-based medicine, epidemiology and nursing. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to dermatology, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

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EDITORIAL

Trichoscopy: Essentials for the dermatologist

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Abstract

Noninvasive *in vivo* imaging techniques have become an important diagnostic aid for dermatology. Dermoscopy, also known as dermatoscopy, has been shown to increase the clinician's diagnostic accuracy when evaluating cutaneous neoplasms. Dermoscope, both hand-held and videodermoscope, are nowadays a basic instrument for almost all the dermatologists around the world. Trichoscopy is the term coined for dermoscopic imaging of the scalp and hair. Routinely using dermoscopy and recognizing the structures and patterns of the different types of alopecia will likely improve the observer's sensitivity for diagnosis and follow up of hair and scalp disorders. Structures which may be visualized by trichoscopy include hair shafts of different types, the number of hairs in one pilosebaceous unit, hair follicle openings (dots), the peri and interfollicular areas and the vasculature. This review summarizes the current knowledge about trichoscopic findings which may aid in the diagnosis of alopecia. Besides diagnosing alopecia, it has the potential for obviating unnecessary biopsies and when a biopsy is still needed it is helpful in choosing an ideal biopsy site. Moreover, trichoscopy can be a valuable tool for evaluating the treatment response photographically at each follow-up. Finally, we have discussed the utility of dermoscopy in inflammatory scalp disorders and infections.

Key words: Alopecia; Dermatosis; Scalp; Dermoscopy; Dermatoscopy; Epiluminiscence microscopy; Diagnosis

Core tip: Trichoscopy refers to the dermoscopy of the hair and scalp disorders. This is a noninvasive, in office technique that can be performed with a hand-held dermatoscope or a digital videodermatoscopy system. Trichoscopy is useful for the diagnosis and follow-up of hair and scalp disorders. In this article, we have briefly described the most important trichoscopic patterns and structures.

Moreno Romero JA, Grimalt R. Trichoscopy: Essentials for the dermatologist. *World J Dermatol* 2015; 4(2): 63-68 Available from: URL: http://www.wjgnet.com/2218-6190/full/v4/i2/63.htm DOI: http://dx.doi.org/10.5314/wjd.v4.i2.63

INTRODUCTION

Non-invasive *in vivo* imaging techniques have become an important diagnostic aid for evaluating hair and scalp disorders. Trichoscopy is the term coined for

Table 1 Hair shafts

> 20% of vellus hairs	AGA, long lasting AA
Exclamation mark hairs	AA, trichotillomania, chemotherapy-induced alopecia
Pohl-Pinkus constrictions	AA, chemotherapy-induced alopecia, blood loss, malnutrition, chronic intoxication
Comma hairs	Tinea capitis
Corkscrew hairs	Tinea capitis
Coiled hairs	Trichotillomania
Flame hairs	Trichotillomania
Tulip hairs	Trichotillomania, AA
Regrowing pigtail hairs	AA, cicatricial alopecia
Zig-zag-shaped hairs	Tinea capitis

AGA: Androgenetic alopecia; AA: Alopecia areata.

Table 2 Dots

Black dots	Active AA, dissecting cellulitis, tinea capitis, chemotherapy-induced alopecia, trichotillomania, after laser depilation, after trichogram, incidental finding in other diseases
Yellow dots	AA: Marker of disease severity Discoid lupus erythematosus: Large, dark yellow to brownish-yellow dots Androgenic alopecia: "Oily" appearance and predominance in frontal area Dissecting cellulitis, trichotillomania: Imposed over dark dystrophic hairs
White dots	Primary folliculocentric alopecias, lichen planopilaris: Fibrotic white dots Dark skin, sun exposed areas: Pinpoint white dots
Red dots	Discoid lupus erythematosus, vitiligo
Pink-grey/grey dots	Frontal fibrosing alopecia (eyebrows)

AA: Alopecia areata.

dermoscopic imaging of the scalp and hair.

Trichoscopy is a simple and non-invasive technique that can be performed with both handheld dermatoscope and digital videodermatoscopy system[1]. The usual working magnifications with videodermatoscope are 20-fold to 70-fold. While the hand-held dermatoscope with 10-fold magnification may give easy and quick evaluation of hair, it does not precisely measure or document the observed findings[2].

The method allows quick identification of hair and shaft abnormalities without the need of hair sampling for *ex vivo* evaluation, *i.e.*, optical or scanning electron microscopy. It is also a helpful tool in differential diagnosis of common acquired hair diseases, such as androgenic alopecia or diffuse alopecia areata[2].

TRICHOSCOPY STRUCTURES AND PATTERNS

Structures which may be visualized by trichoscopy include hair shafts, hair follicle openings, the perifollicular epidermis and the cutaneous microvessels.

Hair shafts

Trichoscopy allows analysing acquired and congenital hair shaft abnormalities.

Dermoscopy of the normal scalp shows regularly distributed follicular units, containing 1-4 hair shafts[1]. A normal terminal hair is uniform in thickness and color throughout its length. However, up to 10% of normal scalp hairs are vellus hairs that are lightly pigmented and measure < 3 mm in length and < 30 μm in thickness[1,3].

Trichoscopy also allows diagnosing most genetic hair shaft dystrophies such as monilethrix, trichorrhexis nodosa, trichorrhexis invaginata, pili torti or pili annulati[4] (Table 1).

Hair follicle openings: Dots

The term "dots" refers to the small, round hair follicle openings seen on trichoscopy. Trichoscopy may distinguish whether hair follicle openings are normal, empty, fibrotic or containing biological material, such as hyperkeratotic plugs or hair residues.

Black dots (cadaverized hairs) represent pigmented hairs broken or destroyed at scalp level.

Yellow dots are follicular infundibula with keratotic material and/or sebum. They vary in color, shape and size[4].

White dots may appear as fibrotic white dots or pinpoint white dots. The classic, big, irregular white dots represent areas of perifollicular fibrosis, observed in primary, folliculocentric cicatricial alopecias, and most commonly in lichen planopilaris[3]. The pinpoint white dots are small and regular, with occasional peripheral hyperpigmentation. They correspond to empty hair follicles or to the eccrine sweat ducts openings. They are observed in sun exposed areas and in dark skin phototypes.

Red dots have been described in discoid lupus erythematosus and in patients with vitiligo.

Pink-grey and grey dots have been observed in the eyebrow area of patients with frontal fibrosing alopecia[3]. This finding is believed to be a favourable prognostic factor for eyebrow regrowth (Table 2).

Peri and interfollicular areas

The classification of peri- and interfollicular skin surface abnormalities in trichoscopy is based on features related to scaling, color, discharge and surface structure[3] (Table 3).

Blood vessels

Appearance of cutaneous microvessels in trichoscopy may vary in type and number depending on disease and activity of the process. Several inflammatory scalp disorders are characterized by a specific pattern of blood vessel arrangement on trichoscopy[3,4].

Table 3 Peri- and interfollicular areas

Epidermal scaling	Diffuse scaling: Healthy individuals, psoriasis, seborrheic dermatitis Perifollicular scaling and tubular scaling structures: Lichen planopilaris, frontal fibrosing alopecia, folliculitis decalvans
Hyperpigmentation	Honeycomb: Sun exposed areas, dark skin phototypes Perifollicular: Androgenetic alopecia Scattered interfollicular: Discoid lupus erythematosus
Yellow or yellow-red discharge	Folliculitis decalvans, bacterial infections, dissecting cellulitis, tinea capitis
Structural changes in the skin surface	Starburst pattern hyperplasia in folliculitis decalvans

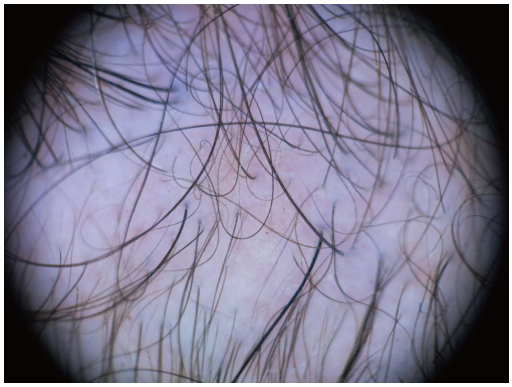

Figure 1 Male androgenetic alopecia. Hair shaft thickness heterogeneity and predominance of follicular units with only one hair (Dermlite photo®).

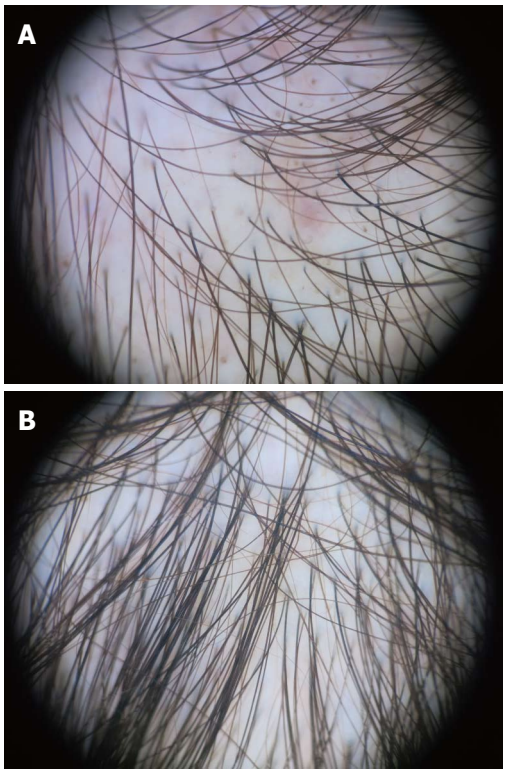

Figure 2 Female androgenetic alopecia. Significant (> 20%) diversity of hair shaft diameter. Note also yellow dots. Higher hair density and less variability in the occipital area (B) compared to the frontal area (A) (Dermlite photo®).

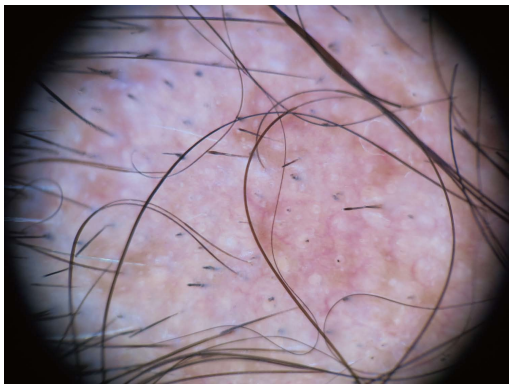

Figure 3 Alopecia areata. Exclamation mark signs and black dots (Dermlite photo®).

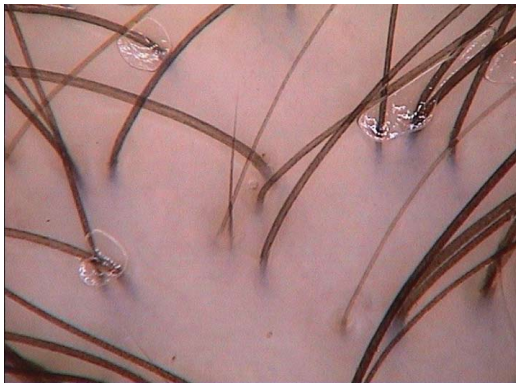

Figure 4 Telogen effluvium. Short regrowing hair (videodermoscopy, 70 x magnification). Photo courtesy of Prof. Lidia Rudnicka.

ALOPECIA

The interest for trichoscopy had greatly increased in the last years. There is an extensive literature on the different types of alopecia. Nowadays it has become an indispensable technique in the evaluation of the hair loss patient.

We have summarized the main trichoscopic findings in the most common types of non cicatricial (Table 4) (Figures 1-5) and cicatricial alopecia (Table 5, Figures 6-8). In addition, there are some diagnostic algorithms in use for alopecia using trichoscopy (Figure 9).

ADVANTAGES AND LIMITATIONS OF TRICHOSCOPY

Standard methods used to diagnose hair disorders are clinical inspection, pattern of hair loss, pull test, trichogram, biopsy, chronology of preceding events, and screening blood test. They vary in sensitivity, reproducibility, and invasiveness. There is accumulated evidence that the use of trichoscopy in the clinical evaluation of hair disorders improves diagnostic capability beyond simple clinical inspection[5-7]. Trichoscopy have the advantages of being a quick and non-invasive, semiquantitative method. Trichoscopy allows to evaluate larger areas than other invasive techniques like biopsy or

Table 4 Trichoscopic findings in common types of non cicatricial alopecia

AGA	AA	Telogen effluvium	Trichotillomania
Hair shaft thickness heterogeneity	Exclamation mark hairs	Empty follicles	Simultaneous, chaotic coexistence of multiple hair shaft abnormalities
Increased proportion of vellus hairs	Broken hairs	Increased proportion of single-hair follicular units	Hairs broken at different lengths
> 10% thin hairs in the frontal area	Clustered short vellus hairs	Short regrowing hairs	Short hairs with trichoptilosis (split ends)
Increased proportion of single-hair follicular units	Pigtail hairs	< 20% hair diameter diversity	Coiled hairs
Yellow dots	Black dots	Brown perifollicular discoloration	Exclamation mark hairs
Perifollicular discoloration (peripilar sign)	Numerous yellow dots	No significant difference between frontal and occipital areas	Black dots
All the trichoscopic features appear most prominently in the frontal scalp area compared to the occipital area			Others: flame hairs, V-sign, hook hairs, hair powder and tulip hairs

AGA: Androgenetic alopecia; AA: Alopecia areata.

Table 5 Trichoscopic findings in common types of cicatricial alopecia

LPP	FFA	DLE
Intense perifollicular scaling, tubular structures	Minor perifollicular scaling	Large yellow dots (follicular keratotic plugs)
Violaceous inter or perifollicular areas	Perifollicular erythema	Mottled dyschromia
Fibrotic white dots	Strong predominance of single-hair follicular units at the hair-bearing margin	Thin and radial arborizing vessels that emerge from yellow dots ("red spider in yellow dot")
Blue grey dots	Absence of vellus hairs	Thick arborizing vessels at the perifery ot the lesion
Small hair tufts	Pink-grey and grey dots in the lateral eyebrow area	Follicular red dots

LPP: Lichen planopilaris; FFA: Frontal fibrosing alopecia; DLE: Discoid lupus erythematosus.

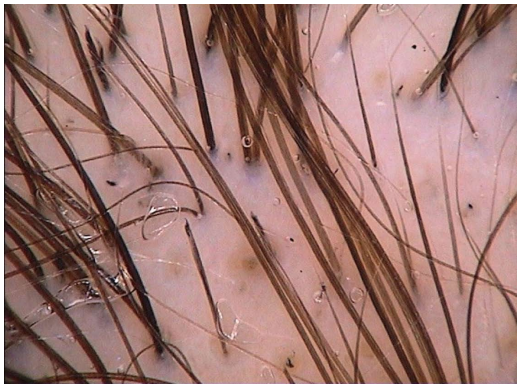

Figure 5 Trichotillomania. Hairs broken at differents lengths, with trichoptilosis (split end) and black dots (videodermoscopy, 70 × magnification). Photo courtesy of Prof. Lidia Rudnicka.

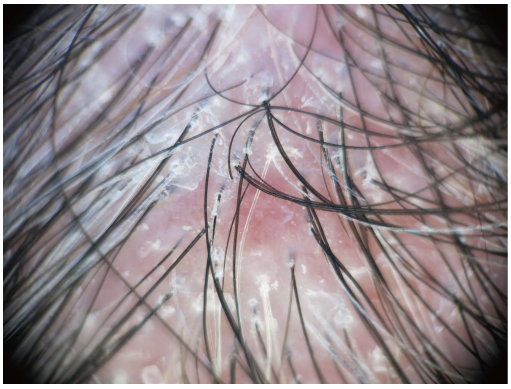

Figure 6 Lichen planopilaris. Intense perifollicular scaling and tubular structures (Dermlite Photo®).

trichogram.

A recent study have demonstrated superiority of trichoscopy as compared to the trichogram, in the diagnosis of female androgenetic alopecia, especially in early cases[8].

An additional advantage of trichoscopy is that it allows digital surveillance and monitoring of the patients. Photographic evaluation at each visit is very appreciated by patients[9].

By the other hand, the use of trichoscopy can result in lower diagnostic accuracy if the physician does not recognize or correctly interpret the significance of structures. Moreover, trichoscopy can lead to lower diagnostic accuracy when patients are diagnosed using dermoscopy alone, without clinical context.

OTHER USES OF TRICHOSCOPY

Dermatoscopy in inflammatory scalp disorders and infections

Psoriasis and seborrheic dermatitis: Dermatoscopy of both cases shows diffuse or localized scales, which tend to be more yellowish in seborrheic dermatitis and

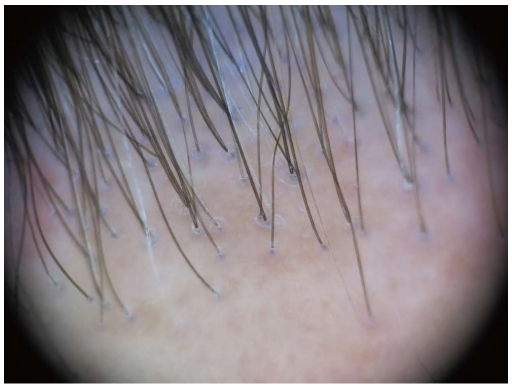

Figure 7 Frontal fibrosing alopecia. Absence of follicular openings, predominance of follicular units with only 1 hair, mild perifollicular scaling and perifollicular erythema (Dermlite photo®).

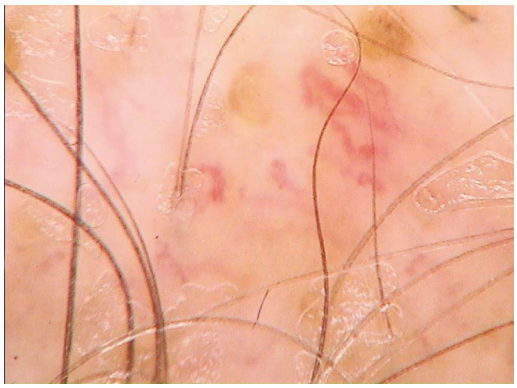

Figure 8 Discoid lupus erythematosus. Characteristic large yellow dots and arborizing vessels (videodermoscopy, 70 x magnification). Photo courtesy of Prof. Lidia Rudnicka.

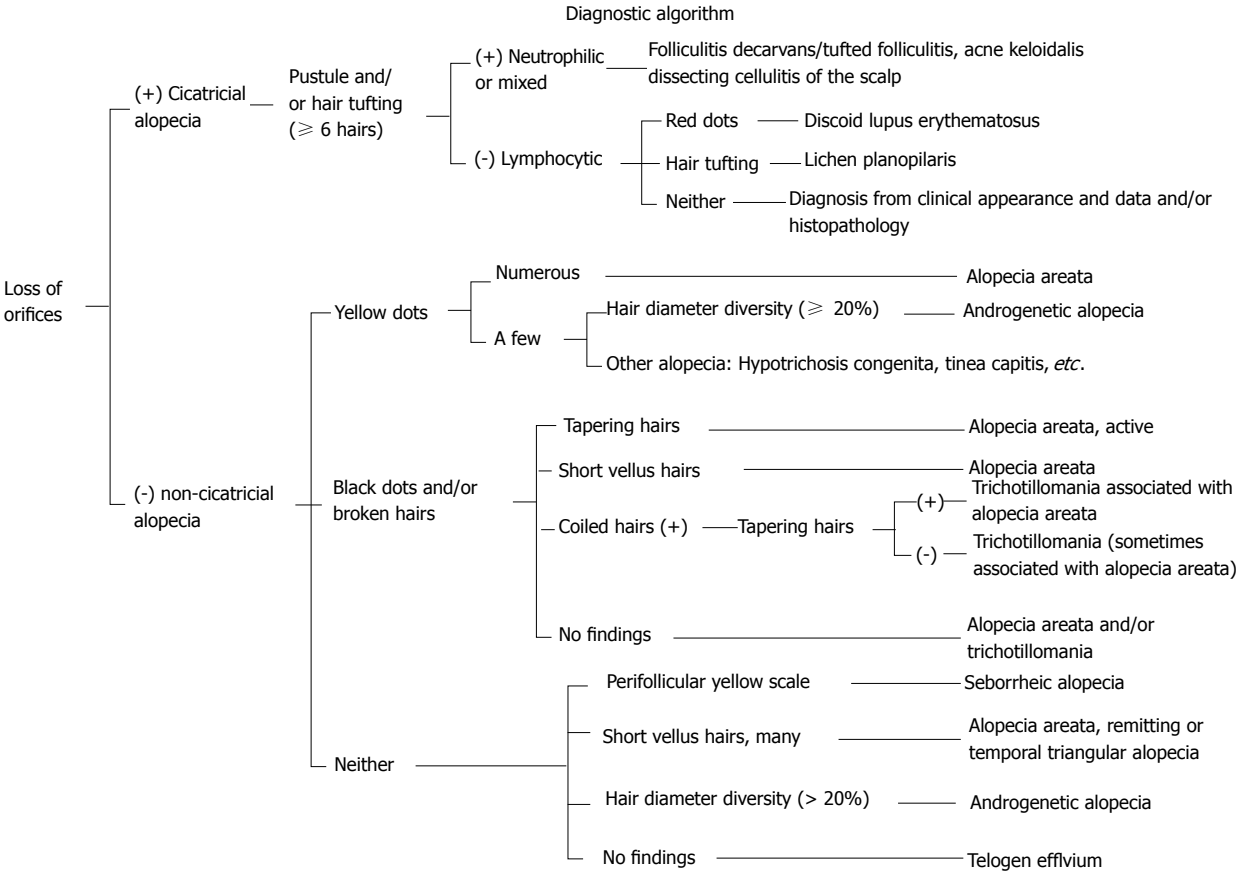

Figure 9 Diagnostic algorithm for trichoscopic findings of hair loss diseases. From Inui S. Expert Rev Dermatol 2012: 7.

more withish in psoriasis.

The major difference in this cases is the vascular pattern. Psoriasis shows red dots, globules and glomerular vessels. In seborrheic dermatitis the most common findings are arborizing and atypical red vessels and the absence of red dots and globules[1].

Pediculosis capitis: Trichoscopy is useful to observe the adult parasites ant to evaluate if the nits are empty or not.

