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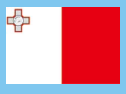

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FIELD OF VISION

Specificity in the alteration of lesional and non-lesional skin lipids in atopic dogs

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Abstract

The present paper is in the same time an overview of the literature concerning the alterations of lipids in the stratum corneum (SC) of atopic dogs and a review of data based on our publications. Knowing the importance of the SC barrier function for against pathogens in atopic dermatitis, we show for the first time a detailed biochemical analysis of lipids corresponding to the same amount of proteins in the successive layers of canine SC taken using tape stripping and their specificity as compared to humans. Also we show new results concerning the changes in the composition for protein-bound ceramides, and for the other lipids in involved and non-involved skin areas in atopic dogs. We show how a topical or oral treatment can restore the SC lipid composition and reconstruct the barrier integrity by up-regulating the biosynthesis of protein-bound ceramides.

Key words: Atopic dermatitis; Dogs; Glucosylceramide; Lipids; Ceramide; Stratum corneum

Core tip: The review concerns the literature on modifications of sphingolipids in the stratum corneum (SC) of atopic dogs. We gave for the first time a detailed biochemical analysis of dog lipids in the successive layers of the SC take by tape stripping, and discussed their specificity by comparison to humans. We showed also the specific composition in protein-bound ceramides and the importance of CerOS in dog skin for barrier integrity. The lipid composition of involved and non-involved skin areas in atopic dogs was described and we showed how a topical or oral treatment can restore the lipid composition of SC and reconstruct the barrier integrity.

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SPECIFICITY OF THE STRATUM CORNEUM ORGANISATION IN DOGS

Stratum corneum (SC) is the outmost layer of the epidermis. It comprises a unique structure made of protein-enriched corneocytes embedded in a lipid-enriched extracellular matrix.

Table 1 Ceramide types of the stratum corneum

Sphingoid base fatty acid	Sphingosine (S)	Phytosphingosine (P)	6-Hydroxy-sphingosine (H)
Normal FA (N)	NS	NP	NH
	Cer 2	Cer 3	Cer 8
Alpha-Hydroxy FA (A)	AS	AP	AH
	Cer 5	Cer 6	Cer 7
Omega-Hydroxy FA (O)	OS	OP	OH
	Cer A		Cer B
Omega Esterified FA (E)	EOS	EOP	EOH
	Cer 1	Cer 9	Cer 4

FA: Fatty acid; NS: Normal fatty acid linked to Sphingosine; NP: Normal fatty acid linked to Phytosphingosine; NH: Normal fatty acid linked to 6-Hydroxysphingosine; AS: Alpha-hydroxy fatty acid linked to Sphingosine; AP: Alpha-hydroxyl fatty acid linked to Phytosphingosine; AH: Alpha-hydroxyl fatty acid linked to 6-Hydroxysphingosine; OS: Omega hydroxyl fatty acid linked to Sphingosine; OP: Omega hydroxyl fatty acid linked to Phytosphingosine; OH: Omega hydroxyl fatty acid linked to 6-Hydroxysphingosine; EOS: Omega esterified fatty acid linked to Sphingosine; EOP: Omega esterified fatty acid linked to Phytosphingosine; EOH: Omega esterified fatty acid linked to 6-Hydroxysphingosine.

SC lipids are composed of polar lipids such as cholesterol-sulphate, neutral lipids such as sterols, fatty acids, triglycerides, wax esters, squalene and extremely hydrophobic species such as ceramides (Table 1). The lipid extracellular matrix containing in few amount the omega-hydroxyceramides (CerOS, CerOP and CerOH), is replacing the plasma membrane of the living cells and it constitutes a scaffold for the intercellular lipid lamellae[1].

Between the terrestrial mammals, the SC thickness and the organisation are variable.

Regarding the canine skin samples, the intercellular lipid content was less than in other terrestrial species[2] and humans[3]. The lipid content also varies among the breeds. The Labrador retriever and Siberian husky are presenting a higher skin lipid content than the poodle[3].

As shown in a previous paper the results performed on the SC of five healthy dogs showed similar molecular species of ceramides as in Figure 1, but in different quantity concerning free and protein-bound lipids[4]. For example, in the Labrador breed, 6-hydroxysphingosine was the major long-chain base of ceramides, The other dogs presented mostly sphingosine- based ceramides and low amounts of phytosphingosine and 6-hydroxysphingosine ceramides.

Within the depth in the SC, we observed a variation in free ceramides but not for protein-bound ceramides as well as it was describes in other studies where it was used the cyanoacrylate method[5,6].

As can be seen from Figure 1, we identified ceramides with omega-hydroxylated long chain fatty acids such as CerOS, CerOP and CerOH, and we showed that CerOS contains omega hydroxy fatty acids species in decreasing order from omega -OH C30:0, omega -OH C29:0, omega -OH C28:0, to omega -OH C32:0.

In conclusion, due to its structure, the Stratum Corneum of healthy dogs show an important role in the skin barrier protection towards environmental factors and trans-epidermal water loss.

SIMILARITIES OF SC OF HUMAN AND CANINE ATOPIC DERMATITIS

Halliwell[7] describes for the first time that from the clinical point of view that the canine atopic dermatitis (AD) show many similarities with the human skin[8]. After 1999, when the American College of Veterinary Dermatology established that any review of AD should be supported by the medically based evidence of atopy, the term "allergic inhalant dermatitis" was replaced by "AD" because of the lack of asthma sign developing in dogs. In this respect, AD is defined as a genetically determined or allergic or inflammatory pathology resulting into a pruritic skin disorder. Environmental allergens[9] or cutaneous Malassezia and Staphylococcus infections[10] are well known to trigger inflammatory changes that are commonly associated with IgE antibodies.

Recently, in a skin model Leiden epidermal model (LEM)[11], it was used IL-4, IL-13, IL-31, and TNF-α to induce AD-like cytokines disorder in skin (spongiosis and alterations of early stage and terminal stage of expression in differentiation-protein in reconstructed skin). Another effect of TNF-α alone or together with Th2 cytokines consisted in a decrease of the level of long chain free fatty acids (FFAs) and ester linked omega-hydroxy (EO) ceramides, leading to an abnormal lipid organization and a defect in skin barrier integrity. Another cause of exacerbating the pathological changes and the impairment of the synthesis of ultra long-chain ceramides in AD results into a higher amount of the interferon gamma which decreases the very long chain fatty acids and ceramide synthase 3 enzymes necessary for the synthesis of the very long-chain ceramides[12].

AD in dog species affects up to 10% of dogs and it has an important breed prevalence[13]. If in humans, mutations in the filaggrin gene accounted for the predisposition to develop AD, in dogs there is no known direct link[14] and a total absence of correlation has been reported in West Highland White Terriers[15].

Previously, it was shown that in AD, the genetic defects in proteins structure or enzymes could impair the synthesis of SC lipids by incomplete extrusion of lipid bodies (LBs)[16,17]. The LBs composition in lipid catabolic enzymes is also changed[18], resulting in an impairment of lateral packing of the inter-corneocytes lamellar lipids (LL) as observed in humans with AD[19]. Compared to normal skin, it was observed in the non-lesional skin of atopic dogs, by transmission electron microscopy (TEM), some ultrastructural changes in SC morphology such as larger intercorneocyte spaces,as well as severely disorganised, sporadic and incomplete lamellar lipids (20).

After topical treatment with SLC[20], or a ceramide-like moisturizer[21], or other extrinsic lipids[22] that would be integrated into the nascent lamellar bilayers, it was observed by TEM a new formation of the SC compactum, an increase in the LLs and an improvement of the SC integrity.

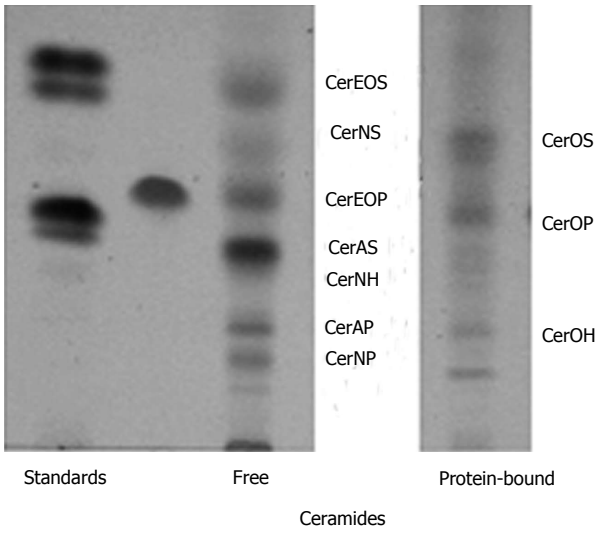

Figure 1 Chromatographic plate with high performance thin-layer of free and protein-bound ceramides from the Stratum corneum of healthy dog skin, Labrador breed. Standards: Left lane; CerNS (ceramide with normal fatty acid and sphingosine): Upper spot; CerAS (ceramide with alpha hydroxy fatty acid and sphingosine): Lower spot; Center lane CerNP (ceramide with normal fatty acid and phytosphingosine); CerEOS: Ceramide with omega esterified fatty acid and sphingosine; CerNS: Ceramide with normal fatty acid and sphingosine; CerAS: Ceramide with alpha-hydroxyl fatty acid and sphingosine; CerNH: Ceramide with normal fatty acid and 6-hydroxysphingosine; CerAP: Ceramide with alpha-hydroxyl fatty acid and phytosphingosine; CerNP: Ceramide with normal fatty acid and phytosphingosine.

EVIDENCE FOR ABNORMAL PRESENCE AND HETEROGENEOUS DISTRIBUTION OF GLUCOSYLCERAMIDE IN THE SC OF ATOPIC DOGS IN NON-LESIONAL AS WELL IN LESIONAL AREAS

An inherent abnormal lamellar structure will cause disorders in cornification as in many ichtyosis, due to a reduced level in protein-bound omega-hydroxyceramides[4], or alteration in the content of other sphingolipids as in psoriasis[23] and AD[5,24-26]. These covalently bound ceramides were first described by Wertz *et al*[27] in 1989.

Recently, a reduction in the free fatty acid chain length was reported in non-lesional and lesional SC of atopic eczema patients[28], associated with a reduced ceramide chain length, suggesting a common synthetic pathway.

This finding could be sustained by the results of Haller *et al*[29] who found that the loss of Abca12 function results in a failure of interaction between glucocerebrosidase and its GlcCer substrate and an accumulation of GlcCer species in SC.

Regarding glucosylceramide, our results[30] show in atopic dogs a near absence of CerOP, a protein-bound ceramide, with the concomitant presence of glucosyceramide in large amount in the SC.

Moreover, Reiter *et al*[5] showed that the ratio cholesterol to ceramide in atopic dog SC is higher than in normal SC dogs, in uninvolved as well as in lesional areas. Also, some results from Sugiura *et al*[31] support the notion that AD in non-lesional skin is associated with an impaired homeostasis in a ceramide-generating process.

Table 2 Protein content of strips taken from normal and atopic stratum corneum dogs

Strip number	Healthy dogs[1]	Atopic dogs	
		Non-lesional areas[1]	Lesional areas
1 + 2	96 ± 11	92 ± 12	56 ± 8
3 + 4	105 ± 12	93 ± 12	58 ± 9
5 + 6	96 ± 10	95 ± 10	57 ± 8
7 + 8	97 ± 13	94 ± 11	59 ± 9
9 + 10	103 ± 15	96 ± 12	52 ± 8
11 + 12	105 ± 14	96 ± 13	54 ± 7

[1]Reproduced from ref.[30]. Values expressed as μg proteins ± SE (n = 5) per 2 strips ($P < 0.05$).

Concerning our work, we reported in 2011 the lipid patterns in non-involved SC of atopic dogs *vs* normal dogs SC that suggested an impaired biosynthesis of the long chain bases of ceramides[30,32]. Here we give the complete analysis of free and protein-bound lipids of lesional and non-lesional SC of 5 atopic dogs.

As shown in Table 2, the amount of proteins taken by tape stripping in non-lesional areas of atopic dogs SC was not significantly different from that of normal dogs, but the protein content was reduced by half compared to the non-lesional areas. The lower protein content of lesional areas was likely to be due to the limited sticking of the tapes on inflammatory areas.

The free lipid content of normal and non-lesional and lesional atopic dog SC is given in Table 3. As compared to their respective contents in normal dog SC, cholesterol and fatty acids showed a moderate (10% to 15%) decrease in both non-lesional and lesional SC of atopic dogs. Free ceramides were reduced by 30% to 40%. However, for glucosylceramides which were absent in normal dog SC, large amounts were detected in non-lesional SC of atopic dogs, with a significant concentration also present in lesional ares, showing a deficient activity of the glucocerebrosidase in the atopic dogs skin.

Table 4 shows the protein-bound lipids of the SC. The amount of Cholesterol, fatty acids and omega hydroxy ceramides of the protein-bound lipids show an important decreasing in atopic dog SC, even higher than that of free lipids. The cholesterol amount was reduced by 30%, the fatty acids by 50% and the omega hydroxyceramides, only 20% compare to the amount found in healthy dog SC. Compare to the normal dog SC which does not contain covalently-bound glucosylceramides, we found an important amount in both non-lesional and lesional atopic dog SC.

In a recent study it was shown that a neutral ceramidase isolated from Pseudomonas aeruginosa (PaCDase) isolated from a patient with AD could degrade the ceramides in the presence of Staphylococcus aureus-derived lipids or neutral detergents in a keratinocyte model[33].

To illustrate the data shown previously[34] and the values from Tables 3 and 4, we analysed comparatively in depth by chromatographic plates the free ceramides of

Table 3 Free lipids of stratum corneum of normal and atopic dogs

Lipid class	Normal dogs[1]	Atopic dogs	
		Non-lesional areas[1]	Lesional areas
Cholesterol	96 ± 28	87 ± 31	86 ± 37
Fatty acids	115 ± 32	91 ± 36	89 ± 43
Ceramides	141 ± 37	112 ± 43	105 ± 56
Glucosylceramides	0	31 ± 17	12 ± 10

[1]Reproduced from ref.[30]. Values expressed as μg ± SE (n = 5) per milligram protein.

Table 4 Protein-bound lipids of stratum corneum of normal and atopic dogs

Lipid class	Normal dogs[1]	Atopic dogs	
		Non-lesional areas[1]	Lesional areas
Cholesterol	12 ± 8	9 ± 5	8 ± 6
Fatty acids	23 ± 12	11 ± 9	15 ± 8
Ceramides	36 ± 10	8 ± 7	8 ± 6
Glucosylceramides	0	8 ± 8	7 ± 6

[1]Reproduced from ref.[30]. Values expressed as μg ± SE (n = 5) per milligram protein.

SC from lesional (line 4) and non-lesional (line 3) spots of atopic dog compared to the heathy one (line 1 and 2) (Figure 2).

It is noticeable that in non-lesional areas (4) the proportion of Cer NP and Cer AS dropped as well as in the lesional side, and moreover, Cer EOS (omega-hydroxy ceramide) is totally absent from lesional areas.

We may noticed an heterogenic distribution in SC depth of protein-bound omega hydroxy ceramides, Cer OS and CerOP, in non-lesional (Figure 3A) and lesional (Figure 3B) SC of atopic dog. Compare to non-lesional SC (Figure 3A), in lesional SC (Figure 3B) an important absence of protein-bound céramides, one reason why the SC integrity is markedly altered.

Figure 4 shows comparatively the presence of glucosyceramide in SC of healthy dog, the precursor of ceramides, (Figure 4A) and its presence in non-lesional (Figure 4B) and the lesional (Figure 4C) SC of atopic dog.

Compare to the healthy dog's SC (Figure 4A), in the successive strips of lesional areas of atopic dogs (Figure 4C), the omega hydroxy ceramides are absent in one sample out of two whereas this does not appear so clearly in non-lesional areas (Figure 4B), responding to question why the alteration of the SC integrity occurs.

Table 4 presents the comparison concerning the whole lipids content of protein-bound lipids of Sc of healty dog compare to atopic dog. We may notice that in atopic dog SC, the whole lipids are strongly reduced as compared to normal dogs. The decreasing in CerOS, which accounts for about 75% of the total omega hydroxy ceramides in normal dog SC, is the only species present in atopic dog SC. Table 4 shows also the amount of glucosylceramide in non-lesional and in lesional areas which confirm the heterogenic profile (Figure 4B and C).

This accumulation of glucosyceramide in SC of

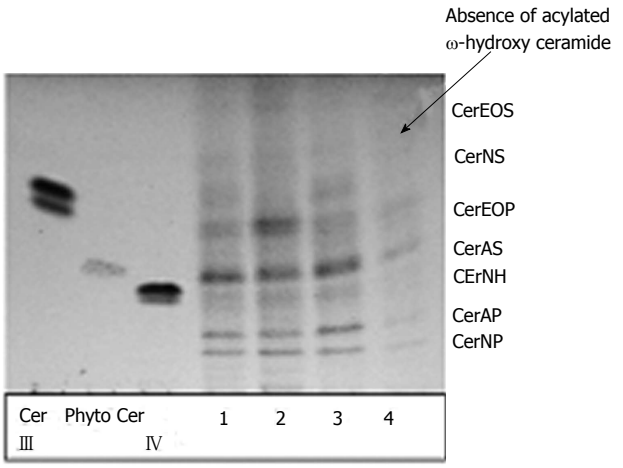

Figure 2 Free ceramides in the stratum corneum of healthy dogs (1, 2) and an atopic dog, non-lesional (3) and lesional areas (4). Standard lipids on the left lanes of the plates: type Ⅲ and type Ⅳ ceramides, phytoceramides.

atopic dogs compared to the normal SC dogs is due to the deficient activity of beta-glucocerebrosidase. This enzyme is known to be essential in acquiring a good SC barrier[18].

Concerning the free glucosylceramide type of lipids, they are completely absent in the normal dog SC. In a similar way, the free glucosylceramides were present in all layers of non-lesional dog SC in an important quantity. In lesional areas, the concentration of glucosylceramides was much lower and there were some variations in the molecular species visualized in these samples, as glucosylceramides with long-chain fatty acids were prominent in pooled strips 5 + 6.

We found in our studies on dog SC, the cholesterol in the protein-bound fraction, as it was reported in human skin[35], Its presence was observed in the successive layers in a striking heterogeneity. In the case of the atopic dogs in non-lesional layers, some layers were more enriched and in lesional layers the content was lowered.

WAYS OF RECOVERY AND TREATMENTS FOR AN EFFICIENT CUTANEOUS BARRIER

One key fact is to restore the barrier function and this requires a decrease to allergen exposure.

Several treatments based on topical application of lipids were designed for patients with allergic contact dermatitis, irritant dermatitis and atopic dermatitits[22]. For exemple, the improvement of the skin barrier in children with AD was accelerated after treatment with a pseudoceramides-based moisturizer[21].

Another study suggested that the application of an emulsion based on an physiological lipid granules would restore the barrier of atopic patients and reduce the clinical symptoms and any side effects[36].

Concerning the dogs, frequent washing and rinsing of the contact zones may help to decrease allergen exposure. In this respect it was shown previously[20] that a mixture of lipid complex SLC® based mainly on ceramides and cholesterol (Allerderm/Derm-1 Spot-on, Virbac

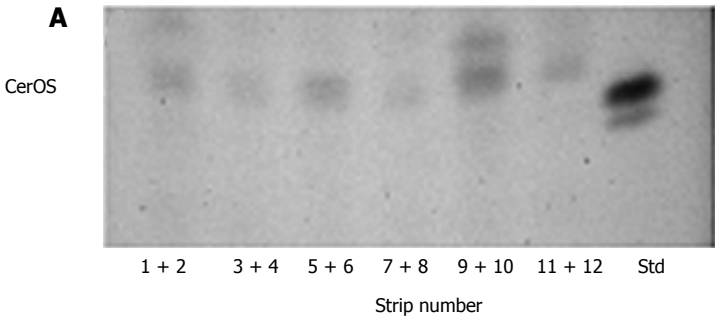

Figure 3 High performance thin-layer chromatography of protein-bound ceramides from non-lesional (A) and lesional (B) stratum corneum of atopic dog (strip tapes taken by two before extraction. Standard ceramide Cer Ⅲ (CerAS). Figure 3A reproduced from ref.[30] (strips tapes pooled two by two before extraction).

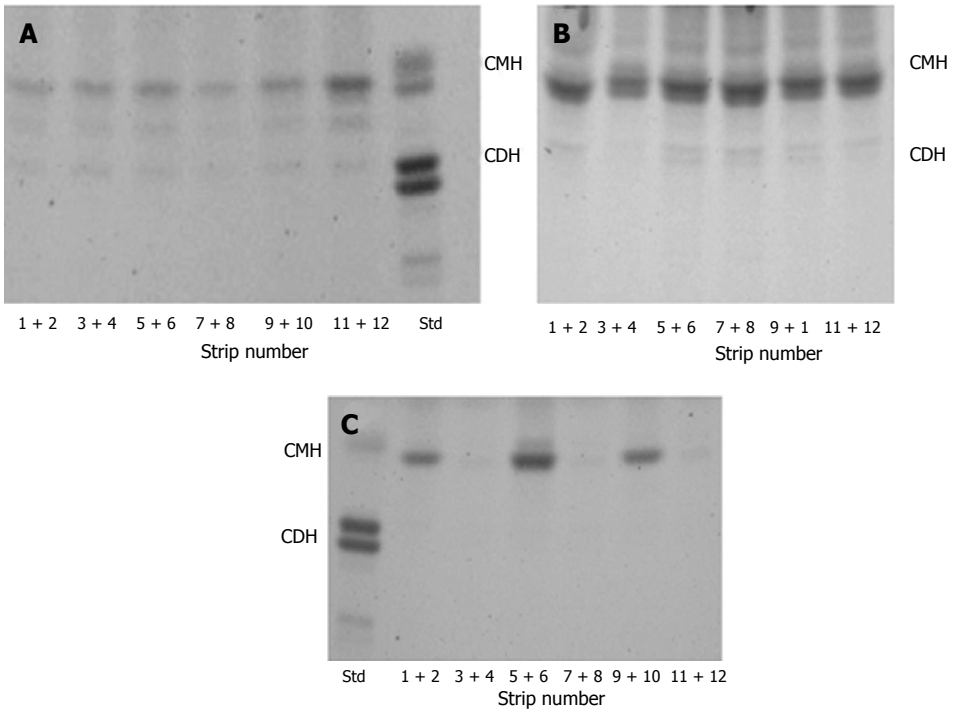

Figure 4 High performance thin-layer chromatography of protein-bound glucosylceramides from non-lesional (B) and lesional (C) stratum corneum of atopic dog compared to healthy dog (A) (strips tapes by two before extraction. Std- mixture of glucosylceramide (CMH) and lactosylceramide (CDH). Figures 4A and 4B reproduced from ref.[30] (strips tapes pooled two by two before extraction).

