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Mini Review Article

An Update on Etiopathogenesis & Management of Lichen Simplex Chronicus (LSC) Alias Neurodermatitis-Recacitrant to Theray

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Abstract

Lichen simplex chronicus delineate's a kind of chronic localized pruritus with a secondary dermatitis, as well as one of the maximum frequent kinds of chronic itch situations, determined to influence greater than 10% of the general population. Nevertheless, although it is prevalent in addition to possesses substantial load, there has been restricted work into the pathogenesis, along with causative factors of lichen simplex chronicus, that, as per history, enabled it to become a bothersome situation in reference to treatment. In recent decade, our insight of this situation, along with that of pruritus as well as the itch-scratch cycle, has escalated substantially, making an extensive escalation of avenues regarding therapy. Additionally, numerous attractive innovative therapies are generational in addition to trials. This mini-review details the definition, epidemiology, clinical properties, pathophysiology, along with present therapeutic opportunities for lichen simplex chronicus, with regards to emphasizing recent advancements in such arena.In milder cases use of emollients like N-palmitoylethanolamine,or with anaesthetic characteristics, for instance polidocanol, /Topical analgesic mixture of ketamine-amitriptyline-lidocaine (KAL) in a lipoderm basemight be of substantial help in contrast to need for systemic therapiesin greater robust cases

KeyWords; *Lichen simplex chronicus; itch-scratch cycle; innovative therapies.*

Introduction

Chronic itch is a considerably bothersome disease with robust repercussions for the health as well as quality of life of impacted persons. Chronic itch situations possess the capacity of being equally draining like chronic pain situations, in addition to result in mood disruption, along with insomnia [1,2]. Of chronic itch situations, lichen simplex chronicus (LSC) is one of the maximum frequent; in certain populations it is the maximum frequent dermatological disorder as well leading to seek appointment of dermatologist [2]. LSC possesses the properties of thick, scaly plaques resulting from indelible modulation of a region with recalcitrant, chronic itch [3].

Despite LSC is generally a non-life-threatening situation, the robust pruritus correlated with the disorder possesses the capacity of robustly affecting patients' well-being [1]. Sufficient therapy of itch is predominantly significant in reference to the treatment of LSC. Additionally, persistent scratching possesses the capacity of resulting in escalated i) skin barricade disturbance as well as ii) the liberation of inflammatory mediators, iii) resulting in sensory impairment in addition to iv) activation of itch-scratch cycles, v) further aggravating itch along with leading to vi) greater scratching [3]. Persistent scratching apart from resulting in greater robust LSC, however might further lead to i) infection in addition to, in occasional cases, ii) malignant conversion [4]. Asssessment of the etiological factors that lie beneath pruritus in LSC is further meaningful regarding determination of diseases which otherwise might be concealed. A plethora of diseases possess the capability of presenting with i) localized pruritus, inclusive of ii) neurological, iii psychiatric along with iv) malignant diseases [1]. Thereby, i) getting insight regarding LSC, ii) its pathophysiology that lies beneath, as well as iii) therapy is imperative for the everyday practice of variety of clinicians.

Definitions, epidemiology along with Clinical properties of LSC

LSC is a localized skin disorder that clinically possesses the properties of lichenified plaques of skin generally associated with overlying abrasions. Such plaques are capable of getting discoloured, with differing erythema shades varying from pink to dark brown. Over a protracted time period, it might convert into a hypopigmented plaque that possesses a darker border. Instead of a diffuse organization, they are positioned to particular regions of the body in the form of one or rare skin plaques which are frequently manipulated (see Figure. 1) [4].