Piedra and tinea capitis: Many features have been described in mycotic infections and dermatoscopy is very useful in these cases.

Trichoscopy guided biopsy

Trichoscopy may be used to select the best area from which to obtain a biopsy specimen[3].

Trichoscopy in general medicine

This includes possible application of trichoscopy in identifying follicular spicules in multiple myeloma, follicular mucinosis in lymphoproliferative disorders, scalp lesions in Langerhans histiocytosis or altered

interfollicular microvessels in dermatomyositis and scleroderma[4].

Ex vivo dermatoscopy of scalp biopsies

Ex vivo assessment of scalp biopsies by dermatoscopy can identify the correct plane of transversal bisection and it is useful to control the tissue processing[10].

Trichogram using dermatoscopy

It has been proposed the use of dermoscopy when performing a trichogram, instead of using the optical microscope, as most of dermatologist nowadays have a dermoscope[1].

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EDITORIAL

Mycosis fungoides and Sézary syndrome: Role of chemokines and chemokine receptors

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Abstract

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma (CTCL), and is characterized by a clonal expansion of malignant $CD4^+$ T lymphocytes with skin-homing properties. Clinically and pathologically, mycosis fungoides can be categorized into patch, plaque and tumor stages. The clinical course of mycosis fungoides is usually chronic and indolent, but a proportion of patients may develop progressive disease with peripheral blood, lymph node and visceral organ involvement. Sézary syndrome is an aggressive leukemic form of CTCL characterized by a clonal population of malignant T cells in the peripheral blood. Various forms of skin-directed and systemic treatments are available for mycosis fungoides and Sézary syndrome. However, current treatments are generally not curative, and can only control the disease. Currently, the etiology and pathogenesis of mycosis fungoides and Sézary syndrome are not well defined. Proposed mechanisms include chronic antigenic stimulation by infectious agents, expression of specific adhesion molecules, altered cytokine production, mutations of oncogenes and tumor suppressor genes, and avoidance of apoptosis. In recent years, a number of chemokine receptors and their corresponding chemokine ligands have been found to contribute to the migration and survival of lymphoma cells in mycosis fungoides and Sézary syndrome, including CC chemokine receptor 4 (CCR4), CCR10, C-X-C chemokine receptor type 4 (CXCR4), CCR7, CCR3 and CXCR3. Since chemokines and chemokine receptors have been found to play important roles in the pathophysiology of mycosis fungoides and Sézary syndrome, they may be potentially useful targets for the development of new treatments for these diseases in the future.

Key words: Mycosis fungoides; Sézary syndrome; Skin-homing; Chemokines; Chemokine receptors

Core tip: Mycosis fungoides and Sézary syndrome are characterized by a clonal expansion of malignant $CD4^+$ T lymphocytes with skin-homing properties. Currently, treatment options for mycosis fungoides and Sézary syndrome are limited. The lack of effective targeted therapy results in part from the poor understanding regarding the pathophysiology of these diseases. Recently, a number of chemokines and chemokine receptors have been found to contribute to the pathogenesis of mycosis fungoides and Sézary syndrome, including the

CC chemokine receptor 4 (CCR4)/chemokine (C-C motif) ligand 17 (CCL17), CCR10/CCL27, C-X-C chemokine receptor type 4/chemokine (C-X-C Motif) ligand 12 and CCR7/CCL21 axes. Therefore, these chemokines and chemokine receptors may be potentially useful targets for the treatment of these lymphomas in the future.

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INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a group of diseases characterized by malignant T lymphocytes infiltrating the skin, and includes mycosis fungoides, Sézary syndrome, lymphomatoid papulosis, anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, cutaneous natural killer/T-cell lymphoma, and primary cutaneous peripheral T-cell lymphoma[1]. This Editorial focuses on mycosis fungoides and Sézary syndrome.

Mycosis fungoides is the most common form of CTCL, and is characterized by a clonal expansion of malignant $CD4^+$ T lymphocytes with skin-homing properties[2]. It is more common in the middle-aged and elderly, and is about twice more common in males than females[3]. However, mycosis fungoides can also occur in children and young adults[4]. Clinically and pathologically, mycosis fungoides can be categorized into patch, plaque and tumor stages. The clinical course of mycosis fungoides is usually chronic and indolent, but a subset of patients may develop progressive disease with peripheral blood, lymph node and visceral organ involvement[5]. Patients with mycosis fungoides also have a higher risk of developing a second malignancy, especially other types of lymphomas[6,7].

Sézary syndrome is an aggressive leukemic form of CTCL showing a clonal population of malignant T cells in the peripheral blood. Traditionally, mycosis fungoides and Sézary syndrome have been regarded as a spectrum of diseases with a common pathogenesis. More recently, investigations have indicated that mycosis fungoides and Sézary syndrome are two different diseases which originate from distinct T-cell subsets[8]. Mycosis fungoides is believed to be a lymphoma arising from skin resident "effector" memory T cells, in which atypical lymphocytes remain confined to the skin. On the other hand, Sézary syndrome is regarded as a lymphoma of "central" memory T cells, in which atypical lymphocytes circulate between the blood, skin and lymph nodes. This may partially account for the differences in biologic behaviors and prognosis between these two diseases.

CLINICAL FEATURES

Classically, mycosis fungoides presents as erythematous patches and plaques, often associated with scaling (Figure 1). The skin lesions are usually located on non-sun exposed areas, such as the chest, abdomen, back, buttocks, groin and thigh. However, any region of the body can be affected. Pruritus is a common symptom. The skin lesions have usually been present for months to years, and they may gradually become thicker and develop into tumors. The three different types of skin lesions (patches, plaques, tumors) can sometimes be seen in a single patient concurrently. In certain patients, mycosis fungoides may progress into an erythrodermic form with generalized erythema and scaling of the skin[5].

Sézary syndrome is an aggressive leukemic form of CTCL. It is characterized by erythroderma (generalized erythema and scaling of the skin involving more than 80% of the body surface area), and a clonal population of malignant T lymphocytes in the peripheral blood[9,10]. Lymphadenopathy may or may not be present. This disease usually develops de novo without preceding mycosis fungoides.

HISTOPATHOLOGY AND IMMUNOPHENOTYPE

On histopathological examination, skin lesions of mycosis fungoides are characterized by atypical lymphocytes infiltrating mainly the dermis (Figure 2). The atypical lymphocytes are usually hyperchromatic, may have a haloed appearance, and show irregular, convoluted, or cerebriform nuclei[11]. They often accumulate in a band-like distribution at the dermoepidermal junction. They show a tendency for epidermotropism (migration into the epidermis without epidermal spongiosis), and may form aggregates with Langerhans cells in the epidermis (Pautrier's microabscess)[12]. There may be an accompanying infiltrate of reactive inflammatory cells.

On immunohistochemical staining, the atypical lymphocytes in mycosis fungoides are usually $CD4^+$, and there is an elevated CD4:CD8 ratio[11,13]. However, in a minority of cases the atypical lymphocytes are $CD8^+$[14]. The atypical cells are also $CD45RO^+$, which is a marker of memory T cells[15]. In addition, there is a loss of T cell antigens (including CD2, CD5, CD7 and CD26)[15]. In Sézary syndrome and certain cases of mycosis fungoides, Sézary cells can be detected in the peripheral blood by flow cytometry, and are identified as $CD4^+CD7^-$ and/or $CD4^+CD26^-$ cells[16,17].

The skin lesions of mycosis fungoides may show a dominant T cell clone. This is demonstrated by the presence of clonal T cell receptor gene rearrangement on polymerase chain reaction (PCR) analysis of the skin[18,19]. In Sézary syndrome patients, a large clonal population of atypical T lymphocytes may be found in the peripheral blood, determined by molecular methods (T cell receptor gene rearrangements by PCR) and flow

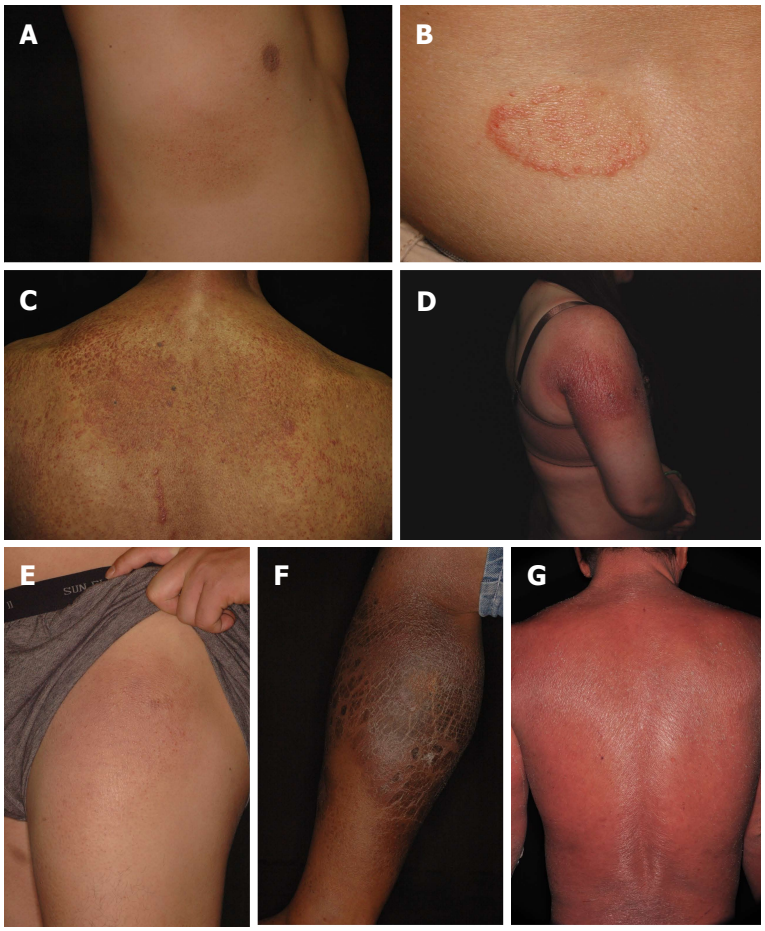

Figure 1 Clinical images showing patch stage (A), plaque stage (B-E), tumor stage (F), and erythrodermic (G) mycosis fungoides.

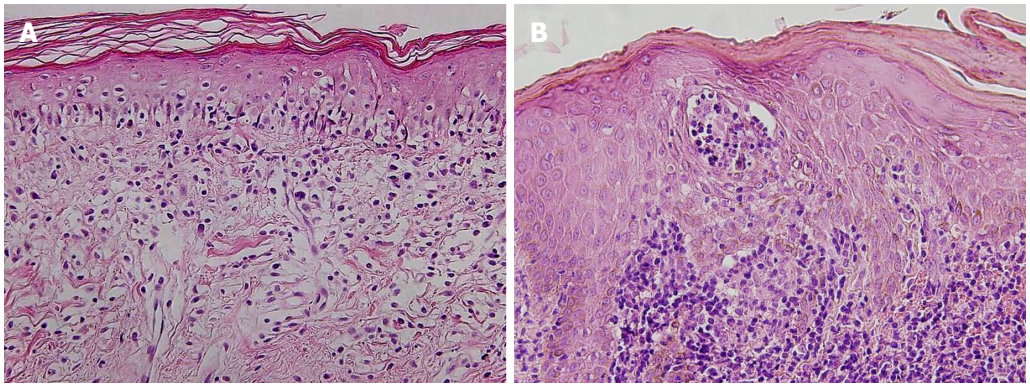

Figure 2 Pathological examination of mycosis fungoides lesions reveals atypical lymphocytes with epidermotropism (A) and formation of Pautrier's microabscess (B).

cytometry (expression of specific T cell receptor Vβ epitopes)[10,20].

EVALUATION OF PATIENTS

Patients should undergo a detailed physical examination to determine the total body surface area involved by lymphoma, as well as the surface area involved by patch, plaque and tumor stages[10]. This provides a measure of the skin tumor burden.

Laboratory tests that should be performed in patients with mycosis fungoides and Sézary syndrome include a complete blood count with differential counts, electrolytes and lactate dehydrogenase. A skin biopsy should be undertaken for histopathological examination, immunohistochemistry and T cell receptor gene rearrangement studies. Peripheral blood should be examined for Sézary cell count and clonality of circulating T cells. Computed tomography scans with positron emission tomography are useful for determining internal organ involvement[21]. Lymph node biopsy should also be performed in cases with lymphadenopathy.

STAGING AND PROGNOSIS

The staging of mycosis fungoides is based on the International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer system, and takes into account the extent of skin involvement (T), lymph node disease (N), visceral involvement (M), and the presence of Sézary cells in the peripheral blood (B). The TNMB classification is converted into a clinical stage[10,22].

The prognosis in patients with early stage mycosis fungoides (stage Ⅰ A) is good, and these patients have a similar life expectancy as the general population[23]. Poor prognostic factors for mycosis fungoides include advanced stage, older age, elevated lactate dehydrogenase levels, presence of erythroderma, large cell transformation, presence of a clonal population of atypical lymphocytes in the peripheral blood, and high Sézary cell count[24-28]. The presence of $CD8^+$ T cells in the skin of mycosis fungoides patients is associated with better prognosis, since this may lead to a host anti-lymphoma response[29].

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of mycosis fungoides and Sézary syndrome is currently not well defined. It has been proposed that mycosis fungoides is caused by chronic antigenic stimulation, which results in lymphocyte proliferation and eventually a clonal expansion of $CD4^+$ T helper cells in the skin. Certain infections, such as Staphylococcus aureus and Chlamydia species, have been implicated in the etiology of mycosis fungoides[30-32].

Atypical lymphocytes in patients with mycosis fungoides and Sézary syndrome have been found to express the adhesion molecule cutaneous lymphocyte antigen, which may mediate the migration of lymphoma cells to the skin[33].

The cytokine profile in mycosis fungoides also changes according to the stage of the disease. In early stages of mycosis fungoides, Th1 cytokines [(interferon-γ, interleukin-12 (IL-12), IL-2] predominate[15,34]. In later stages of mycosis fungoides and Sézary syndrome, a shift from Th1 to Th2 cytokine profile is found, including IL-4, IL-5, IL-10, and IL-13[35-37].

T cell proliferation and cell cycle control may be dysregulated in patients with mycosis fungoides. Amplification and overexpression of the oncogene JUNB were found in a subset of patients with mycosis fungoides and Sézary syndrome[38]. Increased expression of the oncoproteins ras and myc has been implicated in the pathogenesis of mycosis fungoides[39].

Atypical lymphocytes in mycosis fungoides and Sézary syndrome have also been shown to be resistant to apoptosis. Fas is a death receptor which can mediate apoptosis, and studies have shown that low Fas expression and impaired Fas-mediated apoptosis may play a role in the pathogenesis of mycosis fungoides[40-42].

CHEMOKINES AND CHEMOKINE RECEPTORS IN MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

Chemokines and chemokine receptors were initially found to play important roles in mediating the chemotaxis (directional migration) of leukocytes[43]. Chemokines are a family of small polypeptides, and are categorized based on the location of cysteine residues near their amino termini into four families (C, CC, CXC, and CX3C). Chemokines bind to chemokine receptors, which are seven-membrane spanning, G-protein-coupled receptors. There are more than 50 different chemokines and at least 18 different chemokine receptors identified to date[44]. There are redundancies in the binding between chemokines and chemokine receptors, as some chemokines bind to multiple chemokine receptors, and vice versa. The activation of chemokine receptors by chemokines may activate various downstream signaling pathways, including the mitogen-activated protein kinase, phosphoinositide-3 kinase, and mammalian target of rapamycin (mTOR) pathways.

In recent years, various types of cancer cells have been found to express chemokine receptors, which have been shown to play important roles in cancer growth, progression and metastasis[45]. Apart from mediating cancer cell migration, chemokine receptors have also been demonstrated to mediate cancer cell proliferation, survival/apoptosis, and angiogenesis[46,47]. A number of chemokines and chemokine receptors have been found to contribute to the migration and survival of lymphoma cells in mycosis fungoides and Sézary syndrome (Table 1)[48-50].

CHEMOKINE RECEPTOR CC CHEMOKINE RECEPTOR 4

The chemokine receptor CC chemokine receptor 4 (CCR4) has been found to be important in mediating the migration of normal lymphocytes to inflamed skin[51,52]. There are increased percentages of T lymphocytes expressing CCR4 in the blood and skin lesions of patients with CTCL (including mycosis fungoides and Sézary syndrome)[8,53-55]. CCR4 expression is also seen in mycosis fungoides tumors with large cell transformation[56]. Furthermore, CCR4 was found to be expressed by mycosis fungoides cell lines, and activation of the CCR4 receptor promoted migration of lymphoma cells[57]. The CCR4 ligand chemokine (C-C motif) ligand 17 (CCL17) (thymus and activation regulated chemokine) is produced by activated epidermal keratinocytes, dendritic cells and endothelial cells, and its expression is upregulated in the skin lesions and serum of mycosis fungoides patients[58,59]. In addition, serum CCL17 levels were found to correlate with disease activity in patients with mycosis fungoides[59].

Table 1 Role of chemokines and chemokines receptors in the pathogenesis of mycosis fungoides and Sézary syndrome[8,16,51-85]

Chemokine receptor	Chemokine	Role in pathogenesis of mycosis fungoides and Sézary syndrome
CCR4	CCL17 (TARC)	Increased percentages of T lymphocytes expressing CCR4 in the blood and skin lesions of CTCL patients
	CCL22	Activation of CCR4 promoted migration of mycosis fungoides cell lines
		CCL17 expression is upregulated in the skin lesions and serum of mycosis fungoides patients
CCR10	CCL27 (CTACK)	CCR10 is expressed by malignant lymphocytes in skin lesions and peripheral blood of patients with mycosis fungoides and Sézary syndrome
		The level of CCL27 is increased in the serum and skin of patients with mycosis fungoides
CXCR4	CXCL12 (SDF)	CXCR4 is expressed by Sézary cells, and acts as a chemotactic factor for Sézary cells
		Loss of the cell-surface antigen CD26 (which cleaves and deactivates the CXCL12) is a characteristic feature in Sézary syndrome
CCR7	CCL19 (MIP-3b)	CCR7 is expressed on atypical lymphocytes of Sézary syndrome
	CCL21 (SLC)	CCR7 promotes migration of Sézary cells
		CCR7 was expressed in mycosis fungoides skin lesions, and its expression correlated with subcutaneous extension of lymphoma cells
		Activation of CCR7 by its ligand CCL21 promotes MyLa (mycosis fungoides cell line) cell migration through the mTOR pathway
CCR3	Eotaxin-3	Skin lesions of CTCL show higher expression of CCR3 and eotaxin-3
	Eotaxin-1	CTCL patients show higher serum levels of eotaxin-3 and eotaxin-1
CXCR3	CXCL9	CXCR3 is expressed in low-grade mycosis fungoides
	CXCL10	
	CXCL11	

CCR: CC chemokine receptor; CCL: Chemokine (C-C motif) ligand; TARC: Thymus and activation regulated chemokine; CTCL: Cutaneous T-cell lymphoma; CTACK: Cutaneous T-cell attracting chemokine; CXCR4: C-X-C chemokine receptor type 4; CXCL12: Chemokine (C-X-C Motif) ligand 12; SDF: Stromal cell-derived factor; MIP: Macrophage inflammatory protein; SLC: Secondary lymphoid-tissue chemokine.

Therefore, the interaction between CCR4 and CCL17 may play a role in the homing of mycosis fungoides cells to the skin or promote the survival of lymphoma cells.

CHEMOKINE RECEPTOR CCR10

The chemokine receptor CCR10 has been found to be expressed by normal lymphocytes which home to the skin[60,61]. CCR10 has been demonstrated to be expressed by malignant lymphocytes in skin lesions of mycosis fungoides and Sézary syndrome, and mediated migration of Sézary cell line[62,63]. In patients with mycosis fungoides and Sézary syndrome, increased numbers of lymphocytes expressing CCR10 was also found in the peripheral blood[63-65]. The CCR10 ligand CCL27 (cutaneous T-cell attracting chemokine), a skin-specific chemokine, is synthesized by epidermal keratinocytes[66,67]. The level of CCL27 was increased in the serum and skin of patients with mycosis fungoides[63,68], and may act as a therapeutic marker following interferon-α and psoralen and ultraviolet-A (PUVA) treatment[69].

CHEMOKINE RECEPTOR C-X-C CHEMOKINE RECEPTOR TYPE 4

The chemokine receptor C-X-C chemokine receptor type 4 (CXCR4) may also be involved in homing of mycosis fungoides and Sézary cells to skin. CXCR4 has been demonstrated to be expressed by Sézary cells, and acts as a chemotactic factor for Sézary cells[55]. CXCR4 has also been shown to be expressed in mycosis fungoides skin lesions[70]. The ligand for CXCR4 is the chemokine chemokine (C-X-C Motif) ligand 12 (CXCL12) (also known as stromal cell-derived factor 1), which is expressed by skin dermal fibroblasts and endothelial cells[71,72]. In Sézary syndrome, loss of the cell-surface antigen CD26 is a characteristic feature[16,73]. CD26 is a dipeptidyl peptidase which cleaves and deactivates CXCL12, preventing it from activating CXCR4. The downregulation of CD26 and subsequent increased levels of CXCL12 may promote CXCL12-induced chemotaxis of Sézary cells[55].

CHEMOKINE RECEPTOR CCR7

CCR7 is a chemokine receptor which has been discovered to mediate the migration of T lymphocytes and dendritic cells to lymphatic vessels and lymph nodes[74-76]. The ligands for CCR7 are CCL19 (also known as macrophage inflammatory protein-3b, MIP-3b) and CCL21 (also known as secondary lymphoid-tissue chemokine). CCR7 has been found to be involved in the lymph node metastasis of certain cancer cells[77-79]. In addition, CCR7 plays a role in cancer cell proliferation, migration and invasion.