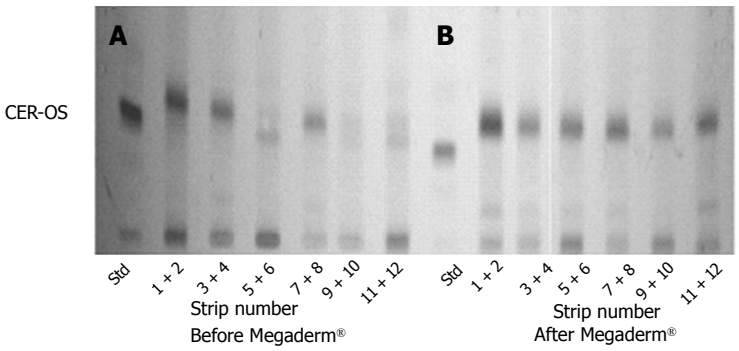

Figure 5 High performance thin-layer chromatography of protein-bounds ceramides from SC of non-lesional skin of an atopic dog before (A) and after treatmanet with Megaderm R (B) (tapes pooled two by two before extraction). Standard-CerOS.

Laboratory) would restructure the SC lipid lamellae. The treatment resulted[32] into an important increase in lipid biosynthesis of keratinocytes (*i.e.*, protein-bound ceramides CerOS and CerOP, and normal and omega-hydroxy fatty acids) and an efficient barrier formation. Another treatment, Megaderm®, designed by Virbac for atopic dogs was a food supplement based on essential fatty acids and vitamin E[33].

Figure 5 shows, as most of our previous publications[30], that the lower lipid content and the marked deficit in protein-liked ceramides (Figure 5A) in atopic dogs may be reversed with the feed supplementation with Megaderm® (Figure 5B). This is the most remarkable feature, accounting for the observed accumulation of the intercorneocyte lamellar lipids[37].

Although it was observed that after feeding for about two months with Megaderm®, the deepest layers of the SC presented several imperfections compared to the SC of healthy dogs, the overall improvement in the lamellar lipid organization and normalization of the protein-bound lipid content did occur, just as with SLC® treatment[20].

It was recently demonstrated with Fourier-transformed infrared spectroscopy and Raman imaging spectroscopy that the stability of the crystalline structure of free fatty acid, ceramide and cholesterol mixtures strongly depends on the length of the fatty acids built into ceramides[38]. It can be that the optimal molecular proportions can be best achieved when living epidermal cells are sufficiently supplied with the essential building bricks provided through the treatments.

Of course, besides the dietary supplementation such as Megaderm® or topical treatment such as SLC®, new treatments used in humans suffering from AD may be also applied in dogs.

These are topical ceramide formulations[39] including targeted CerAP microemulsions[40], that may contain inhibitors of calcineurin[41]. They are all aiming at increasing the epidermal lipid content, supplying filaggrin degradation products[42], regulating the environmental pH[43,44] and the glucosylceramidase activity[45,46], and resulting in a decrease of the transepidermal water loss[47] and inflammation.

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REVIEW

Dermatological conditions of aquatic athletes

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Abstract

Numerous manuscripts have described dermatologic conditions commonly seen in swimmers. This review provides an update on water dermatoses and discusses newly described conditions such as allergic contact dermatitis to chemical ingredients like potassium peroxymonosulate in pool water. In order to organize water related skin conditions, we have divided the skin conditions into a number of categories. The categories described include infectious and organism-related dermatoses, irritant and allergic dermatoses, and sun-induced dermatoses. The vast majority of skin conditions involving the water athlete result from chemicals and bacteria in the differing aquatic environments. When considering the effects of swimming on the skin, it is also useful to differentiate between exposure to freshwater (lakes, ponds and swimming pools) and exposure to saltwater. The risk of melanoma amongst swimmers is increased, and the use of SPF 30 or greater sunscreen and protective clothing is highly recommended. Swimmers should be reminded to generously apply sunscreen and be instructed on proper sunscreen usage. This review will serve as a guide for dermatologists, athletes, coaches, and other medical professionals in recognition and treatment of these conditions. We also intend for this review to provide dermatologist with a basic framework for the diagnosis and treatment of a few rarely described dermatological conditions in swimmers.

Key words: Aquatics; Dermatitis; Athletes; Practice Gaps; Freshwater dermatitis

Core tip: Athletes who spend a significant amount of time in the water are subject to a wide array of diseases that include bacterial and fungal infections. These athletes are often exposed to undesirable environments with excessive humidity, heat, cold, wind, and sunlight. These factors may aggravate or cause different skin conditions that require a dermatologist who has specific knowledge of rare aquatic dermatoses.

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CONDITIONS RELATED TO IMPAIRED SKIN BARRIER AS A RESULT OF CONTACT WITH WATER

Excessive dryness (swimmer's xerosis) is one of the most common conditions seen in water athletes. It is caused by sebum dilution with water, osmotic effect, and stripping off the stratum corneum. Taking long showers with scrubs and soaps after activity also precipitates the problem. Although easy to diagnose, swimmer's xerosis should be differentiated from swimmer's itch and urticaria[1-5]. Preventative measures include decreasing shower duration and applying ointment based moisturizing preparations before and after pool activities[4].

Aquagenic acne occurs due to the rebound effect of sebum over-production after continuously washing off the oils from the skin surface. It may present as an acute exacerbation of a preexisting condition or as a new onset disorder. Other mechanisms include the effect of chlorinated compounds in pool water, occlusion of the sebaceous glands by denuded epidermis, and use of comedogenic moisturizing creams and sunscreens. Aquagenic acne typically presents as common acne and should be treated accordingly. Topical or systemic agents can be used depending on level of severity, but it should be noted that some topical agents may cause additional irritation. Specifically, isotretinoin, commonly used for severe acne treatment, may interfere with performance and cause neuromuscular symptoms and myalgias[6,7].

CONTACT DERMATITIS

Allergic contact dermatitis

Some evidence suggests that swimmers may be more prone to allergic reaction than non-swimmers since swimmers have a higher incidence of positive skin prick tests, asthma, allergic rhinoconjunctivitus, and bronchial hyperactivity[8-12]. Increased allergy rates may be partly explained by the use of chlorinated or brominated disinfectants in swimming pools that may increase sensitization to other allergens[13].

Disinfectants may cause allergic contact dermatitis ("pool water dermatitis"). Compounds proven to cause pool water dermatitis include gaseous chlorine, sodium and lithium hypochloride, 1-bromo-3-chloro-5,5-dimethylhydantoin (BCDMH), potassium peroxymonosulfate, and aluminum chlorohydrate[14-17]. Brominated compounds were previously thought to provide an alternative to chlorine, but have shown an increased potential to cause irritant contact dermatitis. BCDMH is a component that slowly releases bromium and chlorine and is believed to be the causative agent of an outbreak of swimming pool contact dermatitis in the United Kingdom[18-20]. Initially, only negative patch tests to BCDMH were seen, and it was believed to be a solely irritant dermatitis. However, positive patch tests for BCDMH were later reported[16]. It was also proposed that certain individuals may develop an allergic contact dermatitis because of the chlorium, released from BCDMN, but test were negative for BCDMH itself[21].

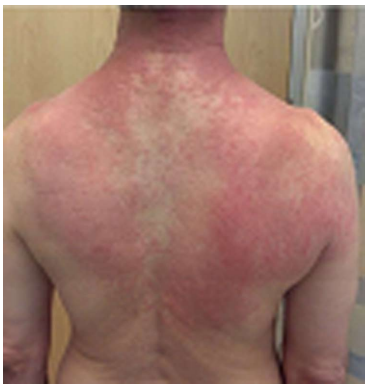

Figure 1 Allergic contact dermatitis to new swim wear.

Allergic contact dermatitis can also be caused by certain clothing and equipment swimmers use (Figure 1). Early reports described reactions to the components of resins (thioureas, benzothiazole, dithiocarbamate and formaldehyde) in goggles, scuba masks, nose clips, earplugs, fins, fin straps, and swimsuits[22-29]. Allergic contact dermatitis to dodecyl diaminoethyl glycine, a diving suit disinfectant, has also been described[30]. Raccoon-like depigmentation was described from use of neoprene goggles in a child, but the etiology (toxic or allergic) was not confirmed[31].

Irritant contact dermatitis

Irritant contact dermatitis in athletes usually develops as a result of chronic friction (Figure 2). Use of caps and goggles that press tightly against the skin may lead to purpura formation[4]. A specific irritant dermatitis known as "pool toes" and "pool palms" is caused by friction of the feet and palms against the pool's rough cement bottom[32-34]. Another form of irritant dermatitis in males is "shoulder dermatitis", which is caused by rubbing an unshaven chin against the shoulder while performing the crawl stroke[35]. In surfers, nodules may develop in the pretibial area due to continuous friction with the surf board[35]. These irritant dermatoses usually resolve spontaneously with cessation of the offending activity, but persistent nodules can be treated with topical keratolytics and intralesional corticosteroids.

SKIN INFECTIONS

Athletes who spend a significant amount of time in the water are subject to a wide array of bacterial and fungal infections. Excessive maceration, dryness, and changes in the skin microflora contribute to the development of

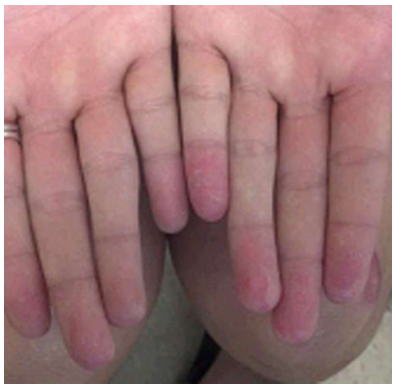

Figure 2 Fingertips that desquamate from the friction of the contact with the sides of the pool.

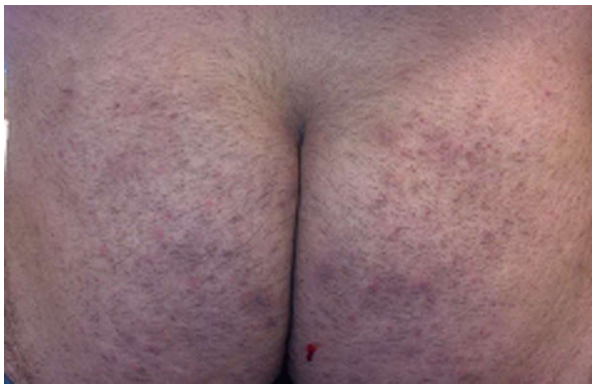

Figure 3 Buttock folliculitis.

the skin infections. Additionally, the risk of disease is increasing because of pool overcrowding and common use of showers and towels.

Bacterial infections

Pseudomonas aeruginosa is able to survive in high temperate water and causes several skin conditions including hot tube folliculitis, otitis externa, and hot foot syndrome. Outbreaks of *Pseudomonal* infections may arise from contact with contaminated water[36-38]. Current studies show that *Pseudomonas* contamination is common in pools and even more so in hot tubs since they are difficult to clean[39]. To decrease the rate of infection, chloride concentration of the water should be monitored daily. Athletes, especially those who train intensely for a prolong period of time, are prone to the colonization of the ear canal by *Pseudomonas*[40].

Hot tub folliculitis presents as a disseminated itchy pustular rash that appears within two days of water exposure. It is prone to localize in the intertriginous areas and may also be seen in a bathing suit distribution. Hot tub folliculitis (Figure 3) is usually a self-limited condition, but systemic symptoms such as low-grade fever, lymphadenopathy, headache and malaise may be rarely seen. It can also be accompanied by other *Pseudomonal* infections including otitis, conjunctivitis, mastitis, and urinary tract infections[41]. *Pseudomonas* folliculitis may also develop under the suit that has led to the aptly suited description of "diving suit folliculitits"[42,43].

Pseudomonas is the most frequently implicated pathogen in the development of otitis externa. Swimmers are five times more likely to develop otitis externa than non-swimmers[44]. Otitis externa presents with pain limited to the external auditory canal, but the ear appears erythematous and swollen with variable discharge (Figure 4). Prophylaxis is generally achieved through proper cleaning and drying of the ear canal in addition to avoidance of excessive moisture in and around the canal. Acidification with a topical solution of 2% acetic acid combined with hydrocortisone for inflammation is effective treatment, although most physicians will also prescribe combination steroid/antibiotic drops. Another dermatoses known as hot foot syndrome has been described as a subcutaneous eruption on the soles of children swimming in the same pool[38,45]. In both reports *Pseudomonas* was isolated from the swimming pool, but a causative relationship (isolation from the skin lesion) was only performed in one child, leaving debates about the etiology of the condition[46,47].

Swimmers also show increased rates of skin colonization by *Staphylococcus* and *Streptococcus*[40]. Bikini bottom is a deep folliculitis of the buttocks that is caused by *Streptococcus* or *Staphylococcus aureus*. It is the result of wearing tight fitting bikinis for prolonged periods of time and presents as firm nodules that manifest along the inferior gluteal crease[48]. Prevention is aimed at early removal of the swimsuit, while treatment consists of oral antibiotics based on sensitivities.

Recent European and American studies have shown that most swimming pools and showers are contaminated with *Mycobacteria*[49-52]. Although not necessarily symptomatic, these bacteria can cause granulomatous disease of the lungs and skin[53]. *Mycobacterium marinum* (*M. marinum*) is ubiquitous in pools, aquariums, freshwater, and saltwater. Since its discovery in Sweden, multiple outbreaks of *M. marinum* outbreaks have been described throughout the world[54-56]. It also causes so-called "fish tank" or "swimming pool" granuloma which has a predilection for the dorsum of the hands, fingers, and elbows, especially when skin trauma or open wounds are present[57]. The predilection for the extremities is due to inhibition of growth of *M. marinum* at 37 ℃ so the organisms tends to infect the cooler parts of the body including the extremities[57]. The granuloma usually presents as a solitary, erythematous papule or nodule and may be mistaken for sporotrichosis or leishmaniasis[58,59]. Disseminated infection is rare, although a case of disseminated *Mycobacterium* that presented as erythema nodosum was previously described in a 12-year-old girl[60]. Histopathology of skin lesions reveal typical tuberculoid granulomas in only 60% of cases, while the other 40% display non-specific inflammation with neutrophils[61]. Frequently, superficial biopsies fail to show specific changes, but granulomas may be seen in the subcutaneous tissue or synovium. Paucity of microorganisms is the characteristic feature of *M. marinum* infections, and the identification of the microorganism is a challenge. Culture and polymerase chain reactions may also be

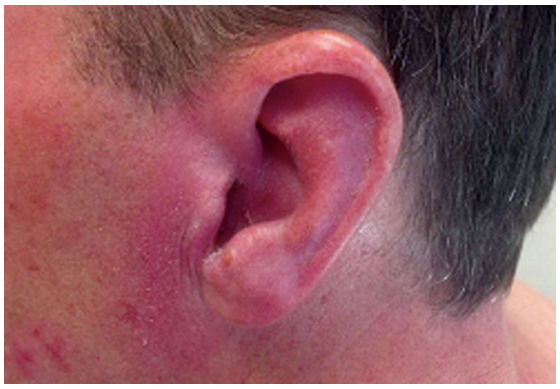

Figure 4 *Pseudomonal* infection of external ear canal.

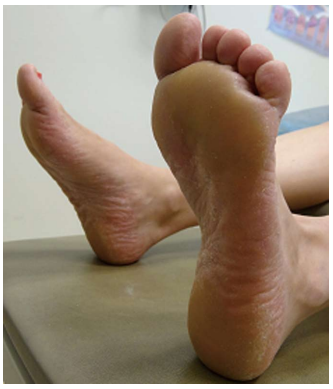

Figure 5 Tinea pedis on the foot of a swimmer.

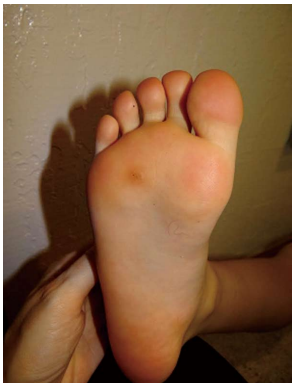

Figure 6 Plantar warts on the foot of a swimmer.

useful for identifying microorganisms[62,63]. Localized lesions of swimming pool granuloma are self-limited and resolve with scar formation. Patients can be treated with clarithromycin, minocycline and trimethoprim-sulfamethoxazole; multidrug therapy with ethambutol and rifampin is needed if disseminated disease is present[57]. Although rare in immunocompetent individuals, other mycobacteria, mainly *M. cheloneae* and *M. fortuitum* may also cause cutaneous granulomas.

Fungal infections

Several studies have shown that swimming pools are contaminated with dermatophytes, which increases the risk of infection[64]. Prolonged contact with water causes increased susceptibility to fungal infections, and Kamihama *et al*[65] found that 63.6% of swimmers are dermatophyte carriers. However, the incidence of tinea pedis among aquatic athletes is not well studied, but early reports have found that it may be up to 10%[52,66]. *Trichophyton mentagrophytes* accounts for up to 85% of infections and has been isolated from swimming pool decks and locker room floors[65,66]. Tinea pedis (Figure 5) should be differentiated from pitted keratolysis, caused by *Corynebacteria,* which presents with the small punched-out depressions and an unpleasant smell. Tinea can be prevented by proper foot hygiene and patient education. Initial treatment involves topical antifungals twice daily for one to two months, but systemic antifungal agents may be used if refractory disease is present.

Viral infections

Swimmers and those who use common showers have a greater incidence of plantar warts (Figure 6) and molluscum contagiosum, although the exact incidence in athletes is unknown[67-69]. Liquid nitrogen, curettage, and salicylic acid are helpful for removal of the lesion. There is not enough evidence to confirm that covering warts helps prevent spread[70].

HAIR CONDITIONS

Aquatic athletes are prone to develop specific hair conditions. Green hair discoloration, often seen in light-haired athletes, is an effect of bleach and copper ion deposition that are used to kill algae[71]. Seborrheic keratosis may also undergo green color change along with the hair due to copper ion deposition[72]. Wetting the hair prior to chlorinated water exposure, prompt bathing after exposure, and use of a copper chelating shampoo may mitigate this problem. Hair discoloration coexisting with nail plate damage has also been described in Japanese swimmers and was considered to be a result of cuticle damage due to water friction and hypochlorus acid penetration[73].

FRESHWATER DERMATITIS

Athletes who swim in marine water may be exposed to conditions transmitted by sea and river microorganisms. Jellyfish, anemones, sponges, corals and rarely Coelenterates (Cnidaria) are known to cause dermatitis and infection if traumatized (Figure 7). Dermatitis can also develop after contact with fish (jellyfish, stingray, weeverfish, stonefish), cones, or sea snakes (Hydrophiidae) due to their venomous toxin (Figure 8). Exposure may result in blistering and skin necrosis along with systemic symptoms, including respiratory muscle paralysis.

Another dermatitis, known as "seabather's eruption", is a pruritic eruption that appears under the bathing suit. It is caused by contact with swimming stages of the thimble jellyfish, *Linuche unguiculata*, and it is seen in Florida, the

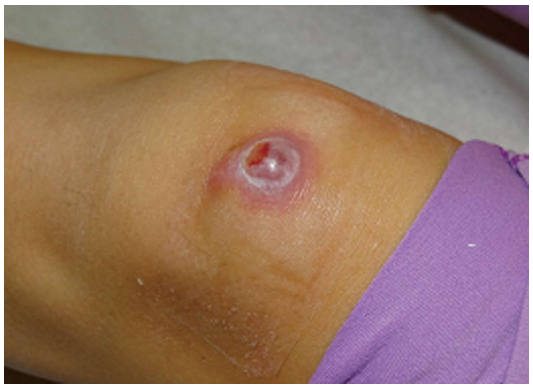

Figure 7 Coral reef dermatitis that became infected secondary to trauma.

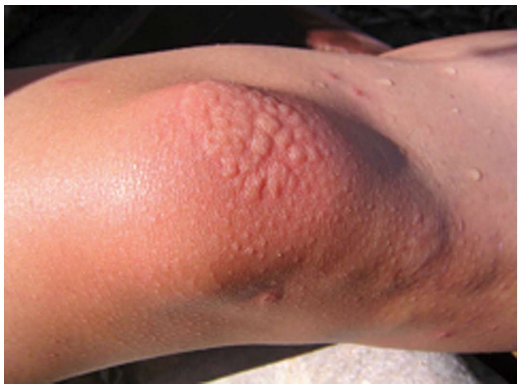

Figure 8 Jellyfish sting on patella.

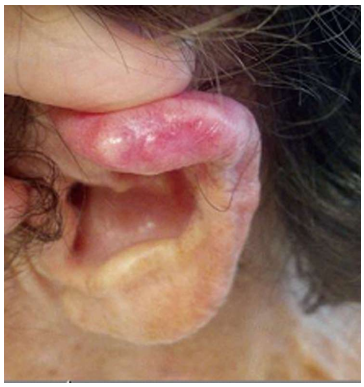

Figure 9 Basal cell carcinoma on superior aspect of ear of swimmer.

Caribbean and Brazil. Cercarial dermatitis (swimmers' itch) develops after penetration of *Shistosoma's* larvae through human skin. The exact species of *Shistosomas* that cause the eruption, their animal hosts, and distribution is still under investigation[74]. The condition is usually self-limited and presents as pruritic papules on exposed body surface areas, usually sparing the bathing suit region.

Onchocerciasis (river blindness) is caused by the filaria *Onchocerca volvulus*. Acquisition of the disease may occur after swimming in the Middle East, Africa or Latin America. Skin changes in onchocerciasis include nodule formation in the area of penetration, a pruritic rash, lichenification, vitiligo-like changes, and atrophy after microfillaria migration. Early detection and treatment of filaria with ivermectin helps prevent river blindness.

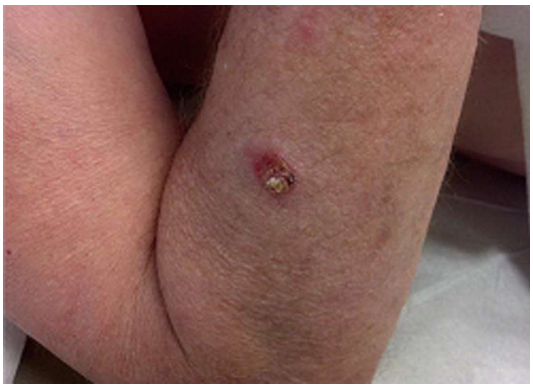

Figure 10 Squamous cell carcinoma on dorsal forearm.

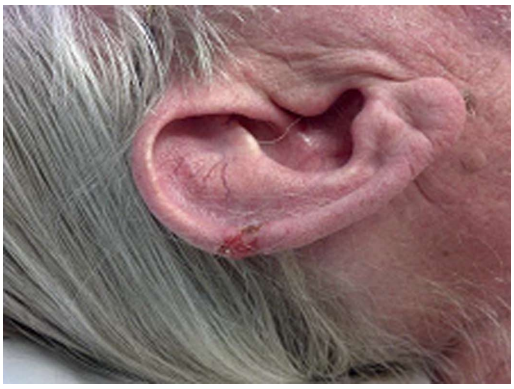

Figure 11 Squamous cell carcinoma on helix of ear.

