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A Concise Narrative Review On The Spectrum Of Lichenification In Association With Atopic Dermatitis

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ABSTRACT
Lichenification consists of epidermal hyperplasia and hyperkeratosis that finally lead to the formation of thickened skin, hyperpigmentation, and exaggerated skin lines in its primary clinical manifestation. Appearance of lichenification has been discussed as a class of secondary skin lesion which is strongly associated with the clinical features and pathological mechanisms of chronic atopic dermatitis (AD) and a few other pruritic (itchy) disorders. Efforts has also been made to identify the role of different inflammatory neuromediators, neurohormones, nerve growth factors, and neuropeptides involved in lichenification and its underlying pathological condition from the previously published literature. A thorough histological examination details for appropriate diagnosis was described in this review for different types of lichenification, with a special mention of allergic contact dermatitis as a common clinical manifestation. In treatment options, monoclonal antibody, topical Calcineurin Inhibitors, corticosteroids, doxepin, derivatives of vitamin A, probiotics, and platelet-rich plasma has been found to be more effective in prior studies regarding this troublesome chronic AD symptom.

INTRODUCTION

Lichenification, a multi-pattern inflammatory skin disease, is classified as a special kind of Atopic dermatitis (AD) with the involvement of several factors. This condition begins with hyperpigmentation, which darkens patches of thick leathery skin, followed by small papules and raised bumps. It can be further clarified as a chronic inflammatory condition of the epidermis and mucus membranes with a very high recurrence rate and the presence of prominent skin markings resembling tree bark signs. It usually happens due to constant scratching and rubbing or without the symptoms of scratching like in case of excoriations and crusting. There are certain conditions that can result in lichenification, such as atopic dermatitis and pruritic (itchy) disorders [1]. Most of the time, skin diseases emerge with a cutaneous surface changes termed as "lesions," have more or less well defined characteristics. Primarily there are three basic types of skin lesions such as primary, secondary, and special. In contrast, lichenification falls under the class of secondary type of skin lesion according to different literature published till date.A primary lichenification, also known as neurodermatitis circumscripta, can be differentiated from a secondary lichenification by considering the cause of the lichenification. It is primarily associated with the formation of lichenified plaques, similar to pruritic dermatosis and capable to intensify the itch symptoms exceptionally. The possibility of getting secondary Lichenification lies on the typical habit of scratching in chronic erythroderma or red skin condition gives a craggy skin in affected area [2]. Therefore, degree of Lichenification could also be related to the duration and intensity of the pruritic dermatoses.Some of the neuropeptides released by lesions may act as mediators of neurogenic inflammation as well as allergic and inflammatory skin reactions. These include substance P, neuropeptide Y, calcitonin-gene-related peptides (CGRP), vasoactive intestinal polypeptide, and somatostatin. [1-6]. Moreover,

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secondary lichenification has been reported to occur when there are other medical conditions present, including infective eczema, dermatophytes, bug bites, xerosis, psoriasis, psoriasiform dermatitis,pityriasis rubra pilaris(PRP), porokeratosis, vegetative growths, anxiety, and obsessive-compulsive disorders. [7]. Limited treatment options, lack of public awareness, less number of reliable readily available clinically identified cases, present a significant obstacle to fight against this disorder. But, as of now several studies failed to provide statistically significant cureness with different treatment option, and especially there is no study about the clear-cut concept on Lichenification exclusively.

EPIDEMIOLOGY

Atopic eczema (AE) is one of the most severe forms of dermatitis with a prevalence of 2% to 5%; in which symptoms include Lichenification or itching. Approximately 12% of the population is reported to have Lichen simplex chronicus (LSC). Most of the LSC cases occur in the middle to late adulthood stage of life and frequently peak around 30 to 50 years of age. Females are two times more likely to suffer from the disorder than males [8-10].

Whereas the occurrence of AD has been increasing and affecting up to 20% of children and 10% of adult in developed countries [9]. Goldstein et al. found a prevalence of vulvar LS in 1.7 % of a general gynaecology patient population. Lichen planus (LP) at any site is estimated to affect 1% of women while it is also involved in commonly observed oral cavity infection. It can also increase the risk of oral cavity cancer as well as hearing loss [10,11]. As one of the most common skin disease, Lichenification may have strong association with the agricultural workers in crop-specific exposures and which is mainly due to their lack of protective equipment. Among grape working crews the prevalence of lichenified hand dermatitis ranged from 0% to 50% and was unrelated to ambient temperature [12].