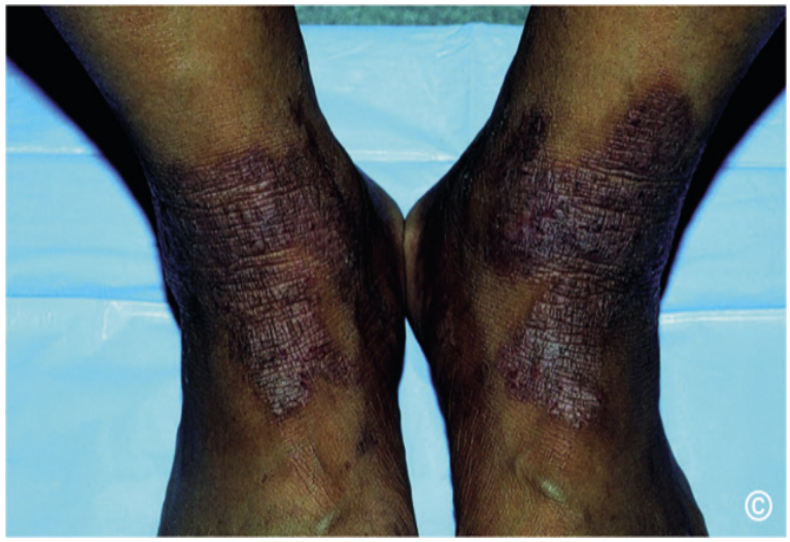


Figure 1

Courtesy ref no.5-Bilateral lichen simplex chronicus plaques on the flexural surfaces of the feet.

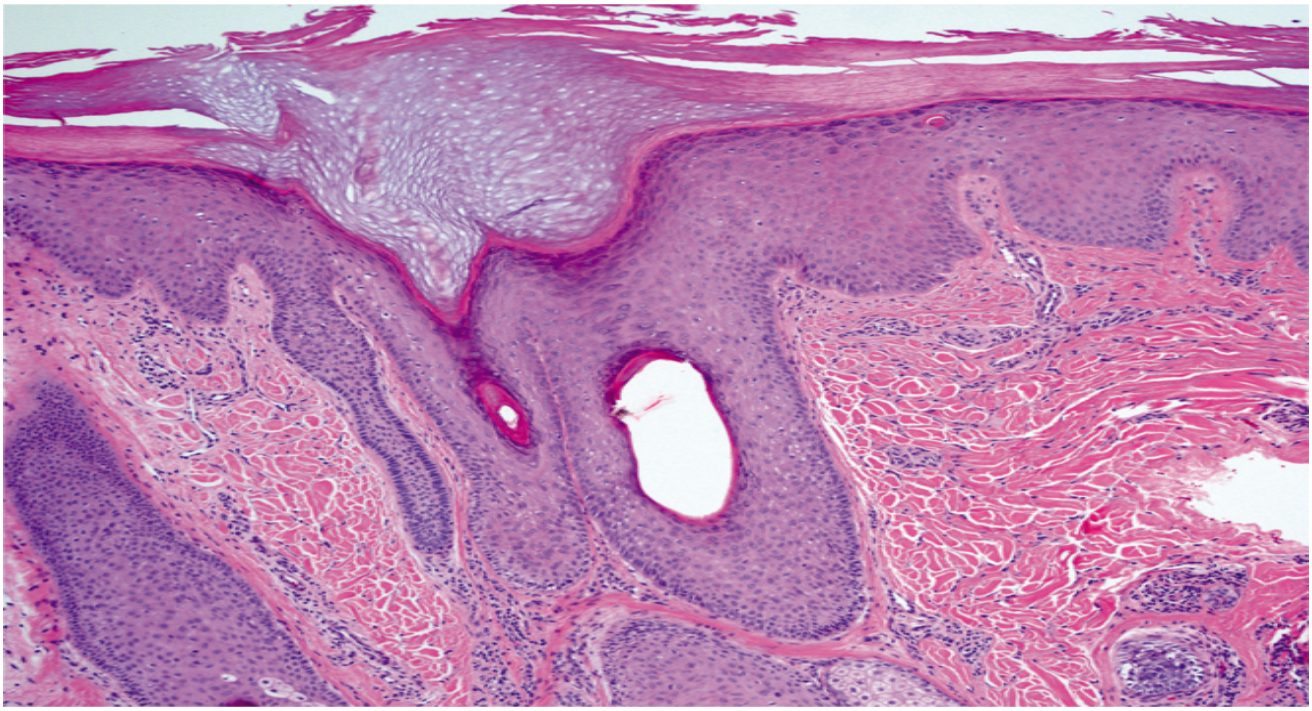
This is compared to i) prurigo nodularis (PN), ii) one more chronic pruritic situations, in addition to iii) secondary dermatitis, that is commonly greater widely organized across plethora of regions of the body in the form of nodules. WhereasLSC might certain times be also known in the form of a neurodermatitis, which embraces other chronic itchy disorders, for instance a) PN, one needs to be careful once naming it with such terminology, since neurodermatitis might further point to b) atopic dermatitis, a different condition which possesses a separate causative factor.