ENVIRONMENT-RELATED CONDITIONS

Outdoor athletes are often exposed to undesirable environmental conditions such as excessive humidity, heat, cold, wind, and sunlight that may aggravate or cause different skin conditions. Sun exposure in athletes may be extreme and can lead to a higher risk of basal cell carcinoma (Figure 9), squamous cell carcinoma (Figures 10 and 11), and melanoma (Figure 12). Moehrle[75] has found that burns were seen in triathletes despite of use of SPF 25+ sunscreens. However, data regarding the incidence of skin cancers in aquatic athletes is limited to several early studies. In 1992, a screening of surfers demonstrated an increased incidence of basal cell carcinomas in surfers, despite of their young age[76]. Nelemans *et al*[77] have shown that the odds of melanoma risk were higher in swimmers, but he contributed it largely to the chlorination of the water in swimming pools.

Use of SPF 30 or greater sunscreen and protective clothing is highly recommended to athletes[78,79]. When counseling swimmers on sunscreen usage, one should advise use of a sunscreen that contains SPF 30 or greater, is water resistant, and provides broad spectrum UVA

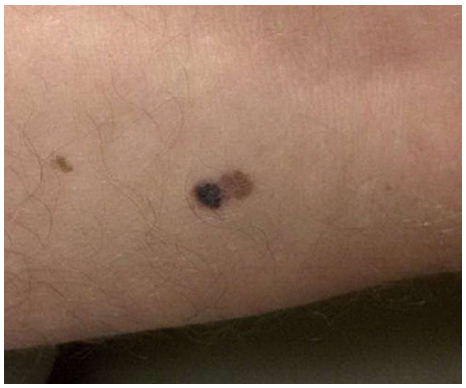

Figure 12 Melanoma on the leg.

and UVB coverage. Swimmers should also be told to generously apply the sunscreen to all bare skin before going outdoors since it can take up to 15 min for skin to absorb sunscreen. Finally, they must be counseled to reapply sunscreen immediately after swimming or every two hours, whichever is sooner.

CONCLUSION

Aquatic athletes present a unique set of challenges for the dermatologist. It is important to educate athletes, parents, and coaches in an attempt to prevent short and long term dermatological sequela.

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REVIEW

From the outside-in: Epidermal targeting as a paradigm for atopic disease therapy

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Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disorder which can precede asthma and allergic rhinitis in a disease trajectory known as the atopic march. The pathophysiology of AD includes cutaneous inflammation, disrupted epidermal barrier function, xerosis and propensity to secondary infections. AD had previously been thought to arise from the systemic atopic immune response and therapies are therefore directed towards ameliorating Th2-mediated inflammation. However in recent years the focus has shifted towards primary defects in the skin barrier as an initiating event in AD. Links between loss-of-function variants in the gene encoding filaggrin and disrupted activity of epidermal serine proteases and AD have been reported. Based on these observations, a mechanism has been described by which epidermal barrier dysfunction may lead to inflammation and allergic sensitization. Exogenous and endogenous stressors can further exacerbate inherited barrier abnormalities to promote disease activity. Pathways underlying progression of the atopic march remain unclear, but recent findings implicate thymic stromal lymphopoietin as a factor linking AD to subsequent airway inflammation in asthma. This new appreciation of the epidermis in the development of AD should lead to deployment of more specific strategies to restore barrier function in atopic patients and potentially halt the atopic march.

Key words: Atopic dermatitis; Eczema; Filaggrin; Skin barrier; Kallikrein; Thymic stromal lymphopoietin; Allergic sensitization; Atopic march

Core tip: Atopic diseases [including atopic dermatitis (AD), allergic rhinitis and asthma] are characterised by Th2-type inflammation. Research over the past decade has highlighted a crucial role for primary skin barrier impairment in the pathogenesis of AD and associated atopic phenotypes. Notably, the epidermal protein, filaggrin, epidermal serine proteases, and the pro-Th2 cytokine thymic stromal lymphopoietin, have been implicated in disease development. We review the evidence upholding a role for epidermal defects in the

initiation of skin inflammation in AD, allergic sensitization and pathogenesis of the "atopic march", and discuss the clinical implications of these findings.

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INTRODUCTION

Atopic diseases are reaching epidemic proportions[1-4], affecting up to 20%-30% of children in developed nations[5-7]. Prominent among these disorders are atopic dermatitis (AD, synonymous with atopic eczema), atopic asthma and allergic rhinitis. Atopic diseases constitute a major source of physical and psychosocial distress[8-10] and account for a large portion of general paediatric practice[11]. Atopic diseases demonstrate complex inheritance patterns and extensive phenotypic variation, and as such their aetiology is poorly understood[12]. However the disorders appear to be underpinned by some common features: they are often associated with elevated levels of total serum IgE and with "atopy" - a personal and/or familial tendency to become sensitized and produce specific IgE against environmental allergens[13] - but this association is hotly debated[14,15]. Atopic diseases are thus presumed to arise as a result of interplay between inherited disposition and environmental factors[16,17].

Longitudinal studies have revealed that approximately half of patients with AD develop asthma later in life and two-thirds go on to exhibit allergic rhinitis[18]. This phenomenon, dubbed the "atopic march" describes the tendency for AD (usually apparent within the first two years of life) to precede the development of food allergies, asthma and allergic rhinitis in a typical temporal sequence[17,19,20]. As AD is now a recognised "gateway" to the atopic march, its diagnosis in infants often prompts parental enquiries about disease prognosis as regards the development of subsequent disorders[17]. AD therefore represents an important focus for interventions which may modify the natural course of atopic disease in high-risk patients.

AD is a chronic, inflammatory skin disease affecting an estimated 10%-20% of children and 1%-3% of adults[6]. The skin of AD patients shows widespread xerosis (dryness) and a disturbance of epidermal barrier function. AD lesions (Figure 1A and B) are additionally characterised by pruritus and a propensity to secondary infections (Figure 1C). Th2-deviated inflammation is widely accepted in the pathogenesis of atopic disease however inflammation in AD may be biphasic, with an initial Th2 response leading to a Th0/Th1 dominated phase in chronic lesions[21]. Traditionally it has been presumed that epidermal barrier dysfunction in AD is a downstream consequence of primary immunologic abnormality (the "inside-outside" hypothesis)[22]. In recent years this view has been challenged, with new evidence shifting the focus towards an "outside-inside" model in which epidermal abnormality is not the result but rather the stimulus of inflammation[23]. In light of this concept, this review will evaluate the evidence upholding a pivotal role for the epidermis in atopic disease pathogenesis, and consider the practical implications for therapy.

BARRIER DISRUPTION IN ATOPIC DERMATITIS

The skin forms an essential barrier between the interior of the body and the external environment. Multiple protective roles are fulfilled by the epidermis and many are mediated by its outermost layer (and end product of keratinocyte differentiation), the stratum corneum (SC; Figure 2)[24,25].

The SC comprises layers of protein-rich anucleate corneocytes interconnected by corneodesmosomes and enclosed within a coat of cross-linked proteins and lipids which together form the cornified envelope (CE)[26]. The CE replaces the plasma membrane during terminal differentiation of keratinocytes into corneocytes and is in turn surrounded by a matrix of intercellular lamellar sheets enriched by 50% ceramides, 25% cholesterol and 15% free fatty acids (FFAs)[27]. This amalgam of highly hydrophobic lipids, together with the CE, provides selective permeability to the epidermis.

Intercellular lipids are secreted as precursors from a unique epidermal organelle, the lamellar body (LB), along with the hydrolytic enzymes required for precursor transformation[24]. At the granular cell-to-corneocyte transition, LBs fuse with the plasma membrane and discharge their contents into the intercellular space by exocytosis. LB extrusion also delivers antimicrobial peptides (AMPs) and the proteases and inhibitors which together orchestrate corneodesmosome cleavage during desquamation. Beneath the SC, the stratum granulosum (SG) provides a second barrier to environmental stressors; keratinocytes in the outer SG layers are intimately connected by tight junctions (TJs) - multi-protein complexes which control paracellular transport.

AD is characterised by widespread skin barrier dysfunction in both lesional and non-lesional skin[28], as indicated by increases in transepidermal water loss (TEWL)[29-31] and percutaneous penetration[32]. This enhanced permeability has been attributed to abnormalities in the composition and architecture of extracellular lipid bilayers, reductions in total lipid and ceramide content[33] and average ceramide chain length[34], as well as an altered ceramide profile[33,35]. The resultant barrier defect renders the skin of AD patients more permissive to the ingress of irritants, allergens and pathogens.

Atopic skin is more susceptible to bacterial and viral infections[10], reflecting defects in the antimicrobial

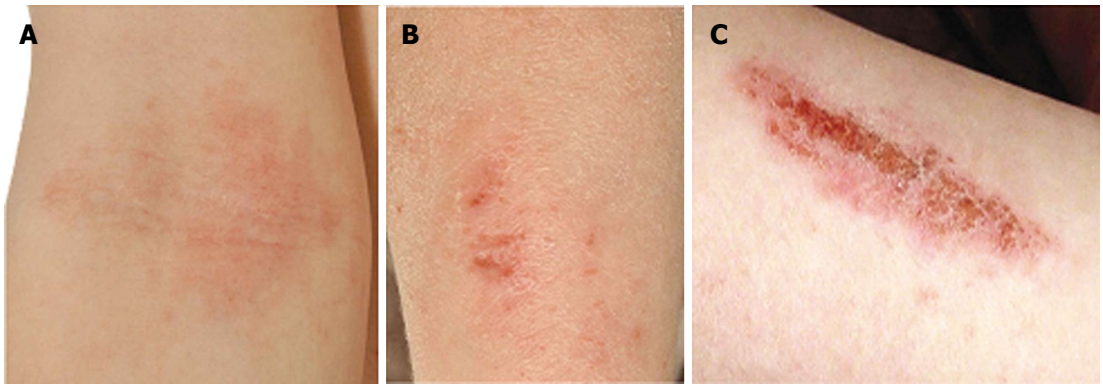

Figure 1 Clinical features of atopic dermatitis. A: Flexural eczema; B: Eczema and ichthyosis; C: Infected excoriation. Clinical photographs (University of Dundee Computing and Media Services, Ninewells Hospital and Medical School) reproduced with patient and/or parental consent.

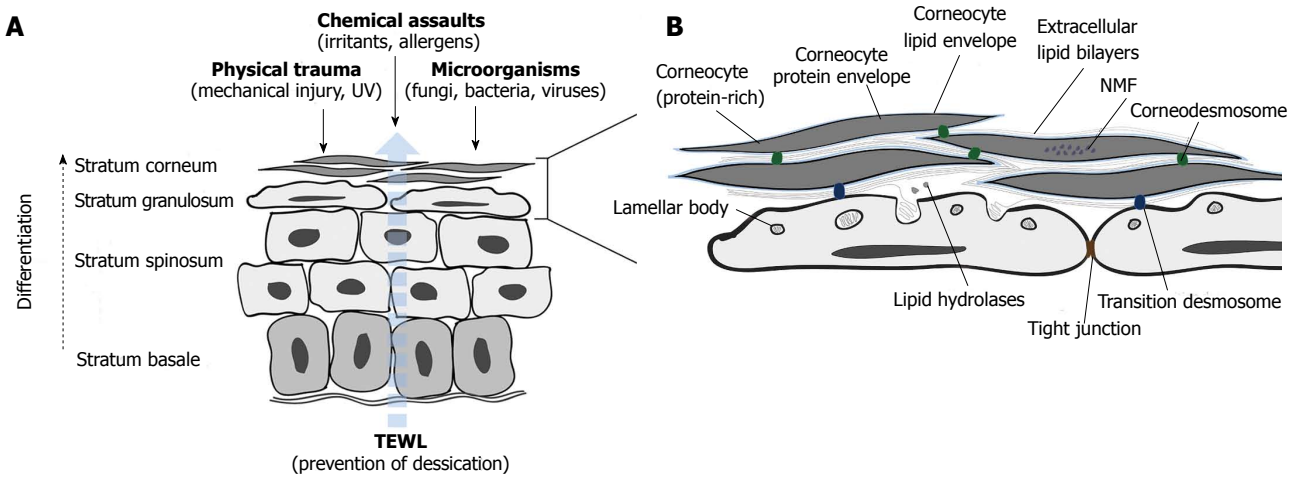

Figure 2 Outside-inside and inside-outside barrier functions of the epidermis. A: The epidermis forms a barrier against multiple external threats and prevents excessive transepidermal water loss (TEWL, indicated by the dashed blue arrow) from the interior of the body; B: Components of the stratum corneum (SC) and stratum granulosum (SG) barriers. During terminal differentiation of SG keratinocytes into corneocytes, lamellar bodies (LBs) fuse with the plasma membrane and their contents is extruded at the SG-SC interface. LB-derived lipids are processed and arranged into continuous bilayers parallel to the corneocyte surface using the covalently bound corneocyte lipid envelope (pale blue) as a scaffold. NMF: Natural moisturising factor.

barrier. 80%-100% of AD patients show colonisation by *Staphylococcus aureus* (*S. aureus*) compared with 5%-30% of non-atopic individuals[36-38]. Flare-ups of AD are often associated with *S. aureus* infection, but whether infection represents a cause or consequence of inflammation remains unclear.

In healthy individuals, the desiccating surface, acidic pH and resident microflora of the skin cooperate with AMPs and lipids to provide protection against invading pathogens[39]. In AD, a number of factors - including the defective epidermal barrier, attenuated innate immune response and increased bacterial adhesion - may promote skin colonisation by *S. aureus*[40]. Among the human AMPs, levels of the cathelicidin, LL-37, and human beta-defensin-2 (hBD-2) are reduced in AD lesions[41], and deficiency of sphingosine - a natural ceramide metabolite and potent anti-*S. aureus* agent - is also evident in the SC[42]. Furthermore, *in vitro* studies have suggested that the Th2 inflammatory response in AD may feed back to the epidermis to promote bacterial colonisation[41,43]. For instance, IL-4, which is over-expressed in AD skin, has been reported to increase skin expression of fibronectin and fibrinogen - receptors which may facilitate attachment of *S. aureus* to the SC[43].

Finally, it should be noted that several other protective functions of the skin barrier are impaired in AD. The skin of AD patients shows disrupted SC integrity (reflected by excess scale[31]) and widespread xerosis, indicated by reduced SC water content[30]. Additionally, pruritus - a prominent characteristic of AD[44] - indirectly aggravates skin barrier impairment *via* the resultant scratching. The itch sensation is believed to result from cross-talk between the SC, keratinocytes, immune cells and nerve fibres[45]. Excoriations directly disrupt the mechanical barrier of skin, creating additional portals of entry for pathogens. Moreover, it has been reported that a subset of AD patients develop serum IgE which is auto-reactive against a variety of keratinocyte proteins[46]. Thus damage to the epidermis may itself intensify pruritus, driving the vicious "itch-scratch" cycle of AD[45].

EPIDERMAL DIFFERENTIATION PROTEINS

Filaggrin-related barrier dysfunction

The outside-inside phenomenon of AD drew sharp attention from the research community when a significant link between loss-of-function variants in the gene encoding filaggrin (*FLG*) and AD was demonstrated in three European case collections[47]. *FLG* mutations were originally identified as the cause of ichthyosis vulgaris (IV)[48] and have since been demonstrated to be the strongest known risk factor for AD in European and Asian populations[49-56]. Cases of AD associated with *FLG* mutations are more likely to be severe, persistent[57-60], and complicated by secondary infections[61,62] than non-*FLG*-related cases. Importantly, *FLG* mutations are now established as an independent risk factor at every step of the atopic march including allergic sensitization[60,63-68], allergic rhinitis[60,64,66-68], food allergies[69,70] and the sub-phenotype of asthma associated with AD[7,60,63,64,66-68].

Profilaggrin is a large precursor molecule (> 400 kDa) containing 10, 11 or 12 tandem repeats of the 37 kDa filaggrin peptide[71]. Insoluble, heavily phosphorylated profilaggrin is the main constituent of keratohyalin granules in the SG. During terminal differentiation, profilaggrin is dephosphorylated and cleaved in a multistep process to release filaggrin monomers, which bind and aggregate keratin filaments, facilitating the collapse of the cytoskeleton and contributing to the flattening of keratinocytes to produce corneocytes[72]. Filaggrin, along with several other cytosolic proteins, is cross-linked into the CE by transglutaminases. As corneocytes move outwards through the SC, filaggrin detaches from the CE and undergoes further degradation within the cytosol, ultimately generating a hygroscopic pool of amino acids and derivatives thereof [including pyrrolidone carboxylic acid (PCA) and trans-urocanic acid (UCA)], contributing to natural moisturising factor (NMF)[73]. NMF appears to play a role in multiple aspects of epidermal homeostasis including SC hydration[73,74], UV photo-protection[75], immunosuppression[76,77] and by acting as a natural acidifier, modulation of enzymatic activity[78-80] and antimicrobial defence[81].

Each of the reported null mutations in *FLG* has an equivalent biological effect, producing a truncated profilaggrin molecule[82]. This precursor cannot be fully processed into filaggrin monomers thus individuals with two *FLG* null alleles (homozygous or compound heterozygous, $FLG^{-/-}$) exhibit an almost complete absence of functional filaggrin[82]. Inherited filaggrin deficiency results in both intracellular and extracellular changes in keratinocyte architecture and altered epidermal physiology. Histological examination of skin from *FLG*-deficient AD and IV patients reveals increased SC thickness[83] and a granular cell layer that is either strongly reduced or absent[84]. At the ultrastructural level, reduction in filaggrin correlates with perinuclear retraction of granular cell keratin filaments, impaired corneocyte integrity and reduced corneodesmosome density, concomitant with reduced SC cohesion[84]. The molecular mechanisms by which deficiency in filaggrin - an intracellular protein - impairs the paracellular skin barrier in AD remains unclear. However it is plausible that the cytoskeletal abnormalities associated with filaggrin deficiency impede the granular cell-to-corneocyte transition and thus formation of the SC extracellular environment. Consistent with this hypothesis, impaired cargo loading into LBs, partially compromised LB secretion and disorganised lamellar bilayers are observed in the skin of AD and IV patients[84,85]. Reduced expression of SG TJ proteins[84] is also likely to further contribute to barrier impairment.

Alternatively or in addition, it may be the biochemical consequences of filaggrin deficiency that are important in AD pathogenesis. *FLG* null mutations effect a dose-dependent reduction in SC NMF levels[86-89], which in turn correlate inversely with skin surface pH[87,89] and TEWL[89]. Additionally, *FLG* exhibits intragenic copy number variation, and a lower number of repeats correlates significantly with AD risk[90], SC UCA levels[90] and the presence of self-perceived "dry skin"[91]. Thus enhanced TEWL in *FLG*-associated AD can be explained in part by reduced SC hydration; deficiency of hygroscopic NMF components would be expected to result in lower SC water content hence a steeper water gradient across the epidermis. In addition, altered skin pH is likely to perturb the natural balance of enzymatic activities in the SC. The elevated pH of AD patient skin would be predicted to favour the net activity of SC-resident serine proteases (SPs)[78,80] whilst reducing that of key SC lipid biosynthesis enzymes. SP hyperactivity drives premature degradation of corneodesmosomes and lipid-processing enzymes[80], likely contributing to defective lamellar bilayer formation. In line with the proposed mechanisms, it has been demonstrated that levels of filaggrin breakdown products correlate with aberrant SC lipid organisation and decreased barrier function in AD patients[34,86,92]. A recent study using a reconstructed human epidermis model has suggested that filaggrin deficiency may also promote enhanced epidermal sensitivity to UVB[93], but this connection remains to be demonstrated in patients.

Finally, filaggrin deficiency in AD has implications for the antimicrobial skin barrier. As described, the natural acidity of the SC in healthy individuals provides innate antimicrobial protection - a function which is likely to be diminished in NMF-deficient AD patients. Furthermore, recent data suggest that filaggrin may play a unique role in protection against *S. aureus* infection, by mediating keratinocyte secretion of sphingomyelinase - an enzyme which reduces the number of *S. aureus* α-toxin binding sites on the keratinocyte surface[94]. These findings indicate a mechanism by which filaggrin-deficient skin may be preferentially targeted by *S. aureus*-induced cytotoxicity. Clinically, the consequences of *FLG* null mutations in AD manifest as a 7-fold increase in the risk of recurrent bacterial infections relative to wild-type *FLG* patients[62].

Thus our understanding of the mechanisms by which *FLG* genotype translates to disease phenotype remains incomplete. Furthermore, recent findings indicate additional levels of complexity to the *FLG*-AD

relationship which are likely to influence the pathogenic mechanisms discussed above. For instance, preliminary data indicate that epigenetic, as well as genetic variation can influence disease outcome. Indeed, a recent study has shown that methylation of a specific CpG site adjacent to *FLG* can modify the influence of *FLG* null mutations on AD risk[95]. Whether inherent variation in enzymes involved in profilaggrin biosynthesis and maturation can also affect atopic disease pathogenesis has yet to be ascertained. Future lines of investigation should clarify how individual variations in filaggrin biology at the DNA, RNA and protein levels interact to determine distinct atopic phenotypes.

Epidermal differentiation genes in addition to FLG

Whilst inherited variation in *FLG* undoubtedly contributes to skin barrier dysfunction in AD, *FLG* null variants are carried by less than one-third of European patients with AD[66] and broad defects in epidermal differentiation are characteristic of the disease regardless of *FLG* genetic status[96]. Taken together, these observations suggest that other factors must modify epidermal homeostasis. Genetic association studies have identified links between AD and gene variants distinct from *FLG* but also located on chromosome 1q21 within the Epidermal Differentiation Complex - a region comprising over sixty genes essential for epidermal structure and function[97]. Of note, a single nucleotide polymorphism (SNP) 7 kb downstream of the gene encoding hornerin (*HRNR*) and an 8-amino acid insertion in the gene encoding small proline-rich protein 3 (*SPRR3*) have been identified as risk factors for AD[98,99]. Additionally, a recent study by Margolis *et al*[100] using whole-exome sequencing and targeted analysis in an African American cohort has identified mutations in *FLG2* (encoding filaggrin-2) that show a significant association with persistent AD - the first established link between a skin barrier gene and AD in subjects of African descent. However, it should be noted that these risk variants lie within a block of linkage disequilibrium and it remains possible that they are tagging unidentified variants within *FLG*. Hornerin and filaggrin-2 are S100-fused type proteins, and thus share a structural organisation similar to filaggrin. Both proteins mirror the subcellular localisation of filaggrin in the differentiating epidermis are believed ultimately (along with SPRR3) to become incorporated into the CE[97]. The precise contributions of these proteins to skin barrier function remain unknown, but available data indicate that filaggrin, hornerin and filaggrin-2 have overlapping or complementary functions in the epidermis[97] and the expression of each may be down-regulated in AD skin[96].

TJs comprise both cytoplasmic and transmembrane proteins, key among which are the claudins, representing the main determinants of barrier selectivity against macromolecules[101]. Claudin-1 expression is down-regulated in non-lesional AD skin and inversely correlated with Th2 cytokines. Variants within the claudin-1 gene, *CLDN1*, have shown association with AD in two ethnically distinct North American populations[102]. Interestingly, this study also demonstrated links between *CLDN1* variants and AD severity, total serum IgE and asthma in subjects of African, but not European ancestry. Given that at present, *FLG* null mutations appear to be considerably less prevalent in African populations relative to European or Asian cohorts[89], these findings (together with those of Margolis *et al*[100] regarding *FLG2*) indicate population specificity in the genetic mechanisms which dominate skin barrier dysfunction in AD.