SIGNS AND SYMPTOMS WITH SECONDARY SKIN LESION

Lichenification can be categorized as a severe skin anomaly based on the location and redundancy of symptoms. It is, however, relevant to mention here that lichenification is strongly associated with the pathognomonic features of atopic dermatitis. There are no specific clinical signs and symptoms for AD, but it may aid in early diagnosis because it is characterized by dry skin, infiltrated erythema, weeping red plaques, lichenification and pruriginous nodules that can be complicated by viral, bacterial and fungal infections. Also known as chronic pruritus, it is characterized by thickening of the skin in areas affected by self-perpetuating scratching. An increase in itching is observed in the evening when the sympathetic nerve activity decreased.Acanthosis can bring two different types of changes in the stratum corneum by means of proliferation of keratinocytes, such as parakeratosis or orthokeratotic hyperkeratosis. Parakeratotic hyperkeratosis displays retained nuclei as a sign of delayed keratinocyte maturation, whereas orthokeratotic hyperkeratosis implies the thickening of the keratin layer with conserved keratinocyte maturation [13]. It may also lead to urticarial or exudative erythema followed by chronic lichenification of the skin in patients with atopic dermatitis [14].

Appearance of either regular or irregular acanthosis is very common in LSC, and this always occurs with hypergranulosis and orthokeratotic hyperkeratosis whereas orthokeratosis is characterized by thickened stratum corneum which is depleted of nuclei in case of LSC and Lichen planus(LP). Multikinase-inhibitors such as VEGF, EGFR, KIT, RET, Flt3, and RAF, are strongly associated with hand-foot skin reaction by modifying the skin homeostasis and giving rise to many different cutaneous manifestations [15].

PATHOPHYSIOLOGICAL BACKGROUND OF LICHENIFICATION

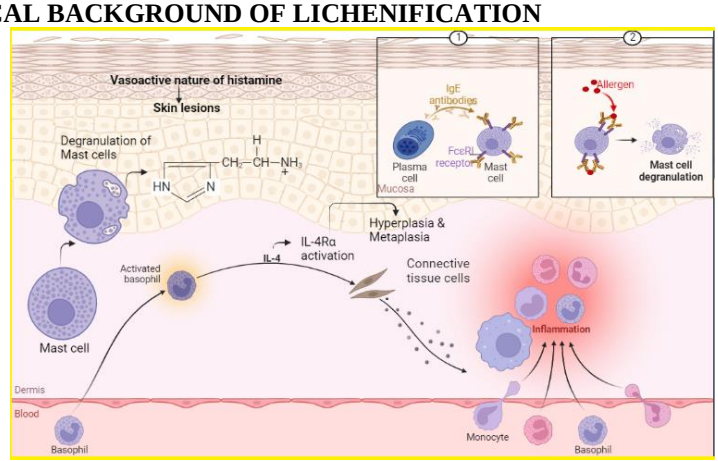

Fig. No. 1: Mechanism of immune response in lichenification.

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Atopy is a physiological propensity toward increase production of IgE due to abnormal overwhelming immune responses against otherwise non allergic substances. Atopic dermatitis (AD) is a chronic relapsing–remitting type inflammatory skin disorder with a tendency to deteriorate and frequently seen in patients with past incident of atopic diseases in personal or family medical history. An acute AD consists of intensely pruritic erythematous papules accompanied by erosions, excoriations, and swollen exudates. Chronic AD is also characterized by thickened, scaly, erythematous papules and plaques (Lichenification), frequent flares, and fibrotic bumps in addition to dry, scaly papules and plaques. Studies have also amply proved that significant baseline increment of histamine concentration took place in overall 20–30% of AD patients. Lichenification, as a minor factor, takes part in the diagnosis guidelines of atopic dermatitis under the Hanifin and Rajka's criteria [5-7]. In addition to histamine 4 receptors, Interleukin 31 and Interleukin 13, various recent studies indicate that itch mediators are associated with severe weakened epidermal skin barriers that allow allergens and microbes to penetrate more easily. There is a high prevalence of FLG mutations among Caucasians. The FLG gene produces a key protein called filaggrin from the development of profilaggrin that makes possible the terminal differentiation of the epidermis and formation of the strong skin barrier matrix. The severity and persistence of AD is worsened by FLG mutations, mostly in early-onset AD. A cytokine capable of increasing or decreasing the production of IgE that is produced by type 1 and type 2 T-helper lymphocytes (TH1 and TH2, respectively), such as IL-12 and IFN-γ from TH1 cytokines and IL-5 and IL-13 from TH2 cytokines.Patients having AD featured with genetically dominance of TH2 cells with higher amount of blood IgE level that may decrease the expression of FLG and other molecules responsible for the skin barrier matrix formation. It has also been advocated in few studies that mutations provide an opportunity for the allergens to penetrate the epidermis and to influence the dendritic cell or macrophage(the primary APC), and leading to the development of symptoms like atopic dermatitis, including asthma [16,17].