Previous studies have indicated that CCR7 is expressed on atypical lymphocytes of Sézary syndrome[8,64,65], and may promote migration of Sézary cells[80]. CCR7 is also expressed in tumor-stage mycosis fungoides[70]. Recently, our research group found that CCR7 was expressed in 62% (13 out of 21) of mycosis fungoides skin tissue specimens, and its expression correlated with subcutaneous extension of lymphoma cells (an indication of lesion thickness). In addition, we showed that CCR7

Table 2 Current treatment strategies for mycosis fungoides and Sézary syndrome

Skin-directed therapies	Systemic therapies
Topical corticosteroids	Oral retinoid (bexarotene)
Topical nitrogen mustard	IL-12
Topical retinoid (bexarotene)	Interferon-α
Ultraviolet light phototherapy (PUVA, narrowband UVB)	Histone deacetylase inhibitors
	Extracorporeal photopheresis
Radiation therapy	Methotrexate
	Chemotherapy
	Hematopoietic stem cell transplantation

PUVA: Psoralen and ultraviolet-A; IL-12: Interleukin 12.

expression was increased on the surface of MyLa cells (a human mycosis fungoides cell line) compared to peripheral blood mononuclear cells. Activation of CCR7 by its ligand CCL21 promoted MyLa cell migration but not proliferation. We also demonstrated that the CCL21-induced MyLa cell migration was mediated through the mTOR pathway[81].

OTHER CHEMOKINE RECEPTORS

It has been demonstrated that in skin lesions of CTCL (mycosis fungoides), keratinocytes, endothelial cells and dermal fibroblasts showed higher expression of eotaxin-3 compared to normal skin. In some advanced cases of CTCL, atypical lymphocytes in skin lesions were found to express CCR3, the chemokine receptor for eotaxins. These patients also show higher serum levels of eotaxin-3 and eotaxin-1. Therefore, the interaction between eotaxins and CCR3 may play a role in the pathogenesis of mycosis fungoides[82].

In addition, the chemokine receptor CXCR3 has been found to be expressed in low-grade (patch and plaque stage) mycosis fungoides, especially in the epidermotropic lymphoma cells[83-85].

MANAGEMENT: SKIN-DIRECTED THERAPIES

There are a variety of different treatment strategies available for mycosis fungoides and Sézary syndrome (Table 2), depending on the severity of the disease and patient factors[86-89]. Since mycosis fungoides and Sézary syndrome are generally not curable, chronic management is required in order to control the disease. In early stage mycosis fungoides, (stages ⅠA-ⅡA), lymphoma cells are mainly confined to the skin, and skin-directed therapies are usually used. In advanced stage mycosis fungoides (stages ⅡB-ⅣB) and Sézary syndrome, systemic therapies may be selected, including immunotherapy, targeted therapies and chemotherapy[90]. Each of the different treatment strategies are associated with various adverse effects, the discussion of which is beyond the scope of this Editorial.

In early stage mycosis fungoides, topical corticosteroids is the most commonly used form of treatment[91]. It can also be used in combination with other therapies in advanced stages of disease. Topical nitrogen mustard (a DNA alkylating agent) or topical retinoids (bexarotene, tazarotene) may also be used in early stage mycosis fungoides[92,93].

Phototherapy with ultraviolet light may be effective for patients with early stage (stages ⅠA-ⅡA) mycosis fungoides. Forms of phototherapy include PUVA with oral 8-methoxypsoralen, and narrowband ultraviolet B (311 nm)[94-96].

Ionizing radiation therapy has deeper penetration compared to ultraviolet phototherapy[97]. Total skin electron beam therapy may be used for patients with rapidly progressive or refractory disease, and plaque or tumor lesions involving large body surface area[98,99]. Localized radiotherapy may be suitable for patients with localized tumor lesions[100].

MANAGEMENT: SYSTEMIC THERAPIES

The oral retinoid bexarotene is used for the treatment of refractory mycosis fungoides and Sézary syndrome in all stages[101,102]. Bexarotene acts by modulating cell differentiation and apoptosis, and also decreases the expression of CCR4 on malignant lymphocytes, which may inhibit their ability to migrate to the skin[103,104].

In mycosis fungoides and Sézary syndrome, there is an increased expression of Th2 cytokines (including IL-4, IL-5, and IL-10). IL-12 is a Th1-promoting cytokine, and has been shown to be efficacious in some patients[105]. Interferon-α may also be effective for different stages of mycosis fungoides, and act by inducing Th1-mediated immune responses to atypical lymphocytes[106].

In extracorporeal photopheresis, the circulating lymphocytes are separated from the patients' peripheral blood, 8-methoxypsoralen is added, and the cells are treated with ultraviolet-A light. This treatment is indicated for erythrodermic mycosis fungoides and Sézary syndrome[107,108].

Chemotherapy drugs may be used for refractory or progressive mycosis fungoides and Sézary syndrome. Methotrexate is an antifolate agent which acts by

inhibiting dihydrofolate reductase and thereby inhibits proliferation of lymphocytes[109]. Hematopoietic stem cell transplantation may be used in advanced stage mycosis fungoides and Sézary syndrome, and have the potential for curing the disease[110].

CONCLUSION

Mycosis fungoides and Sézary syndrome are characterized by a clonal expansion of malignant $CD4^+$ T lymphocytes with skin-homing properties, and have potential for lymph node, blood and visceral organ dissemination. Currently, treatment strategies for mycosis fungoides and Sézary syndrome are limited. The lack of effective targeted therapy results in part from the current poor understanding regarding the pathophysiology of these diseases. Since chemokines and chemokine receptors have been found to play important roles in the pathogenesis of mycosis fungoides and Sézary syndrome, they may be useful targets for the development of new treatments for these diseases[111]. Previously, antibodies against CCR4 which induce antibody-dependent cellular cytotoxicity have been used in the treatment of mycosis fungoides and Sézary syndrome[112]. In addition, chemokine-toxin fusion proteins (for example CCL17 ligated to the Pseudomonas exotoxin 38) have been demonstrated to selectively target and kill lymphoma cells which express CCR4[113]. Therefore, further investigations are warranted to determine whether modulation of chemokines and chemokine receptors may be potentially useful for the treatment of mycosis fungoides and Sézary syndrome in the future.

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REVIEW

Review of the cutaneous manifestations of autoimmune connective tissue diseases in pediatric patients

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Abstract

Autoimmune connective tissue diseases are chronic inflammatory disorders associated with complex genetic and environmental interplay resulting in a variety of cutaneous and systemic manifestations. Pediatric onset of these disorders carries a unique diagnostic pressure for the clinician due to the potential years of disease burden and complications. Mortality and morbidity from these disorders has fallen dramatically over the past fifty years due to increasing awareness of these disease sequelae and utilization of systemic treatment modalities when necessary. This review highlights the clinical features that are unique to pediatric presentations of lupus erythematosus, juvenile idiopathic arthritis, juvenile dermatomyositis, juvenile onset systemic sclerosis and morphea. Each of these disorders has a distinct appearance corresponding to a particular cutaneous and systemic clinical course and prognosis. Awareness of the associated potential systemic complications can also alert the clinician to make astute management decisions when confronted with a probable rheumatologic case. Cutaneous symptoms may predate onset of systemic symptoms and by keeping the rheumatologic differential diagnoses in mind, the dermatologist can play a key role in potentially offsetting autoimmune disease burden in children.

Key words: Lupus erythematosus; Juvenile idiopathic arthritis; Juvenile dermatomyositis; Systemic sclerosis; Morphea

Core tip: Early recognition of cutaneous manifestations of connective tissue disease can positively impact disease course. This review summarizes key cutaneous findings of some of the more common pediatric autoimmune connective tissue disorders, including lupus erythematosus, neonatal lupus, juvenile idiopathic arthritis, juvenile dermatomyositis, systemic sclerosis, and morphea.

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INTRODUCTION

Autoimmune connective tissue diseases are complex

multisystem disorders. These disorders are associated with genetic and environmental factors, triggering intricate interactions between inflammatory cell responses and mediators, ultimately resulting in clinical manifestations. Dermatologists have the unique opportunity to diagnose some of these autoimmune disorders based on cutaneous findings which may predate systemic symptoms. The patient then benefits from close surveillance for complications and related conditions. Early recognition is of particular importance in the pediatric population as prompt intervention can often positively impact disease course.

The purpose of this review is to highlight the cutaneous manifestations of several of the more common pediatric autoimmune connective tissue diseases, including lupus erythematosus, juvenile idiopathic arthritis (JIA), juvenile dermatomyositis, systemic sclerosis, and morphea. We describe the disease course, highlighting the unique aspects of the pediatric presentation, potential complications seen in these disorders, key dermatologic and serologic findings, and offer a brief review of management options.

LUPUS ERYTHEMATOSUS

Lupus erythematosus (LE) was initially described as a disorder limited to the skin by Cazenave in 1851[1] Subsequently, Kaposi clarified the skin findings as one component of a disease that can potentially affect multiple organs, hence coining the term systemic lupus erythematosus (SLE)[2]. Today, cutaneous lupus erythematous (CLE) is considered a subset of SLE and is further sub-characterized based on the various cutaneous morphologies that are observed. Cutaneous LE is 2-4 times more common than SLE in the pediatric and adult populations[3,4]. Recognition of CLE is essential as a subset of patients, particularly pediatric patients, may have or develop systemic involvement.

SLE is a chronic autoimmune disorder that can affect multiple systems including the skin, joints, kidneys, heart and central nervous system and therefore can incur significant morbidity. More recently, it has been reported that patients are also at increased risk for atherosclerosis[5]. The pathogenesis is complex, involving genetic predisposition as well as environmental triggers, particularly medications and ultraviolet (UV) radiation exposure. Furthermore, UV radiation has been implicated in triggering and exacerbating cutaneous LE[6,7]. About 80% of patients with SLE will display cutaneous involvement at some time during the disease course, with up to 60% for whom it is the presenting symptom[8,9]. Although the majority of patients are adult women within their childbearing years, approximately 20% of patients are diagnosed prior to the age of 16 years of age[10]. Pediatric onset SLE is a special subset of this disease and portends a more severe and aggressive disease course, particularly among non-Caucasian patients[11-13]. Approximately 50 years ago, pediatric onset SLE was associated with a 100% mortality rate. However, with the utilization of more aggressive therapy, pediatric patients currently have been able to achieve survival rates > 90% with systemic anti-inflammatory medications to restrain and manage immune dysregulation[14]. Underscoring the severity seen in the pediatric population, systemic medications are used almost 4 times more frequently than in the adult populations[9,15,16].

Diagnosis of SLE was recently updated in 2012 by the Systemic Lupus International Collaborating clinics[17]. Eleven clinical and 6 immunologic criteria were identified and currently the diagnosis of SLE requires fulfillment of at least 4 criteria, with at least 1 from either category (Table 1). These criteria would allow for a diagnosis of SLE based on skin findings alone (acute cutaneous lupus, chronic cutaneous lupus, oral or nasal ulcers and non-scarring alopecia) in the setting of positive serologic markers. Early diagnosis is imperative to minimize potential end organ damage[18]. This is particularly critical for pediatric patients as this group is more likely to have associated renal and neurologic disease[9]. Serology can be helpful in predicting disease course. In pediatric patients, anti-dsDNA, anti-ribosomal P and anti-histone antibodies are more frequently seen. Anti-dsDNA autoantibodies are associated with significant renal disease while the presence of anti-ribosomal P autoantibodies appears to be inversely correlated with kidney involvement[19]. The presence of antiphospholipid antibodies is generally associated with a poorer prognosis[20].

Cutaneous lupus erythematosus can be categorized into three major forms which are described as acute, subacute CLE (SCLE) and chronic cutaneous lupus[21]. Within the chronic category, several subtypes are included: discoid lupus erythematosus (DLE), lupus erythematosus tumidus (tumid lupus), lupus panniculitis, and chilblain lupus erythematosus. Importantly, the three major types of cutaneous lupus are not mutually exclusive and more than one subtype of cutaneous disease may occur in the same person[22].

Acute cutaneous lupus is commonly associated with active SLE and can be further categorized into localized and generalized forms[3]. The classic localized form manifests as what is known as the "malar rash" extending over the nasal bridge with sparing of the nasolabial folds. This finding can be as subtle as mild erythema, or more pronounced with features of intense edema and scaling (Figure 1). This finding may last from a few hours to several weeks. A malar rash is associated with the onset of SLE in 61% of pediatric cases[8]. The malar rash may be misdiagnosed as seborrheic dermatitis, rosacea, parvovirus B19 infection, sunburn or other facial dermatoses[23]. The generalized form of acute cutaneous lupus is rare and appears as widespread symmetric erythematous macules and papules on the torso and extremities, sometimes associated with pruritus[3] (Figure 2). Involvement of the dorsal hands can provide diagnostic clues.

Table 1 Cutaneous findings, diagnostic criteria, and treatments for juvenile systemic connective tissue disease

Disease	Cutaneous findings	Diagnostic criteria	Treatment
Lupus erythematosus	Acute cutaneous lupus Malar rash Generalized erythematous macules and papules, sparing the knuckles on dorsal hands Mucosal ulcerations Bullous lupus Subacute cutaneous lupus Photodistributed annular eczematous or psoriasiform plaques Chronic cutaneous lupus Discoid lupus Lupus panniculitis Chilblain lupus Tumid lupus	Systemic lupus erythematous requires fulfillment of ≥ 4 criteria with at least 1 criterion from either category: Clinical criteria: Acute cutaneous lupus; Chronic cutaneous lupus; Oral ulcers; Nonscarring alopecia; Synovitis; Serositis; Renal disease; Neurologic disease; Hemolytic anemia; Leukopenia; Thrombocytopenia Immunologic criteria: ANA; Anti-dsDNA; Anti-Smith; Anti-phospholipid antibody; Low complement; Direct Coombs' test	Mild skin-limited disease Photoprotection Topical corticosteroids Calcineurin inhibitors Hydroxychloroquine Refractory skin disease and systemic disease Hydroxychloroquine Systemic corticosteroids Methotrexate Dapsone (bullous lupus) Other steroid sparing immune modulators
Systemic juvenile idiopathic arthritis	Transient salmon-pink macules and edematous papules Flagellate erythema	Onset before 16 yr of age, ≥ 6 wk of arthritis, ≥ 2 wk of fever At least one of the following: Evanescent eruption Generalized lymphadenopathy Splenomegaly Serositis	Systemic corticosteroids Methotrexate Biologic agents Supportive symptomatic measures for skin manifestations
Juvenile dermatomyositis	Gottron's papules–lichenoid papules overlying phalangeal joints, elbows, knees Heliotrope rash of eyelids Poikiloderma of upper back and chest Hyperkeratosis and fissuring of fingertips Mucosal ulcers Gingival telangiectasia Calcinosis cutis	Fulfillment of all five criteria: Symmetric proximal muscle weakness Elevated skeletal muscle enzymes Electromyography changes[1] Muscle biopsy abnormalities[1] Characteristic skin findings	Photoprotection Hydroxychloroquine Systemic corticosteroids Methotrexate IVIG Other steroid sparing immune modulators
Juvenile onset systemic sclerosis	Limited Sclerosis limited to distal extremities and face CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias) Diffuse Diffuse sclerosis	Skin sclerosis and ≥ 2 of the following: Sclerodactyly; Raynaud's phenomenon; Nailfold capillary abnormalities; Digital tip ulcers; Dysphagia; Gastroesophageal reflux; Neuropathy; Carpal tunnel syndrome; Tendon friction rubs; Arthritis; Myositis Arrhythmias; Heart failure; Renal crisis; New-onset arterial hypertension; Pulmonary fibrosis; Decreased DLCO; Pulmonary arterial hypertension; Antinuclear antibodies; SSc-selective autoantibodies	Avoidance of vasospasm triggers Methotrexate Physiotherapy Other immune modulators
Morphea	Linear Linear erythematous indurated plaques En coup de sabre–indurates plaques affecting forehead and scalp Parry Romberg–indurated plaques of the face with ipsilateral facial atrophy Circumscribed Isolated indurated plaques Generalized 4 or more circumscribed type plaques that are larger than 3 cm in diameter Involving at least 2/7 anatomic sites: head-neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, anterior trunk or posterior trunk Pansclerotic Diffuse involvement of the limbs, trunk, face and scalp with fixation of underlying structures Mixed 2 or more different types of morphea present	No sclerosis of internal organs, except for rare involvement of underlying fascia, muscle and bone	Topical corticosteroids Calcipotriene UVA1 phototherapy Severe or critical location of lesions Systemic corticosteroids Methotrexate

[1]These tests are typically not done in children and have been clinically replaced with MRI evidence of muscle inflammation and autoantibodies compatible with juvenile dermatomyositis.

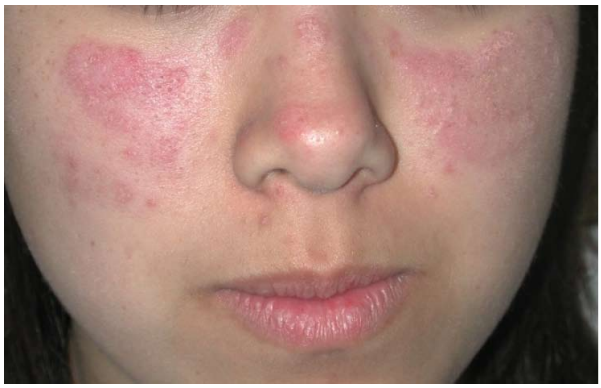

Figure 1 Acute cutaneous lupus erythematosus. The facial erythema on the malar cheeks appears as erythematous plaques with scale. There is distinct sparing of the nasolabial folds.

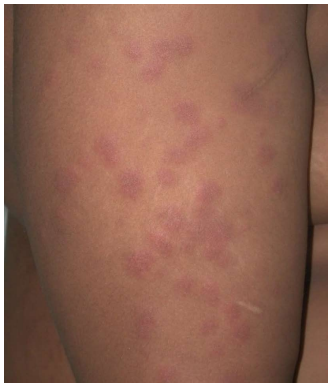

Figure 2 Acute cutaneous lupus erythematosus. Pink edematous papules on the extremities.

Erythematous plaques characteristically involve the skin between the joints more than the skin overlying the knuckles. Cuticle overgrowth and dilated cutaneous blood vessels may be seen underlying the proximal nail fold (Figure 3). Mucosal involvement in acute cutaneous lupus manifests as mucosal ulcerations, gingivitis, or silvery white changes on the vermilion border, gingiva, buccal and nasal mucosa. These findings may be seen in 3% of patients with cutaneous LE and up to 30% of pediatric patients with SLE[24]. Mucosal findings may be severe in acute SLE flares and have even been mistaken for drug-induced toxic epidermal necrolysis[25]. A rare, but distinctive, variant of acute CLE is bullous lupus erythematosus. This condition is characterized by localized or generalized tense subepidermal vesicles and bullae arising on normal or erythematous skin. The bullae herald the presence of circulating auto-antibodies to collagen Ⅶ[26]. Sun-exposed sites of the trunk, limbs and face are particularly affected; small blisters along the vermillion border of the lips can be seen in up to 30% of cases[27,28].

SCLE is typically limited to sun-exposed skin. This form of cutaneous lupus is the least common type presenting in the pediatric population, however when present, is more frequently associated with systemic disease as compared to the adult population[22,29].

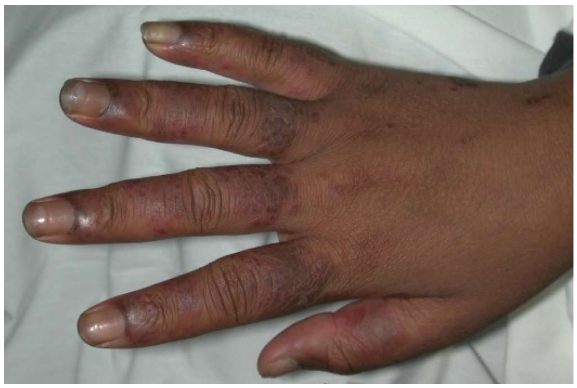

Figure 3 Acute cutaneous lupus erythematosus on the dorsal hands. Note the erythematous edematous papules coalescing into plaques on the dorsal fingers with sparing of the phalangeal joints. Note the dilated cutaneous vessels under the proximal nail fold particularly of the index finger.

The lesions of SCLE tend to demonstrate an annular configuration, often with raised red borders, and manifesting eczematous to psoriasiform epidermal features. Due to the superficial location of the inflammation, these lesions rarely result in scarring. Interestingly, the midface skin is usually spared, with more frequent involvement of the sides of the face, upper trunk and extensor aspects of the arms; lip involvement has also been described[25]. The differential diagnosis of SCLE in children includes urticaria, eczematous dermatitis and erythema multiforme. Anti-Ro and La autoantibodies are often associated with SCLE, and subsequently patients may also have dry eye and dry mouth symptoms and organ involvement consistent with Sjogren's syndrome[22].

Chronic cutaneous lupus is the most common subtype of cutaneous LE among pediatric patients, specifically the morphology known as discoid DLE. Children with DLE have an increased risk of developing SLE as compared to adults, with approximately 23%-26% developing SLE, *vs* 5%-20% of adults[30,31]. Discoid LE is most often localized to the face, scalp and ears as it preferentially appears on sun-exposed areas and is found to be exacerbated by UV radiation[4,24]. A generalized form of DLE has been described where there is widespread distribution including mucosal surfaces. The latter presentation is associated with a higher rate of progression to SLE[4,6]. The lesions are typically round to annular, slightly indurated, erythematous to violaceous plaques with adherent scale, often with follicular plugging which is described as "carpet tack-like." Older lesions will demonstrate atrophy, dyspigmentation resulting in scarring, and alopecia in hair bearing areas (Figure 4). Lip involvement can be present with lesions blurring the sharp vermillion border[25]. Linear presentations following the lines of Blaschko have also been described in children[32,33]. Squamous cell carcinoma has been reported in longstanding lesions of DLE[34].