Finally, protein regulators of lamellar bilayer formation have been implicated in the pathogenesis of AD. Mutations in the gene encoding fatty acid transporter 4 (*FATP4*)[103] and *MATT* (encoding mattrin, a component of the LB secretory system in flaky tail (*maft*) mice[104]) are associated with increased risk of AD[105]. *Maft* mice harbour mutations in both *Flg* and *Matt* genes, and have been used for many years as an experimental model of AD. However, it has recently been shown that *ma/ma* mice, which carry mutations in *Matt* but not in *Flg*, exhibit enhanced TEWL and decreased SC hydration, and develop the spontaneous dermatitis and atopy exhibited by *maft* mice to a greater extent than the filaggrin-null ($Flg^{-/-}$) mice[104-106]. *Matt* may therefore play a greater role than *Flg* in driving the dermatitis phenotype in *maft* mice, supporting a key role for SC lipid secretion in the development of AD.

Thus skin barrier genes may act alone or in combination with *FLG* to modify AD pathogenesis. Whether or not the same genes are also associated with subsequent steps of the atopic march remains to be elucidated.

Epidermal proteases and protease inhibitors

Maintenance of epidermal physiology is dependent on the coordinated activities of skin-resident proteases and anti-proteases. Perturbation of this balance in favour of protease hyperactivity can result in pathogenic barrier disruption, as exemplified in Netherton syndrome (NS). NS is an autosomal recessive disorder featuring ichthyosis and atopic manifestations, which is caused by loss-of-function mutations in *SPINK5*[107] - the gene encoding lympho-epithelial Kazal-type-related inhibitor (LEKTI)[108]. In healthy skin, proteolytic LEKTI fragments specifically co-localise with and regulate the activity of multiple SPs, including members of the kallikrein (KLK) family. KLKs are central to desquamation[109] and also indirectly promote profilaggrin proteolysis[110]. In the skin of NS patients, residual LEKTI expression correlates inversely with enhanced KLK activity[111] resulting in dramatic SC thinning and attenuation of the permeability barrier through unrestricted degradation of corneodesmosomes[109] and lipid-processing enzymes [111] respectively. Permeability barrier function may additionally be compromised through activation of protease-activated receptor 2 (PAR-2), which is expressed in nucleated epidermal layers and can be induced by specific SPs to down-regulate LB secretion[112-114].

A number of association studies have identified SNPs in *SPINK5* which are associated with AD risk in different ethnicities[115-119]. In particular, one such variant, LEKTI E420K, has also been linked to elevated serum IgE[118], food allergies[116], AD severity[116] and AD-

associated asthma[120]. *In vitro* analysis has shown protease hyperactivity resulting from the E420K mutation to result in increased corneodesmosomal destabilisation and premature profilaggrin proteolysis[121], suggesting a functional pathway by which E420K may contribute to filaggrin deficiency and the development of AD. In addition to *SPINK5* polymorphisms, a mutant allele of the *CSTA* gene (which encodes the skin-resident cysteine protease inhibitor, cystatin A) has been reported to associate with AD in a small UK cohort[122]. Fewer data exist for associations between AD and epidermal protease genes; an association between AD and a putative gain-of-function insertion in the 3' UTR of *KLK7* has been described in a British case-control study[122] but failed to be confirmed in subsequent investigations[123,124].

BASIS FOR BARRIER-INITIATED INFLAMMATION

The above pathways together may account for the skin barrier phenotype in AD, but the mechanisms linking epidermal disruption and concomitant allergic inflammation remain unclear. The *maft* and more recently generated *Flg*$^{-/-}$ mouse models[106,125] serve as useful systems in which to study the aetiology of the immune response in the context of inherited barrier impairment. Although showing differences in disease phenotype, both mice exhibit increased percutaneous allergen penetration and a reduced inflammatory threshold to skin irritants and allergens[106,126]. Based on these observations, it is widely postulated that inflammation in AD is a secondary reaction to increased entry of allergens and irritants through the compromised skin barrier. Whilst this is yet to be confirmed in human subjects, it is worth noting that AD patients with *FLG* null mutations have a significantly increased risk of allergic sensitization[60] and irritant contact dermatitis[127], and display elevated numbers of allergen-specific CD4$^+$ T cells compared with wild-type *FLG* patients[128]. Furthermore, it seems likely that in addition to the inflammatory response to penetrating antigens, barrier impairment itself may intrinsically promote downstream inflammation. For instance, elevated SP activity (induced in AD along the pathways described above) not only promotes epidermal barrier breakdown but leads to increased release of active IL-1α and IL-1β[129,130] from the corneocyte cytoplasm, thereby initiating inflammation. Furthermore, SP hyperactivity may stimulate inflammation indirectly by accelerating the degradation of transition desmosomes, leading to secretion of IL-1β, IL-8 and TNF-α from mechanically stressed keratinocytes[131]. Finally, accumulated data indicate that following activation by SPs, PAR-2[131], together with pro-inflammatory cytokines, induces NF-κB-mediated over-expression of the pro-Th2 cytokine, thymic stromal lymphopoietin (TSLP)[132], and IL-6[133]. Evidence in support of the latter pathway has been observed in studies of *maft* mice and *FLG* knock-down keratinocytes *in vitro*[134], suggesting that this immunologic cascade may operate downstream of a primary filaggrin deficiency.

Whilst these data are compelling, the same pathogenic mechanisms have yet to be demonstrated in human AD. Nonetheless, the strength and number of independent associations between *FLG* and atopic disorders greatly surpass those of any other gene expressed in the skin to date[123]. As such, filaggrin deficiency is widely regarded as a primary abnormality leading to skin inflammation in AD[135-138]. Leading on from this, a putative pathogenic pathway has been described in which the reduction in filaggrin acts as a central stimulus for increased SP activity, which in turn triggers the inflammatory response[139]. AD patients with *FLG* null mutations exhibit increased skin levels of IL-1 cytokines, in a manner inversely correlating with NMF levels[87]. This observation has been attributed to pH-induced stimulation of SPs, which can promote inflammation by the mechanisms described above[139]. However, no correlation between SC pH and levels of either IL-1α or IL-1β could be demonstrated in the same study, and recent findings have indicated that *FLG* status is not an essential determinant of SC pH[79,93,106]. Thus whilst these data do not rule out a role for skin pH changes in initiation of inflammation in *FLG*-related AD, it is likely that protease activity and consequently IL-1 levels are modulated by additional factors. For instance, Kezic *et al*[87] have proposed that increased SC calcium concentration (resulting from reduced SC hydration) may favour the activation of calcium-dependent SPs, but based on our current knowledge, this pathophysiological pathway remains entirely speculative.

INSIDE-OUTSIDE PATHOGENIC MECHANISMS

Despite the undisputed involvement of *FLG* null variants in the atopic march, it is important to note that filaggrin deficiency is observed in AD patients even in the absence of known *FLG* mutations[96]. Whilst this may be explained in part by other forms of genetic regulation, it is apparent that a number of additional factors can reduce expression of functional filaggrin, resulting in barrier disruption. In particular, accumulating evidence points to components of the acquired immune response as key players in endogenous barrier impairment, prompting the proposition of a self-sustaining "outside-inside-outside" pathogenic loop in AD[139].

Studies in *maft* mice have shown that following initial sensitization, further defects in barrier function occur, suggesting exacerbation of the primary barrier impairment by the induced inflammatory response[126]. Consistent with this, the Th2 cytokines, IL-4, IL-13, IL-22 and IL-25, which are over-expressed in AD lesions, have been shown to inhibit expression of filaggrin[136-138] and profilaggrin-processing enzymes[140,141] *in vitro*. Inflammation in AD may also compromise skin barrier function by a number of filaggrin-independent mechanisms. The epidermal AMPs, LL-37, hBD-2 and hBD-3, are down-regulated in a Th2-dependent manner[41,142-144] and roles for Th2 cytokines in disruption of SC lipid synthesis[145-147], SC protease activity[148,149] and multiple processes in epidermal

differentiation[147,149-151] have been reported. Finally, whilst not endogenously perturbing the skin barrier *per se*, the cytokines TSLP and IL-31 induce itch[152,153], thereby aggravating the itch-scratch cycle.

ENVIRONMENTAL STRESSORS PLAY UPON BARRIER DEFECTS TO EXACERBATE DISEASE ACTIVITY

The avoidance of exogenous irritants is an important part of atopic disease management. Diverse environmental factors are known to exacerbate atopic disorders, but several are now recognised as having detrimental effects on the skin barrier. For instance, prolonged exposure to reduced ambient humidity (as may occur in centrally heated homes) has been shown to accelerate TEWL and promote profilaggrin proteolysis[73], potentially driving further depletion of cutaneous filaggrin[139]. External modifiers of skin surface pH may also aggravate disease activity *via* enzyme-mediated pathways; use of neutral-to-alkaline soaps is known to induce SC thinning and precipitate flares of AD[154]. Protease activity in the epidermis of AD patients may be further intensified by airborne proteins; proteolytic allergens produced by house dust mites and cockroaches have been shown to penetrate the skin and can exacerbate barrier dysfunction[155,156] both directly, by degrading barrier components[157,158] and indirectly, through activation of PAR-2[159-161]. Staphylococcal infection also has a number of implications for skin barrier function. Essential *S. aureus* surface proteins confer resistance to the bactericidal action of human epidermal FFAs and AMPs[162] and once established on the skin, coagulase-negative staphylococci can secrete peptidases and lipid hydrolases[163] which may further erode the skin barrier. Indeed it has been shown that elevated levels of the enzyme ceramidase (which catalyses the degradation of ceramide to sphingosine and FFAs) are secreted by the bacterial flora of AD patient skin relative to healthy controls[164]. Finally, psychological stress (PS) may precipitate atopic diseases[165] by disturbing the permeability barrier[166,167], SC integrity[166] and antimicrobial defences[168] in the skin of mouse models, *via* a mechanism thought to be mediated by increased production of endogenous glucocorticoids[167-169].

ALLERGIC SENSITIZATION AND TSLP: THE ATOPIC MARCH

The mechanistic link between AD and subsequent phenotypes in the atopic march remains unclear and has been the subject of intensive research in recent years. Generally, current data favour a model in which the downstream systemic effects of allergen penetration through the impaired skin barrier cause immune cells to mount an exaggerated inflammatory response at any allergen-exposed epithelial surface[136,154,170]. This theory fits with several observations: (1) AD is usually the first manifestation of atopy[18]; (2) *FLG* is not expressed in bronchial airways[171] nor the oesophageal epithelium beyond the oro-pharyngeal mucosa[172], suggesting that filaggrin does not directly influence permeability of these epithelia; and (3) allergic sensitization induced by epicutaneous exposure to peanut allergen inhibits subsequent oral tolerance in mice[173].

Central to the uncertainty over the atopic march is the strength of the connection between early allergic sensitization in AD and the risk of allergic airway disease, with the epidemiological data being somewhat inconsistent[14]. Functional studies on the atopic march have identified a prominent role for the cytokine TSLP as a promoter of the Th2 response in AD and a trigger linking epicutaneous sensitization to subsequent asthma[174,175]. TSLP is expressed primarily in lung and skin epithelia[176] where it is recognised as a "master switch" from epithelial barrier disruption to Th2 inflammation[177,178]. Accordingly, TSLP expression is up-regulated in the SC of AD patients compared with healthy subjects[179]. Notably, a recent study using mice in which TSLP is selectively and inducibly ablated in epidermal keratinocytes suggests that skin-derived TSLP is essential for skin allergic inflammation and epicutaneous sensitization, which in turn leads to allergic asthma[180]. This study, in contrast to previous findings[181,182], indicated that keratinocyte-derived TSLP acts as an essential "adjuvant" to the Th2 response induced by topical allergen treatment, but that skin expression of TSLP caused by barrier disruption alone (*i.e.*, without allergen) is not sufficient to promote the full inflammatory phenotype. It is also noteworthy that in this model sensitization was achieved through barrier-defective skin (as opposed to intraperitoneal or intradermal injection of allergen[181,183]), followed by airway challenge, conditions representative of those in human AD. Airway inflammation appears to require an antigen-specific memory $CD4^+$ T cell response[180,183], but occurs independently of TSLP presence in the lung[175,180,183] and circulating TSLP[183], suggesting that skin-derived TSLP is both necessary and sufficient for manifestation of asthma symptoms.

The relative importance of TSLP in the human atopic march remains to be clarified. A recent study in an American paediatric AD cohort identified the *TSLP* variant rs1898671 (which produces attenuated TSLP) as protective against the development of persistent AD[184] however no association with comorbid asthma was identified[184]. It has further been demonstrated that risk of childhood asthma is influenced by epistasis between *SPINK5* and *TSLP*[185]. The authors postulate that *TSLP* and *SPINK5* function in a common pathway in which LEKTI deficiency ultimately leads to TSLP production, an exaggerated Th2 response and allergic lung inflammation[185]. Although the analysed cohort comprised both asthmatic patients with and without concomitant AD, these findings support the view that the systemic consequences of an epidermal pathway are sufficient to induce inflammation at remote epithelia in the human atopic march (Figure 3). Thus it will be interesting to see if evidence for a similar pathway in patients with AD-associated asthma emerges in the

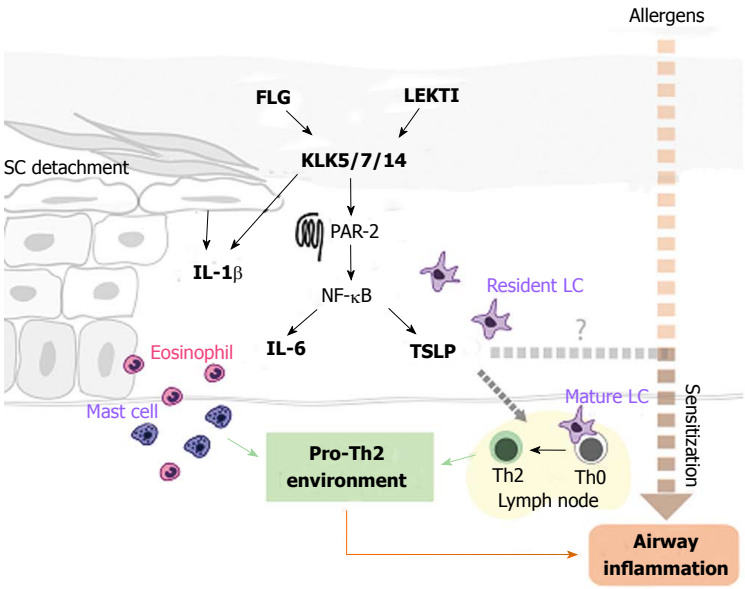

Figure 3 Hypothesised pathways from skin barrier impairment to inflammation and the atopic march. Deficiencies in FLG and LEKTI promote enhanced activity of KLKs, which induce over-expression of TSLP and IL-6 through the PAR-2-NF-kB pathway. KLK hyperactivity also degrades transition desmosomes, inducing the release of pro-inflammatory cytokines from mechanically stressed keratinocytes. The pro-inflammatory environment triggers eosinophil and mast cell recruitment and activation. TSLP activates LCs which promote the differentiation of naïve (Th0) T cells into Th2 cells in lymph nodes. Allergen ingress (dashed red arrow) promotes allergic sensitization and may, with TSLP, stimulate downstream airway inflammation. FLG: Filaggrin; LEKTI: Lympho-epithelial Kazal-type-related inhibitor; KLKs: Kallikrein proteases; TSLP: Thymic stromal lymphopoietin; IL-6: Interleukin-6; IL-1β: Interleukin-1β; LCs: Langerhans cells; SC: Stratum corneum; PAR-2: Protease-activated receptor-2; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells.

coming years. Together, the above findings reinforce the attractive idea that early and aggressive intervention directed towards the skin barrier may impede the progression from AD to subsequent airway inflammation in atopic patients.

CLINICAL IMPLICATIONS: A PARADIGM FOR THERAPY?

The pathogenic mechanisms described above create a strong case for prioritising protection and restoration of the skin barrier in atopic individuals. The current foundations of general AD management include the avoidance of triggering factors and optimal skin care[165], with efforts to address epidermal barrier defects centred on the regular use of emollients. Emollients help to hydrate the skin and soothe pruritus[186]; when applied liberally, they can provide a short-term artificial barrier to reduce TEWL and protect against the penetration of allergens and irritants. The benefits of emollient therapy in controlling the cutaneous symptoms of AD are accepted on the basis of clinical experience[186]. A recent feasibility study of early emollient therapy for AD prevention has shown promising preliminary results[187], but further trials are warranted before the efficacy of this approach can be confirmed. Thus far, emollient monotherapy has rarely proved sufficient for disease resolution in moderate-to-severe AD, in which the use of anti-inflammatory agents is often necessary for exacerbation management[165].

However, corticosteroids and topical calcineurin inhibitors are associated with a spectrum of cutaneous and systemic side effects[165,188] including the impairment of both permeability and antimicrobial barrier functions in AD skin[189-191]. Interestingly, selected emollients have also been reported to disrupt the skin barrier. The majority of over-the-counter (OTC) moisturisers contain non-physiological ingredients (*e.g.*, petrolatum and lanolin) which function by undefined biological mechanisms and in certain cases have been found to compromise SC integrity, permeability barrier function[192] and epidermal differentiation[193]. The above findings, together with recent advances in our understanding of skin pathophysiology, have shifted interest towards novel "barrier replacement strategies". Such therapies aim to correct underlying biochemical abnormalities; they are based upon physiological components and may therefore minimise the likelihood of an unfavourable response[194]. For instance, prescription barrier repair creams (BRCs) are based on SC lipids and differ from their non-physiological counterparts in that they are taken up by keratinocytes, packaged into LBs and ultimately secreted to form lamellar bilayers[195]. In accordance with the lipid deficits in AD skin, a number of "designer" ceramide-dominant and triple-lipid-based barrier repair formulations have now been tested in AD patients[196]. Trials of one ceramide-dominant BRC demonstrated significant reductions in disease severity[197,198] and marked restoration of the epidermal barrier when used as adjunct to topical anti-inflammatories[197]. Moreover, improvements in severity, pruritus and sleep were comparable to the effects of the TCS fluticasone[198], suggesting that BRCs hold potential steroid-sparing effects. However small study size, variation in study design, commercial pressures and the possibility of publication bias make such data difficult to interpret. Furthermore, it is worth noting that the direct comparison of OTC emollients with BRCs has demonstrated equal efficacy for the treatment of mild-to-moderate AD[199], with a notably significant cost disparity between the two treatments. Thus the prescription of BRCs over cheaper and simpler OTC alternatives remains contentious. Large-scale randomized control trials will be necessary to determine whether BRCs are indeed superior for long-term management of AD.

The identification of filaggrin deficiency as a strong predisposing factor for atopic disorders has opened the prospect of filaggrin or NMF restoration as another barrier repair strategy. Topically applied recombinant filaggrin peptide has been shown to penetrate to the SG of reconstructed human epidermis, and is internalised and

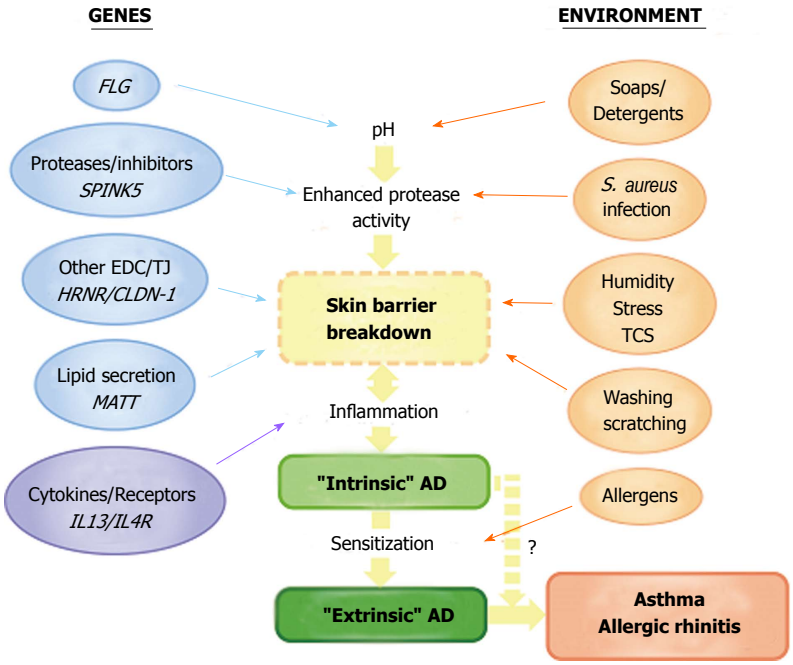

Figure 4 The combination of genetic and environmental factors in the natural history of atopic disease. Note that some allergens (*e.g.*, house dust mite allergens) can also contribute to total protease activity in the skin. Stress: Psychological stress; TCS: topical corticosteroids; *S. aureus*: *Staphylococcus aureus*.

processed to restore epidermal structure in *maft* mice[200]. Furthermore, a recent study has identified a candidate drug that promotes filaggrin mRNA and protein expression *in vitro*, and suppresses the development of skin inflammation when administered orally in the NC/Nga mouse model of AD[201]. These findings, whilst preliminary, hold promise for filaggrin restoration as part of future AD therapy. Clarification of the relative importance of the functions of profilaggrin, filaggrin and filaggrin degradation products will be useful in directing research in this area[202].

Thus the new appreciation of skin barrier pathophysiology should encourage greater clinical emphasis on the optimization of skin care and avoidance of barrier-breaching products in neonates and children. Yet a number of important questions remain. For instance, can restoration of the permeability barrier alone help to normalise epidermal gene expression? Will barrier-based interventions also protect against inflammation and the development of comorbid atopic disorders in patients with AD? Long-term follow-up studies with examination of treatment efficacy at the molecular level will be required. Finally, additional potential treatment avenues (*e.g.*, selective inhibition of SPs and TSLP) have yet to be explored and it is expected that further elucidation of the mechanisms of skin barrier dysfunction in the coming years will identify practicable therapeutic targets.

CONCLUSION

The discovery of loss-of-function mutations in *FLG* has led to a new appreciation of skin barrier dysfunction as primary pathogenic mechanism in atopic disease. Undoubtedly one of the greatest challenges for future research is the dissection of the complex interactions between multiple genetic, environmental and immunologic factors which influence disease pathogenesis (Figure 4). Some interactions with *FLG* have already been identified. Of note, the combined occurrence of mutations in *FLG*, an epidermal gene, and in the genes encoding IL-10 and IL-13, mediators of acquired immunity, have been shown to have a multiplicative effect on AD risk[203] and inter-regulation by SC and SG skin barriers at the mRNA and protein levels has been reported[101,204]. These interactions, whilst yet to be demonstrated in human patients, may present further difficulties in determining the relative importance of individual barrier components in AD pathogenesis. Progress in the molecular genetics of atopic disease has been accelerated by advances in next-generation sequencing techniques, but the additional complexity of multiple gene-gene and gene-environment interactions requires further development of bioinformatics analysis. The integration of genetic, transcriptomic and proteomic analyses is also computationally demanding. However, a recent transcriptomic analysis of AD skin used *FLG* genotype to stratify data and has offered insight into novel pathways and predicted functional networks[205]. The expanding understanding of epigenetic variation is also predicted to contribute further novel mechanistic insights in the coming years.