LSC is a substantially prevalent disorder, affecting a determined 12% of the general population, as well as is specifically prevalent in middle-aged patients amongst the ages of 30 in addition to 50 years[4]. Women are more commonly impacted in contrast to men, with a 2-to-1 ratio[4]. Such disorder is further common in Asia, particularly in elderly patients [2].Those with a family or personal history of atopy might possess greater predisposition to LSC. Around 20–90%of people affected by LSC document a personal or immediate family history of i) atopic dermatitis, ii) allergic rhinitis, as well as /or iii) asthma [6]. Psychosocial stress is further associated with robustly pruritic dermatoses for instance LSC, in addition to patients demonstrate a meaningfully greater prevalence of i) psychosomatic, along with ii) psychiatric comorbidities, for instance iii) clinical depression as well as iv) anxiety. LSC is usually existent in i) ambitious with ii) stressful in addition to iii) enterprising, lifestyles[7]. In the form of a secondary dermatitis, LSC results from mechanical modulation of a recalcitrant itch resulting in a compacting , along with scaling of the skin. Because it gets stimulated by scratching by habit as well as rubbing, LSC is generally observed in regions of the body that are self-accessible, for instance the i) ankles, ii) shins, iii) elbows, iv) dorsal hands, v) upper back, v)i neck in addition to vii) anogenital regions. Disfigurements are usually symmetrically organized , especially on the extensor surfaces of the extremities[4].

A study on the pleasure obtained from scratch of different pruritic dermatological situations observed that LSC possesses one of the maximum frequent ratings for pleasure from scratching, subsequent to just notalgia paraesthetica. Additionally, greater scores pleasure obtained from scratch were observed to be analogous with regions where LSC is commonly existent. Regions for instance the scrotum , along with vulva, where scores associated with scratch were observed to be greater, are a frequent placement for LSC, whereas regions for instance the scalp, where scores associated with scratch was observed to be lesser, is occasionaly implicated other than that on the posterior scalp[8].

The histopathology of LSC illustrates a hyperkeratotic plaque, certain times with i) centers of parakeratosis, ii) a pronounced as well as compacted iii) granular layer, iv) remarkable acanthosis, v) lengthened in addition to thickset rete ridges, vi) pseudoepitheliomatosus hyperplasia, vii) papillary dermal fibrosis , along with viii) mild spongiosis. Evaluation of the superficial dermis might document vertically directed , compacted collagen bundles with perivascular as well as interstitial inflammation which possesses the properties of i) histiocytes,

ii) lymphocytes in addition to iii) eosinophils in the superficial dermis (Figure. 2) [4].