CAUSATIVE FACTORS

Different factors which lead to LSC, can be broadly classified in four groups such as dietary (including allergic), traumatic, racial, and psychogenic. According to some observer's insight, eastern world people who follow an occidental diet that is highly enriched with red meat, animal fat, dairy products and sugar, and deficient in legumes, vegetables and fruits, might have a higher incidence of the LSC infection [18]. In chronic forms, erythroderma or 'red skin' can become lichenified with permanent skin alterations, which may require careful clinical management [2]. It has been described that nodular lichen simplex can develop in sites like the scrotum, where a lax skin could result in the formation of lichenified masses with large nodules the size of pinheads. [19].

Table 1: To summarize the spectrum of well mentioned factors associated with lichenification.

Sr. No.	Causative factors mentioned for lichenification associated skin diseases	Study Author
1.	Pain relievers involved in hypersensitivity drug reactions such as ibuprofen (Advil, Motrin IB, others), diclofenac and naproxen (Aleve, others)	[20]
2.	Alkaline substances which eliminate surface lipids	[21]
3.	HMG-CoA reductase inhibitors(Statins) and derivatives of fibric acid.	[22, 23]
4.	Photosensitivity the result of phototoxicity or photoallergy: Lichenification and hyperpigmentation may occur	[21, 24]
5.	Certain pigments, chemicals like benzocaine, tea-tree oil, Aloe vera, and ubiquitous metal like Nickel.	[25, 26]
6.	33 Flu vaccine related LP from July 1990 to November 2014 in the United States.	[27]
7.	Hepatitis C infection: Necrolytic acral erythema presents distinct hyperkeratosis and lichenification.	[28, 29]
8.	Specific medications for heart disease, high blood pressure like Amiodarone and calcium channel blockers.	[30]
9.	Neuropeptides or Opioid peptides are endogenous neuromodulators play a vital role in itch sensation.	[31]

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SPECIAL TYPES OF LICHENIFICATION AND UNDERLYING DISEASES

Contact dermatitis

It is a kind of inflammation that manifests in your skin as a red, itchy rash whenever it is exposed to an allergen or irritant. Further, exposures to chemicals or any other external factors from diverse sources of widely-differing types continue to induce sensitization in a large section of our population and may result in allergic contact dermatitis. Depending on the cause it either can be irritant or allergic contact dermatitis(ICD or ACD). Exogenous vulvar dermatitis is kind of contact dermatitis where vulva may be erythematous, edematous, scaly, fissured, hyperkeratosis in exhibition.Common culprits include fragranced and antibacterial soaps, bath products, feminine sprays, and OTC anti-itch preparations containing benzocaine (eg. benzocaine/resorcinol made topical products Vagisil [Combe Inc] and vagicaine) [32].

Lichen Sclerosus

Lichen sclerosus (LS) is kind of chronic inflammatory autoimmune dermatosis linked with several other autoimmune diseases, often described as “cigarette paper” skin. They were found in 74% of women with anogenital LS and 7% in healthy controls. A man with LS showed significantly higher anti-ECM1 antibody concentrations than a control. Antibodies specific to the basement membrane zone (BMZ) have been reported to be present in one-third of patients with vulval LS whereas anti-BMZ antibodies lacks any significance. Human leukocyte antigen (HLA) DQ7, DQ8, DQ9 have also been frequently seen in both women and men with LS[31].

Lichen planus

This chronic inflammatory disorder has been prevalent in 1% of world population with a poor understanding of its etiology. It is a type of infection in the oral cavity that can increase the risk of oral cancer. In addition, if left untreated, it also can lead to hearing loss by infecting the ear canal. Nine out of ten LP cases (90%) were hypertrophic, and three exhibited pseudoepitheliomatous hyperplasia; none were erosive. Perivascular lymphocytic infiltration and focal melanophages exist in the upper dermis.

Pityriasis lichenoides (PL)

The term pityriasis literally means a predominant scale. While about 20% of PL cases occur in the pediatric age, children are more likely to show an unremitting course, frequent dyspigmentation, and poorer response to conventional treatment modalities. Antibiotics like tetracycline, erythromycin, and minocycline have been succeeded because of their anti-inflammatory properties and as infectious agents are reports as the plausible factor of PL [34,35].