Understanding the interplay between atopic genes and environmental factors will be vital to explaining (and perhaps controlling) the rising prevalence of atopic diseases. This will require long-term epidemiological studies in which early genetic profiling of *FLG* and other disease genes is coupled with careful monitoring of patient environment. Such studies may help to explain how specific gene variants act in the context of different external insults to induce a range of related yet distinct atopic phenotypes. Evaluation of *FLG* genetic status is not commonplace in pharmacogenetic studies or current clinical management of AD. However careful clinical examination can identify *FLG* null genotype[206] and as the multiple influences of filaggrin on atopic disease trajectory are clarified, this will benefit clinical care and

prognostic predictions. More detailed knowledge of genotypes associated with atopic phenotypes could in the future help to direct the prescription of personalised therapeutic regimes, including focused instructions for disease prevention and targeted treatment. Thus early control of skin barrier function in high-risk patients may in future prevent allergic sensitization and what had previously been considered the inevitable path through the atopic march.

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REVIEW

Frontal fibrosing alopecia update

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Abstract

Frontal fibrosing alopecia (FFA) is a recently described form of primary cicatricial alopecia, characterized by progressive recession of the frontotemporal hairline and eyebrow loss, occurring predominantly in postmenopausal women. The incidence of FFA has increased significantly during the last decade and we may be facing an epidemic of the disease. Because this condition causes permanent hair loss, prompt diagnosis and treatment are essential for obtaining optimal outcome. This article reviews existing knowledge on epidemiology, etiopathogenesis, clinico-histological features, diagnosis, and treatment modalities of FFA.

Key words: Cicatricial alopecia; Scarring alopecia; Frontal fibrosing alopecia; Lichen planopilaris; Hair loss

Core tip: Frontal fibrosing alopecia (FFA) is a recently described form of primary cicatricial alopecia, characterized by progressive recession of the frontotemporal hairline and eyebrow loss, occurring predominantly in postmenopausal women. The incidence of FFA has increased significantly during the last decade and we may be facing an epidemic of the disease. Because this condition causes permanent hair loss, prompt diagnosis and treatment are essential for obtaining optimal outcome. This article reviews existing knowledge on epidemiology, etiopathogenesis, clinico-histological features, diagnosis, and treatment modalities of FFA.

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INTRODUCTION

Frontal fibrosing alopecia (FFA) is a relatively recently recognized form of primary cicatricial alopecia (PCA), characterized by progressive recession of the frontotemporal hairline and eyebrow loss, occurring predominantly in postmenopausal women. It was described by Kossard[1] in 1994. The number of patients with this condition has markedly increased over last decade and there are dermatologists who believe that we are facing a possible epidemic of this challenging disease[2-7]. Due to the clinical and histologic similarities with lichen planopilaris (LPP), many dermatologists consider it to be a clinical variant

of LPP with marginal distribution. Both entities show perifollicular erythema and follicular hyperkeratosis, and lichenoid lymphocytic infiltrate along with perifollicular fibrosis leading to hair follicle destruction[1,4,5,7-11]. The cause of "marginal march" in FFA is unknown and therefore whether it is an LPP variant or a distinct entity with shared clinical features, remains to be determined[4,12,13]. The pathogenesis of FFA is poorly understood, although an autoimmune reaction and hormonal androgen-driven factors seem to play a role[4,9,13]. Several familial cases have been reported that raise the possibility of a genetic inheritance factor[3,14,15]. Some researchers have also suggested that there may be an environmental trigger for the disease[16,17]. The natural history of FFA is variable, although slow progression with spontaneous remission is the most frequently reported outcome[2,8,13,18]. The general uncertainties with this entity begin with an unknown origin and pathogenesis and continue with the difficulty of finding effective treatment. A range of topical as well as systemic treatments has been disappointing. Several researchers have reported stabilization with topical and intralesional corticosteroids, antibiotics, hydroxychloroquine, immunomodulators, and 5-alpha-reductase inhibitors[2-5,7,11,13,18-21].

EPIDEMIOLOGY

In 1994 Kossard[1] described 6 postmenopausal women with distinctive progressive scarring alopecia affecting the frontal hairline and frequently extending to the temporal and parietal regions. This contrasted with the usual multifocal appearance of LPP, yet had similar histopathological features. Kossard[1] named this entity "postmenopausal frontal fibrosing alopecia" and further characterized it clinically and histologically in subsequent studies[1,8]. Since 1994, numerous case reports and studies on FFA have been published. Several reports have included men and premenopausal women, and it has been proposed that "postmenopausal frontal fibrosing alopecia" is better termed "frontal fibrosing alopecia". The incidence of FFA is unknown, although most dermatologists agree that there has been an increase in the number of patients with this condition in recent years[2-7]. A ten-fold increase in the number of cases seen annually over the last decade was described by MacDonald *et al*[5]. According to reports published to date, over 85% of the patients reported were white postmenopausal women[2-5,17,18,20]. However, this condition has also been reported in Black, Asian, and Hispanic male and female patients[3,4,20]. Several studies showed a high incidence of early menopause, up to 17%, compared with an incidence of 6% in the general population[2,3]. In addition, several reports described that in a considerable number of women the menopause had been surgically precipitated, post-hysterectomy[2,3]. The course of the disease does not seem to be affected by the onset of hormone replacement therapy[4,21]. Age of onset of the disease ranged from 18 to 87 years with the highest incidence in the sixth decade[2-5,7,20]. One study showed an earlier age of onset of FFA in black patients, with 74% of those cases starting prior to menopause[22], yet another study described the age of onset to be similar to that in a white population[23]. There have been several reports of familial cases of FFA mentioned as well[3,14,15]. A family history of FFA in 8% of patients was recently described in a multicenter review consisting of 355 patients[3]. Most researchers found no association between previous medical background and administered medications, except for the increased incidence of autoimmune diseases[3,5-7,9,13]. One recent study described dyslipidemia, hypothyroidism, hypertension, and osteoporosis as the most frequent comorbidities[3]. Another study described an association between beta-blockers and nonsteroidal anti-inflammatory drugs, with a possible protective effect of angiotensin-converting enzyme inhibitors[5]. Concurrent female pattern hair loss or senescent alopecia has been described in 0%-68% of patients[3-5,7,13]. Thyroid abnormalities are probably the main association described, with an incidence between 9% and 23%[3,4]. Previous or concurrent lichen planus (LP) was reported in FFA patients, with a frequency ranging from 2% to 17%. Compared to LPP, in which LP is found in 28%-50% of cases, the association between cutaneous and mucosal lichen planus and FFA seems to be less common[4,5,20]. Other autoimmune diseases reported to be associated with FFA include vitiligo, alopecia areata, atopy, psoriasis, rheumatoid arthritis, lupus erythematosus, and polymyositis[3-5,20]. FFA has also been described in patients following hair transplantation and face-lift surgery[24]. One study assessed the socioeconomic and smoking status of patients with FFA and showed an association with the higher affluent group and significant preponderance of nonsmokers within the cohort of Scottish patients comparing with national data[5]. Another study from Spain showed 87% were nonsmoking patients, but it was found to be similar to the percentage of Spanish women matched by age, so their results did not support the protective effect of tobacco against FFA[3]. Laboratory work-up that included hormonal profile evaluation was unremarkable in several studies[3,12,13,19].

ETIOLOGY AND PATHOGENESIS

The etiopathogenesis of FFA remains uncertain. A key element seems to be destruction of the epithelial hair follicle (HF) stem cells located in the bulge region of the HF leading to permanent hair loss.

RELATION TO LPP/LP

Most authors consider FFA as a clinical variant of LPP in a patterned distribution that primarily affects postmenopausal women. In fact, the North American Hair Research classification system currently classifies FFA as a lymphocytic primary cicatricial alopecia within the spectrum of LPP. This hypothesis is based on similar histopathologic features. Both entities show a lichenoid

lymphocytic inflammatory infiltrate involving the upper and midportion of the hair follicle, with perifollicular fibrosis, and hair follicle destruction. Several authors reported coexistent mucosal or cutaneous lesions of LP in patients with FFA and postulated the phenotypical relation of these two conditions[1,4,5,7,8,10]. Previous or concurrent LP was reported in FFA patients, with a frequency ranging from 2% to 17%, in comparison to LPP, in which LP is found in 28%-50% of cases[4,5,20]. This indicates that the association between mucosal and cutaneous LP and FFA seems to be less common than in LPP. Poblet *et al*[12] examined the clinicopathological features of FFA as well as the similarities and differences between FFA and LPP. No clear-cut histological differences between these two entities were reported; however, their study demonstrated that, in general, FFA tends to show more apoptosis and less lichenoid tissue reaction and damage to basal cells, along with spared interfollicular epidermis. In their opinion, whether FFA can be considered a variant of LPP just because they share a common inflammatory pattern, or it is a distinct entity, is still questionable[12]. Several studies have shown patchy fibrinogen deposition and globular deposits of IgM or IgA along the epidermal or infundibular basement membrane zones (BMZ) in direct immunofluorescence (DIF) in LPP patients, but these findings were not observed in FFA[6,12,19]. In addition to these histological findings, it appears that there are differences in treatment response, indicating that FFA and LPP should be considered two separate entities. High and moderate potency topical corticosteroid preparations and systemic corticosteroid preparations and hydroxychloroquine were reported as effective in LPP patients, whereas in the cases of FFA the response to these treatments was less impressive if at all. On the other hand, there are several reports of the effectiveness of anti-androgenic drugs such as dutasteride and finasteride in FFA patients[3-5,7,9-11,13,20,21].

HORMONAL INFLUENCE

Next to an inflammatory process caused by infiltrating lymphocytes, hormonal influence has been also suggested as a potential factor in the pathogenesis of FFA. It is argued that the FFA is a scarring variant of pattern hair loss[13]. The role of androgens was suggested due to involvement of the androgen-dependent HF at the frontal line and onset of the disease after menopause. It was further supported by reported clinical improvement with anti-androgen therapy, such as 5-alpha-reductase inhibitors (finasteride and dutasteride)[3,7,13,18]. However, several studies have examined the hormonal profile of patients with FFA and did not show increased levels of androgens or any other hormonal abnormalities[3,13,19]. According to existing reports, hormone replacement therapy did not cause an improvement in patients with FFA[7,8,13]. A lack of any correlation to peripheral sex hormone levels or the use of hormone supplementation may suggest that regional factors of the frontotemporal scalp are involved. In addition, FFA has also been reported in men and premenopausal women[3-5,7,9,20]. The majority of patients with FFA have experienced progressive hair loss from the frontal hairline that was not preceded by progressive miniaturization of HF. In addition, FFA targets the follicles not linked to the areas of patterned hair loss. For example, involvement of the eyebrows typical of FFA does not occur in cases of androgenetic alopecia. In summary, according to existing data there is not enough evidence to implicate a hormonal basis as the cause of FFA.

GENETIC FACTORS

The occurrence of familial cases of FFA points to a possible genetic contribution[3,14,15,17]. It is also well documented that inherited genetic traits codetermine susceptibility to autoimmune diseases as well as the influence of different environmental factors. On the other hand, one could argue that the accumulation of a number of cases in the same family simply indicates exposure to a common environmental trigger. The development of FFA in transplanted HF also raises the issue of whether the influence of local factors in the frontal area determines follicular destruction rather than the inherent qualities of the follicles at this site[24]. Further accumulation of familial cases may allow assessment of the role of genetic factors and identification of gene mutations predisposing to FFA.

AUTOIMMUNITY AND INFLAMMATION

Several studies showed that in FFA the lymphocytic infiltrate and fibrosis selectively affect the HF of the frontal margin and eyebrows. The disease concomitantly involves hair follicles of different types: terminal, intermediate, and vellus hairs, and different stages of the cycling (from anagen to telogen)[13,25]. Preferential involvement of vellus and intermediate HF is supported by several authors[13,26]. The reason for this selection is still unknown. A T-cell-mediated autoimmune reaction against follicular keratinocytes appears to play a major role in this process. Important mechanisms implicated in the irreversible follicular destruction include collapse of the HF immune privilege, cytotoxic cell-mediated follicular damage along with increased proinflammatory response, and increased apoptosis[12,17,27]. The inflammatory cells attack and destroy keratinocytes expressing particular antigens. These target follicular antigens have as yet not been defined. The inflammation is mostly located around the bulge area, where the stem cells are present, thus causing permanent hair loss. The fact that several autoimmune diseases have been associated with FFA also suggests an autoimmune pathogenesis[3,5-7,9,13].

EPITHELIAL-MESENCHYMAL TRANSITION

Epithelial-mesenchymal transition (EMT) may contribute

to fibrosis in FFA. Previous studies suggested a possible contribution of EMT in renal, liver, and pulmonary fibrosis. Recently, Nakamura *et al*[28] demonstrated that an EMT marker, snail 1, was expressed in the fibrotic dermis of FFA patients. This observation suggests a possible role of EMT conversion of HF epithelial cells to fibroblasts regulated by transforming growth factor-β in the pathogenesis of the FFA[17,28].

PPARγ DEFICIENCY AND SEBACEOUS GLAND DESTRUCTION

Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of the nuclear receptor super-gene family that regulates the expression of genes involved in lipid homeostasis and inflammatory responses and has a crucial role in maintaining the pilosebaceous unit. Recent gene expression studies identified a deficiency in PPARγ-mediated signaling in LPP patients and suggested that the loss of this function may trigger the pathogenesis of LPP. Several authors reported the efficacy of PPARγ-agonists in treatment of LPP. The deficiency of PPARγ has yet to be studied in FFA[16,29].

ENVIRONMENTAL TRIGGERS

The epidemiology of FFA strongly suggests a role of environmental factors in its development. The occurrence of the disease in several members of the same family may indicate exposure to common environmental triggers. A contact sensitizer, environmental toxin, dietary factor, or infectious agent could be responsible for triggering the process in predisposed subjects. For example, photoallergic reaction to pyridoxine hydrochloride found in a wide variety of hair care products, needs to be evaluated as potential trigger for scarring alopecia. Up to date a role of application cosmetic products and hair-care practices in the pathogenesis of FFA were not documented and their role remains unclear. The possible role of microbial antigens or super-antigens in this context remains to be elucidated. Recently the possible link between the aryl hydrocarbon receptor (AHR) and its overexpression in cicatricial alopecia was suggested. Since the ligand for the AHR is activated by dioxin, the possibility that dioxin-like substances can trigger the disease *via* the AHR was discussed recently, but remains unproven[16,17,29]. Dioxin-like chemicals are environmental pollutants that are ingested mostly with food of animal origin: meat, dairy products, or fish predominate, depending on the country. These toxins persist in the environment and are very slowly eliminated from the human body. Chronic low-dose exposure may lead to the accumulation of dioxins in lipid-rich regions such as sebaceous glands, causing loss of PPARγ expression and thereby scarring alopecia in susceptible individuals.

In conclusion, future investigation is needed to clarify the pathogenesis of FFA and to define the role of genetic, autoimmune, hormonal, and environmental factors and lipid metabolism in this challenging condition.

CLINICAL FEATURES

FFA has a distinct clinical presentation characterized by recession of the anterior hairline with loss of follicular orifices in the area of hair loss. The band-like zone of alopetic skin appears pale, shiny, and smooth contrasting to the mottled, photo-aged skin of the forehead. Although the frontal area is most commonly affected, and despite the name "frontal" fibrosing, FFA may appear on other sites, such as the temporo-parietal as well as the retroauricular and occipital areas. Hairline recession usually occurs symmetrically and bilaterally, giving rise to a band of alopecia between 0.5 and 10 cm from its original site (Figure 1A-C). Although the progression is relatively slow, distribution can be widespread, involving the entire hairline and leaving only a band of hair on the top of the scalp, which is described as "clown alopecia". Increased venous vasculature on the temples is also a common observation (Figure 1B). Perifollicular erythema and papules along the new hairline indistinguishable from that seen in LPP are common findings as well (Figure 1D). Degree of erythema and scaling may be variable, being marked in some, but minimal in others[1-11,13,18-20]. The striking feature is the unnatural appearance of the hairline caused by loss of both terminal and vellus hair (Figure 1D)[13,30]. The presence of "lonely hair" described by Tosti *et al*[31] is also a useful diagnostic clue (Figure 1E). This sign describes the presence of isolated terminal hairs in the middle of a bald band marking the original hairline prior to hair loss. This is a common but non-specific sign of FFA. While some patients can present with associated itching, pain, and burning sensations, it is not unusual to see patients who are completely asymptomatic without frank inflammation. Most patients with FFA exhibit some degree of eyebrow diminution, recognized as a characteristic feature of this disorder. It can occur either before or after the onset of frontotemporal recession. Hair loss from the lateral third of the eyebrows is typical, but in some cases, there may be diffuse thinning or total loss of eyebrows (Figure 1E). Eyelash involvement was also reported, albeit less frequently (Figure 1E)[1-11,13,18-20]. Recently, non-inflammatory asymptomatic facial papules, mainly confined to the temporal area of the face, were reported as possible sign of facial vellus hair involvement (Figure 1F)[32]. Several authors described decrease or absence of facial vellus hair as well as loss of hair from peripheral body sites and generalized hair loss[2,6,8,13,18]. It should be noted that despite frequent reports of axillary and pubic hair loss, it cannot be clearly attributed to the disease process considering that this is also a common symptom in postmenopausal and older women.

Findings on trichoscopy include the absence of follicular openings, absence of vellus hairs, white dots (corresponding to the follicular fibrosis seen in dark-skinned individuals), and brown halos (expressing the inflammation). Reduced hair density, follicular

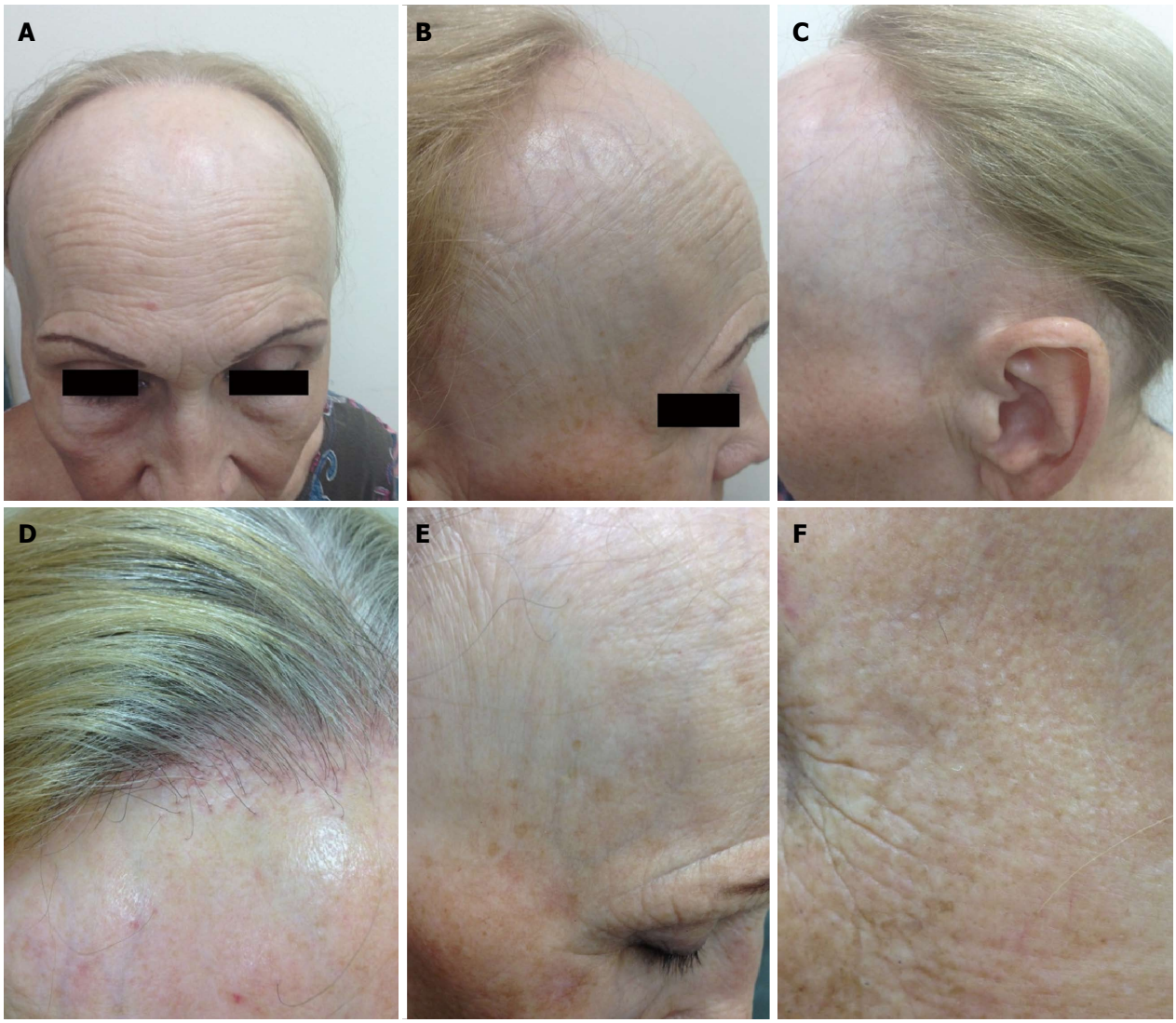

Figure 1 Clinical presentation of frontal fibrosing alopecia. A: Fronto-temporal hairline recession in a band-like distribution. The pale, smooth, and atrophic skin of the alopetic area contrasts with the sun-damaged and pigmented skin of the forehead; B: Lateral view: Increased visibility of veins on the forehead; C: Retroauricular area involvement; D: Absence of vellus hairs, perifollicular erythema and hyperkeratosis over the frontal hairline; E: Eyebrow loss and isolated hairs in the middle of the alopetic band ("lonely hair sign"); F: Facial papules over the temporal area indicating vellus hair involvement.

plugging, perifollicular scale (also called peripilar casts), and perifollicular erythema are frequent around the existing hairs at the anterior hairline[30,33]. Follicular red dots on the forehead corresponding to another sign indicating vellus hair involvement were described recently[34].