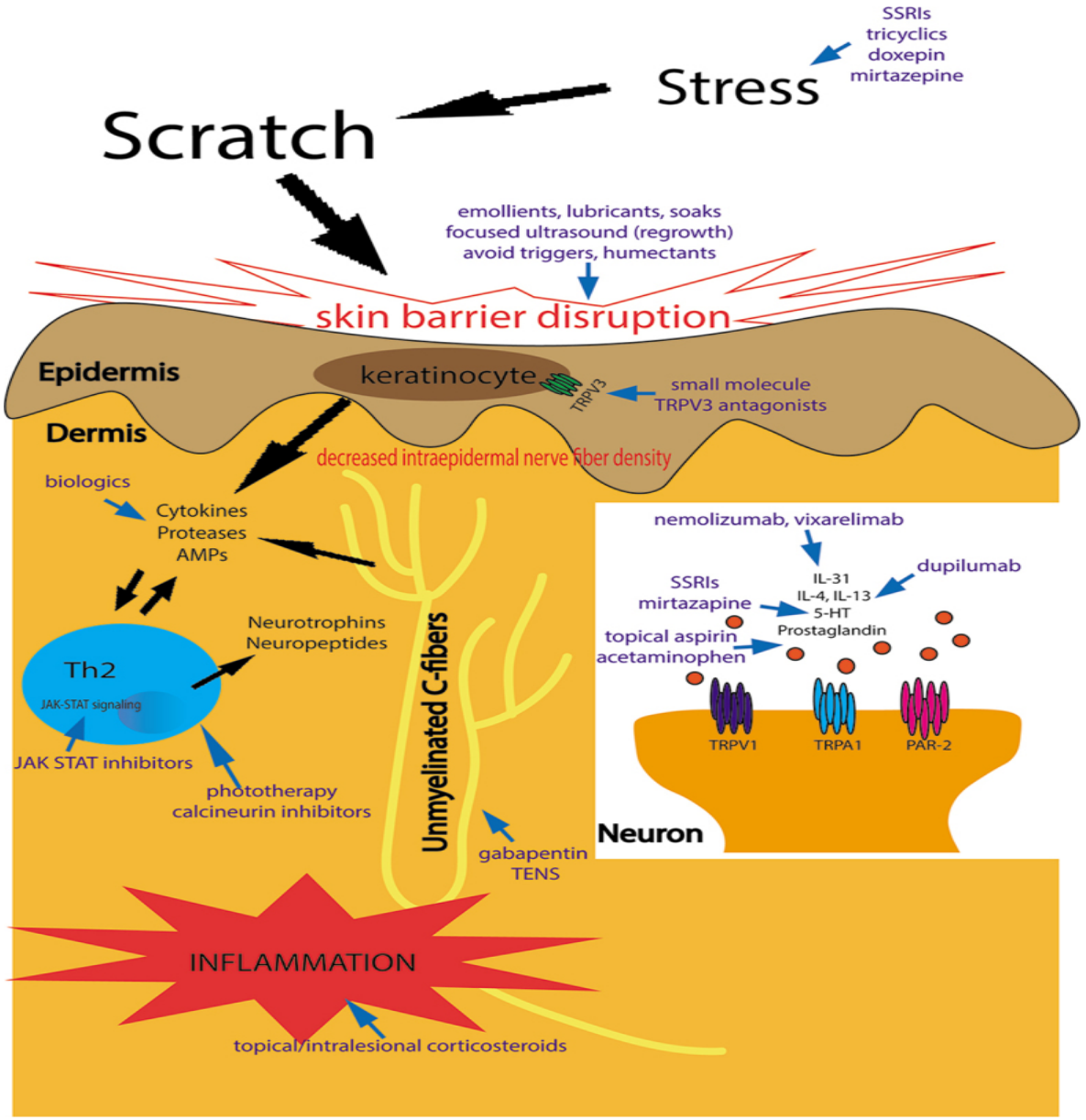


Legend for Figure 2.

Courtesy ref no.5-Lichen simplex chronicus of the posterior scalp showsirregular acanthosis with hypergranulosis and pronouncedhyperkeratosis reminiscent of the acral skin. There is an increasednumber of fibroblasts in the upper dermis, and mild perivascular lymphocyticinfiltrate (haematoxylin and eosin, ×10). Credit to and permission obtainedto publish from Dr Mariya Miteva.

Pathophysiology of LSC

Whereas the precise pathophysiology of LSC have yet to be identified,LSC has been believed to be a chronic event, caused by i) primary psychological or ii) factors correlated with surrounding milieu or iii) secondary to **other dermatoses eliciting an a) itch as well as resulting in b) powerful itch-scratch cycle (Figure 3).**



Legend for Figure 3.