Other subtypes of chronic cutaneous lupus include lupus panniculitis, chilblain lupus erythematosus and

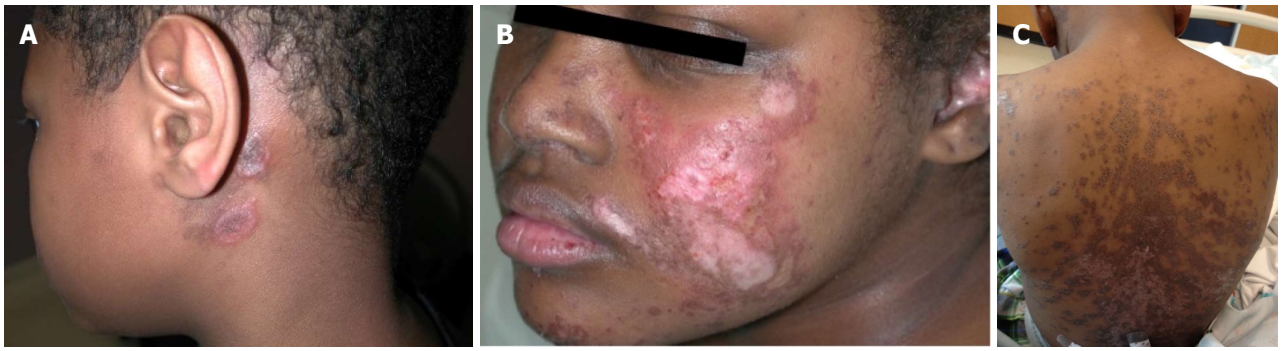

Figure 4 Discoid lupus erythematosus. These lesions will typically favor the head and neck. A: Earlier lesions can present as erythematous papules and annular plaques with scaling; B: This patient had more chronic lesions involving her cheek, nose, chin and conchal bowl with significant dyspigmentation; C: Widespread symmetric involvement can be seen in generalized discoid lupus.

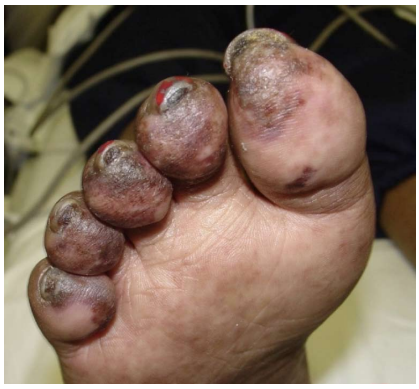

Figure 5 Chilblain lupus erythematosus. Violaceous plaques with overlying scale on the distal toes.

tumid lupus, all of which are rare in children. Lupus panniculitis results in firm subcutaneous nodules and can present in association with DLE. Lesions tend to involve areas of increased fat deposition such as the chest, upper arms and thighs and sometimes in areas where patients report a history of trauma[3,28]. Lupus panniculitis can last for many years, and due to the deep nature of the inflammation, the lesions can leave disfiguring atrophic scars. Chilblain lupus appears as painful, itchy, violaceous papules, plaques, or erosions on cold-exposed surfaces such as the tips of the digits (Figure 5). This finding represents cold-induced vasospasm of the hands and feet and may even resemble frostbite. Twenty percent of adult patients with chilblain lupus are reported to evolve into SLE[35]. A dominantly inherited familial form of chilblain lupus erythematosus has been described due to a mutation in TREX1[36]. Tumid lupus presents as red to purple edematous plaques without epidermal change that remain fixed in shape, often in a polycyclic pattern, on sun exposed sites. These lesions tend to heal without scarring.

The major histologic findings associated with most forms of cutaneous lupus erythematosus include basement membrane thickening in the setting of an interface lymphohistiocytic infiltrate and increased dermal mucin deposition[37]. In acute cutaneous lupus the dermal infiltrate can be subtle, while in SCLE there can be significantly more superficial dermal involvement. In DLE lesions, liquefactive degeneration of the basal layer with lymphohistiocytic involvement of periadnexal structures, follicular plugging and fibrosis is notable. Lupus panniculitis exhibits lobular infiltrates within the subcutaneous fat. In contrast, lupus tumidus will not exhibit the epidermal changes, but demonstrates notably increased dermal mucin deposition. Direct immunofluorescence of lesional and nonlesional skin in the setting of LE will typically exhibit a granular deposition of IgG and/or IgM along the dermal epidermal junction and around hair follicles[37].

Special mention needs to be made of non-specific skin findings observed in LE patients. These findings may be suggestive of SLE and when they coincide with systemic symptoms suggestive of SLE, such as joint pain, the physician must be alert for additional signs of lupus (Table 2). The most common non-specific findings are those representing cutaneous vascular disease such as Raynaud phenomenon, livedo reticularis, and cutaneous vasculitis. Other nonspecific findings which may be associated with SLE include urticaria, erythema multiforme, and nonscarring alopecia.

The management of pediatric cutaneous LE is dependent on extent of disease. In general, patients should be advised to avoid the sun as much as possible and to employ UV protection at all times. If the disease is localized, treatment with topical corticosteroids or calcineurin inhibitors may be adequate; however, the routine use of hydroxychloroquine in all LE patients, including those with skin-limited disease, is becoming more strongly favored. Hydroxychloroquine has been shown to increase survival and lengthen remission in adults and to specifically reduce the prevalence of renal disease[3,38,39]. Refractory cutaneous disease may require additional antimalarial agents, systemic corticosteroids, and steroid sparing agents such as methotrexate and mycophenolate mofetil[3].

NEONATAL LUPUS

Neonatal lupus is a passively acquired autoimmune

Table 2 Nonspecific cutaneous findings suggestive of systemic lupus erythematosus (modified from Bolognia)[1]

Diffuse non-scarring alopecia
Raynaud's phenomenon
Nailfold telangiectasia and erythema
Vasculitis
Urticarial vasculitis
Small vessel vasculitis (*e.g.*, palpable purpura)
Polyarteritis nodosa-like lesions
Ulcerations
Cutaneous signs of antiphospholipid syndrome
Livedo reticularis
Ulcerations
Acrocyanosis
Atrophie blanche-like lesions
Degos'-like lesions
Livedoid vasculopathy
Palmar erythema
Papular and nodular mucinosis

disorder of neonates born to mothers with circulating connective tissue autoantibodies Ro, La, and less commonly, U1-ribonucleoprotein[40]. Approximately 50% of mothers are asymptomatic at the time of the infant's diagnosis, therefore diagnosis in the child can alert the clinician to recommend connective tissue disease evaluation for the mother[40]. The data suggests that approximately 50% of mothers who are asymptomatic at the time of their child's diagnosis will develop symptoms of connective tissue disease within 3 years[41,42]. Only 10% of these women will meet full criteria for SLE within 6 years of follow up[42]. Cutaneous lesions of neonatal LE are transient. Cutaneous manifestations typically resolve within 6-8 mo after birth, as maternal autoantibodies disappear from the infant's circulation[42,43]. The gravest complication of neonatal lupus is cardiac conduction abnormalities which are typically permanent. Conduction abnormalities occur in 15%-30% of cases[42]. The developing fetal heart undergoes a complex pattern of growth, programmed apoptosis and folding, during which Ro and La antigens are expressed on fetal myocytes. These myocytes are targeted by the maternal autoantibodies causing scarring within the fetal conduction pathway and resulting in dysrhythmias and/or complete heart blocks without structural anomalies. Almost all patients with this complication will require a pacemaker at some point in their life[42]. Other potential complications of neonatal lupus include liver involvement with conjugated hyperbilirubinemia, splenomegaly, hematologic abnormalities, hydrocephalus, hemorrhagic strokes and seizures[42,44,45].

Cutaneous features of neonatal lupus typically appear at a mean of 6 wk after birth, though it can be present at the time of delivery in some cases[46,47]. The classic facial lesions are erythematous annular and polycyclic plaques with or without scale located on the scalp and periocular region of the face. Confluent erythematous papules or even pustules are also seen[44]. The pattern noted on the face is often referred to as "owl

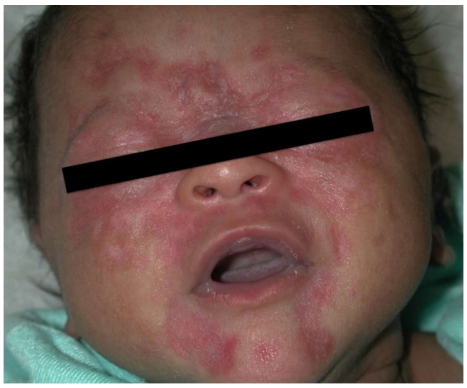

Figure 6 Neonatal lupus. Annular lesions with central atrophy particularly concentrated around the eyes.

like" or "raccoon like" (Figure 6). Annular plaques may also be found on the trunk and extremities and in the groin region, thus involving non-sun-exposed sites[47,48]. Many lesions resolve without sequelae over a mean duration of 17 wk, however approximately 25% can leave residual dyspigmentation, persistent telangiectasia and atrophic scarring of the affected areas. It is unclear if treatment with topical steroids prevents lingering skin findings. Strict UV protection is recommended as it is in all forms of CLE[47]. All patients with neonatal lupus should be followed regularly as long term follow up studies have reported cases of autoimmune thyroiditis, type 1 diabetes mellitus and JIA. To date, there have been no reports of cases of SLE, dermatomyositis (DMS), or systemic sclerosis in patients with a history of neonatal lupus[47,49].

SYSTEMIC JIA

JIA is a term that refers to a group of six chronic arthritides in children less than 16 years of age. Of these six subtypes, only two are associated with cutaneous findings, systemic onset arthritis and psoriatic arthritis. Due to the connective tissue disease focus of this review, skin manifestations of psoriatic arthritis will not be discussed here. Systemic JIA is considered a subset of JIA and is a diagnosis of exclusion defined as arthritis with, or preceded by, daily fevers of at least 2 wk duration in the setting of specific systemic signs of inflammation (Table 1). Cutaneous findings are found in 25%-50% of patients and may precede fevers, arthritis or organ involvement by several years[24]. Pathophysiology of this disease remains obscure, and current theories point to an autoinflammatory etiology. A genetic component has been identified as subgroups of patients have been identified to have mutations in MEFV and LACC1[50,51].

Joint involvement will result in severe, recalcitrant and destructive progressive polyarticular disease in 50% of patients. Other complications of systemic JIA include serositis, uveitis, hepatosplenomegaly, pleuritis, and pericarditis. A particularly severe complication is macrophage activation syndrome which can be life

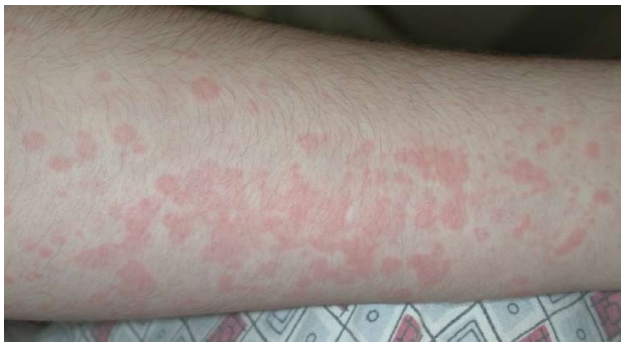

Figure 7 Juvenile idiopathic arthritis. Erythematous papules coalescing into plaques with surrounding pallor, typically evanescent in nature.

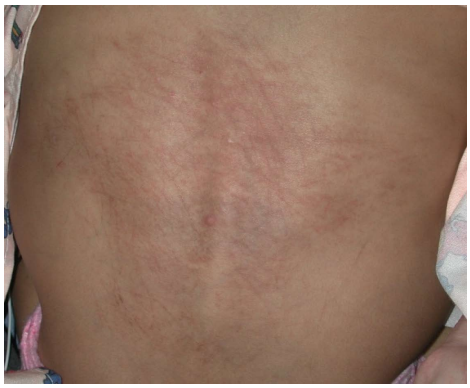

Figure 8 Juvenile idiopathic arthritis presenting as flagellate erythema. Erythematous and hyperpigmented persistent plaques in a flagellate pattern.

threatening.

The classic evanescent cutaneous eruption associated with systemic JIA is described as 2-5 mm salmon-pink macules and edematous papules that arise with fevers and typically resolve within hours of defervescence. This eruption is not usually pruritic and can involve the chest, proximal extremities and pressure points[52] (Figure 7). These cutaneous findings will coincide with an elevation in acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, ferritin and platelets. Biopsy findings are variable and non-specific[37]. Adult-onset Still's disease is typically considered the adult version of systemic onset JIA. An eruption of persistent pruritic papules and plaques variably associated with a flagellate erythema has been described in adult-onset Still's disease. The histologic findings in these cases are notable for a characteristic pattern of dyskeratotic keratinocytes in the upper layer of the epidermis and extending into the stratum corneum[53-58]. A similar eruption with consistent histologic findings has been observed in a child with systemic onset JIA (authors' experience) (Figure 8).

Management of the cutaneous features of systemic onset JIA is contingent on treatment of the systemic disease. First line treatment includes non-steroidal anti-inflammatory medications in association with physical therapy. For severe cases, systemic corticosteroids, methotrexate, other steroid-sparing medications or biologic agents may be necessary. Recently, genetic variations in patients with systemic onset JIA has helped to elucidate treatment response patterns[59,60] Earlier aggressive therapy is associated with longer remission[61,62].

JUVENILE DMS

DMS is an immune-mediated process triggered by exposure to various exogenous factors in genetically predisposed individuals. The skin, striated muscles and internal organs may be affected. It is the most common inflammatory cause of myopathy in children[63]. Traditional diagnostic criteria for juvenile DMS include cutaneous findings in conjunction with serologic findings and signs and markers of myopathic disease, including muscle electromyographic changes and histopathologic features (Table 1). Radiographic studies to document muscle involvement are often substituted for the more invasive diagnostic procedures[64,65]. A subtype known as amyopathic DMS is diagnosed when cutaneous findings are present in the absence of muscle symptoms for at least 6 mo. Amyopathic disease is thought to represent an estimated 20% of all dermatomyositis cases[66]. In children, it has been suggested that a quarter of patients with amyopathic DMS will progress to classic DMS in a mean follow up period of 4 years[67]. Dermatomyositis is rarely associated with malignancy in children, whereas in adults associated malignancy is present in 14%-30% of cases[66-68]. Females are at higher risk for DMS overall. A bimodal pattern of onset is seen in childhood with peak ages of onset between 2-5 years of age and 12-13 years of age[63]. Recent literature suggests that patients who present at the younger age peak may have a milder disease course[69].

Onset of DMS can be insidious in up to 43% of the cases and by the time the diagnosis is made, the patients may have experienced subtle weakness, anorexia, malaise, and abdominal pain in addition to cutaneous findings for over 2-6 mo[63,67,70]. Male gender and proximal muscle weakness evidenced by a positive Gower's sign is associated with poor prognosis for complete clinical remission[71]. Complications of DMS include hypertriglyceridemia with insulin resistance, calcinosis cutis, muscle weakness and atrophy, lipodystrophy, and infections, particularly from gram negative organisms. Lipodystrophy and small vessel vasculitis affects an estimated 10% of the pediatric disease population and these patients demonstrate an increased incidence of concomitant insulin resistance and hyperlipidemia[72].

Most patients will present with proximal muscle weakness and the hallmark dermatologic findings of Gottron's papules and heliotrope rash around the eyes. Gottron's papules are small purple or pink lichenoid papules on the dorsum of the hands, overlying the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints (Figure 9). These

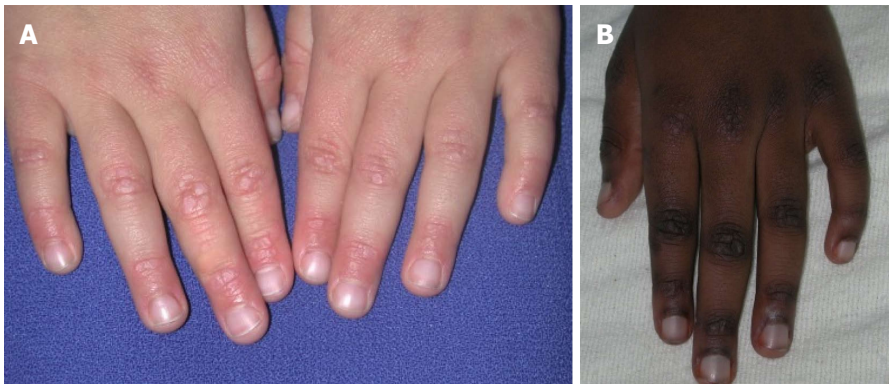

Figure 9 Dermatomyositis. Gottron's papules with (A) pink to (B) violaceous flat-topped papules overlying the dorsal joints of the fingers with sparing of the skin in between the joints, a finding occasionally mistaken for flat warts. Also note the erythema noted around the proximal nail folds.

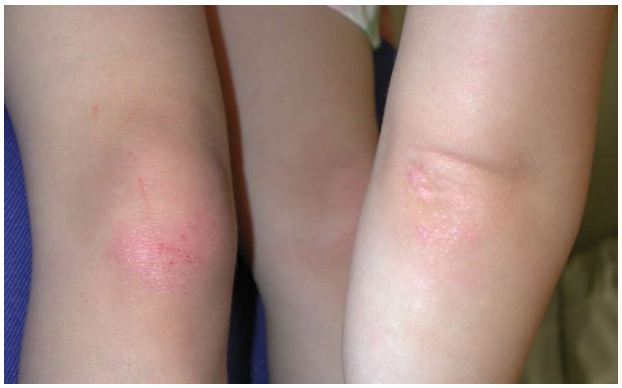

Figure 10 Dermatomyositis. Lichenoid papules and plaques over bony prominences of the knees and elbows.

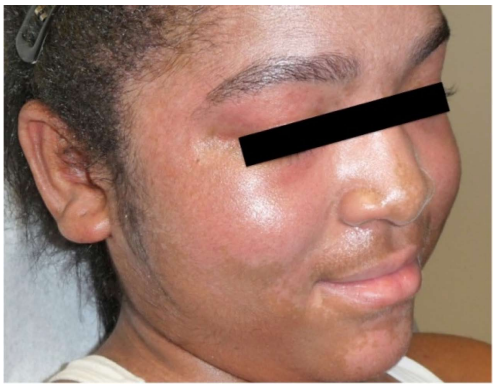

Figure 11 Dermatomyositis. Heliotrope sign with prominent capillary vasculature around the eyelids and characteristic pink-purple patches involving the cheeks, chin and temples.

papules may resolve with atrophy, telangiectasia and dyspigmentation. Similar small pink to purple papules, almost psoriasiform in nature, can be found on bony prominences over the knees, elbows and ankles (Figure 10). The heliotrope rash is a purplish red discoloration that involves the eyelids most commonly. The notable purple red patches are sometimes accompanied by edema. Temples, forehead, cheeks and ears can be similarly affected[24] (Figure 11). Erythema with scaling may involve the scalp and can be mistaken for seborrheic dermatitis, psoriasis or even CLE[73]. The histologic findings that correlate with most of these clinical features demonstrate vacuolar changes of basal keratinocytes, dermal mucin accumulation and a mild to moderate dermal lymphocytic infiltrate, sometimes with features of dermal sclerosis[37].

In the setting of chronic DMS, poikiloderma (dyspigmentation, telangiectasia and epidermal atrophy overlapping in the same region) is often present. Poikilodermatous change involving the upper back and anterior chest in a photodistributed manner is classically referred to as the "shawl sign". Ragged cuticles and nail fold telangiectasia can be appreciated in up to 68% of patients. "Mechanic's hand" is a phrase that describes hyperkeratosis and fissuring at the fingertips with associated palmar erythema. Mucosal findings include mouth ulcers, gingival telangiectasia and gingival bleeding.

Calcinosis cutis is a complication associated with significant morbidity and is more prevalent in juvenile DMS as compared to adult counterparts, affecting 18%-25% of pediatric patients. This finding correlates with disease chronicity. Fortunately, with newer management regimens focusing on early aggressive therapy, the incidence is steadily decreasing[63,70,72]. Lesions of calcinosis cutis are hard nodules in areas that are prone to trauma such as the buttocks, elbows, knees, fingers and shoulders. The nodules are occasionally deeply seated into the fascia and intramuscular connective tissue. These lesions may connect to the skin surface and result in chalky drainage. Complications such as cellulitis and ulceration may ensue[24].

Prior to the use of corticosteroids in the treatment of juvenile DMS, the disease had a mortality rate of 30%. Standardized treatment protocols have resulted in lowered mortality rates of 0.7%-3.1%. The mainstay of treatment is systemic corticosteroids, methotrexate and IVIG. Other treatments include hydroxychloroquine and cyclosporine[64]. Studies using biologic therapies including etanercept and rituximab have demonstrated mixed results[64,74,75]. Patients with amyopathic DMS can be treated with hydroxychloroquine, topical corticosteroids and photoprotection[76]. Treatment of calcinosis cutis can be unsatisfying. The most promising treatments in children include bisphosphonates, calcium channel

blockers and surgical excision of larger lesions[77].

JUVENILE ONSET SYSTEMIC SCLEROSIS

Juvenile onset systemic sclerosis (jSSc) is a rare disorder of unclear etiology that causes vascular dysfunction, immune dysregulation and finally tissue fibrosis due to deposition of collagen and other extracellular matrix proteins. The organs prominently affected are skin, blood vessels and internal organs. Of the organs, the lungs are of particular concern as almost all patients will exhibit pulmonary function test abnormalities resulting in significant morbidity and mortality[78]. The onset of this disease is insidious and it can take 1-4 years on average until the diagnosis is made, highlighting the importance of disease awareness. Ten percent of all patients with this disease will present in childhood[79]. Diagnostic criteria set forth by the Pediatric Rheumatology European Society and American College of Rheumatology require the presence of cutaneous sclerosis proximal to the metacarpophalangeal joints in addition to 2 minor criteria involving extracutaneous organs[80,81] (Table 1). There are two known types of jSSc, limited and diffuse. The limited type is characterized by distal extremity disease and facial involvement. These patients may also fulfill criteria for CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia). The diffuse type involves both the distal and proximal portions of the extremities including the hands and face. The limited subtype appears to have a more benign course. In both subtypes, the diseases will often affect the fingers and hands first, with subsequent spread to the proximal extremities and trunk in symmetric fashion. Compared to adults, juvenile onset systemic sclerosis has a higher survival rate (98% *vs* 75%), is more likely to be involved in rheumatologic overlap syndromes, and is less likely to be complicated by pulmonary artery hypertension and renal crisis[82].