HISTOPATHOLOGY

A 4-mm punch biopsy from an active inflammatory lesion within the hair-bearing margin of the alopetic patch is preferred for pathological study. Horizontal sections seem more informative than vertical orientation. Typical histopathological findings in FFA show lymphocytic infiltrate mainly localized to the isthmus and infundibular regions with the lower portion of HF being spared. The inflammatory infiltrate shows lichenoid characteristics of variable severity, with a follicular interface dermatitis pattern, whereas the overlying interfollicular epidermis is spared. The number of HFs is reduced, perifollicular lamellar fibrosis is evident, and HFs are often replaced by fibrous tracts. The sebaceous glands are absent or only focally present, and the external root sheaths may show vacuolar degeneration of the basal layer and apoptosis of follicular keratinocytes. Perivascular and periadnexal inflammation is absent. Histopathologic findings are variable according to disease progression. In its active stage the inflammation is much more prominent, while in the "burned-out" stage the specimen may show only a follicular scar. Most authors consider FFA as a clinically distinct variant of LPP with patterned distribution, based on their similar histopathological findings[1,6,8]. However, recently a number of subtle histopathological differences between these two entities were described[12]. In general, the lichenoid tissue reaction was shown to be milder in FFA than in LPP. While LPP cases may show intense damage of the basal cell layer, this feature is not observed

in FFA. The involvement of interfollicular epidermis was not found in FFA, but it is common in LPP. FFA cases tend to show much more apoptosis than LPP. The foreign body reaction to the follicular destruction of the external root sheath and the hair shafts trapped in the dermis were found to be more frequent and more prominent in FFA[12]. In addition, immunofluorescence tests are negative in FFA, while they can show patchy fibrinogen deposition and globular deposits of IgM or IgA along the epidermal or infundibular basement membrane zones in LPP[6,12,19]. It was also reported that there may be a predilection for the involvement of intermediate and vellus follicles in FFA[13]. Recently, the sign of "follicular triad" was suggested as a possible diagnostic clue to the diagnosis of FFA[26]. This sign describes the simultaneous involvement of HF of different types: terminal, intermediate (0.03-0.06 mm), and vellus (< 0.03 mm) and in different stages of cycling (anage, catagen, and telogen) with inflammatory infiltrate and perifollicular fibrosis. Although clinically noninflammatory, several studies have shown that histologically eyebrow, facial, and peripheral hair loss demonstrate inflammation and fibrosis, suggesting that the process of permanent hair loss is generalized rather than localized only to the frontal scalp[2,6,13].

DIAGNOSIS

In most cases the diagnosis of FFA can be made on clinical grounds and supported by trichoscopy. When the clinical diagnosis is not conclusive, for example, in the early stages when the follicular density is almost normal, in partially treated cases, or in advanced cases when clinical signs of inflammation are subtle, a dermoscopy-guided biopsy from a site of disease activity is indicated to provide for histopathological confirmation[2,5,10,13].

Key features of FFA that help to make clinical diagnosis are as follows: (1) largely affects postmenopausal women; (2) symmetric and progressive band-like recession of the fronto-temporal region with loss of follicular ostia; (3) pale and atrophic skin devoid of follicular orifices in the zone of alopecia, contrasted with the hyperpigmented sun-damaged skin of the forehead; (4) perifollicular erythema and follicular hyperkeratosis around the existing hairs at the margin of alopecia; (5) presence of isolated terminal hairs in the bald band on the forehead ("lonely hair" sign); and (6) marked decrease or complete loss of the eyebrows.

On trichoscopy: (1) absence of follicular openings; (2) reduced hair density, absence of vellus hair at hairline margins; (3) follicular plugging, perifollicular scale, and erythema around the existing hairs at the margin of alopecia; and (4) peripilar white dots and brown halos (incontinentia pigmenti).

Histopathological features include: (1) lichenoid lymphocytic infiltrate mainly localized to the isthmus and infundibulum; (2) follicular interface dermatitis pattern, with sparing of interfollicular epidermis; (3) reduced number of HFs, perifollicular lamellar fibrosis, replacement of HFs by fibrous tracts; (4) the sebaceous glands are absent or only focally present; (5) vacuolar degeneration of the basal layer and apoptosis of follicular keratinocytes in the external root sheaths; (6) absence of perivascular and periadnexal inflammation; and (7) follicular triad sign: simultaneous involvement of different types of hairs (terminal, intermediate, and vellus) and in different stages of cycling (anage, catagen, and telogen).

DIFFERENTIAL DIAGNOSIS

FFA should be differentiated from several conditions that cause marginal scalp hair loss. In some cases it is difficult to distinguish between FFA and alopecia areata involving hairline, for example in sisaipho or ophiatic pattern alopecia areata. Presence of follicular orifices, exclamation mark hairs, yellow dots, black dots, and dystrophic hairs on dermoscopy can help establish the diagnosis of alopecia areata. On the other hand, lack of follicular ostia, perifollicular inflammation, and symmetric eyebrow involvement appear in FFA. When it is difficult to differentiate between the diseases clinically, skin biopsy is recommended.

Frontotemporal form of female pattern hair loss (FPHL) is another condition that may be confused with FFA. Unlike FFA, female pattern hair loss is not a cicatricial process. In FPHL, the vellus hair is present, and there is no perifollicular inflammation or scale.

Another condition that can cause hair loss in the periphery of the scalp is traction alopecia. Differentiation from traction alopecia can usually be made from the history of traction or chemical straightening, and supported by the finding of broken hairs of various lengths in the affected area. There is no eyebrow and peripheral hair loss or perifollicular inflammation, and vellus hair is preserved. The lichenoid follicular inflammation and fibrosis are absent and sebaceous glands are preserved in histologic sections.

Cicatricial marginal alopecia was recently described by Goldberg[35] in women who presented with hair loss limited to the periphery of the scalp. There was no history of traction. The clinical picture revealed hair thinning or almost complete alopecia of the scalp margin and eyebrows were not involved. Dermoscopic features were characterized by low hair density with loss of follicular ostia, reduced diameter of remaining hairs, and absence of perifollicular erythema or hyperkeratosis. Histological sections revealed a decrease in HF density with normal sebaceous glands and no signs of inflammation.

There are cases where the possibility of genetic family high hairline should be considered. In this condition, the front line of hair can be located relatively high, but it has a natural appearance, and contains all types of hair (terminal, intermediate, and vellus). There are no clinical signs of inflammation or eyebrow involvement.

The differential diagnosis with other diseases from the PCA group can be challenging. The distribution

pattern of alopecia (single plaque, multifocal, hairline recession), the involvement of other hairy sites (eyebrows, axillae, body hair), and the presence of other associated cutaneous manifestations may allow clinical distinction in a large number of cases.

While FFA patients are mostly asymptomatic and only rarely have mild itching, intense pruritus, pain, burning, and scalp tenderness are common in LPP patients. The distribution of the hair loss also differs. There is a multifocal disease with a predilection to central scalp in LPP. The involvement of hair in the peripheral portion of the scalp typical for FFA is uncommon. Histologic sections of LPP show less apoptosis and more inflammation. DIF is not uncommonly negative, with some cases showing patchy deposition of fibrinogen and IgM, or less commonly IgA and C3, along the follicular BMZ. Elastin staining reveals a superficial, wedged-shaped scar associated with loss of the upper follicular elastic sheath.

Piccardi-Lasseueur-Graham-Little Syndrome is classically considered a type of LPP; however, several researchers suggest that it is a distinct entity. It is characterized by a triad of scarring patchy scalp alopecia, nonscarring alopecia of the axillae and the pubic area, and grouped or disseminated follicular papules with spinous scale on the trunk and extremities. Face and eyebrows can be also affected. Pathology shows features of both LPP and keratosis pilaris atrophicans.

Fibrosing alopecia in a pattern distribution was described by Zinkernagel *et al*[36]. This entity shares clinical and histologic features similar to LPP, but is limited to an area of androgenic hair loss. The centrovertical scalp is usually diffusely affected, but some patients also have frontotemporal loss similar to that seen in FFA. Biopsy specimens demonstrate the HF miniaturization and a lichenoid inflammatory infiltrate targeting the upper follicle region.

Discoid lupus erythematosus (DLE) is usually multifocal and does not have a predilection for the marginal scalp. In contrast to FFA, the center of lesion, rather than the hair-bearing periphery, is affected in the active disease stage. A search for DLE elsewhere on the body or for coexisting signs of systemic lupus erythematosus is essential. The histologic presentation of DLE is also different. Superficial and deep perivascular and perieccrine inflammation and dermal mucin deposition are typical features of DLE and are not found in FFA. In addition, the interface change is vacuolar and not lichenoid, often with a thickened basement membrane. The interfollicular epidermis is generally not spared. The dermal sclerosis is usually less severe than in FFA and telangiectases are present. The DIF of DLE is usually specific with deposition of immunoglobulin (Ig) G or IgM and C3 in a granular or homogenous band-like pattern at the dermal interface with the follicular epithelium and epidermis. Elastin staining reveals a diffuse dermal uptake that spares the fibrous tracts of extinct follicles.

Pseudopelade of Brocq is another type of PCA that predominantly affects the vertex and parietal areas of scalp with irregular multifocal areas of scarring alopecia. The lesions are asymptomatic, limited to the scalp, with no visible perifollicular inflammation or follicular hyperkeratosis. Multifocal coin-sized plaques and larger polycyclic or irregular plaques of alopecia coalesce and create a "footprints in the snow" pattern. There are no pathognomonic features on histology. In early lesions, massive lymphocyte-mediated apoptosis of the follicular sheath has been observed. Lymphocytic perifollicular infiltrate around the infundibulum without interface changes, and prominent concentric lamellar fibroplasia are described as established disease features. Findings on DIF are usually negative, but scanty IgM deposition along the follicular infundibular basal membrane zone can be seen. Elastin stains reveal hyalinized dermis with markedly thickened elastic fibers throughout and broad follicular fibrous tracts with intact elastic sheaths, unlike the pattern seen in LPP and DLE.

Central centrifugal scarring alopecia predominantly occurs in adult black women and presents with asymptomatic, noninflammatory alopecia that begins in the midline central scalp, with gradual centrifugal spread over the years. The histologic features are not specific in this type of PCA and resemble Pseudopelade of Brocq.

Alopecia mucinosa has a polymorphous presentation and can be nonscarring or scarring. Histology is diagnostic showing mucinous degeneration of the follicular and sebaceous epithelium associated with perifollicular and perivascular lymphocytic infiltrate.

Keratosis Follicularis Spinulosa Decalvans (KFSD) may also share features similar to FFA. Unlike FFA, it usually begins in infancy and may improve during puberty. There are sporadic and familial cases. Men are more likely to present with a more severe disease. Triad of KFSD includes widespread keratotic papules succeeded by atrophy, cicatricial alopecia, and photophobia. Alopetic plaques have multifocal distribution with patchy involvement of the scalp, eyebrows, and eyelashes, with perifollicular hyperkeratosis and erythema at the edges. It can be associated with focal palmoplantar keratoderma. In some cases, follicular pustules appear at the hair-bearing margins, resembling folliculitis decalvans. The histopathology shows a mixed inflammatory infiltrate with follicular plugging, hypergranulosis, and neutrophilic spongiosis of the infundibulum and adjacent epidermis in acute disease and perifollicular lymphocytic infiltrate thereafter.

Neutrophilic type cicatricial alopecia can also simulate FFA, especially in advanced stages of the disease, when pustules and crusts are absent, and neutrophilic infiltrate of folliculitis decalvans disappears. Multifocal distribution without predilection to marginal scalp and presence of tufted HFs are characteristic of folliculitis decalvans.

TREATMENT AND PROGNOSIS

Because the disease has been described relatively recently, little is known about the natural history of FFA. The

rate and extent of frontal recession is highly variable. According to several studies an average rate of recession is 0.9-1.05 mm per month[2,3,5]. It has been described that FFA may advance slowly and stabilize over time regardless of treatment continuation, whereas in some patients the recession progresses despite therapeutic intervention and eventually involves the entire scalp[2,8,13,18]. One recent study demonstrated that eyelash loss, presence of facial papules, and body hair involvement may be associated with poor prognosis, while eyebrow loss as the initial clinical presentation was associated with mild forms of FFA[3]. It has also been described that visible erythema does not always correlate with alopecia progression[5]. Because the alopecia is cicatricial, hair regrowth is not possible, except when therapy has been started at the very beginning of the disease; therefore, early diagnosis is crucial. The treatment goals are to abort the disease progression, prevent further alopecia, and reduce symptoms. The fact that FFA progression is slow, with spontaneous cessation of the disease years after onset, makes both treating the disease and assessing the effectiveness of the administered treatment difficult. Given the tendency of FFA for spontaneous stabilization, some apparent responses may simply have been part of the natural course of the disease. The available evidence on the treatment of FFA comes from retrospective observation studies. There are no controlled clinical trials to evaluate the available modalities. It should be noted also that there is currently no standardized outcome measure for the evaluation of treatment efficacy in FFA. Several researchers have used LPP activity index in order to assess treatment efficacy in FFA patients[20,37]. In view of the differences that exist between FFA and LPP, such as a lower weight of subjective symptoms and clinical signs of inflammation in FFA, the relevance of this index in FFA patients is questionable. Recently, a clinical severity scale of FFA was suggested, basing on measuring the area of hairline recession. It includes 5 grades of severity: I (< 1 cm), Ⅱ (1-2.99 cm), Ⅲ (3-4.99 cm), Ⅳ (5-6.99 cm), and Ⅴ (≥ 7 cm, also called clown alopecia), which are grouped as mild FFA (grades I and Ⅱ) and severe FFA (grades Ⅲ, Ⅳ, and Ⅴ)[3]. We believe that the main measure to be considered in evaluating the treatment efficacy in FFA is progression of hairline recession. Changes in erythema or subjective symptoms should be evaluated separately. Treatment of FFA has been disappointing. It is unclear whether treatments alter the natural history of the disease. Several topical and systemic therapeutic options have been reported to have some efficacy in halting the disease progression in retrospective studies.

TOPICAL CORTICOSTEROIDS

According to previous reports, almost all patients had been treated with moderate to high potency topical corticosteroids. Although in some cases this treatment resulted in reduced inflammation, it did not halt progression of alopecia in most cases[7,11,21].

INTRALESIONAL CORTICOSTEROIDS

Intralesional corticosteroid injections have been considered as first-line treatment by most researchers. Triamcinolone acetonide at a concentration of 5-10 mg/mL (to a maximum of 2 mL) for the scalp and 2 mg/mL for the eyebrows (location is more susceptible to atrophy) every 4-8 wk produced a response rate of up to 60%[21]. Higher concentrations of triamcinolone acetonide were reported as well, and in these cases the time intervals between injections were longer. For example, triamcinolone acetonide injections at a concentration of 20 mg/mL were made every 3 mo[13,18]. However, most researchers prefer to employ a lower concentration in order to reduce the risk of cutaneous atrophy. Intralesional corticosteroids are more effective in the early stages of the disease, especially in patients with prominent clinical and histologic inflammation. Once alopecia has advanced to the fibrotic phase, it provides no benefit and may even worsen the fibrosis and atrophy that characterize the advanced stages of FFA[18,19]. It should be noted that in most reported cases this treatment was given in combination with other treatment modalities, which makes it difficult to judge its own efficacy. Several researchers have emphasized that the results of this treatment are less impressive compared with those in the cases of LPP[2-5,29].

SYSTEMIC CORTICOSTEROIDS

Administration of oral prednisone may be useful in rapidly progressive diseases, especially when the signs of inflammation are prominent. However, after the discontinuation of treatment a relapse is common. There are different protocols in the literature. Usually oral prednisone is administered in the dose of 0.5-1 mg/kg per day for a period of 1 to 18 mo and tapered to discontinuation over 2-4 mo[1,8,32,38]. There are researchers who preferred intramuscular triamcinolone pulses of 0.5-1 mg/kg every 3-4 wk for 3-4 mo[13,29]. The combined treatment of systemic corticosteroids with other topical or systemic treatments was also described. Existing literature indicates that, like with other anti-inflammatory treatments, corticosteroids in FFA are less effective than in LPP.

ANTIMALARIALS

Because there is an opinion that FFA is a clinical variant of LPP, antimalarial medications known to be effective in LPP were one of the frequently used systemic medications in FFA patients. According to existing reports, results are inconclusive. There are studies that show the disease stabilization in more than 50% of cases[3,7,20,29,37]. Other studies have noted less impressive results or simply a lack of efficacy[2,6,11,39]. Protocols described include administration of hydroxychloroquine in a dose of 200-400 mg per day, or chloroquine diphosphate 250 mg per day, for at least 6 mo[3,7,32].

TETRACYCLINE ANTIBIOTICS

Several reports describe treatment with tetracycline 500 mg twice daily or minocycline 100 mg twice daily in FFA patients. Like other anti-inflammatory treatments, tetracyclines caused a decrease in inflammation in some cases, but their efficacy in controlling the alopecia was uncertain[4,20].

TOPICAL CALCINEURIN INHIBITORS

Topical tacrolimus and pimecrolimus were used with disappointing results in most patients[2,5,7,11].

5-ALPHA-REDUCTASE INHIBITORS

Although the hormonal basis of FFA has not been proven, several retrospective studies have shown efficacy of anti-androgen therapy with 5-alpha-reductase inhibitors, finasteride and dutasteride. A number of studies comparing the efficacy of various treatments in patients with FFA suggest that this treatment is more effective than others in halting the disease progression. Due to its teratogenic potential (pregnancy category X) this treatment needs to be combined with oral contraceptive therapy in premenopausal women. Several open label studies demonstrated the efficacy of finasteride at a dose of 2.5 mg daily given for at least 6 mo[3,4,7,13,18]. Treatment with dutasteride was also reported to be effective, producing even more impressive results than with finasteride, probably due to its ability to achieve greater suppression of dihydrotestosterone[7,25]. Therapeutic protocols of treatment with dutasteride reported in the literature include treatment at a dose of 0.5 mg per day for at least six months[40] or loading dose of 0.5 mg per day for 2 wk and reducing to maintenance dose of 0.5 mg per week thereafter[2-4,7,25]. Some authors question the effectiveness of 5-alpha-reductase inhibitors in treatment of FFA. They argue that in all cases reported, the treatment with 5-alpha-reductase inhibitors was combined with other medications, such as topical or intralesional corticosteroids[40], calcineurin inhibitors[40], or minoxidil[13,18,40], thus making it difficult to judge which of medications given can be associated with the outcome. Some authors also suggest that the improvement obtained may be related to a positive effect of medications on accompanying female pattern hair loss by preventing miniaturization and stimulating of remaining hairs[5,11]. Therefore, although several preliminary reports are promising, further evaluation of the therapeutic role of dutasteride with randomized controlled trials is warranted.

TOPICAL MINOXIDIL

Limited reports on the use of topical minoxidil solution did not slow the progression of FFA in most patients[3,9,19,21]. It should be noted that in several reports the treatment with minoxidil was combined with topical steroids and 5-alpha-reductase inhibitors. These studies showed positive results. It is unclear whether the results are related to the effect of minoxidil or to the additional medication that had been taken, and if the improvement is due to the influence on FFA or on an accompanying female pattern hair loss.

OTHER

Limited reports on the use of PPPAR-γ agonists, methotrexate, cyclosporin[29], mycophenolate mofetil[20], griseofulvin[9], isotretinoin, acitretin, and UVB[3,21] on FFA preclude any conclusion regarding efficacy.

HAIR TRANSPLANTATION

There is some concern about hair transplantation in FFA patients because of reported cases of FFA that began after hair transplantation in patients with androgenetic alopecia[24,37]. There is also a description of the development of FFA following face-lift surgery[37,41]. However, several reports have shown promising results[21,42]. It was suggested that hair transplants might be proposed when there is no progression of the disease for at least 1 year.

COSMETIC CAMOUFLAGE

Different methods of camouflage including wigs, hairpieces, scalp micropigmentation, and eyebrow tattooing may be recommended to cover hair loss in severe refractory and end-stage cases of FFA[2,5].

CONCLUSION

FFA is form of PCA, characterized by progressive recession of the frontotemporal hairline and eyebrow loss, occurring predominantly in postmenopausal women. The pathogenesis of FFA is poorly understood, although an autoimmune reaction and hormonal androgen-driven factors seem to play a role. Typical histopathological findings of FFA show lichenoid lymphocytic inflammatory infiltrate localized to the upper portion of hair follicle, perifollicular fibrosis, and HF destruction. Therapeutic options are limited. Long-term prospective cohort studies are needed to further elucidate the etiopathogenesis, to evaluate the effectiveness of existing treatments, and to find new treatment options. Until then, management of this fascinating disorder remains unsatisfactory.

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MINIREVIEWS

Knowledge explosion for monogenic skin diseases

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Abstract

During the past few decades, the investigative technologies of molecular biology - especially sequencing - underwent huge advances, leading to the sequencing of the entire human genome, as well as the identification of several candidate genes and the causative genetic variations that are responsible for monogenic skin diseases. These advances provided a solid basis for subsequent studies elucidating mechanisms of monogenic skin diseases and improving our understanding of common skin diseases. Furthermore, these discoveries also contributed to the development of novel therapeutic modalities for monogenic skin diseases. In this review, we have used the disease spectrum caused by mutations in the *CYLD* gene - Brooke-Spiegler syndrome, familial cylindromatosis and multiple familial trichoepithelioma type 1 - as a model for demonstrating the knowledge explosion for this group of diseases.

Key words: Familial trichoepitheliomatosis; Familial cylindromatosis; Brooke-Spiegler syndrome; Monogenic skin diseases

Core tip: Although dermatology is a morphology-orientated specialty, genetic investigation can help understand the events taking place in the skin of the affected patients. Genetic investigation of Brooke-Spiegler syndrome, familial cylindromatosis and multiple familial trichoepithelioma type 1 further supported the clinical hypothesis that these monogenic skin diseases are not different entities, but rather clinical variants of a disease spectrum caused by mutations in the cylindromatosis (*CYLD*) gene. In addition to understanding the underlying mechanisms of these allelic variants, genetic investigation can also accelerate the development of novel therapeutic modalities, such as therapy using tropomyosin-receptor-kinase specific lestaurtinib for patients with germline *CYLD* mutations.

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INTRODUCTION

From ancient times to the present, the basic approach for diagnosing skin diseases has been to classify the diseases according to their visible signs and symptoms. This approach highlights that dermatology is still a highly morphology-orientated specialty. The end of the 18th century saw great breakthroughs in dermatology: the first comprehensive textbook of modern dermatology was published in 1799 by Francesco Bianchi[1] and the first great school of dermatology was established in Paris in 1801[2]. Since that time, the desire to understand the nature of observed skin lesions constantly drives the development of dermatology and the incorporation of novel investigative methods into its everyday practice.

Among these methods, dermatohistopathology has had the highest impact on the diagnosis of skin diseases. Although the microscope was invented by Anton van Leeuwenhoek as early as 1673, the first standardized and classified nomenclature of dyes and stains was prepared only in 1924[3,4]. Since that time, enzyme histochemistry, electron microscopy, polarizing microscopy, immune-histochemistry and *in vivo* confocal microscopy have all become diagnostic tools in dermatohistopathology and have been integrated into everyday dermatology practices[3,4]. In recent decades, developments in the investigative fields of clinical genetics and genomics have further accelerated our knowledge about skin diseases.

Breeding agricultural plants and animals characterized the pre-Mendel era of genetics[5,6]. After Gregor Mendel established the basic rules of heredity in the nineteenth century[7], several major discoveries, such as the identification of DNA as the material encoding inheritable information, of the genetic code and of the mechanisms of gene expression, have initiated the era of molecular genetics[8,9]. Very recently, the enormous technical development of sequencing methods and platforms has resulted in large-scale genomic projects, which produce amounts of data that were unimaginable a few decades ago[10,11].

These discoveries and techniques have been used to identify several normal genetic variations, as well as candidate genes and their disease-causing mutations, accelerating the elucidation of the genetic background of several monogenic skin diseases. In this review, we present the knowledge explosion for monogenic skin diseases, using as an example the disease spectrum caused by mutations in the *CYLD* gene, which involves Brooke-Spiegler syndrome (BSS) (OMIM 605041), familial cylindromatosis (FC) (OMIM 132700) and multiple familial trichoepithelioma type 1 (MFT1) (OMIM 601606) (Table 1).