Courtesy ref no.5-Pathophysiology of lichen simplex chronicus and its therapeutic targets. AMPs: antimicrobial peptides; JAK-STAT: janus kinase-signal transducer and activator of transcription; IL: interleukin; PAR-2: protease-activated receptor 2; SSRIs: selective serotonin reuptake inhibitors; TENS: transcutaneous electrical nerve stimulation; Th: T-helper cell; TRPV: transient receptor potential vanilloid; 5-HT: serotonin.

Pruritogens portray molecules which, once established into the skin, stimulate itching. i) Binding of such pruritogenic molecules with their respective receptors on C-nerve fibres, result in ii) neuronal activation as well as iii) transmission of an itch signal to the dorsal root ganglion in addition to iv) spinal cord. Taken together pruritus possesses the capacity of being categorized in the form of i) histaminergic (usually correlated with acute itch) , along with ii) non-histaminergic (usually correlated with chronic itch), with every itch possessing their own neuronal correlated pathway. The specific pruritogens implicated in LSC continues to be uncharted; nevertheless, owing to LSC represent ‘s a chronic event, the pathophysiology is believed to be basically non-histaminergic itch modulated by binding of pruritogens to i) G-protein coupled receptors (GPCR) in addition to /or ii) ion channels, specifically a) transient receptor potential(TRP) channels. TRPs might react to a) capsaicin, along with to b) temperature. Two calcium-permeable ion channels expressed in sensory nerve fibres, i) transient receptor potential vanilloid 1 (TRPV1) as well as ii) ankyrin-1 (TRPA1),were advented to possess a meaningful part in the crosstalk with iii) pruritogens in addition to iv) nociceptive stimuli, along with might be imperative in T-cell modulated IL-31- stimulated itch as well [9]. TRPA1 serves in the form of the downstream molecule to variable histamine - autonomous, chronic itch pathways.

A study exploring 21 biopsies from patients with LSC in addition to 28 healthy controls illustrated meaningfully down-regulated expression of TRPA1 in LSC disfigurements, pointing that TRPA1 might possess a part in pathogenesis of the disease[10].

TRPV3 delineate warm temperature-sensitive channels, which possesses enrichment in keratinocytes. They are correlated with itch signalling through protease-activated receptor-2 (PAR-2), a GPCR receptor found in sensory nerve fibres as well as keratinocytes [11]. TRPV3 in addition to PAR-2 portray pivotal actors in other pruritic situations inclusive of atopic dermatitis. Activation of TRPV3 in conjunction withPAR-2 results in the liberation of plethora of cytokines, along with chemokines[12], whereas hampering leads to diminished inflammation as well as itch amelioration [11]. LSC pathophysiology possesses the probability of implicating certain facets of such TRPV channelsin addition to GPCRs.

Additionally, escalating corroboration points that LSC implicate neuroimmune crosstalks. Skin is an enriched innervated organ, as well as where nerve fibres come in touch with cells of the immune system, there are avenues in reference to localized neuroimmune crosstalk, specifically via the liberation of i) neurotrophins in addition to ii) neuropeptides from immune cells. i) At the times of stress as well as ii) chronic inflammation, iii) neurotrophin quantities, along with the iv)quantity of neuropeptidergic nerve fibres in the skin as well as their touch points with immune cells often escalate [13]. Such reaction results in i) cutaneous inflammation in addition to generation of pruritus.This might be analogous to the higher rates of LSC in patients with potentiated quantities of stress, for instance ambitious (6). Plethora of studies have shown escalated quantities of the neurotrophins i) nerve growth factor (NGF)or ii) brain-derived neurotrophic factor (BDNF) in atopic