The cutaneous manifestations of jSSc underscore the vascular dysfunction central to this entity. The most common initial presentation of jSSc is Raynaud's phenomenon, present in approximately 75% of cases, followed by proximal skin induration (66%), sclerodactyly (55%), and digital tip ulcers (35%)[79]. Raynaud's phenomenon is characterized by vasospasms causing pallor, cyanosis, pain, numbness, tingling, swelling, and hyperhidrosis of acral surfaces, most typically affecting the hands and feet and occasionally the nose, lips, cheeks and ears[24]. Episodes can be precipitated by cold and emotional stress. Sclerodactyly in children tends to appear edematous at first, with progression to shiny skin overlying tapered fingertips associated with decreased range of movement. In addition to the sclerotic changes, calcifications, ulcerations, and matted telangiectasias will develop[79,83]. Dyspigmentation of the overlying skin has been described to have a "salt and pepper" appearance due to retained pigment in a perifollicular pattern within areas of hypopigmentation[24]. Ichthyotic skin changes of the proximal extremities have been reported as a prodromal presentation of jSSc[84]. Histologically, skin biopsy reveals compact or hyalinized collagen in the dermis with atrophic adnexal structures and thinning of the overlying epidermis. The different subtypes of systemic sclerosis cannot be differentiated on microscopic exam[1].

Lifestyle recommendations are critical to the management of the cutaneous symptoms in this disorder. Patients must be advised to avoid vasospasm triggers such as stress, cold and smoking. Currently most treatment modalities are based on adult studies. In adults, there have been randomized controlled trials that support methotrexate in managing and treating the early stages of disease[85,86]. For patients with recalcitrant disease, human autologous stem cell transplants have been reported to improve symptoms in a limited number of cases[87]. Due to the risk of contractures with jSSc, physiotherapy is critical.

MORPHEA

Morphea is a distinct inflammatory disease affecting the skin and underlying tissues leading to localized sclerosis. For this reason, another term for morphea is "localized scleroderma." However, morphea displays a clinical course distinct from that of systemic sclerosis and thus "morphea" is the preferred term to prevent confusion. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) recently reported baseline data of 259 patients within their registry. The majority of patients were female (71%) and were more likely to be Caucasian (81%). Here they reported that the mean age of onset was 9.5 years, however almost 40% had at least a 5 year delay in diagnosis[88]. Approximately half of all cases of morphea present in childhood. In children, disability due to the disease and associated extracutaneous complications is more severe than it is in adult patients[89].

When a patient presents with morphea, the differential diagnosis of systemic sclerosis may be entertained. The distinction between morphea and systemic sclerosis is a clinical one with the latter characteristically exhibiting Raynaud's phenomenon and sclerodactyly as mentioned in the previous section (Table 1). Morphea is non-life-threatening, but can be significantly debilitating and disfiguring. Limb involvement, particularly when overlying a joint, can cause permanent limb asymmetry, contractures, ulcerations and joint immobility. Ocular and central nervous systemic manifestations have been reported in cases where there is underlying disease focused on the face or scalp. Esophageal involvement is not uncommon in children[90]. Restrictive lung disease can result from generalized morphea subtypes[91,92]. Other potential complications include calcinosis cutis and rarely squamous cell carcinoma in lesions of morphea, particularly of the pansclerotic type[93,94].

Morphea is classified into 5 groups: Linear, circumscribed, generalized, pansclerotic and mixed. Mixed

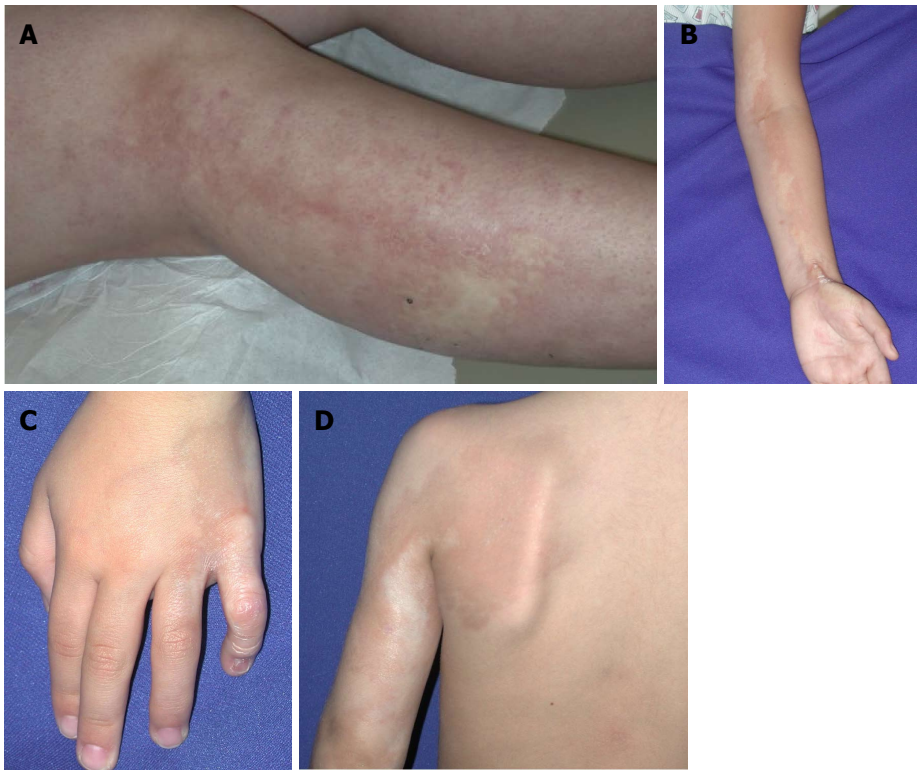

Figure 12 Linear morphea overlying joints. Early indurated plaques with lilac-colored border (A); (B) Advanced sclerotic and hypopigmented plaques on the left arm (C) with flexion contraction of the left fifth finger; (D) residual hyperpigmentation on the left shoulder.

type refers to presentations where 2 or more different types of morphea present on the same patient[92]. In children, linear morphea is most common; in adults the circumscribed type is more common. Approximately 51%-65% of pediatric cases are of the linear subtype, followed by circumscribed morphea (26%), generalized morphea (7%) and pansclerotic morphea (2%). Histologically, the hallmark of well-developed lesions of morphea is thickened dense bundles of collagen in the dermis. Additionally, vascular changes of endothelial swelling and edema with a perivascular lymphocytic infiltrate and plasma cells may be appreciated[1,37]. Slightly over 10% of pediatric patients will report an inciting event that is attributed to the onset of the morphea, such as trauma, infection, vaccination or insect bite[91,92].

Linear morphea is the most common subtype in children and is divided into 2 subtypes by area of involvement: trunk/limbs and head[95]. Linear morphea presents as a linear, erythematous strip that extends longitudinally in a series of indurated plaques, ultimately joining into a scar-like band. When linear morphea involves skin overlying a joint, there is risk of involvement of the underlying fascia, muscle and tendons (Figure 12). The inherent stiffness of the skin, as well as any deeper manifestations, can ultimately impact the joint mobility. Linear lesions can also extend circumferentially and produce significant limb size discrepancies[24]. When linear morphea affects the head, various presentations, including en coup de sabre and Parry-Romberg syndrome, are described. En coup de sabre is a term used for linear morphea affecting the forehead and scalp (Figure 13). Underlying findings on brain MRI/CT scans, including T2 hyperintensities, calcifications and ipsilateral cerebral atrophy, can be found in up to 73% of patients and can be associated with neurologic symptoms including seizures[96]. Parry-Romberg syndrome (progressive hemifacial atrophy) describes a subset of facial morphea cases involving the lower half the face with associated ipsilateral atrophy (Figure 14). In this particular presentation, the entire distribution of the trigeminal nerve, including the eye and tongue, may be affected. Associated symptoms can include alopecia, seizures and headaches[24,95].

Circumscribed morphea is characterized by slightly elevated, flesh colored or erythematous edematous plaques with an advancing border. The active border classically appears "lilac", or violaceous, in color leaving a trail of central sclerotic, scar-like tissue (Figure 15). There can be associated hair and sweat gland loss. The lesions can be asymptomatic or slightly pruritic and are often initially not noticed by the patient. The trunk is the most common location, affected by one or multiple asymmetric lesions. Clinical activity correlates with the presence of the lilac border. The active period of disease is felt to be on average 3-5 years. Once the lilac hue at the border disappears, the progression also seems to arrest[1]. Residual atrophy and dyspigmentation are commonly observed. The term generalized morphea is used when there are 4

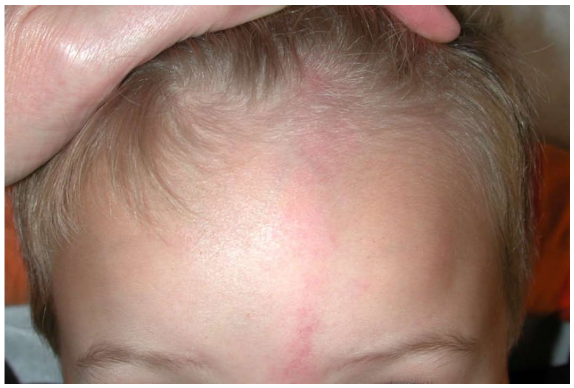

Figure 13 En coup de sabre morphea. Early presentation with an erythematous patch in paramedian forehead location extending into the scalp with hair loss.

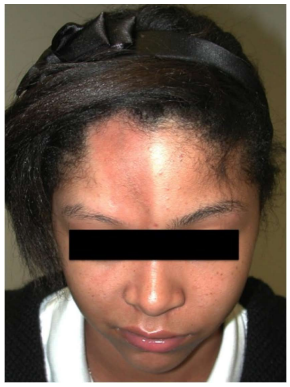

Figure 14 Parry-Romberg syndrome. Note the resulting asymmetry of the right lower face due to loss of subcutaneous fat.

or more circumscribed plaques of morphea that are larger than 3 cm in diameter and involve at least 2 out of 7 anatomic sites: head-neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, anterior trunk, and posterior trunk[95].

Pansclerotic morphea is a rare disabling variant more commonly seen in children than in adults. Diffuse involvement of the limbs, trunk, face and scalp occurs. In contrast to systemic sclerosis, pansclerotic morphea notably spares the fingertips and toes (Figure 16). Superficial and deep involvement by the sclerotic process leads to fixation of underlying structures. Internal organ involvement is notably absent, differentiating this entity from systemic sclerosis. Onset is usually before 14 years of age. Severe disability may result due to persistent atrophy of the underlying musculature[24,95].

Treatment of morphea depends on the site of involvement, extent of disease and level of disease activity. Aggressive treatment is indicated for linear morphea overlying joints or near joints, facial disease, generalized and pansclerotic morphea. The standard treatment protocols involve use of systemic corticosteroids initially while bridging to longer term management with methotrexate. Randomized controlled studies have demonstrated response rates to be as high as 75% with this protocol[97]. Increased relapse rates

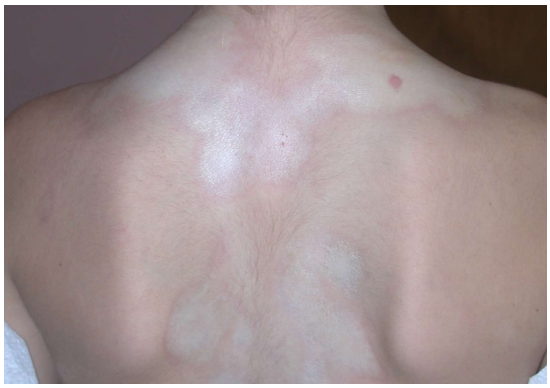

Figure 15 Circumscribed morphea. Inflamed lilac border around indurated sclerotic plaques.

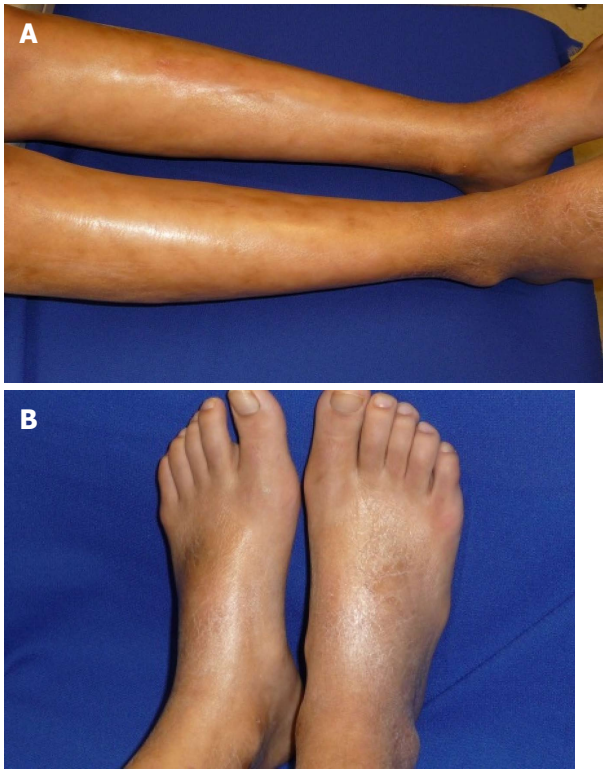

Figure 16 Pansclerotic morphea. A: Sclerosis of the skin bound down to underlying skin making the skin appear wooden with an uneven, taut shiny texture to the skin; B: Note the sparing of the toes which differentiates pansclerotic morphea from systemic sclerosis.

have been associated with shorter methotrexate courses (< 2 years) and shorter tapering regimens[98]. Milder presentations of morphea may be managed with topical regimens including calcipotriene and corticosteroids. UVA1 phototherapy has recently been shown to have efficacy in morphea[99,100]. Any consideration of surgical reconstructive procedures must be delayed until evidence of active disease has been thoroughly ruled out[101].

CONCLUSION

In summary, there is a wide array of cutaneous findings

observed in the setting of autoimmune connective tissue diseases affecting pediatric patients. Timely diagnosis of these entities can be challenging as many symptoms are of gradual onset. Dermatologists have the opportunity to provide critical assistance by early recognition of suggestive findings, allowing for prompt treatment of disease and improved clinical outcome.

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MINIREVIEWS

Review of allergic contact dermatitis: Scratching the surface

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Abstract

Contact dermatitis-including allergic contact dermatitis (ACD)-n and results in over four million lost work days per year in the United States alone. ACD is a classic example of a type IV delayed hypersensitivity reaction, and represents a significant burden on the health system, economy, and patient quality of life. Thorough history taking, clinical examination, histologic evaluation, and patch testing are keys to diagnosing contact dermatitis. Patch testing, especially with comprehensive and customized panels based on the patient's exposure history, is particularly useful in identifying potential allergens in the case of allergic contact dermatitis. ACD management requires a combination of direct medical intervention, patient education, and appropriate environmental modification to prevent exposure to offending allergens in the home or workplace. Continuing advances in the study of ACD has led to an increased understanding of the disease processes, new methods for diagnosis, and improved management. This article reviews ACD-aiming to connect recent investigational data with the current clinical understanding of disease pathophysiology, diagnostic techniques, and management strategies.

Key words: Allergic contact dermatitis; Occupational dermatitis; Skin sensitization; Contact allergens; Patch testing

Core tip: Allergic contact dermatitis (ACD) affects approximately 20% of the adult population and results in over four million lost work days per year in the United States. Continuing advances in the study of ACD have led to an increased understanding of the disease processes, new methods for diagnosis, and improved approaches for treatment. This article discusses ACD holistically, aiming to connect recent investigational data with current clinical understanding to review disease pathophysiology, diagnostic techniques, as well as management strategies.

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INTRODUCTION

Contact dermatitis (CD) is a common inflammatory skin

reaction that follows direct contact of substances with the skin[1,2]. Contact dermatitis affects approximately 20%[3,4] of the adult population and is responsible for over eight million outpatient visits to dermatologists per year in the United States alone[5]. Occupational related CD represents 90% of all occupation related skin disorders and results in over four million lost work days per year[6,7]. CD represents a significant burden on the health system, economy, and patient quality of life[4,7,8].

Contact dermatitis is divided into two distinct disease processes: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is characterized by solitary or cumulative exposure to irritants (both chemical and physical) that induce direct keratinocyte damage and local inflammation, regardless of prior exposure[2,4]. In contrast, ACD is an example of type Ⅳ delayed-type hypersensitivity, which is divided into distinct phases: sensitization, elicitation, and inflammatory regulation[2,4,9,10]. Sensitization is the immunologic priming response following the initial topical exposure of a chemical allergen. Subsequent exposures at the same or distant sites on the skin result in a more vigorous secondary immune response at the point of contact, referred to as elicitation[1,4]. The extent and severity of these hypersensitivity responses are controlled by underlying inflammatory regulation pathways. The clinical presentation of these phases is referred to as ACD[4]. Continuing advances in the study of ACD have led to an increased understanding of the disease processes, methods for diagnosis, and approaches for treatment. This ACD review article will aim to connect investigational data with current clinical understanding to review disease pathophysiology, diagnostic techniques, as well as management strategies.

MECHANISM OF ACD

ACD is a multifactorial disease, resulting both from genetic and environmental factors[2,5]. ACD is characterized as a type Ⅳ delayed hypersensitivity reaction[10]. Once one or more potential allergens come in contact with the skin, a series of phases-sensitization, elicitation, and inflammatory regulation-occur that lead to an inflammatory response to the allergen(s)[1,2,5,9]. The precise roles these phases play in ACD are still under investigation. ACD in humans typically develops in response to repeated subthreshold exposures to contact allergens with clinical signs and symptoms of dermatitis developing gradually overtime[5,9]. Interestingly, our current understanding of ACD pathophysiology is primarily based on animal studies using the contact hypersensitivity (CHS) model[5,10]. In CHS studies, potent lipophilic compounds are applied directly to a rodent's skin. This serves as the sensitization phase. Five to seven days later the same compound is applied to a different location, resulting in the elicitation response. Given the short time course and potency of compounds used for priming an immunologic response, the CHS model depends on innate inflammatory mechanisms more than ACD. Regardless, it requires T cell antigen specific response, and is recognized as an analogous delayed-type IV hypersensitivity reaction[5].

For a cutaneous immune response to be induced, contact allergens must be able to penetrate the stratum corneum, the water impermeable outer layer of the skin, in order to gain access to the deeper living layers of the epidermis[1,4,11]. Filaggrin proteins are critical for maintaining epidermal homeostasis, aiding in the alignment of keratin filaments in the corneocytes and hydration of the stratum corneum[10]. Without these proteins, there is impaired skin barrier function, allowing for easier penetration of chemical irritants and allergens. Patients with a history of atopic dermatitis and filaggrin mutations have an increased risk, four to seven fold, of developing contact dermatitis[12].

Contact allergen characteristics also play a critical role in developing ACD. Most contact allergens are small organic chemicals or metal ions with molecular weights of < 500 daltons and lipophilic residues. These compounds are small enough to reach the horny layer of the epidermis, but too small to be immunogenic on their own[1,4,10]. Allergen sensitization potential depends on forming stable reactions with proteins and creating hapten-protein conjugates[4]. Sensitizing metals (*e.g.,* nickel, chrome, cobalt, *etc.*) react readily to form stable non-covalent protein-metal complexes. However, a majority of contact allergens cannot bind directly to host proteins and require either environmental or direct enzymatic changes in order to transform into reactive metabolites capable for forming covalent bonds[2,9,10,13]. Allergens that undergo activation from the external environment such as photosensitizers with ultraviolet radiation or auto-oxidizing agents such as the fragrances D-limonene or linalool are referred to as pre-haptens. Alternatively, allergens that are modified through the natural detoxification processes of keratinocytes (*e.g.,* cytochrome P450 isoenzymes, UDP glucuronosyltransferase, glutathione S-transferase, *etc.*) into highly reactive intermediates are termed pro-haptens[14]. Some familiar pro-haptens include natural products (urushiol), dyes (paraphenylene diamene, disperse blue), fragrances (eugenol), drugs (sulfamethoxazole), and industrial chemicals (styrene, ethylenediamine)[1,13]. Once haptenated proteins are formed, they activate an inflammatory cascade attracting dendritic cells (DCs) to the contact site[2]. Haptens are phagocytosed by DCs triggering the first phase of ACD, sensitization[1].

As part of the sensitization process, the protein-allergen complexes are broken down and expressed as peptide epitopes on the grooves of MHC class Ⅰ and Ⅱ molecules. These antigen bearing DCs migrate from the initial contact site to regional lymph nodes where $CD8^+$ and $CD4^+$ T-lymphocytes in the paracortex are primed. Here T-cells undergo differentiation into effector T-helper (Th) cells, cytotoxic T-cells, and

Table 1 Key points in allergic contact dermatitis history taking[18-20]

Topic	Details
Demographics	Age, sex, race, ethnicity
Past medical history	Personal history of atopic dermatitis, asthma, allergic rhinitis or other allergic diseases, co-morbidities, current medications, and medical device implantation (including dental implants such as braces, crowns, or fillings)
Family history	Atopic dermatitis, allergic rhinitis, or asthma
Occupational history	Current job description, materials handled at work, type and regularity of chemical exposures, previous employment history, and symptoms at work
Dermatitis specific history	Initial rash: date/duration, area(s) affected, symptoms, pattern/progression of eruption, frequency of recurrence, and treatments attempted Current rash: areas affected, severity, and changes during work week vs weekend
Home environment	Location (urban, suburban, or rural), pets (Dogs, cats, birds, rodents, livestock, *etc.*), house cleaning activities, and detergents used
Personal care	Hand washing frequency, deodorant, lotion, cream, perfume/cologne, hair styling aides, nail polish remover, makeup use, *etc.*
Sports/hobbies	Type of equipment used, indoor vs outdoor, and symptoms with activity
Jewelry/piercing/tattoos	Type, location and frequency of jewelry use, type and location of piercings, history of temporary or henna based tattoos

T-regulatory (Treg) cells, which over the course of weeks to months begin to circulate into the peripheral blood[2,5,10].

Future re-exposure to sensitized contact allergens are recognized by DCs and result in a vigorous immune response (elicitation) and a classic inflammatory rash typically within 12 to 72 h[4,9]. Resolution and regulation of the inflammatory response involves clearance of haptens and activation of $CD4^+$ regulatory T cells[2,5,10]. Studies have found haptens may remain in the for skin weeks to months following the initial exposure, suggesting the importance of anti-inflammatory cytokine production from local skin cells in addition to regulatory cells[15]. While their precise action remains unknown, increasing evidence suggests $CD4^+$ Treg cells control the priming and expansion of hapten specific $CD8^+$ cells in the skin[16]. Other mechanisms, including MicroRNA have been found to have a regulatory component[17]. MircoRNA segments bind to sections of inflammatory sequences of mRNA, blocking and thereby inhibiting their effective translation. The accelerated turnover and breakdown of the transcripts alters gene expression and likely contributes to the dysregulation of inflammation in allergic contact dermatitis[17].