DISCUSSION

BSS is a rare monogenic skin disease characterized by the development of a wide variety of benign skin appendageal tumors, such as cylindromas, trichoepitheliomas and/or spiradenomas[12,13]. BSS was named after the two physicians who first reported these neoplasms in 1892 and 1899: Henry G Brooke and Eduard Spiegler, respectively[14,15]. FC, which was originally considered a separate rare disease, is characterized by the development of cylindromas[16]. FC was first reported in 1842 and 1899 by Henry Ancell and Eduard Spiegler, respectively[15,17]. MFT1, which was also reported as another rare entity, is characterized by the development of trichoepitheliomas[16] and was first reported in 1892 by Brooke[14] and Fordyce[18].

Comparing the clinical features of these tumors, cylindromas are benign, skin-colored tumors usually present as multiple turban-like protrusions on the scalp, trichoepitheliomas are small, benign, skin-colored tumors, typically located at the center of the face, and spiradenomas are purple, benign, nodular tumors, usually located on the trunk or limbs[19]. The histological characteristics of cylindromas are dermal nodules of epithelial cells lined by membrane-like basement material and arranged in a "jigsaw puzzle" pattern, of trichoepitheliomas are dermal nodules of basaloid cells with peripheral palisades arranged in nests or cribriform patterns and of spiradenomas are dermal nodules comprised of large light-colored epithelial cells with abundant cytoplasm at the center and small darker epithelial cells at the periphery[20-22]. Hybrid tumors can also occur, such as spiradenocylindromas, which exhibit the characteristics of both cylindromas and spiradenomas[23].

The candidate gene for BSS was first mapped to chromosome 16q12-q13 in 2000[24], and the causative *CYLD* gene and its first pathogenic mutation was identified in an affected German pedigree in 2002[25]. The candidate gene for FC was first mapped to chromosome 16q12-q13 in 1995[26]; however, the causative *CYLD* gene and the first 21 pathogenic mutations were identified as late as 2000[27]. It was first suggested in 1995 that MFT1 and FC may be caused by the dysfunction of the same gene, since both type of tumors can occur in the same patient or in different patients within a single family[28]. The causative gene for MFT1 was identified as *CYLD,* and the first pathogenic mutation was detected in an affected Turkish family in 2003[29].

These clinical variants - BSS, FC and MFT1 - were originally described as distinct clinical entities. However, due to their overlapping clinical symptoms and their manifestation within the same family, they are currently considered as part of a phenotypic spectrum of the same entity[30-32]. This hypothesis is supported by genetic evidence: several mutations - the c.1112C/A p.S371X, the c.2272C/T p.R758X and the c.2806C/T p.R936X nonsense mutations - lead to the development of all three clinical variants (Table 2)[33-42].

Presumably, this is due to the fact that the nonsense mutations of the *CYLD* gene are in general recurrent ones and develop due to *de novo* events indicating mutational hotspots on the gene[35]. Patients carrying the same nonsense mutation from different mutational events often exhibit extreme phenotypic differences, which might be the consequences of yet unknown genetic factors that modify the development of the phenotype.

To date, a total of 99 disease-causing *CYLD* mutations have been reported worldwide (Figure 1)[43-46]. The majority (82%) of *CYLD* mutations identified to date

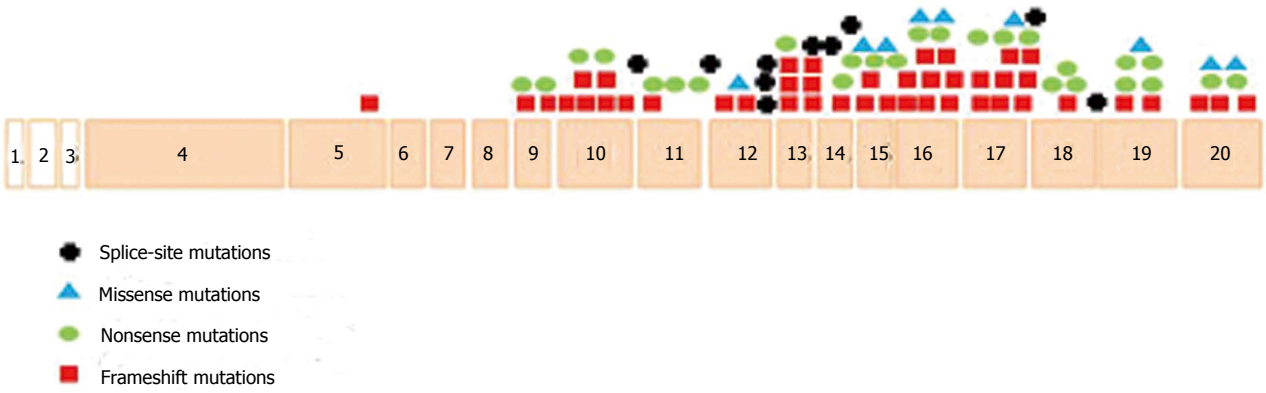

Figure 1 ***CYLD*** **gene mutations identified to date.**

Table 1 Classification of the clinical variants within the disease spectrum caused by *CYLD* mutation

Name of clinical variant	Familial cylindromatosis	Brooke-Spiegler syndrome	Multiple familial trichoepithelioma type 1
Clinical symptoms	Cylindromas	Cylindromas Trichoepitheliomas Spiradenomas	Trichoepitheliomas
Genetic background	Any type of mutation	Any type of mutation	Any type, but mainly missense mutations

Table 2 Reported clinical variants and geographic distributions of the most common recurrent mutations of the *CYLD* gene

CYLD cDNA	CYLD protein	Detected in patients with	Nationality	Ref.
c.1112C > A	p.S371X	BSS, FC, MFT1	American, African American, Irish, Dutch, Austrian, Czech, Slovak, Chinese	Bignell *et al*[27], 2000; Bowen *et al*[30], 2005; Saggar *et al*[32], 2008; Linos *et al*[40], 2011; Kazakov *et al*[39], 2011; Grossmann *et al*[33], 2013; Kacerovska *et al*[51], 2013; Lv *et al*[41], 2013; Van den Ouweland *et al*[36], 2011
c.2272C > T	p.R758X	BSS, FC, MFT1	American, South African, Austrian, Czech, Dutch, Chinese, Japanese	Bignell *et al*[27], 2000; Kazakov *et al*[38], 2009; Kazakov *et al*[39], 2011; Grossmann *et al*[33], 2013; Oiso *et al*[42], 2004; Zhang *et al*[37], 2006; van den Ouweland *et al*[36], 2011
c.2806C > T	p.R936X	BSS, FC, MFT1	American, Canadian, Anglo-Saxon, Czech, Hungarian, Chinese	Bignell *et al*[27], 2000; Bowen *et al*[30], 2005; Saggar *et al*[32], 2008; Kazakov *et al*[38], 2009; Grossmann *et al*[33], 2013; Young *et al*[31], 2006; Nagy *et al*[35], 2013

BSS: Brooke-Spiegler syndrome; FC: Familial cylindromatosis; MFT1: Multiple familial trichoepithelioma type 1.

are located between exon 12 and 20. This finding has a significant diagnostic relevance, as mutation screening of the affected individuals should begin with examination of the exon 12-20 region. Within this region, exons 16 and 17 contain the highest number of mutations (16%). Now that, because the causative mutation can be identified prenatally as well as preimplantation, diagnosis can be offered to affected families. This information can have a huge impact on family planning, since the symptoms of all clinical variants can be very stigmatizing[35].

Several functional studies have been performed to elucidate the underlying mechanism of the *CYLD*-mutation disease spectrum. The *CYLD* gene encodes an enzyme with deubiquitinase activity, which is involved in the post-translational modification of its target proteins by removing Lys63-linked ubiquitin chains[47]. CYLD interacts with several members of the NF-κB signaling pathway, including the TRAF2, TRAF6, NEMO and BCL3 proteins, acting as a negative regulator[48]. Mutations of the *CYLD* gene, in general, result in decreased activity of the CYLD enzyme. The reduced activity leads to the hyperubiquitination of interaction partners and influences several signaling pathways, such as the NF-κB pathway, as well as affects several biological processes, such as the development of the skin appendages and tumor formation[34].

It is interesting to note that, although the CYLD protein is expressed in a wide range of human tissues, the reason why dysfunction manifests only in skin symptoms is still unclear[49-51]. Moreover, patients carrying the same mutation from different mutational events often exhibit extreme differences in their clinical and histological manifestations[35]. These differences might be the consequences of yet unknown genetic, environmental and/or lifestyle factors that modify the development of the phenotype. Further

studies are needed to elucidate the putative factors that are responsible for the observed late onset of the symptoms, for the development of only skin manifestations and for the great variation in phenotypes and histological findings.

To date, no causative therapy is available for BSS. However, recent gene expression studies demonstrated that tumors with somatic *CYLD* mutation have impaired *TRK* signaling and treatment with a small *TRK*-inhibiting molecule, lestaurtinib, can reduce colony formation and proliferation of tumor cells with somatic *CYLD* mutation[52]. These data may have huge clinical significance, since lestaurtinib treatment might be a novel therapeutic modality for patients suffering from symptoms caused by germline *CYLD* mutations.

CONCLUSION

Although dermatology and genetics are considered separate disciplines, the combination of these two fields has already resulted in enormous improvement in the understanding of monogenic skin diseases, such as the skin-disease spectrum caused by mutations in the *CYLD* gene. Genetic studies have proved that BSS, FC and MFT1, which were originally considered different entities, result from mutations of the same gene. Moreover, mutations of the *CYLD* gene have been reported in patients presenting all clinical variants. Genetic screening and the identification of the disease-causing mutation have already been of great significance for family planning in prenatal and preimplantation diagnosis. Furthermore, molecular biological investigation demonstrated that all known *CYLD* mutations lead to decreased activity of the encoded CYLD deubiquitinase enzyme and, thus, influence several signal transduction pathways. Currently, only symptomatic surgical treatment is available for patients with BSS, FC or MFT1. Gene expression studies of solid tumors carrying the *CYLD* mutation identified modifications in the TRK signaling pathway and raised the possibility that treatment with lestaurtinib could potentially be a novel therapeutic modality for patients with germline *CYLD* mutation. Future genetic studies could also provide a solid basis for the development of novel causative therapies that will be more specific and effective than the symptomatic treatments currently available for patients with the FC, BSS and MFT1 variants.

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MINIREVIEWS

Primary cutaneous B cell lymphoma: Clinical features, diagnosis and treatment

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Abstract

Primary cutaneous B cell lymphoma (PCBCL) is defined as B cell lymphomas that presents in the skin without any evidence of extra-cutaneous involvement at diagnosis. They are the second most common type of primary cutaneous lymphomas accounting for 25%-30%. Since the prognosis and treatment differ from systemic lymphomas involving the skin, differential diagnosis is very important. PCBCL is a heterogeneous group of disease comprising different B cell lymphomas with distinct treatment and prognosis. PCBCL is divided into 5 subclasses according to World Health Organization and European Organization of Research and Treatment of Cancer classification. Primary cutaneous marginal zone lymphoma and primary cutaneous follicle center lymphoma are indolent forms and often confined to skin at presentation and during the course of the disease. But primary cutaneous diffuse large B cell lymphoma, leg type and intravascular large B cell lymphoma are more aggressive forms that may disseminate to extra-cutaneous tissues. There is not a treatment consensus since they are rare entities. Local therapies like radiotherapy, surgery or intralesional steroids are options for localized disease in indolent forms. More disseminated disease may be treated with a systemic therapy like single agent rituximab. However combination chemotherapies which are used in systemic lymphomas are also required for aggressive PCBCL. Although indolent forms have relatively better prognosis, early relapses and disseminated diseases are mostly observed in aggressive form with a consequent poor prognosis.

Key words: Primary cutaneous lymphomas; Diagnosis; Treatment; Bcell lymphoma

Core tip: Primary cutaneous B cell lymphoma is a type of lymphoma that presents in the skin without evidence of extra-cutaneous involvement. Prognosis and treatment being different from systemic lymphomas involving the skin makes differential diagnosis very important. It is a heterogeneous group of diseases that consists of indolent (primary cutaneous marginal zone lymphoma, primary cutaneous follicle centre lymphoma) and aggressive forms (primary cutaneous diffuse large B cell lymphoma, leg type and intravascular large B cell lymphoma). The indolent forms are mostly confined to the skin and have good prognosis whereas aggressive forms present with disseminated disease and are treated mostly with systemic combination chemotherapies.

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INTRODUCTION

Primary cutaneous lymphomas (PCL) are neoplastic proliferation of lymphocytes in the skin. They are the second most common extranodal non-Hodgkin lymphomas. PCL can be divided into two main groups; primary cutaneous T cell lymphoma and primary cutaneous B cell lymphoma (PCBCL).

PCBCL is defined as B cell lymphomas that present in the skin without any evidence of extra-cutaneous involvement at diagnosis. They are the second most common type of PCL, accounting for 25%-30%[1-5]. Since the prognosis and treatment differ from systemic lymphomas involving the skin, differential diagnosis becomes crucial.

PCBCL is a heterogeneous group of diseases consisting different B cell lymphomas with distinct treatment and prognosis. Their clinical presentation is relatively uniform, mostly manifested by nodules (Figure 1). The indolent forms, primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL) are often confined to the skin during the course of the disease. Although all body parts can be affected, specific distribution of the subtypes may provide information for differential diagnosis[6].

CLASSIFICATION

PCBCL are divided into 5 subclasses according to World Health Organization and European Organization of Research and Treatment of Cancer (WHO-EORTC) classification[2] (Table 1).

In WHO classification of tumours of hematopoietic and lymphoid tissues, primary cutaneous diffuse large B cell lymphoma, leg type (PCLBCL-LT) is classified under the heading of diffuse large B cell lymphoma not otherwise specified, NOS. PCFCL and intravascular large B cell lymphoma (IVL) are considered specific entities. PCMZL can be classified under the heading of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)[7].

DIAGNOSIS AND INITIAL EVALUATION

Thorough physical examination including the inspection of all the parts of the skin and detailed history giving special attention to B symptoms (weight loss, fever, night sweats), laboratory tests including serum antibodies or polymerase chain reaction based analysis for bacterial aetiologies should be performed. An adequate biopsy of the lesion, preferably excisional biopsy or a punch biopsy of at least 4 mm for routine histology and immunohistology is crucial for the diagnosis of PCL (Figures 2 and 3). Pathological lymph nodes should be biopsied for possible involvement. Bone marrow aspiration and biopsy is optional for most of the PCBCL with indolent course but is required in more aggressive CL like PCLBCL-LT and IVL[6,8-10]. However, differentiating early stage and rare variants of PCL from benign lymphoproliferative diseases can sometimes be complicated. Molecular analysis by demonstrating the clonality of B cells is an option[11]. Demonstration of monoclonal rearrangement of immunoglobulin by polymerase chain reaction (PCR) is a useful diagnostic tool when used in conjunction with data from the clinician and pathologist. Flow cytometric immunophenotyping is also a feasible and reliable method for detecting clonality in PCBCLs and can provide additional prognostic and therapeutic information[12]. Radiologic examinations [chest X-ray, ultrasonography, computed tomography (CT), and positron emission tomography combined with CT (PET/CT)] are contributory tools to exclude skin involvement of a systemic lymphoma[6].

Table 1 World Health Organization and European Organization of Research and Treatment of Cancer classification of primary cutaneous B cell lymphoma (2005)

Primary cutaneous B cell Lymphoma
Primary cutaneous marginal zone B cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B cell lymphoma, leg type
Primary cutaneous diffuse large B cell lymphoma, other
Intravascular large B cell lymphoma

STAGING

TNM classification for cutaneous lymphomas other than mycosis fungoides and Sezary syndrome was established by International Society for Cutaneous Lymphomas (ISCL) and Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) in 2007 (Table 2). However this classification does not give much information about the prognosis and survival[8,13].

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA

PCMZL is an indolent B cell lymphoma characterized by infiltration by a combination of small B cells, marginal zone cells, lymphoplasmacytoid cells, and plasma cells[2]. According to WHO classification it is listed under the heading of extranodal marginal zone lymphoma of MALT lymphoma[7]. Cases formerly known as "immunocytoma" as well as "non-myelomatous plasmacytomas" of skin are now included in this category. It makes up approximately 7% of all PCL[13,14]. It is mostly presented as red to violaceous nodules sometimes surrounded by an erythematous halo, mainly on the trunk and extremities although papules and plaques have also been reported[2,6]. Lesions may be solitary (51%), localized (26%), or multifocal (23%)[14]. It usually presents in the fifth or six decade and more common in men than women[14]. Extra-cutaneous involvement at the time of diagnosis and dissemination to extra-cutaneous sites

Table 2 International Society for Cutaneous Lymphomas and European organization of Research and treatment of cancer TNM classification staging for cutaneous lymphomas other than mycosis fungoides and Sezary syndrome

T
T1: Solitary skin involvement
T1a: A solitary lesion less than 5 cm diameter
T1b: A solitary lesion greater than 5 cm diameter
T2: Regional skin involvement
T2a: All disease in a 15-cm-diameter circular area
T2b: All disease in a 15 and 30 cm diameter circular area
T2c: All disease in a 30-cm-diameter circular area
T3: Generalized skin involvement
T3a: Multiple lesions involving 2 noncontiguous body regions
T3b: Multiple lesions involving 3 or more body regions
N
N1: Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
N2: Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3: Involvement of central lymph nodes
M
M0: No evidence of extra-cutaneous disease (other than lymph node)
M1: Extracutaneous disease is present (other than lymph node)

T: Tumor; N: Lymph node; M: Metastasis.

are uncommon but recurrence in the skin is frequent[14]. Elevated lactate dehydrogenase, beta-2-microglobulin levels, abnormal complete blood count values and B symptoms are uncommon and considered as clues for a systemic disease[14].

Although there is no clearly identified risk factor or hereditary tendency, associations with infectious agents, especially Borrelia burgdorferi, and autoimmune diseases have been reported. A link between the PCBCL and Borrelia burgdorferi has been documented in some studies in Europe and healing of the lesion with antibiotic treatment has been reported by some researchers. However, this could not be confirmed by other studies carried out especially in the United States and Asia[15-21].

The diagnosis of the disease can be established by histopathologic examination of the skin biopsy and exclusion of a systemic disease. Excisional biopsy is preferred but if an excisional biopsy is not appropriate, it can be substituted by a punch biopsy of an adequate length[9]. Morphologically, skin biopsy specimens depict nodular to diffuse infiltrates with sparing of the epidermis[2,21].

The differentiation of PCMZL from reactive skin changes and other cutaneous lymphomas is important. Morphologic and immunophenotypic features and demonstration of clonality will aid in the differential diagnosis.

Treatment

Treatment depends on the symptoms of the patient, stage of the disease and the number of the lesions. The treatment options include antibiotics, rituximab, chemotherapy, intralesional interferon alfa, radiotherapy and excision.

Radiotherapy is a rational option especially for patients with solitary lesion or a few lesions that can be treated in one radiotherapy field[6,22-25]. The margins of the radiation

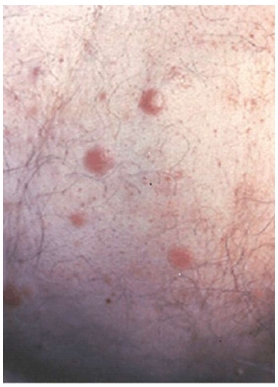

Figure 1 Primary cutaneous B-cell lymphoma. Red-brown nodules scattered on the trunk.

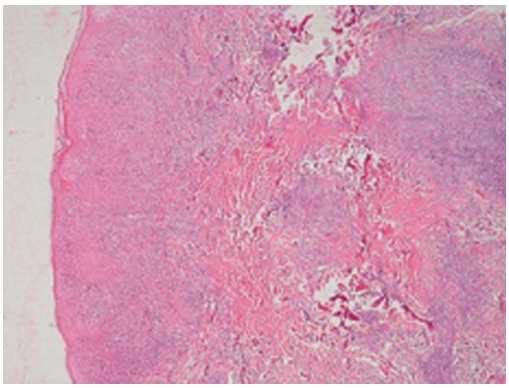

Figure 2 Widespread lymphoid infiltration with clusters of mononuclear cells involving the dermis (HE, × 10).

field should be clinically free of the disease[6]. With local radiotherapy, complete remission (CR) and 5 year disease specific survival (DSS) rates are over 95%[6,22,24]. Even though approximately half of the patients experience cutaneous relapses, extra-cutaneous relapses are very rare.

Surgery is used frequently in patients with local lesion. CR rate is nearly 100% but skin relapses are not so uncommon[6]. In an Italian study, CR and relapse rates were reported as 97.4% and 31.6%, respectively. In the same study, 97.6% of the PCMZL patients achieved CR and 46.9% of them had relapse after radiotherapy[24].

Topical steroids, triamcinolone, nitrogen mustard and cryotherapy are other local therapies with good responses[13,25,26]. Intralesional interferon treatment is another alternative strategy. In small case series of 8 patients, CR was 100% but two of them relapsed and second CR was achieved with another cycle of IFN-α[25,27]. There is very limited data on intralesional[28] or systemic rituximab[29] treatment. Three of 5 patients achieved complete (1 patient) and partial (2 patients) responses[29]. Although the experience with rituximab is very limited it can be an alternative treatment option.Treatments with chemotherapy with a single agent such as chlorambucil or combination of medications have also been reported in the literature, especially in multifocal diseases. The response rates are relatively good in patients with disseminated disease[6,25]. In asymptomatic patients with disseminated disease a close

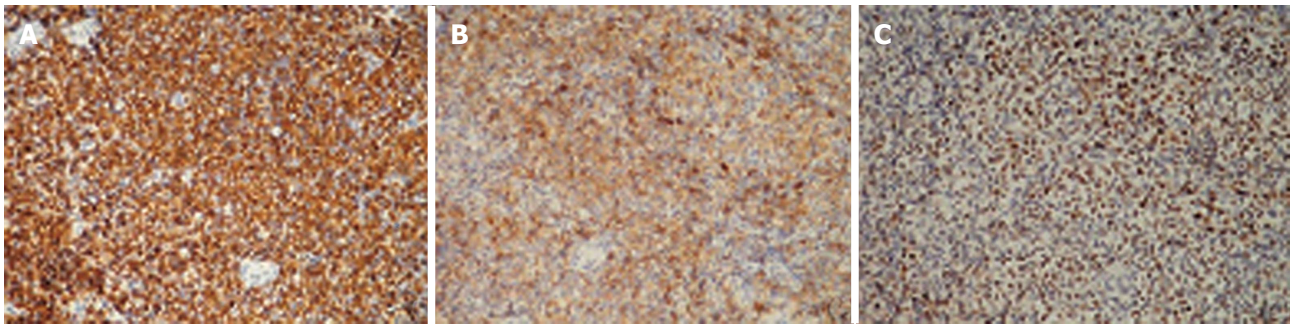

Figure 3 Immunophenotype of lymphoid cells: Immunohistochemical staining shows expression of CD20 (A), CD10 (B), and Bcl-6 (C) (Original magnifications × 20).

follow up/wait-and-see strategy and treatment of only symptomatic lesions can also be performed.

A trial with an antibiotic treatment may be a rational option for *Borrelia burgdoferi* positive patients before more aggressive therapies[6,25].

PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA

It is a tumour of neoplastic follicle centre cells, centrocytes and centroblasts. It is the most common type of PCBCL, accounting about two thirds of all cases[30]. It typically presents with solitary or multiple firm, erythematous, painless, papules, plaques, or tumours in middle ages with a slight predominance in males. It has a predilection for the head, neck, and trunk. Multifocal presentation is a rare entity[2,24,31]. It is an indolent lymphoma with a very slow progression rate and long latent period[32]. Extra-cutaneous dissemination is a rare, just like PCMZL cases.

The diagnosis is based on the histological and immunohistochemical examination of biopsy material and ruling out the systemic disease. PCFCL shows nodular or diffuse infiltration of the dermis and subcutaneous tissue; sparing of the epidermis is almost a rule. Microscopically, typically large, often multilobulated centrocytes and large centroblasts with prominent nucleoli in variable numbers are present[6]. Tumours show 3 different growth patterns; follicular, follicular and diffuse (mixed) and diffuse.

Differential diagnosis from systemic lymphomas and reactive follicular hyperplasia is critical since the treatment and prognosis are completely different. Strong expression of Bcl-2, Bcl-6, and CD10 and t(14,18) should raise the suspicion of systemic follicular lymphoma with skin involvement[33]. Unlike the follicles seen in cutaneous follicular hyperplasia, the follicles in PCFCL are ill-defined, have a decreased mantle zone and lack tingible body macrophages.

According to ISCL/EORTC guidelines, bone marrow evaluation is optional for staging in PCFCL[13]. However, bone marrow involvement is demonstrated in 11% of the patients with PCFCL presenting in the skin. Among them, bone marrow was the only extracutaneous involvement in 9 patients. Their prognosis is worse in comparison to patients presenting only with skin involvement[34]. Although there is not a consensus, these results indicate that BMB/A should be included in the staging system in PCFCL patients presenting with skin lesions[6,34].

TREATMENT

Surgery and radiotherapy are the first line treatment options for single or localized lesions. Multifocal lesions can be treated with many different modalities including radiotherapy, intralesional or local therapies. Close follow up and observation may also be an option in asymptomatic patients since it is a very slowly progressive disease.

In patients presenting with solitary or localized skin lesions, radiation therapy covering also the clinically normal margins around the lesion is the preferred mode of treatment[9]. Although radiotherapy is mostly preferred in patients with solitary or localized disease, multifocal disease can also be treated with radiotherapy[35]. PCFCL is highly sensitive to radiotherapy with a 99% CR rate and 100% 5 year over-all survival[9,36]. Solitary lesions that are small and well-demarcated can be treated with surgical excision but relapse rate is as high as 40% after excision[9]. Other local treatment options with good results are topical or intralesional steroids, cryotherapy, intralesional interferon alpha[9,27,37].

In patients with very extensive skin lesions, systemic rituximab is the first choice of treatment. Rituximab, systemic or intralesional, have been used in limited number of patients with PCFCL in the literature. CR has been achieved in 10/11 PCFCL patients treated with systemic rituximab while 3 patients had relapse after achieving CR[38]. Intralesional rituximab also have similar effectiveness that is confirmed only in small number of cases[9,39].

Combination chemotherapy should be considered only in patients with progressive and disseminated disease or patients with large tumour burden who do not respond to other treatment modalities[9,23,25]. Almost one third of the patients had relapse after an initial treatment and most of the relapses occurred in the skin and can be treated with the initial treatment strategy. Dissemination to extra-cutaneous sites is uncommon[9]. Even though it is an indolent lymphoma, lesions presenting in the leg

has poorer prognosis and these lesions should be treated more aggressively[9].

PRIMARY CUTANEOUS LARGE B CELL LYMPHOMA, LEG TYPE

Primary cutaneous large B cell lymphoma, leg type (PCLBCL-LT) is a PCBCL with predilection to legs that is histologically characterized by infiltration by centroblasts and immunoblasts. It is classically a disease of patients in their seventies with a female predominance[7]. It mostly occurs on legs unilaterally or bilaterally but, less than one third of the patients may present with lesions in an area other than the leg[2,6,40,41]. The prognosis is worse compared to other PCBCLs with higher relapse rates of extra-cutaneous dissemination. Rapidly growing red or red to bluish skin lesion especially on the lower leg is typical[2,30,40].

The differential diagnosis especially from PCFCL is important; PCFCL typically comprises centrocytes which don't express bcl2 or MUM1 in contrast to PCLBCL - LT. The site of presentation is also different since PCFCL has a predilection to trunk and head.

In contrast to indolent cutaneous lymphomas, BMB/A should be examined before initiating the therapy to exclude a systemic involvement.

Nearly all of the PCBCL-LT cases have at least one genetic alteration and half of them have combined several alterations. These mutations support lymphomagenesis with NF-κB activationand guide for targetted therapis[42].

Treatment

PCLBCL-LT is a more aggressive disease with extra-cutaneous progression, lower remission and higher relapse rates[24,41]. Multiple skin lesions, bcl-2 expression, are independent prognostic factors in these patients[43]. Patients who presents with multiple lesions on the leg has worse prognosis than lesions on other sites or single lesions[43]. Another factor with a high prevalence associated with poor prognosis in PCLBCL-LT patients is MYD88L265P mutation[44]. This mutation activates the nuclear factor-κB pathway and is associated with shorter survival rates. Patients harboring this mutation will be candidates for new targeted therapies in the future[44].

Local disease control methods like radiotherapy or topical treatment are not effective in PCLBCL -LT patients. Five year overall survival and disease free survival have been calculated as 67% and 33%, respectively, when treated with radiotherapy[36]. More than half of the patients relapse after RT[9]. Radiotherapy is an option as a palliative regimen especially in elderly patients who cannot be treated with systemic therapies[6,25].

Single agent rituximab is a reasonable therapy for elderly who can't tolerate combination chemotherapies. In a retrospective analysis of 60 PCLBCL-LT patients, all but one patient achieved CR (91.6%), with a 2 year survival of 81%when treated with combination chemotherapies plus rituximab. Two year survival rate was 59% in the group of patients who were treated with other therapies and CR rate was 62%[41].

Similar to systemic diffuse large B cell lymphomas, PCLBCL-LT should be treated with antracyclin based combination chemotherapies with or without rituximab. RT can supplement systemic chemotherapies. RCHOP ± rituximab should be considered as first line chemo-therapy[2,9,41]. Since large randomized clinical trials are lacking, the efficacy of the treatment options are not well documented.

Primary cutaneous DLBCL others, are lymphomas rather than DLBCL-LT[2]. It is a rare entity including morphologic variants of diffuse large B-cell lymphoma, such as anaplastic or plasmoblastic subtypes or T-cell/histiocyte rich large B-cell lymphomas and[2] intravascular large B cell lymphoma cutaneous variant.

INTRAVASCULAR LARGE B CELL LYMPHOMA

Intravascular large cell lymphoma (ILCL) is a rare subtype of large cell lymphoma that is characterized by the proliferation of lymphoma cells within the lumina of small blood vessels. They are more common in elderly patients, with a predilection to central nervous system and skin[2,45-47]. It has poor prognosis. The diagnosis is difficult because of divergent clinical presentation and absence of lymphadenopathy. Random skin biopsy is beneficial for early diagnosis in ILCL[48].

Cutaneous variant of the disease presents with nodules, plaques, or maculesin younger female patients[47]. The clinical presentation is diverse with painful, indurate, erythematous eruption, poorly circumscribed plaques, large solitary plaques, painful blue-red palpable nodules, tumours, ulcerated nodules, small red palpable spots, and erythematous and desquamated plaques. Lesions may be single or multiple, mostly on the leg, thigh and trunk[47]. Pain and oedema usually accompany the lesions. The differential diagnosis from inflammatory diseases and erythema nodosum is critical.

Patients mostly present with a disseminated disease even though there are also cases with lesions confined to the skin only. Blood vessels are filled with neoplastic B cells that cause occlusion of the venules, capillaries and arterioles. Immunophenotypically, the neoplastic cells are mature B cells but rarely T cell phenotype can be seen[47]. B symptoms and bone marrow involvement are less common in cutaneous variant. Cutaneous variant has a better prognosis with a 3 year survival of 56% and better performance status[47]. Multiagent chemotherapies are the preferred therapies in these patients[9].

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Salivary gland disease in human immunodeficiency virus/ acquired immunodeficiency syndrome: A review

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Abstract

The effect of human immunodeficiency virus (HIV) infection on salivary glands has diagnostic and prognostic significance. HIV-salivary gland disease (HIV-SGD) is comprehensively ascertained amongst the major critical acquired immunodeficiency syndrome (AIDS)-related oral manifestation and causes substantial morbidity. Parotid gland swelling due to sicca syndrome, parotid lipomatosis, sialadenitis, diffuse infiltrative lymphocytosis syndrome, benign lymphoepithelial lesions, neoplasms (benign or malignant) of salivary gland, parotid gland inflammation, diminished flow rates of saliva and xerostomia have been documented that also affects the health- associated characteristics of life in subjects infected with HIV. There is a necessity for health care researchers to diagnose it, particularly as it might worsen if left undiagnosed. The precise characteristic of alterations in dynamics of salivary gland structure and functionality with long-standing usage of highly active anti-retroviral therapy still remains unknown. HIV positive children also present with bilateral parotid enlargement and the syndrome state with classical clinical and cytological features of predominated lymphoid hyperplasia. Though various case reports and studies have been extensively published on different aspects of HIV-SGD, it has not been described solely, thus leading to occasional confusion of nomenclature and clinical presentation of HIV-SGD. This article reviews the pathogenesis of HIV-related SGD and its components and various other miscellaneous disorders affecting the salivary glands in HIV/AIDS.

Key words: Human immunodeficiency virus; Acquired immunodeficiency syndrome; Salivary gland diseases; Antiretroviral therapy; Highly active; Xerostomia

Core tip: Since the discovery of human immunodeficiency virus (HIV), the world has kept acquired immunodeficiency syndrome high on the agenda, rallying around global and regional commitments to turn the tide on HIV infection. There is limited data on the documentation of HIV salivary gland disease and the influence of highly active anti-retroviral therapy occurring on various components of salivary gland disorders in HIV. The purpose of

writing this article is to review the clinical manifestations and the pathogenesis of salivary gland disorders in HIV in era of antiretroviral therapy and provide an update on latest treatment modalities in the management of various salivary gland disorders.

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INTRODUCTION

Since the discovery of human immunodeficiency virus (HIV), the world has kept acquired immunodeficiency syndrome (AIDS) high on the agenda, rallying around global and regional commitments and goals to address and turn the tide on HIV infection. HIV affects almost all the structures in the body. Patients with HIV infection are prone to salivary gland disease. The initiation of highly active antiretroviral therapy (HAART) has coincided with reduced prevalence of oral manifestations in HIV/AIDS infected patients in the developed and developing countries. These oral manifestations can act as markers of immune reconstitution or as a marker of HAART failure. However, there is limited data on the documentation of HIV salivary gland disease (HIV-SGD) and the effect of HAART on various components of salivary gland disorders in HIV. In resource constrained nations, the relatively easier diagnosis of HIV-SGD can help in the early diagnosis of HAART failure, thus helping in an early initiation of other drugs in HAART. The purpose of writing this article is to review the clinical manifestations and the pathogenesis of salivary gland disorders in HIV in era of antiretroviral therapy and provide an update on the latest treatment modalities in the management of various salivary gland disorders.

HIV-SGD

The latest criteria given by the Oral HIV/AIDS Research Alliance (OHARA) gives description of SGD as asymptomatic long standing enlargement of parotid glands, usually bilaterally[1]. The clinical presentation of HIV-SGD simulates Sjögren's syndrome. There are however noticeable serologic and histopathological distinctions concerning both the diseases[2]. There is absence of anti-Ro (SS-A) and anti-La (SS-B) antibodies in subjects with HIV-SGD. HIV-SGD is typically seen in young males as compared to Sjogren's syndrome that occurs predominantly in middle aged females[2]. In HIVSGD, minor salivary gland histopathology constitutes predominantly periacinar, perivascular, and periductal lymphocytic infiltrates with most of the penetrating cells being CD8 cells[2]. With the advent of HAART, the prevalence of HIV-SGD has increased in developed countries. The prevalence has been reported to be 5% (Patton *et al*[3]) - 10% (Mandel *et al*[4]). Navazesh *et al*[5] had found an increased prevalence of HIV-SGD in a study of HIV infected women where HAART primarily comprised of Protease inhibitors. In contrast, in developing countries there have been few cases of HIV-SGD following HAART[6-8]. The probable association between HIVSGD pathogenesis and BK polyomavirus (BKPyV) has been validated with demonstration of HIVSGD-derived BKPyV oral tropism and proficient viral copying in salivary gland cells[9]. The presence of lymphoid tissue within a salivary gland capsule has been observed only in parotid gland while the submandibular lymph nodes lie adjacent to, but outside the glandular capsule[9]. An awareness of HIV-SGD may prevent unnecessary surgeries in these patients, a biopsy being necessary only in those cases suspected of harboring a malignancy[10]. The homeostasis of the oral cavity is altered in subjects with HIV-SGD due to quantitative variations ensuing in the saliva such as reduced secretory levels of lysozyme, sodium, calcium chloride, total anti-oxidant capacity and cystatin[11].

XEROSTOMIA AND HAART

HIV infected patients have been reported to be having a considerably greater possibility of salivary gland hypofunction and xerostomia as compared to patients who are not infected[12]. Xerostomia has been documented in HIV subjects with varying prevalence ranging from 10% in American homosexual males, 9% in 74 Dutch patients, 35.5% of 200 Indian patients, and 80% patients from Peru[13-16]. The reduced absolute CD4 cell counts were substantially correlated with a greater frequency of zero unstimulated salivary flow rates in HIV patients[17]. Lin *et al*[18] had reported that there is reduction in unstimulated salivary flow rates and stimulated salivary flow rates even in early stages of HIV infection. Reduced salivary flow rates have also been attributed to HIV infection, side effect of HAART, or in correlation to considerable salivary gland disease[19,20]. It is difficult to determine whether the subjective alterations related to salivary flow (hyposalivation, xerostomia, and dysgeusia) can be attributed to HIV disease or HAART[21]. Among HAART, protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTIs) have been especially been known to induce xerostomia probably by exertion of an anti-secretory effect on acinar cells[12]. Other researchers had suggested that the PIs changes adipose tissue deposition within the salivary gland[22]. However López-Verdín *et al*[21] and Nittayananta *et al*[6] found no significant difference in salivary flow rates when they compared HAART with PIs and HAART without PIs.

HIV p24 antigen in the salivary gland and a viral load of greater than 10000 copies were also found to correlate with a higher prevalence of xerostomia[23]. There was a reduction of stimulated and unstimulated salivary flow rates in HIV patients on HAART[6,12]. A considerable diminution of saliva in response to proportion of the increased number of years of usage of antiretroviral therapy has

also been reported[21]. However documentation in all the epidemiologic studies has relied on the presumptive criteria of EC-Clearinghouse classification which will not give the true prevalence of xerostomia. Most studies have been done on limited sample size, have been cross sectional and the terminologies of salivary gland hypofunction and xerostomia have been interchanged frequently for subjective signs and objective clinical observations[12]. The subjective (finding negligible saliva) and objective (*i.e.*, clinical presentation of major salivary glands, stimulated and unstimulated salivary flow rates) processes have been comprehensively documented in very few studies[6,12,17]. However, studies have taken different parameters like unstimulated and chewing gum stimulated whole saliva and parotid gland saliva. Wang *et al*[24] had found unstimulated whole salivary flow rates to be more sensitive to dry mouth complaints rather than stimulated whole salivary flow rate. Therefore research should be conducted on unstimulated whole saliva in a preferably longitudinal study to understand the exact effects of HAART and HIV on salivary gland hypofunction.

The sequelae of reduced salivary flow are increased caries prevalence, increased oral candidiasis, dysguesia and periodontal diseases[17,21]. The Usage of crystal methamphetamine is frequented with greater HIV acquisition, and it is correlated to sudden generalized dental caries recognized as "meth mouth" in HIV positive patients[25]. Lithium, muriatic and sulfuric acids and lye, the constituents of crystal methamphetamine, have been considered as causative factors. In a study conducted in 2009, high concentrations of the HIV p24 antigen in the salivary gland and a viral load of greater than 10000 copies were found to correlate with a higher prevalence of xerostomia[5].

PAROTID LIPOMATOSIS

Abnormal fat deposition in HIV patients on HAART (PI) has been documented in abdomen, dorsal cervical areas and Parotid gland[26]. Olivé *et al*[27] were first to document parotid lipomatosis in two patients on Protease Inhibitors. The protease inhibitors stimulate peripheral lipodystrophy that is triggered by inhibition of proteins which control metabolism of lipids[26]. The above process ensues in decreased differentiation and a rise in peripheral adipocytes's apoptosis with impaired fat storage[27].

LYMPHOEPITHELIAL CYSTS

A rare condition of Lymphoepithelial lesions observed in the parotid gland is correlated with a greater frequency in HIV patients[28]. The persistent generalized lymphadenopathy (PGL) is a characteristic feature of HIV patients. Lymphoepithelial lesions represent a probable confined or limited expression of PGL[28]. However, the etiopathogenesis of lymphoepithelial lesions is still unknown. The lymphoepithelial lesions may originate from inclusions of the major salivary gland located in lymph nodes (mainly intra-parotid lymph nodes). Another possibility of lymphoepithelial lesion developing from the parenchymal component of the salivary glands has also been postulated[28-30]. Parotid lympho epithelial cysts are easily diagnosed by ultrasonography. These lesions often become large leading to societal stigmata[28]. The lymphoepithelial lesions are typically benign. However there is always a distinct possibility of their conversion to lymphomas. Thus, continuous and periodic follow-up should be conducted for these lesions and should not be disregarded[31]. There are also bilateral parotid swellings observed in diffuse infiltrative lymphocytosis syndrome (DILS), a condition typified by a penetration of constant CD8 cells lymphocytosis that results in swelling of the gland[4,28].

DiGiuseppe *et al*[32] postulated persistent generalized lymphadenopathy to be a cause of benign lymphoepithelial lesions in parotid gland. An increased viral load is also known to be associated with salivary gland enlargement by altering the expression of strategic cellular genes[33]. Ihrler *et al*[30] had demonstrated a secondarily lymphoid penetration of parenchymal component of the salivary gland that induces a lymphoepithelial reaction of striated salivary gland ducts. Owotade *et al*[34] had reported 5 cases of parotid gland enlargement and had managed them with different modalities like Fine needle Aspiration, Anti-retroviral therapy and parotidectomy.

The conditions that can simulate lymphoepithelial cysts are salivary gland duct retention cyst (mucocele), mucosa associated lymphoid tissue lymphoma that may possess cystic constituent and polycystic parotid disease[35]. The possibility of papillary cystadenoma lymphomatosum should also be excluded in these patients[36].

RANULA

The involvement of ranula as an oral manifestation in HIV patients has been suggested which still has not been established. However, Syebele *et al*[37] had demonstrated a mixed and delayed response (3-6 mo) of ranulas for regression to HAART. The precise etiopathogenesis of the association amongst these dual dissimilar pathological conditions is ambiguous. Chidzonga *et al*[38] had documented a high prevalence rate (88.5%) of HIV subjects within a cohort of 38 patients with sublingual ranula. A case report documented that without any surgical intervention, sublingual mucocele had entirely lapsed after initiation of HAART[39]. Syebele *et al*[39] had also proposed research on association between ranulas and HIV infection to establish the likely result of HAART on ranula. Case control studies are required to evaluate the degree of periductal lymphocytosis, isolation of viral particles and chemical analysis of the mucus present in ranula[40].

SALIVARY GLAND NEOPLASMS

Patients with HIV/AIDS demonstrate augmented possibility of malignancy, predominantly viruses triggered cancers[41]. The greatest risk for salivary gland carcinoma was found to be lymphoepithelial carcinoma, which is

an undifferentiated carcinoma associated with Epstein Barr virus and also having a prominent non-neoplastic lymphoplasmacytic infiltrate[41]. The most common site of involvement is parotid gland. The common histological subtypes of salivary gland malignancy like mucoepidermoid carcinoma and adenoid cystic carcinoma seen in general population are not commonly seen in HIV patients[41]. High grade Non-Hodgkin's lymphoma and Kaposi's sarcoma are the other frequent malignancies associated with salivary glands in HIV patients[42]. The greater probability of squamous cell carcinomas of both nasopharynx and salivary glands could be ascribed to tobacco or alcohol usage, which are frequent in HIV subjects and related to other malignancies in the head and neck region[43]. Rare case reports of primary squamous cell carcinoma affecting Stensen's duct and developing from Cheilitis glandularis were documented in subjects infected with HIV[44,45].

HIV-ASSOCIATED SIALADENITIS AND SICCA COMPLEX

In a study conducted in 2009 in 105 AIDS patients the researchers found the most common infectious conditions affecting the sublingual and submandibular glands were mycobacteriosis followed by cytomegalovirus (CMV) and cryptococcosis[46]. HIV p24 was observed in lymphocytes and macrophages correspondingly[46]. The highest prevalence of cells seen in chronic nonspecific sialadenitis were CD8 lymphocytes, while CD68 macrophages were predominant in the mycobacteriosis-associated granulomatous and nonspecific diffuse macrophagic sialadenitis[46]. Parotid gland histopathological changes were observed in more than half of the HIV infected patients in a research conducted by Vargas *et al*[47]. Chronic sialadenitis of non-specific origin (29 cases) was the frequent change observed followed by various conditions of infectious origin (22 cases). Amongst the infectious conditions, 10 patients had Mycobacteriosis, followed by nine patients with cytomegalovirus infection, cryptococcosis in three patients and lastly histoplasmosis in two patients[47]. Wax *et al*[48] had reported three patients of CMV sialadenitis who clinically had nodules in parotid gland in HIV/AIDS patients. A possible complication of sialolithiasis in HIV positive patient with the usage of HAART drug atanavir was suggested[49].

SALIVARY GLAND DISEASE IN CHILDREN

HIV positive children often present with bilateral parotid enlargement and the syndrome state with classical clinical and cytological features of lymphoid hyperplasia predominated[50]. Parotid gland enlargement is a common condition found in pediatric patients with HIV infection. In the pediatric HIV population, its prevalence is 1% to 10%[51]. DILS or Sjogren syndrome- resembling condition, first seen in pediatric HIV infection, is a CD8 lymphocyte facilitated syndrome that might involve the submandibular as well as parotid salivary glands[52]. HLA-DR11 and HLADR5 have been associated with salivary gland enlargement in HIV infected children signifying a possible genetic predilection[53].

RECENT ADVANCES IN RESEARCH AND MANAGEMENT OF SALIVARY GLAND DISEASE

More studies need to be done for exact association between HAART and hypo salivation. Longitudinal studies documenting xerostomia need to be done measuring the salivary flow subjectively prior to HAART and after HAART. There should be more research on the role of Ranula as an oral mucosal finding in HIV patients. Artificial salivary glands are also being formulated[54]. HAART's success has resulted in patients with xerostomia, a risk factor for caries and its potential sequelae, thus affecting the patient's quality of life.

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