DIAGNOSTIC REVIEW OF LICHENIFICATION

A thorough history and examination are required for vulvar dermatitis-related different types of lichenification. In addition to patch testing for allergens, cultures may also be performed to exclude secondary infections caused by bacteria or Candida [36,37]. As a characteristic feature of LS, dermal homogenization is characterized by a band of oedematous, hyaline, or fibrotic collagen in the superficial dermis beginning at the dermo-epidermal junction. When the epidermis shows acanthosis the diagnosis of LS will get superimposed with LSC [33].

DIFFERENT REPORTED TREATMENT OPTIONS FOR LICHENIFICATION

Reported Cases	Year of Publication	Trial Drug	Effect
(Simonart, Lahaye et al. 2008)	2008	topical corticosteroid cream 0.1% betamethasone valerate	Postmenopausal 34 women were treated, once daily for 1 month treatment with a moisturizing cream improved overall and seventy-one percent became symptom free and 29 % experienced a partial response
(PIAMPHONGSANT 1974)	1974	Tetracyclines	Complete remission occurred in five patients within 2–4 weeks, and seven patients reported
Observational, non-controlled, prospective			

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cohort study of patients between 2 and 70 years of age (Eberlein, Eicke et al. 2008)	2007	Emollient cream with a unique lamellar matrix containing N-palmitoylethanolamine (PEA)	partial response and continued at the dosage of 1 g daily for 4 weeks. Intensities of erythema, pruritus, excoriation, scaling, lichenification and dryness were significantly reduced with a combined score reduction of 58.6% in the entire population
Treatment of Lichenified Atopic Eczema with Tacrolimus Ointment (Granlund, Remitz et al. 2001)	2001		
A Statistical Model to Predict the Reduction of Lichenification in Atopic Dermatitis (Glazenburg, Mulder et al. 2015)	2015	0.1% tacrolimus or a vehicle control (tacrolimus ointment base) based on a 1:1 randomization for a period of 2 weeks.	Percentage decrease in the combined symptom score in the 0.1% tacrolimus group (68.5%) whereas in the vehicle control group (13.4%) (p =0.002).
(Tan, Firmansyah et al. 2021)	2021	Fluticasone propionate cream or ointment, once or twice daily for 4 weeks	In total, 749 patients and 3 different FP treatment studies lichenification significantly improved ($p < 0.005$) within one week compared to placebo treatment in the lichenification scores.
A Case of Neurodermatitis Circumscipta of Scalp Presenting as Patchy Alopecia(Ambika, Vinod et al. 2013)	2013		
Thirty-seven subjects were enrolled, mean age 38 years (range 17–73) (Berth-Jones, Takwale et al. 2002)	2002	Combination of 0.05 percent clobetasol, halobetasol propionate, mometasone furoate and 3% liquor carbonis detergent, and 2% salicylic acid	A cure rate of 88.9% was obtained in combination formulation, while standard therapy containing 0.05% Clobetasol obtained a cure rate of 77.5%
		Intralesional injection of triamcinolone acetonide 2.5 mg/ml weekly for 4 weeks along with doxepin hydrochloride 10 mg at night.	Marked reduction in itching in the 1st week and complete regrowth of hair at end of 4 weeks
		Azathioprine, or matching placebo, was used at the dose of 2.5 mg/kg/day	The SASSAD score fell by 26% during treatment with azathioprine vs. 3% on placebo ($P < 0{\cdot}01$).

Table 2 : To summarize major well mentioned case reports associated with lichenification.

CONCLUSION

In conclusion, there have been major advances identified indeed in our understanding of the mechanisms responsible for lichenification throughout approx 100 years interval of literature studies. Different keywords have been used in search engine to fully abstract the internet resources that, resulted in 68 overall references mentioning this disease. It is our obvious observation that lichenification has been so far understood as a characteristic feature of chronic AD

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with thickened allergic skin. In particular, there is an abnormal and overwhelming immune response that results in increased production of IgE against any naturally inert substances. That antigen-antibody complex brings basophils and mast cells, responsible for the release of different chemical mediators, namely histamine and influence the inflammatory responses and accumulate microscopic cellular infiltrate in the skin. Excessive amount of IgE level in blood also decreases the expression of FLG, responsible for the formation of a strong skin barrier matrix. Maximum efforts have also been made to get meaningful insight with evidence from the available treatment approaches and therapeutic perspective for this disorder. It was also carefully observed that treatment cannot cure entirely in many cases but helps to keep the condition under control. Moreover, an incomplete understanding still exists with this condition. Still, we expect the collection of reported cases and opinions from different authors will help to solve some critical aspects of lichenification and associated disorders like disease identification, proper treatment selection, and better prognosis.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

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