DIAGNOSIS

Timeliness of diagnosis for ACD is essential for improved outcomes in the management of this disease. Making a diagnosis of ACD entails the following steps: (1) detailed history; (2) suggestive physical exam findings; (3) supportive histological evidence, and (4) patch testing[3].

Clinical history and physical

Recognizing the clinical symptoms, exposure history, morphology, and distribution of lesions are important in the diagnosis of ACD. The first step in diagnosis is a obtaining a detailed history in order to determine the clinical relevance of various patch test allergens. This may require extensive questioning. Standardized screening questionnaires are helpful to ensure comprehensive data collection regarding demographics, past medical history, family history, occupational history, home environment, hobbies, jewelry, tattoo use, use of personal care products, disease course and response to previous treatments (see Table 1 for key topics and relevant details to discuss when screening patients for ACD)[18-20].

Many ACD cases can be traced to occupation[20]. Certain professions-*e.g.,* health professionals, construction/factory workers, machinists, cooks, janitors, farmers, hair dressers, among others-have an increased risk of developing occupational ACD[21]. However, exposure to common industrial allergens, including cements, glues, plasters, and solvents, may also occur at home[20]. Gathering a history should include information about temporality (*i.e.,* when do symptoms worsen or improve) and location (*i.e.,* where is the patient when symptoms worsen or improve)[22]. For example, if symptoms improve on weekends or vacations, it suggests occupational relation. In contrast, symptoms that worsen during holidays or weekends may indicate recreational exposure to allergens.

Physical exam also provides important diagnostic clues. While dermatitis can have various morphologies, lesions typically present acutely as erythematous, edematous, or urticarial appearing papules, plaques, vesicles and bullae that become increasingly eczematous and weeping[18,23]. In areas with thinner skin (*e.g.,* eyelid, penis, and scrotum), lesions are more edematous, with fewer superimposed vesicles[18,23]. Intense pruritus leads to secondary changes of excoriation; subsequent impetiginization may also be observed. With persistent or repeated exposure, sub-acute or chronic ACD may develop. In sub-acute ACD, the skin remains erythematous and edematous as vesicles are replaced by erosions, oozing, crusting, and desquamation. With chronic exposure, the skin becomes dry, thick, and scaly with dermal infiltration, lichenification, and fissuring[23].

Table 2 Allergic contact dermatitis distribution and commonly associated sources of exposure[18,23]

Location	Type of exposure
Face/eyelids	Cosmetics, topical medications, or airborne allergens (volatile chemicals, sprays, dust, *etc.*)
Scalp/neck/posterior auricular folds	Hair dyes or shampoos
Sun exposed (face, upper chest, neck, arms)	Phototoxic or photoallergic reaction
Neck/upper chest	Fragrance in perfume or lotions
Hands	Occupational dermatitis (wet work or chemicals)
Trunk and axillary folds	Cloth dyes or textile exposure
Waist band	Rubber component of elastic waistband, nickel from belt buckle or buttons
Dorsal feet	Shoe chemicals (*e.g.*, rubber accelerators, potassium dichromate)

The inflammatory response is typically localized to areas directly in contact with the allergen. However, depending on the allergen sensitivity, the inflammatory response in ACD is well known for its ability to extend beyond areas of direct contact-a feature which distinguishes it from ICD[23]. Additionally, allergens have the potential for secondary transfer, leading to inflammatory presentation beyond the area of initial contact. This is typically seen as "kissing lesions" in flexor regions or areas touched by contaminated hands[23]. While the hands are the most common site for ACD, other common areas include the face, eyelids, lips, upper chest, arms, trunk and axilla, and dorsal feet. Recognizing distribution patterns can be a helpful in understanding ACD exposure (see Table 2 for examples of ACD location and distribution, as well as commonly associated sources of exposure)[18,23].

Histology

Cutaneous changes in ACD can also be observed histologically via light microscopy. Histologic evaluation is important to rule out other conditions that may otherwise clinically resemble contact dermatitis on physical exam. Characteristic findings depend on the severity of response to offending allergens and the time of biopsy after contact with allergen[18,24].

In acute ACD, the epidermis is normal in thickness, and significant inflammatory infiltrates can be observed perivascularly in the dermis[24,25]. Additionally, eosinophilic spongiosis is also a prominent feature - characterized by intercellular edema leading to disruption of intercellular bridging between keratinocytes[24,25]. Fluid accumulation progresses into intra-epidermal vesicles, while dermal perivascular lymphocytic infiltrate and blood capillary dilation result in dermal edema[25,26]. Other common histologic features include, hyperkeratosis, spindled and stellate dermal dendritic fibrohistiocytic cells scattered in the interstitium, and occasional Langerhans cell microgranulomas[24-26].

In sub-acute and chronic cases of ACD, histology is difficult to distinguish from nummular dermatitis or lichen simplex chronicus. Furthermore, while the histologic criteria of ACD occur reliably, they are relatively non-specific and are not readily distinguishable from ICD[18,24]. Sub-acute ACD is characterized by acanthosis and parakeratosis in the superficial cornified layer. Untreated or chronic cases are notable for epithelial ridges that become elongated and broadened. Biopsy is used most commonly for scientific research and is only clinically indicated in patients presenting with atypical symptoms in order to rule out alternative diagnoses (*e.g.,* cutaneous T Cell lymphoma). While histology can aid in diagnosis, current methods do not allow pathologists to readily differentiate ACD from other types of spongiotic dermatitis[27]. Ultimately, diagnosis relies on a combination of history, clinical findings, histology, and positive epicutaneous patch test results[23].

Patch test

Epicutaneous patch testing is the gold standard method for identifying contact allergies[14,28]. Initially a very time consuming process, a majority of patch testing now relies on emulsified gel systems with pre-loaded allergens coated on water impermeable polyester backings. Once applied, allergens are released onto the skin as the dehydrated gel becomes moisturized by transepidermal water. Exposure reactions are then examined at 48 h and re-examined at 72-96 h, directly linking particular contact allergens with hypersensitivity reactions.

Established in 1995, the thin layer rapid use epicutaneous (TRUE) test pioneered this new generation of standardized patch testing. Currently, it remains the only patch test system approved by the Food and Drug Administration. The TRUE test contains a negative control and 35 antigens which includes allergens responsible for up to 80% of clinical allergic contact dermatitis cases[29,30]. The convenience of the TRUE test has allowed for widespread use of diagnostic patch testing in academic centers and private practice dermatology offices. However, with over 4000 known contact allergens, relying on such a limited number of antigens will predictably result in missed diagnoses of ACD[14,29]. Many studies have highlighted this concern, such as Saripalli *et al*[31] who showed that only one quarter of patients would have all clinically relevant allergens identified with the TRUE test, while another quarter would have none identified at all. Similarly, a 2009 study by Warshaw *et al*[32] found that the 36 chamber TRUE test missed 26.7% of contact antigens, particularly common rubber and perfume allergens typically included in an extended 70 antigen panel. Given the TRUE test's restricted diagnostic power,

there is a growing emphasis on more comprehensive screening[19,29,30].

The North American Contact Dermatitis Group (NACDG) was among the first groups to pool ACD data in order to generalize the prevalence of reactivity to allergens in patch tests[7,30]. Based on these results, the most common allergens are selected biennially by consensus for the North American series panel-a larger 70 antigen patch test series[7]. An example of a popular addition to this larger series is fragrance mix Ⅱ (a combination of 6 perfume allergens), which in combination with fragrance mix Ⅰ has been shown to increase fragrance allergy detection by 30% more than fragrance mix Ⅰ alone[33]. Other efforts to raise awareness for contact allergens includes the dubious recognition of "Allergen of the Year," awarded annually by the North American Contact Dermatitis Society to draw attention to common, but under recognized contact allergens. Various dermatology organizations offer alternative patch test series, for example the International Contact Dermatitis Research Group utilizes the widely accepted European Standard patch test series[7]. Other series include the Minimum International Standard, British Baseline, and Japanese Standard.

Logistics and expense prevents including many allergens in a baseline panel. However, supplemental panels should be selected in order to include contact allergens with a higher pre-test probability of being positive according to a given patient's exposure risk (*e.g.,* bakery, dental technicians, hair dressing, metal implants, photochemicals, or metal working, *etc*). Hence, a detailed history is essential for identifying potential allergens. For example, if an allergen in the workplace is suspected, the occupational history needs to include details about the worker's job, their exposures at work, their use of personal protective equipment, work and skin care practices, the relationship of the symptoms to work, and whether other workers are also affected[22]. Examples of specialized series focused on particular industries or jobs include: bakery, dentistry, hairdressing, metal working, and photochemical panels. Examples of specialized series focused on particular chemicals include: acrylates, epoxy, isocyanates, metals, oils and coolants, plastics and glues, and rubber. Specialized trays have been found to have a clear added value, with studies finding 5% of plastics and glue allergies as well as 11% of rubber allergies going undetected by standard screening trays[34,35].

Despite the availability of patch testing and the relative technical ease of administering the test, there are limitations[14,29]. Reading patch test results in particular is dependent on practitioner skill and experience. The NACDG estimates the sensitivity and specificity of patch testing to be both below 85%, with a false positive range of 15%-18%[36]. This confusion often arises during evaluation of weak positive results. Cases of extensive erythema and induration make differentiation between ICD and ACD difficult, particularly in the face of unclear clinical relevance[14]. While ICD tends to decrease by reading at 72 compared to ACD, many cases will not change in appearance, stretching the limits of morphologic interpretation. According to guidelines for interpretation, ICD cannot be definitively ruled out, and ACD cannot be definitively ruled in[14]. In cases with unclear positivity or unclear clinical relevance, alternative tests such as repeated open application test (ROAT) and usage testing should be considered.

The ROAT utilizes one test allergen at a time without occlusion, minimizing rates of ICD and false positive reactions[3,14,37]. It requires the application of 0.1 mL of the test allergen to a pre-specified area (usually the antecubital fossa) twice daily for up to 28 d, or until an eczematous reaction pattern develops[37]. The ROAT allows practitioners to test the clinical relevance of previous patch test results. It is important to note that although a patient might display negative results when the allergen is applied on normal skin, ACD may still manifest during episodes of skin disease or damage[37].

Another alternative for negative or unclear patch test results is usage testing. This involves having the patient use a product with specific ingredients, in order to test sensitivity under real world conditions. This method allows for all factors that may predispose a patient for ACD (friction, damaged or pre-sensitized skin) to be tested[38]. However, this method of testing is limited because it is unable to distinguish an ICD *vs* ACD response. A discussion of proper methodology for patch testing with non-standardized allergens has been reviewed thoroughly by De Groot (2009)[39] Despite these limitations, patch testing remains the most reliable method of diagnosing ACD.

Confocal microscopy

A proposed alternative to patch testing is reflectance confocal microscopy (RCM)[40,41]. RCM is a relatively new non-invasive *in vivo* imaging technique that allows for real-time imaging of the epidermis and superficial dermis[11,40,41]. ACD and ICD are histologically very similar, and are not easily differentiated with traditional histologic methods. However, subtle differences do exist-with deeper, more prominent infiltrate and follicular spongiosis in ACD compared to ICD[11]. These distinctions are deemed less reliable and not histologically definitive given the risk of specimen damage during biopsy collection and the introduction of handling artifacts during fixing and staining[25,26]. In contrast, RCM allows evaluation of cellular and subcellular changes over time with serial observations of affected areas. Astner *et al*[40,41] demonstrated the ability to distinguish ACD from ICD, offering RCM as a promising alternative method of diagnosing ACD.

Once patch testing and clinical history both confirm ACD, measures should be taken to treat symptoms and prevent further exposure.

MANAGEMENT

Successful management of ACD necessitates both prevention and therapy, initially managing symptoms with corticosteroids, while allergen identification and avoidance education are completed[19].

Prevention

ACD prevention relies on allergen avoidance[19]. This requires eliminating exposure to substances clinically suspected and diagnostically confirmed to be causative from the home and work environment. Avoidance of the offending allergen(s) can drastically reduce incidence and severity of ACD[20]. However, even with avoidance, ACD can persist-this is particularly notable in patients with ACD caused by chromate in which less than 20% of cases clear after 10 years[42]. Protective equipment at work should be considered if symptoms or risk of allergen exposure persist. Barrier protection, such as gloves, safety goggles, and respirators, are effective for some workers[20,22]. If occlusive gloves are used regularly they may cause skin irritation. Cotton liners should be recommend to prevent the development of impaired skin barrier function[32].

In addition to barrier equipment, protective creams may also improve skin barrier function. Topical skin protectant (an emulsion with perfluroalkylpolyether) and quaternium 18-bentonite lotion can prevent urushiol-induced dermatitis, while creams containing the chelator diethylenetriaminepentaacetic acid can prevent nickel, chrome, and copper dermatitis[43]. However, in general there is mixed evidence for the effectiveness of pre-work barrier creams[44]. They may be more effective if used in combination with cleansing and after-work creams or emollients. Pre-work barrier creams should not be used by workers who wear latex gloves, because they may increase allergen uptake from gloves[19,43].

Education is an essential part of prevention. Holness *et al*[45] found that workers seldom receive health and safety training related to skin protection. Thus, it is important for practitioners to set aside ample time to counsel patients on allergen avoidance and barrier protection methods. Encouraging patients to read product labels in order to screen for ingredients is an important part of behavior modification. However, practitioners should recognize that ingredient names are complex and may make compliance difficult[19,46,47]. Physicians should consider using free web-based resources (*e.g.,* www.contactderm.org, www.allergyfreeskin.com, or www.mypatchlink.com) that provide patient-friendly education, including detailed lists of products free of patients' particular allergens in order to help improve allergen avoidance and quality of life[19,43,46]. While the efficacy of various forms of education remains unknown, failure to educate patients on how to avoid, or protect against, contact allergens may result in therapy regimens that are ineffective at controlling chronic ACD and episodes of relapse.

Therapy

Topical steroids are the mainstay of ACD symptomatic therapy. The spectrum of potency and ingredients allows the titration of treatment to match the severity and location of the dermatitis. The combination of barrier creams with moderate to high potency steroids have repeatedly been shown to successfully control ACD symptoms[43]. However, long term topical steroid use is often discouraged. In widespread or poorly controlled cases, short term pulse therapy paired with systemic corticosteroids may be considered to bring dermatitis under control rapidly. Additionally, in cases of secondary impetiginization, topical antibiotics (*e.g.,* mupirocin) or oral antibiotics, such as cephalosporin or penicillinase resistant penicillin, are appropriate[43].

Less well studied alternatives treatments include topical calcineurin inhibitors, ultraviolet light therapies (PUVA or UVB), or systemic immune modulating therapies (azathioprine, cyclosporine, methotrexate). Interestingly, since histamine is not a primary inflammatory mediator responsible for pruritus in ACD, anti-histamine treatments are less effective, and are often only prescribed for their sedating side-effects[14].

CONCLUSION

ACD is one of the leading causes of occupational skin diseases and significantly impacts quality of life. The best prognostic indicator for treatment of ACD is early recognition and intervention. Accurate identification of an offending allergen requires a detailed history of potential exposures and a physical examination to confirm the signs of ACD. Patch testing remains the gold standard for diagnosis, but is ultimately limited by the expertise of the clinician and the availability of relevant contact allergens. Management of ACD is multifactorial, relying on both prevention (eliminating allergen exposure, using protective equipment, and educating the patient) and medical therapy (typically topical corticosteroids).

While there continue to be significant improvements in our understanding of ACD, there is still much to be learned, particularly in the arenas of prevention and treatment. Patient education is critical for compliance with ACD prevention strategies. Future ACD management research should focus on the efficacy of various forms of patient education (handouts *vs* online resources *vs* healthcare led seminars, *etc.*). Additionally, ACD treatment is relatively limited to traditional corticosteroid regimens. The field would benefit from large, prospective longitudinal studies of alternative treatment techniques. Regardless of the research focus, studies that evaluate functional outcomes measures, such as time to return to work, would go far to enhance our understanding of the practical effectiveness of current management and treatment methods.

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MINIREVIEWS

Nicolau syndrome: A literature review

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Abstract

Nicolau syndrome (NS) is a rare cutaneous adverse reaction after intra-muscular or intra-articular injection. Clinical features of NS are presented by three typical phases (initial, acute and necrotic phases). The cause of NS is acute vasospasm, inflammation of arteries and thromboembolic occlusion of arteriole related various drugs. Many results of laboratory test, imaging studies and histopathology are reported and are associated with disease status. Three phase treatment is recommended for the patients with NS. Initially pain control and rule out differential diagnosis and in acute phase steroid therapy, heparin and pentoxifylline are useful. In necrotic phase, surgical treatment is needed depending on size of the affected site. NS is not well understood so far, however three phase treatment could lead to good result on basis of literature review.

Key words: Nicolau syndrome; Livedoid dermatitis; Embolia Cutis Medicamentosa; Drug hypersensitivity; Dermatitis; Diclofenac

Core tip: To our knowledge, there is no literature review of nicolau syndrome (NS) and we report this review article for understanding NS.

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INTRODUCTION

Nicolau syndrome (NS) (Embolia Cutis Medicamentosa or Livedoid dermatitis) is an uncommon cutaneous adverse reaction after intra-muscular or intra-articular injection of various drugs. NS was first reported in 1925 after the muscular injection of bismuth for the syphilis in the gluteal area[1,2]. The usual characteristics of the injected lesion are pain immediately after injection, subsequently erythematous lesion, livedoid and hemorrhagic patch, and NS leads to necrosis of skin, adipose and muscle layers. The syndrome has been related to the injection of various drugs, including non-steroidal anti-inflammatory drugs

Table 1 Clinical features and three phase treatment of nicolau syndrome

Phase	Clinical features	Treatment
Initial	Intense pain	Analgesics
	Erythema	Systemic antibiotics[1]
	Radiating pain	No ice pack
	Faintness, syncope	
Acute	Livedoid plaque	Systemic steroid
	Violaceous patch	Anticoagulant agent
	Non-necrotic	
Necrotic	Necrotic indurated plaque	Surgical debridement
	Ulceration with necrosis	Plastic surgery

[1]Systemic antibiotics: Until rule out cellulitis.

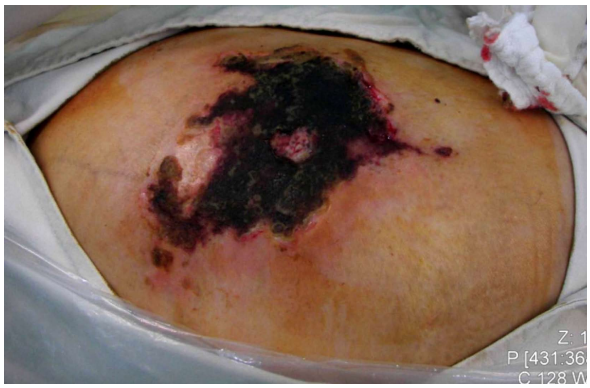

Figure 1 Photography of right gluteal lesion three weeks post injection illustrating the nature and extent of the eschar.

(NSAIDs), etancercpt, pethidine, antibacterial agents, chlorpheniramine maleate, corticosteroids, vitamin, sulphonamide, lidocaine, phenobarbital, chlorpromazine, thiocolchicoside and vaccines. To our knowledge, there were no literature review of NS and we report this review article for understanding NS.

RESEARCH

Literature search and selection criteria

The expansion of the search for this review was conducting during the last week of August 2014 using the MEDLINE (December 1966 to August 2014). The following medical terms were searched: "Nicolau syndrome", "Embolia Cutis Medicamentosa", "Embolic Cutis Medicamentosa", and "Livedoid dermatitis". Results were limited to human subjects, written in English (except one which is first described report by France), and published in peer-reviewed journals. There is one review article that is limited to children cases[3]. And 80 cases less than 12 years old was reported in Italian[4].

Clinical features

Clinical features of various patients suffering from NS are divided to three steps; initial, acute and necrotic phases (Table 1).

Initial phase of NS is presented by intense pain immediately or soon after the injection with a bluish discoloration[5]. Some patient complaints radiating pain to affected extremity or neurologic symptom such as peroneal neuropathy[6-9]. Faintness or syncope may occur[10]. Pain at the injection site is first sign subsequently erythema or hemorrhagic lesion and cutaneous necrosis or soft tissue and of the muscle develop eventually.

Acute phase occurs 24 h to 3 d later. In this phase, erythematous lesion develop at the injection site[11] or indurated painful livedoid plaque with the border of the violaceous and reticular plaque[12] develop. That is non-necrotic plaque or patch.

Necrotic phase as a final stage reveals that the injection site progress to violaceous, necrotic, crusted, indurated plaque. The lesion is progressing to erythema, swelling and tender induration with central necrosis. Finally necrotic phase comes 5 d to 2 wk. A painful indurated erythematous plaque with black necrosis[11,13] or a large necrotic skin patch with ulceration over the injection site is observed[6] (Figure 1).

The most common sites are the buttocks however NS also has been reported on the shoulder[10], thigh[14-19], knee, ankle, breast[20] and abdomen[21,22]. In some complicated cases, critical complications such as extensive skin necrosis, transient or persisting ischemic changes of the ipsilateral limb and several neurological deficit may occur.

Pathogenesis and etiology

Pathogenesis of NS is not clear but a vascular origin is the most reasonable hypothesis. Acute vasospasm, inflammation of arteries and thromboembolic occlusion of arteriole are the key mechanisms[12]. The leakage of around artery and neural space has been suggested as cause of intense pain. Moreover, sympathetic nerve stimulation and vasospasm lead to ischemic change and skin necrosis. Unintended intravascular injection of drugs also has been proposed as causing inflammation or thromboembolic occlusion of the arterioles. These may cause arterial intimal necrosis, destructure the arterial membrane and induced subsequently cutaneous necrosis[12,23]. Few patients with NS after intramuscular injection of diclofenac have been reported even though which is a commonly used NSAIDs. Diclofenac as a cyclo-oxygenase inhibitor inhibits prostaglandin synthesis and causes vasoconstriction. Therefore, a vasospastic effect of diclofenac is the suggested pathogenetic mechanism of NS[24].

Many drugs (Table 2) related to NS have been reported such as cyanocobalamin (vitamin B_{12})[12], lidocaine[20], vitamin K[17,18], etanercept[21], naltrexone[25], ketorolac[26], ketoprofen[27,28], meperidine[27], gentamycin[29], chlorpheniramine maleate[30], Trabit (phenylbutazone, salicylamide, dexamethasone and lidocaine)[31], triamcinolone[31], benzathine penicillin[23,31,32], salicylate bismuth[2], ibuprofen[2], Interferon β[5], penicillin G[12], thiocolchicoside[7], glatiramer acetate[22,33], piroxicam[8], DPT(diphtheria-tetanus-pertussis)[15], DTP-polio-Hib[14],

Table 2 Drug list related to nicolau syndrome

Drug	Target disease or symptom of using drug	Ref.	Duration of necrosis	Affected site
Naltrexone	Alcohol dependency	Perli *et al*[25]	Over 7 d	Buttock
Etanercept	Psoriatic arthritis	Guarneri *et al*[21]	10 d	Abdomen
Ketorolac	NS	Marangi *et al*[26]	2 wk	Buttock
Ketoprofen	Knee pain	Kim *et al*[27]	NS	Buttock
	COM	Lee *et al*[28]		
Meperidine	Operation site pain	Kim *et al*[27]		Buttock
Gentamycin	Elbow sprain	Kim *et al*[29]		Buttock
Chlorpheniramine maleate	Pruritus	Nischal *et al*[30]	7 d	Arm
Trabit	Back pain	Ruffieux *et al*[31]		Buttock
Triamcinolone acetonide	Lichen planus of scalp	Ruffieux *et al*[31]		Buttock
Salicylate bismuth	Syphilis	Corazza *et al*[2]	A few days	Buttock, thigh
Ibuprofen	Coxarthrosis	Corazza *et al*[2]		Buttock
Interferon β		Ozcan *et al*[5]	3 d	Arm
Benzathine penicillin	Cellulitis	Ruffieux *et al*[31]		Buttock,
	NS	De Sousa *et al*[32]	1 d	L/Ext.
		Ocak *et al*[23]		
Penicillin G	Fever and cough	Luton *et al*[12]	2 d	Buttock, L/Ext.
Cyanocobalamin		Luton *et al*[12]		Buttock
Thiocolchicoside	Back pain	Guarneri *et al*[7]	2	Buttock
Glatiramer acetate	Multiple sclerosis	Harde *et al*[22]	2 d	Lower
		Koller *et al*[33]		abdomen
Piroxicam	Ankle sprain	Lee *et al*[8]		Ankle
DPT	Vaccination	Erkek *et al*[15]	2 wk	Thigh
DTP-polio-Hib	Vaccination	Bégin *et al*[14]	2 wk	Thigh
Hydroxyzine	Itching	Gayken *et al*[16]		Thigh
Calcium hydroxide	Bleeding in the distal root canal	Willbrand *et al*[34]		Cheek
Lidocaine	Core needle biopsy on breast	García-Vilanova-Comas *et al*[20]		Breast
Vitamin K	Prematurity	Puvabanditsin *et al*[18]	2 wk	Thigh
Mesotherapy injections	Tendinopathy	Zaragoza *et al*[35]	3 wk	Knee

NS: Non-specific; COM: Chronic otitis media; Trabit: Phenylbutazone, salicylamide, dexamethasone and lidocaine; L/Ext: Lower extremity; DPT: Diphtheria-tetanus-pertussis.

hydroxyzine[16], calcium hydroxide[34] and mesotherapy injections[35]. However, diclofenac sodium is the major drug of NS.

Laboratory test

Blood result is unremarkable[6]. Initially there was no evidence of cellulitis. Some studies reported that The biologic markers suggesting muscle damage such as creatine kinase, myoglobin, aspartate transaminase, alanine transaminase and lactate dehydrogenase are elevated although white cell count, inflammatory markers and renal function were unremarkable[36]. Otherwise leukocytosis, increased serum glutamic oxalacetic transaminase, lactic dehydrogenase and myoglobinuria were found[12].

Imaging studies

Ultrasonography do not identify any definite abscess or sign of fluid collection[19,25] but shows an evidence of an area of diffuse edema within the muscles[2]. Necrotic lesion reveals a diffuse hyperechogenic area with inflammation involving the subcutaneous area and the muscles[11].

Computed tomography reveals a well-defined lesion of the diffuse adipose inflammation with central gas collection[25,37] However the muscle tissue is uninvolved and there is no liquid collection[24]. Extension of involved lesion is usually limited out of the muscular fascia[13,37].

Magnetic resonance imaging reveals a subcutaneous liquid collection up to the fascia and muscle tissue appears uninvolved[11] or only diffuse change of signal intensity in the adipose layer at the injection site showing extensive edema in the subcutaneous fat[36] in acute phase. Progressing to necrotic phase, MRI reveals focal muscle necrosis and the residual muscle edema[36] however the muscle is spared and there is no liquid collected under the eschar tissue in some case[38].

Histopathology

Histopathologic findings are mainly reported in necrotic

phase because surgical debridement is performed in this phase. Histopathology revealed fibrosis of adipose tissue, fat necrosis and predominantly eosinophilic infiltration[25] and inflammation infiltrating subcutaneous adipose tissue without any vasculitis or granuloma[5]. There is no evidence of malignancy or vasculitis[6].

Cultures

Bacterial, fungal and mycobacterial cultures were negative[8,,25,38] or resident flora[7,39]. Pseudomonas aeruginosa and Staphylococcus aureus[5,6,16,19,27,30]. Pseudomonas aeruginosa leads to use piperacillin intravenously[6].

Differential diagnosis

Initial differential diagnosis includes a local toxic reaction to drugs, acute bleeding and acute compartment syndrome[16,36]. Especially shoulder region is differentiated from cardiac problem checking an ECG, cardiac enzyme levels, and a chest radiograph[10]. Also the differential diagnosis includes vasculitis, fat embolism, left atrial myxomas and Hoigne syndrome[12]. Patients would be admitted for presumed cellulitis[12,16,25]. Misdiagnosis of cellulitis lead to use antibiotics and it can be failure of treatment for NS[12]. Suspicious malignancy has to be checked by surgical extirpation of the plaque of the lesion and biopsy for macroscopic examination[20].

Treatment

There is no consensus of treatment of NS so far. However we suggest the treatment of NS step by step as the three phases (Table 1). Phasic treatments depend on the extent of the necrotic lesion and ranges from medication to surgical debridement.

Initial phase: Because of severe pain, conservative pain control with analgesics and dressings is usually recommended. And differential diagnosis is most important in the initial phase. Ice pack application increases the acute focal vasospasm and can aggravate the disaster[10,40]. Until cellulitis of affected site is ruled out, systemic antibiotics are suggested. After any signs of cellulitis ruled out such as fever, elevated white blood cell count, C-reactive protein and erythrocyte sedimentation rate, prophylactic antibiotics might be useful.

Acute phase: Hypothesis of vascular origin and inflammatory sequelae is most reasonable. For this reason systemic steroid and anticoagulant agent are usually used[12,36]. Hyperbaric oxygen treatment was given to patient with the assumption of microarterial thrombi as well as heparin and pentoxyphilline[23]. Subcutaneous injection of heparin 5000 to 10000 U b.i.d.[12] and intravenous infusion of betamethasone diphosphate 24 mg/d induce improving symptom within 2 d[12]. Patient responses rapidly to methylprednisolone 1g IV q.d. or dexamethasone 32 mg intravenous injection for three days and pentoxifylline 400 mg PO t.i.d.[12]. Warm intermittent compression[12] is also recommended.

Necrotic phase: The patients with NS undergo surgical debridement of the affected skin, subcutaneous tissue and muscle in case of clinical and radiographic evidence of tissue necrosis[2,6,13,16]. And after the ulcerative necrotic lesion was filled with healthy granulation, split-thickness skin graft or reconstructive surgery were performed. Finally the wound healed well and uneventfully with atrophic skin scar or wound contraction[30].

Special condition

If the patient is necessary to maintain following drugs, continuation of treatment with glatiramer acetate at other injection sites is recommended[22,33]. Also further injection of etanercept at other site is tolerated without complication[21].

Prevention

Confirmation to extra-vascular leakage of the drugs is necessary to perform injection after having aspirated with the syringe[2]. And upper outer quadrant of the buttock area is the recommendable site for the intramuscular injection, which has fewer vessels[41].

CONCLUSION

Clinical differentiation alone is difficult to make a diagnosis of NS and the imaging and laboratory tests assist in the clinical decision[36]. By this literature review, three phase treatment is recommended for NS.

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MINIREVIEWS

New innovation of moisturizers containing non-steroidal anti-inflammatory agents for atopic dermatitis

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Abstract

Atopic dermatitis is a chronic, relapsing and extremely pruritic eczematous disease which commonly affects children. The standard management consists of a combination of anti-inflammatory drugs in adjunctive with skin care management particular moisturizer application. A concern for the side effects associated with long term use of corticosteroids has also been considered. There has been an emerging interest in moisturizer containing non-steroidal anti-inflammatory agents such as herbal extracts, vitamins, mineral and lipids. The *in vitro* and the *in vivo* studies of each agent were reviewed. The clinical study on the efficacy of moisturizers containing these agents were also demonstrated including the author's studies and clinical experience. These moisturizers might be considered as an alternative treatment in acute flare of mild to moderate atopic dermatitis.

Key words: Non-steroidal anti-inflammatory agents; Moisturizer; Atopic dermatitis

Core tip: The skin care management particular moisturizers play an important role in atopic dermatitis. The side effects of corticosteroids are limited in their use in this disease. Take together, a new moisturizer containing various anti-inflammatory substances have been developed to be used as an alternative treatment to avoid the side effects of corticosteroids. These agents are divided into herbal extracts, vitamins, minerals and lipids. The clinical trials on the effectiveness of these moisturizers were reviewed. The author's clinical experience also discussed.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing and extremely pruritic eczematous disease which commonly affects children and influences the quality of life.

The etiology of AD seems to result from a combination of barrier dysfunction, immunodys function, genetics, autoimmunity, *Staphylococcus aureus* and environmental factors[1].

The standard management of AD consists of a combination of anti-inflammatory drugs in adjunction

Table 1 Type of anti-inflammatory agents

Herbal extracts
Licorice
Glycyrrhiza inflate (Licochalcone A)
Glycyrrhiza glabra (Glycyrrhetinic acid)
Chamomile
Matricaria recutita (Bisabolol, chamazalene, apigenin)
Vitamins and minerals
Provitamin B5 (Dexpanthenol)
Vitamin B3 (Niacinamide)
Zinc
Lipids
Natural sources of lipids
N-palmitoylethanolamide extracted from palm oil
Linoleic acid extracted from:
Shea butter (*Butyrospermum parkii*)
Canola oil
Argar oil
Kernel oil
Spent grain wax
Portulaca oleracea Linn
Phytosterol extracted from shea butter
Synthetic lipids
Ceramides
Pseudoceramides

with skin moisturization and avoidance of triggering factors. A concern for the side effects associated with long term use of corticosteroids has also been considered.

For the past five years, there has been an emerging interest in moisturizer containing non-steroidal anti-inflammatory agents such as herbal extracts, vitamins, minerals and lipids. The anti-inflammatory property of these agents are demonstrated in *in vitro*, *in vivo* studies, as well as the clinical trials on the patients with AD, psoriasis and seborrheic dermatitis.

From the literature reviews of clinical researches on these moisturizers, they are divided into 3 groups according to the active ingredients of anti-inflammatory agents as follows: herbal extracts, vitamins, minerals and lipids (Table 1). The evidence of the clinical studies on the effectiveness of moisturizers containing anti-inflammatory agents are summarized in Table 2.

HERBAL EXTRACTS

There are two active ingredients extracted from two species of Licorice: (1) Licochalcone A (LA), extracted from *Glycyrrhiza inflate*; and (2) Glycyrrhetinic acid, extracted from *Glycyrrhiza glabra*.

There is an *in vitro* study that demonstrates that LA, a major phenolic component of *Glycyrrhiza inflate*, has anti-inflammatory as well as antimicrobial effects[2,3]. It could inhibit cytokines production from T cells and monocytes as well[2-4]. The study shows that LA could reduce shave-and ultraviolet (UV)-induced redness[4]. Moreover, the improvement of the rosacea patients is also reported in a clinical study in which skin care product containing LA was applied for 8 wk[5].

In 2010, Udompataikul *et al*[6], conducted a comparative trial of moisturizer containing LA and linoleic acid *vs* 1% hydrocortisone (HC) for the treatment of childhood AD. It was a randomized controlled-investigator blind study. LA lotion were applied on one side of the patients' body and HC lotion on the opposite side, twice daily for 6 wk. The clinical outcome was assessed using the scoring of AD (SCORAD) score. The relapse rate was recorded and analysed using survival analysis. Thirty patients were enrolled, 26 patients completed the protocol. The mean age was 5.8 years old. The average baseline SCORAD score was 28 on both sides (moderate severity). The response rate of both agents was 73.33%. There was no statistical significant group difference in the reduction of SCORAD score. Though the edema and erythema score in HC treated area had more rapid improvement than that of LA treated side, there was no significant difference. The relapse rate of HC-treated side was higher than that of LA-treated side. However, there was no significant difference. No side effect was observed from both agents. It was concluded that the effectiveness of moisturizer containing LA was equal to that of HC lotion. It could be used as an alternative treatment for both acute flare and in maintainance phase of mild to moderate childhood AD.

There was also a multicenter, randomized,split-side double blind study in 55 children between the age of 3 mo to 14 years with mild to moderate AD. It was shown that LA had a similar result in terms of improved SCORAD and reduces transepidermal water loss (TEWL) compared with 1% HC[7].

In 2014, Angelova-Fischer *et al*[8], designed a comparative study of moisturizer consisted of LA, linoleic acid, decanediol and menthoxypropanediol (LALDM) *vs* 1% HC for mild to moderate AD treatment. Twenty patients were included. The mean age was 26.2 years old (16-65 years old). It was discovered that LALDM and 1% HC can reduce SCORAD scores, pruritus, erythema, TEWL and increase in skin conductance without statistically significant difference between two groups. Moreover, LALDM can reduce *Staphylococcus aureus* colonization with statistically significant difference from 1% HC. Decanediol has antibacterial activity. Menthoxypropanediol, a synthetic derivative of menthol can improve the pruritic symptom by triggering cold-sensitive receptors in the skin which is responsible for cooling sensation.

Glycyrrhetinic acid also possesses anti-inflammatory property[9]. Abramovits *et al*[10], conducted a randomized, vehicle-controlled clinical trial to examine the effectiveness of MASO63DP cream, which composed of shea butter and Glycyrrheticnic acid, in the management of mild to moderate AD. 218 patients, age between 18-84 years old, were included in this 50-d study. The clinical outcomes were assessed using Eczema Area and Severity Index score and Investigator's Global Assessment. It was found that the incidence of rash

Table 2 Evidence of the clinical studies on the effectiveness of moisturizers containing anti-inflammatory agents

Ref.	Active ingredients	Design + Population + Age	Outcome measurement	Results
Udompataikul *et al*[6]	Licochalcone A, LA	Randomized controlled-investigator blind; *n* = 28, mean age = 5.8 yr old (2-15 yr old)	SCORAD score	Response rate 73.33% The effectiveness of LA was equal to 1% HC
Wananukul *et al*[7]	Licochalcone A, LA	Randomized, double-blind, split-side, study *n* = 55, age 3 mo-14 yr old	SCORAD score, TEWL	The effectiveness of LA was equal to 1% HC
Angelova Fischer *et al*[8]	LALDM	Randomized controlled-investigator blind, study; *n* = 20 mean age = 26.2 yr old	SCORAD score, TEWL, skin -conductance, *Staphylococcus aureus* colonization	LALDM was equal to 1% HC, and LALDM can reduce *Staphylococcus aureus* colonization
Abramovits *et al*[10]	Glycyrrhetinic acid, shea butter (MASO63DP)	Randomized, vehicle-controlled study; *n* = 218, age 18-84 years old	EASI score, IGA	The effectiveness of MASO63DP was more effective than vehicle
Boguniewicz *et al*[11]	Glycyrrhetinic acid, shea butter (MASO63DP)	Randomized, vehicle-controlled study; *n* = 142, age 18-84 yr old	EASI score, IGA	The effectiveness of MASO63DP was more effective than vehicle
Udompataikul *et al*[20]	Dexpanthenol, petrolatum	Open label; *n* = 30 mean age 7.19 yr old	SCORAD score	The effectiveness of dexpanthenol ointment was equal to 1% HC
Eberlein *et al*[30]	PEA, phytosterol ceramide in dermal membrane structure	Multicenter study (moisturizers as adjuvant treatment) *n* = 2456 (adult 1533, children 923)	Clinical and pruritic VAS	Pruritus reduction (VAS), Improvement of sleep quality, Reduction of previous use of topical corticosteroid were significant difference
Udompataikul *et al*[20]	Linoleic acids from Spent grain wax, shea butter, argan oil; phytosterols (LP)	Randomized investigator blind; *n* = 31, age = 4.24 yr old	SCORAD score	The effectiveness of LP was equal to 1% HC
Lee *et al*[40]	Multilamellar emulsion – pseudoceramide, type III synthetic ceramide (PC)	An open crossover study	Clinical	PC cream was more effective than urea cream

LA: Linoleic acid; SCORAD: Score of Atopic Dermatitis; EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment; TEWL: Transepidermal Water Loss; VAS: Visual Analogue Scale; LALDM: Licochalcone A, linoleic acid, decanediol menthoxypropanediol; PEA: N-palmitoyl ethanolamine.

was 2.1% in MASO63DP group *vs* 5.5% in the vehicle group. MASO63DP was statistically more effective than vehicle. Two patients discontinued using MASO63DP because of an adverse effect[10]. Boguniewicz *et al*[11], also conducted the same clinical study in 142 childhood AD patients. It was concluded that MASO63DP is an effective monotherapy for mild to moderate AD in infant and children[11].

Chamazulene (terpenoids) is a major active ingredients extracted from chamomile (*Matricaria recutita*). It possesses anti-inflammatory property by inhibiting histamine release from mast cells and leukotriene B4 from white blood cells[12,13]. In addition, Apigenin, flavonoids agents found in chamomile also has anti-inflammatory and antioxidant effect[14]. It was discovered that these active agents decrease UV induced erythema[15]. Chamomile is commonly used as an active ingredient in combination with Zinc or dexpanthenol (DT) in protective cream for irritant contact diaper dermatitis.

VITAMINS AND MINERALS

DT, an alcoholic analog of pantothenic acid, as water-in-oil emulsion, is rapidly penetrated through the skin[16]. Pantothenic acid is essential for normal epithelial function and is a component of coenzyme A, a cofactor for catalytic enzyme in carbohydrate, fatty acid, protein, sterol and porphyria metabolism[17], 2%-5% of DT acts like a humectant moisturizer[17-19]. It was shown that DT has anti-inflammatory action on UV-induced erythema and irritation model[17]. Furthermore, DT plays an important role in wound healing by activation of fibroblast proliferative and acceleration of re-epithelization. The ointment consisted of 2%-5% DT is effective for the treatment of burns, anal fissures, leg ulcers, diaper dermatitis, and sodium lauryl sulfate induced irritant contact hand dermatitis in AD patients[17]. The comparative study of 5% DT in w/o emulsion *vs* 1% HC ointment in the treatment of mild to moderate childhood AD was also investigated[20]. Thirty patients with mean age of 7.19 years old enrolled.

Twenty-six patients completed the study. The results exhibited that the efficacy of DT and HC to reduce SCORAD scores were not significantly different at the end of the study (week 8). However, HC could relieve edema faster than DT with a significant difference (within week 1 *vs* week 2 respectively). Hence, this study also demonstrates that DT has a beneficial role as an alternative treatment in mild to

moderate severity of childhood AD.

Niacinamide (vitamin B3) demonstrates anti-inflammatory action by inhibiting the histamine release from mast cells[21]. It also increases ceramides biosynthesis and other stratum corneum lipids to improve the epidermal barrier function[22]. Zinc exhibits the anti-inflammatory response by blocking cytokine release from monocytes[23]. It is commonly used in the barrier cream for the treatment and prevention of irritant contact diaper dermatitis.

LIPIDS

Lipids with the occlusive effect, help prevent TEWL from the skin. As a result, it keeps the skin moist. The types of lipids which possess anti-inflammatory properties are as follows.

Natural sources of lipids

N-palmitoylethanolamine: N-palmitoylethanolamine (PEA), a fatty acid derivative that belongs to the family of N-acylethanolamines. PEA used in commercial moisturizers, is extracted from palm oil. It is physiologically produced by keratinocyte and is found in the stratum granulosum of human skin. The major roles of PEA are to be used as an anti-inflammatory, antioxidant and analgesic compound. The mechanism of action is *via* cannabinomimetic action on cannabinoid receptors (CBR) located on mast cells and cutaneous nerve fibers[24,25]. CBR agonists significantly decrease histamine induced pruritus and vasodilatation after they are topically applied on the skin[26]. An anti-inflammatory action of PEA was clinically demonstrated. PEA was incoperated into a lamellar matrix cream which was used in these studies. It was shown that this cream could alleviate the irritative facial skin lesions[27] and uremic pruritus[28]. Moreover, HC cream and this cream were equally effective in 18 patients with mild to moderate AD[29]. A recent 6-wk multicenter trial study illustrated that intensities of erythema, pruritus, excoriation, scaling, lichenification and dryness were significantly reduced with a combined score of 58.6% among the whole group of patients according to the doctors' reports. A pruritus reduction on visual analogue scales from 6 d through 6 wk of treatment with significant difference from baseline was reported, and the patients' sleep quality was significantly improved as well. Previous use of topical corticosteroids were significantly reduced by 56% while the average weekly application rate decreased by 62%. Therefore, this cream demonstrates a benefit in the AD management[30].

ESSENTIAL FATTY ACIDS AND STEROLS

Essential fatty acids like Omega 3, Omega 6 and sterols as phytosterols possess an anti-inflammatory property. They help reduce the production of prostaglandins. They are found in the seeds of many plants, including shea butter, spent grain wax, argan oil, kernel oil, canola oil[31], as well as in the roots, leaves and stems of purslane *(Portulaca oleracea* Linn)[32,33].

Recently, the study of moisturizing cream consisted of linoleic acids from spent grain wax, shea butter, argan oil and phytosterols from shea butter has been conducted in 31 patients with mild to moderate AD. The mean age was 4.24 years old. It was also shown that this cream is equally effective to HC. Thus, it is considered as an alternative monotherapy for childhood AD with mild to moderate severity[34].

Synthetic lipids

Natural stratum corneum ceramides structurally consist of a polar amide group and non-polar alkyl chains. They are capable of assembling to form the lamellae[35]. However, since the natural ceramides are extremely expensive and difficult to formulate, the new pseudoceramides, for example 1,3-bis-(N-(2-hydroxyethyl)-palmitoylamino)-2-hydroxypropane, have been developed[35]. Pseudoceramides have similar molecular properties to ceramides. The synthetic ceramides have been developed as well.

Park *et al*[36], discovers that the molecular organization of multilamellar emulsion-pseudoceramide and type Ⅲ synthetic ceramide as characterized as the lateral hexagonal phase are similar to the human stratum corneum intercellular lipid. Moreover, synthetic ceramides show anti-inflammatory effect both in *in vitro* and *in vivo*, and prove to be beneficial in an animal model of AD[37-39].

There was a clinical comparative study on anti-inflammatory property of multilamellar emulsion containing pseudoceramide and synthetic ceramide (ME) *vs* urea cream. It concluded that ME cream was more effective than that of urea in mild to moderate childhood AD[40].

AUTHOR'S CLINICAL EXPERIENCE AND COMMENTS

From author's clinical practice experience, corticosteroids, calcineurin inhibitors and moisturizer skin care are standard treatment for AD patients. Nevertheless the moisturizers containing anti-inflammatory agents can be used as an alternative treatment instead of corticosteroids or calcineurin inhibitors in mild to moderate severity of AD patients, and in the maintenance phase as well. They are particularly suitable for some selected cases whose parents are corticosteroid phobia. However, the anti-inflammatory responses especially, the edema and erythema parameter might be slower than corticosteroids. This information should be informed to the patients. In these particular cases, when these moisturizer that contained anti-inflammatory agents were used to treat as an alternative first line of treatment for a couple of weeks with slow response rate, the

corticosteroids should be added on. It was found that these moisturizers could reduce the frequency of corticosteroids use in the treatment.

CONCLUSION

Because particular skin care moisturizers play an important role in AD management, the side effects of an anti-inflammatory agents like corticosteroids are limited in their use in AD. Taken together, new moisturizers containing various substances have been developed to be used as monotherapy in mild to moderate AD. These agents are herbal extracts, vitamins and minerals and lipids. They can be used as an alternative treatment and in the maintenance phase of AD. The further researches for new anti-inflammatory substance should be conducted.

However, the long term side effect of the treatment with these moisturizers should be warranted, and the pricing of these moisturizers should also take into consideration.

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CASE REPORT

Identifying and managing naevus dysmorphia in clinical practice

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Abstract

Naevus dysmorphia is a form of appearance concern/body image dissatisfaction, which describes a preoccupation with the appearance of a clinically small melanocytic naevus. The naevus is perceived by the patient to be disfiguring. Such perception leads to maladaptive behaviours and is often associated with low mood, as well as high levels of anxiety and social avoidance. Affected individuals form a diverse group. However, what they have in common is that the distress experienced is disproportionate to the objective visual appearance of the mole. There is a range of severity of the impact on the individual's well being. Naevus dysmorphia may or may not be a cutaneous manifestation of body dysmorphic disorder (BDD). It is essential that patients with naevus dysmorphia are identified and distinguished from patients requesting removal of a mole for other uncomplicated cosmetic reason. Patients with naevus dysmorphia can be challenging to treat and communicate with. Surgical excision of the naevus will not address the underlying psychopathology and so it may not result in long-term positive outcome. Ideally, a detailed psychological assessment and formulation can be made potentially followed by psychological therapy tailored to the needs of the individual. A therapeutic trial of appropriate psychopharmacological course may be indicated in certain cases, *e.g.*, when symptoms of a depressive disorder, anxiety disorder or BDD are present. A case series of 10 patients with naevus dysmorphia is presented, in order to highlight the above issues.

Key words: Naevus dysmorphia; Body dysmorphic disorder; Body image dissatisfaction; Psychological distress

Core tip: Naevus dysmorphia is a form of body image dissatisfaction. A preoccupation with a simple melanocytic naevus that causes significant distress to the individual and impacts on their wellbeing are central features. Symptoms are often consistent with body dysmorphic disorder but the impact can be less severe. Patients tend to present to dermatology or

cosmetic surgery requesting removal of a mole. An extended history is needed to fully assess the perceived "problem". Excision alone will not necessarily address the underlying psychological issues. Liaison with clinical/health psychology and/or psychiatry can be desirable in individual cases.

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INTRODUCTION

Naevus dysmorphia is a specific form of body image concern/appearance concern, which describes a morbid preoccupation with the appearance of a clinically small melanocytic naevus, which the individual is convinced is unsightly resulting in distress, behavioural adaptations and negative impact on their wellbeing. An extended history is desirable including assessment for associated psychiatric disorders including body dysmorphic disorder (BDD), depressive disorder and suicidal ideation. Patients often present to general or cosmetic dermatology or cosmetic surgery clinics requesting surgical removal of the "offending" mole. Simple excision does not necessarily address the underlying reasons for the person's overvalued perceptions of their appearance and preoccupation with the feature. A detailed psychological assessment and appropriate psychological therapy is recommended.

We are not aware of any previous detailed descriptions or case series of naevus dysmorphia *per se*.

CASE REPORT

Patient 1

A 16-year-old girl presented with 2 moles on her right arm and 2 moles on right lower leg which she had found "disgusting". The appearance of the moles had distressed her to such an extent that she bought Dermatend®[1] on the internet and treated the areas in an attempt to remove them. Dermatend® contains the escharotic agent *Sanguinaria canadensis* which has been marketed as a skin tag and mole remover. On attendance at clinic it became apparent that she was generally distressed by the appearance her skin (cutaneous dysmorphia) stating that "she hated her pale skin and all her moles" and wished to have 3 further moles removed from her face.

Excision of the pink plaques at the site of the Dermatend® application was performed in order to obtain a histological diagnosis. A discussion around body image disorders appeared to be productive and a referral to health psychology was made. However, the patient did not attend for psychological therapy and was lost to follow-up.

Patient 2

A 36-year-old man presented with a small intradermal naevus above his left eyebrow. He had previously undergone multiple minor surgical procedures to correct perceived defects including 2 rhinoplasties and removal of a chickenpox scar. The index mole was small and inconspicuous, but was causing him such a high level of anxiety and distress that he stated he would "remove it himself with a kitchen knife", if he was not offered excision. Significantly, he had been recently removed from his GP register for aggressive behaviour.

He had had a shave excision of the naevus due to the favourable risk:benefit ratio. He was also referred to health psychology, but he failed to attend.

Patient 3

A 29-year-old woman presented with multiple small melanocytic naevi on her left check, neck and left lower lip. She appeared very self-conscious of the appearance of the moles and described them as "ugly". She had adopted safety behaviours, such as covering her face with her hands regularly to hide the moles and constantly checking her appearance in the mirror. Her husband reassured her constantly that she "looked fine" and that he did not notice the moles.

Interestingly, she had a skin graft on her left neck following a burn in childhood adjacent to one of the problematic moles. However, the appearance of the graft did not seem to concern her, despite it being more obvious to the onlooker than the mole (Figure 1). She retained good insight of the fact that other people did not view the moles in the same way as she did. She had a shave biopsy of one mole and engaged in a course of cognitive behavioural therapy with good outcome.

Patient 4

An 18-year-old girl presented with a 1 cm congenital melanocytic naevus on her left thigh which she found "repulsive".

She had become more concerned with the appearance over the past 4 years and had started to adopt avoidance behaviours, such as wearing tights and avoiding swimming, in order to conceal the appearance of the mole. She reported doing gymnastics as a child and being ashamed to wear a leotard out of fear that the mole would be exposed. She recalled that her mother had advised her to "cover it with a plaster". She was reassured of the benign nature of the mole and warned of the risks of excision including unpredictable scarring, bleeding and surgical site infection. Nevertheless, she remained adamant that she "must have the mole removed". She did not wish to undergo a psychological assessment. A separate referral was made by the GP to plastic surgery, who excised the mole.

Patient 5

A 16-year-old hairdresser presented with a mole on

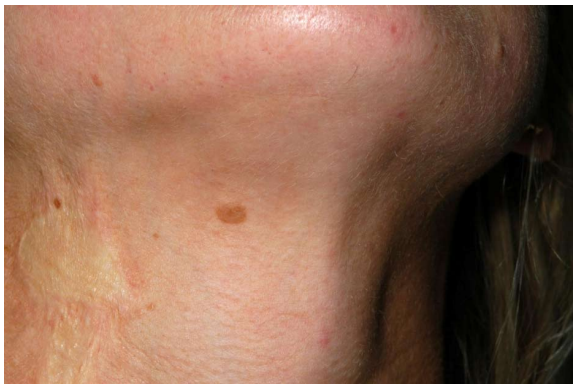

Figure 1 The skin graft following childhood burn is more obvious to the onlooker than the neighbouring naevus that this 29-year-old woman perceives as "ugly".

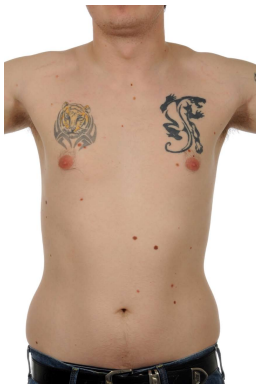

Figure 2 Multiple small, banal naevi on trunk and 2 large, conspicuous tattoos on right and left chest.

her left cheek. Over the past year she had become more aware of the mole. She described it as "dirty and horrible." She stated that the mole was "all she could see when she looked in the mirror" and that she would be keen to remove it herself, if this was possible. She always wore heavy make-up and smiled as much as possible to try to hide the mole in the left nasolabial fold. She was advised of the risks of unpredictable scarring on a prominent part of the face and surgical intervention was not performed. She was offered referral to health psychology for further assessment and psychological therapy, but she declined.

Patient 6

A 16-year-old school girl presented with concern about the appearance of a small mole on her left infraclavicular skin which she had "hated" for 6 years. When she said or heard the word "mole" she her felt nauseous. She refused to expose the mole in public. She missed physical education classes and avoided wearing low-cut tops. On further enquiry, she also had significant concerns about several other aspects of her appearance, including "a big nose", "large forehead, and "oily skin", despite minimal objective findings. Depressive symptomatology with suicidal ideation were present. She did engage with clinical psychology and psychiatry and her psychological symptoms improved using a multidisciplinary approach (excision of the naevus, Cognitive Behavioural Therapy, and oral fluoxetine).

Patient 7

A 48-year-old woman presented with distress about the appearance of a mole on her cheek which had several terminal hairs growing within it. She thought about this mole every day and became anxious with social avoidance behaviours and ideas of reference, *i.e.*, that people were noticing it and thinking it was "horrible". She lived with a daily fear of negative evaluation of this mole. She had a past history of depressive disorder and panic attacks. A simple excision biopsy was performed. A discussion and psycho-education about body image and appearance distress was provided. The patient reported increased wellbeing 2 mo post-treatment at review.

Patient 8

A 28-year-old single woman demanded removal of multiple small moles from her body. She described these as "disgusting". She claimed they had caused her to become depressed and unable to take appropriately care of her 3-year-old daughter on holiday. She said she had always "hated" her moles since her early teens. She avoided socialising and attributed this to her moles, which she considered "very ugly" and "making her look like a Dalmatian". She blamed her moles for the fact that she can't look after her child properly. She had a history of depressive disorder, self-harm and recreational drug misuse. She felt that removing all her moles would "fix" many of her problems in life. She threatened with suicide if she was refused excision. It was felt that her expectations were not realistic and a referral to health psychology was suggested in the first instance. However, she declined psychology referral and was lost to follow-up.

Patient 9

A 24-year-old single man, had asked his GP if he could have all his moles removed as he "hated" them so much. He said he'd "rather have lots of scars than lots of moles". He was very anxious about going on holidays abroad, because he felt unable to take his top off at the beach or swimming pool. He attributed this to the shame he felt about his appearance. He avoided communal changing rooms or showers. He had a significant history of childhood psychological trauma.

On skin examination of his torso, several large tattoos were noticed (Figure 2). On further discussion he disclosed that he used tattoos to distract attention from the moles. In specific, he said that he "got tattooed to try and take people's eye off the moles", so they "noticed the tattoos more than the moles". An excision biopsy of a naevus on the right flank was

Figure 3 Muscular body habitus, several small melanocytic naevi and 4 tattoos.

performed. This mole was particularly troubling him aesthetically. Efforts were also made to engage him in psycho-education about body image concerns. Referral to a Clinical/Health Psychologist was also suggested. However, the patient was lost to follow up.

Patient 10

An 18-year-old man presented as extremely self-conscious about moles on his trunk, especially on his back, since the age of 13 years old. He said he had avoided swimming ever since. He exhibited several avoidance behaviours, *e.g.*, persistently avoiding mirrors and refraining from using communal changing rooms. He was a body builder and had developed striae distensae around anterior axillary folds. On enquiry, he presented with considerable insight into his unhelpful perception about his skin and felt that his concerns may appear "stupid" to others. However, he was unable to change his beliefs and behaviours. He had a large circumferential tattoo on his left arm and another group of tattoos across his shoulders and right wrist (Figure 3). He said the reason for his tattoos was to distract his and others' attention from the moles. However, despite this, he still thought about his moles every day, including the ones in the tattooed areas. Two naevi were excised from his back. Discussions around his body image were productive and advice on coping mechanisms was provided, whereas web-based cognitive behavioural therapy was suggested mainly to improve self-confidence and help reframing his negative thoughts about appearance.

DISCUSSION

This case series illustrates a range of manifestations of naevus dysmorphia. The discrepancy between objective/clinical (visibility of the naevus) and perceived "severity" is common to all cases, as are obsessive thoughts, preoccupation, and social anxiety/avoidance. The use of emotionally charged language, such as "horrible" or "disgusting", to describe the appearance of the naevi is another common feature. Non-attendance at clinic follow-up was common, which may be due to avoidance or denial of underlying emotional issues perhaps. In some cases there was a history of negative life events. In some cases there was associated low mood, self-harm and suicidal ideation, as well as anger/frustration. In our clinical experience, in most cases, the issues around the egosyntonic nature of naevus dysmorphia were striking, *i.e.*, the statements and experiences about the naevi and the skin are actually reflective of basic cognitions and emotions about the self. This is further demonstrated by the use of emotionally charged language these patients use to describe their naevi, *i.e.*, "hate, ugly, horrible, disgusting, repulsive", *etc.*, which are indicative of their low self-worth and point towards deeply seated feelings of shame about the self. When such feelings are verbalised during appropriate treatment positive outcomes can occur with great relief[2].

As depressive symptomatology, anxiety, shame and guilt can be indicative of psychological trauma, one could suggest that the above presentations might be manifestations of previous or ongoing complex and relational psychological trauma presentations. Psychological trauma in skin disorders and dermatology in general is largely under-researched. Some of the authors are currently undertaking a pilot study to establish the prevalence of psychological trauma in dermatology (AF and ZC). The findings of this investigation will be presented elsewhere.

In put clinical experience, the self-concept of the individual underlies their presentation and may explain the range of reactions and prognosis. The self-concept, *i.e.*, how we see ourselves and how we think others see us, is very complex and evolves across the lifespan, with many factors both genetic and acquired contributing. The self-concept may be especially brittle in adolescence when a degree of appearance concern is common[3].

Modern society's rigid "Barbie doll" stereotypes of health and beauty likely contribute to unrealistic expectations regarding appearance, which contribute to appearance-related concerns[4]. Children and adolescents are exposed to images of certain body sizes and shapes portrayed by the media, where some features are depicted as more beautiful and desirable than others, *e.g.*, being very slim, having "flawless skin", no body or facial hair and looking eternally youthful[3]. Other influences on body dissatisfaction include parents' beliefs and behaviours and peers/social interaction. Genetic and neurochemical factors may have a role to play. Previous psychological trauma, which may not have been previously disclosed, may also contribute to body image anxiety and associated low self-esteem. Psychological trauma could also account for persistent and treatment resistant symptoms of depression and anxiety. By adolescence, some individuals are so anxious about their appearance that they seek to alter it by seeking cosmetic surgery, dieting to lose

weight, taking supplements or even anabolic steroids to increase muscle mass or performing excessive exercise regimens to try and achieve "the perfect figure". These behaviours are thought to be a response to an internalised sociocultural appearance ideal[5].

"Clear" skin is considered beautiful and desirable by many adolescents especially girls. Any minor blemish, such as a mole, may be considered undesirable. In certain individuals, their beliefs, feelings and behaviours around the mole start to impact considerably on daily life.

When meeting a patient with disproportionate concern about the appearance of a small naevus, the dermatologist is called to be psychologically-minded and take a detailed history. Relational skills are vital with good communication being crucial in developing a therapeutic relationship based on person centred care, *i.e.*, developing trust, empathy and acceptance of the patent's individual circumstances and needs.

A discussion around the topic of "body image concern" is useful in patient engagement. Appearance value and valence are important topics. In specific, a person may think he/she is not good looking, but, if appearance does not matter that much to them, then they will not be as distressed as someone else for whom appearance is a key aspect they use to define their self-worth. When "red flags" are found that suggest severe appearance distress and BDD[6], *e.g.*, significant preoccupation, marked distress, lack of insight into the unrealistic nature of the cognitions about the naevus, extreme behaviours or avoidance related to the mole, regular checking behaviours, and large negative impact on daily life, then referral to psychiatry is desirable. However, in practice, the threshold for diagnosing BDD remains subjective and differentiation from "normal"-albeit excessive-appearance concern can be difficult.

The three diagnostic criteria for the diagnosis of BDD are[7]; (1) Preoccupation with some imagined defect in appearance or markedly excessive concern about a slight physical anomaly; (2) The preoccupation causes clinically significant distress or impairment in social, occupational or other important areas of functioning; and (3) The preoccupation is not better accounted for by another psychiatric disorder.

The presence of disabling anxiety or depressive symptomatology, excessive concern about other aspects of body image, history of psychological trauma, history of mental illness, history of extreme dieting or self-induced vomiting/use of laxatives and/or diuretics for weight control, suicidal ideation[8]/self harm or suicidal attempts should prompt further assessment by clinical psychology or psychiatry. An empathic non judgemental approach is needed to facilitate engagement. A discussion around and psycho-education about the pros and cons of surgically excision of the mole is necessary. In individual cases when the risk: benefit ratio is favourable then excision might be a reasonable and even beneficial course of action.

It is desirable for Dermatologists to have a good up-to-date understanding of the psychology of appearance and appearance concerns, over and above BDD alone. A proportion of 65% of patients with BDD will present with a perceived defect on their skin and will attend Dermatology outpatient clinics[9].

A study by Phillips had shown that 11.9% of 268 patients attending dermatology outpatients screened positive for body dysmorphic disorder which is significantly higher than the general population level of 1%-2%[10].

BDD is undoubtedly a serious concern in dermatology. However, an understanding of the wider range of appearance distress and body image dissatisfaction is also very important, if we are to make effective, safe and person centred clinical decisions. Management of patients with naevus dysmorphia is challenging. On one hand, simply reassuring the patient and discharging will often result in "doctor-shopping" for another opinion, in seeking private treatment or in often risky attempts of "home treatment". On the other hand, simply excising the lesion will not cure the problem as it does not address the underlying body image concern and the vicious circle of anxiety, low mood and anxiety, which can eventually lead to "revolving door" effects or disengagement with health services. The situation needs to be handled gently and empathetically. It is essential that the patient feels that you are on their side and want to help, rather than against them. Therefore, engaging the patient is the first step, whereas normalization, *i.e.*, explaining that other people have similar problems and have managed to manage effectively, as well as psycho-education about appearance distress and how best to cope with it are essential. Psychology referral might also be required for some patients. There are several treatment options which need to be tailored to the individual and the level of insight that they retain. These include surgical removal of the lesion, psychological therapies, and use selective serotonin uptake inhibitors. Several of these options can be used alone or in in combination and a pragmatic approach is often required.

Physical removal of a mole BBD is controversial. A study carried out by Philips examined medical or physical treatment, *e.g.*, removal of a lesion in patients with BDD. Twelve out of 16 patients in the study had a lesion excised and 75% of these did not report a change in symptoms of BDD. However, a second study by Mühlbauer *et al*[11] showed that there was a subset of patients that would benefit from removal a lesion and derived criteria for excision of lesions in BDD patients. They found patients with mild BDD, and a minor lesion, with realistic expectations of a simple procedure for a real, albeit minor defect would benefit from surgical excision[11].

COMMENTS

Case characteristics

Ten patients with obsessive thoughts, social anxiety and behavioural changes

related to a disproportionate distress about the appearance of a clinically small mole.

Clinical diagnosis

Patients with naevus dysmorphia clinically have a small benign naevus or a number of naevi.

Differential diagnosis

The differential diagnosis is severe and often complex appearance concern or body dysmorphic disorder.

Treatment

Removal of the naevus may be considered, but is cautioned when patient expectation is unrealistic and psychological "red flags" are present.

Related reports

Readers can get further information from texts on body dysmorphic disorder and the psychology of appearance.

Term explanation

Dysmorphia–a disproportionate concern regarding an aspect of appearance [as been used in conjunction with muscle, acne and skin (cutaneous) previously in the literature].

Experiences and lessons

The paper highlighted main challenges in patient engagement, the blurred boundary between expected and pathological appearance concern and the lack of evidence to know when excision of the mole is safe, reasonable and justified, and when it is cautioned or contraindicated. Dermatologists need to be aware of the discrepancy between perceived and clinical severity and how this is manifested in patients with suspected naevi dysmorphia and other similar types of appearance disturbances. Being able to assess psychological "red flags" within the context of a non-judgmental and trusting therapeutic relationship are key for safe, effective and person centred clinical management of patient with such difficulties.

Peer-review

This is an interesting case series report concerning one naevus dysmorphia which is a traumatic problem of many people in "postindustrial society". The considerable value of this work is presentation of psychological and sociological aspects of this body dysmorphic disorders, because these questions are often passed over in publications concerning somatic diseases.

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