dermatitis as well as uraemic patients with pruritus[14]. Nevertheless, a recent study of 36 patients illustrated reduction in quantities of i) serumneurotrophin-3 (NT-3), ii) NGF, iii) glial cell line derived neurotrophic factor (GDNF), in addition to iv) BDNF in patients with LSC in contrast to healthy controls, despite quantities were not associated with disease robustness[15]. One additional study of 33 patients with LSC illustrated a meaningful decreased intraepidermal nerve fibre density in sample tissue from the disfigurement region compared with a contralateral control region [16]. This was correlated with decreased sensitivity to i) warm in addition to ii) cool stimuli. Such damaged fibres in the epidermis were posited to become i) aberrantly sensitive as well as ii) generate pathological spontaneous action felt in the form of an itch[16]. Chronic scratching further possesses the capacity of aggravating epidermal denervation. Sandoval et al. [16] ,illustrated that the small fibre neuropathy in such patients with LSC possesses the capability of resulting in improvement with i) lidocaine plasters,either ii) via diminished transmission of action potentials or iii) reduced neurogenic inflammation, iv) despite inflammatory mediators were) v) not meaningfully changed .

Scratching transitionally attenuates the discomfort associated with itch sensation i) by activating pain-sensory fibres that ii) hamper itch at the magnitude of the spinal cord. Nevertheless, scratching is capable of resulting in a pathological event, called the itch-scratch cycle. Scratching gets caused by i) epithelial injury , ii) the liberation of cytokines, iii) proteases, along with iv) antimicrobial peptide, that activate immune cells as well as v) stimulate itch sensory neurones along with vi) channels, in the manner detailed aforementioned . This results in a vicious itch- scratch cycle[3].

Diagnostic strategy

The manner with maximum dermatological situations, an exhaustive patient history is imperative to generating a diagnosis of LSC. A complete dermatological examination needs to be performed in reference to rule out purely primary inflammatory dermatoses in addition to evaluate for disfigurements which are secondary to scratching, for instance the canonical solitary lichenified plaques. A biopsy might possess the capacity of aiding in discriminating LSC from other disorders with analogous clinical manifestations , for instance i) hypertrophic lichen planus, ii) psoriasiform rashes, iii) contact dermatitis, iv) squamous cell carcinoma, along with v) mycosis fungoides. The degree of the pruritus might be assessed with subjective scales, for instance the visual analogue scale. In the form of a secondary dermatitis, getting insight in reference to the initiation of itch in LSC, in case owing to i) psychological, ii) encompassing milieu factors,or iii) secondary to other dermatoses, might be substantially of utility in the therapy of the disorder.

Guidelines for management

There are plethora of therapeutic strategies regarding treatment of LSC .Therapies are generally targeted towards i) isolating as well as ii) managing the disease lying beneath, iii) healing the barricade layer working,

iv) diminishing inflammation, in addition to v) breaking the itch-scratch cycle. i) Nevertheless, treating LSC possess the capacity of getting bothersome , ii)because we have just recently started to gain insight regarding its pathophysiology. iii) At the time of the beginning of asssessment , iv) clinicians need to take into account , v) along with tackle any plausible non-dermatological causative factors of LSC[1]. A) In reference to healing the barricade layer working to diminish the exposure of nerve endings, i) patients need counselling ii) regarding avoidance of any stimulating factors, for instance i) heat or ii) irritants, as well as iii) to wear iv) looser, v) cotton blend clothing for avoidance of aggravating their disease. Emollients with i) ceramides, ii) soaks, iii) lubricants for instance a) sitz baths in addition to b) utilization of wetted towelling need to be encouraged. iv) Low pH emollients have been illustrated to diminish the activation of proteases. v) Emollients possessing supplementary therapy , for instance N- palmitoylethanolamine or vi) with anaesthetic characteristics, for instance polidocanol, have been illustrated to result in improvement of chronic itch in clinical studies. vii) Emollients possessing pilodocanol, specifically, have been observed to diminish non-histaminergic itch in double-blind, placebo-controlled clinical trials[17]. Humectants, for instance i) lactic acid, ii) glycolic acid, along with iii) urea, are not advocated owing to they are capable of irritating the skin. iv) Diminishing inflammation is one additional benchmark to the therapy of LSC. v) Greater robustness possessing topical corticosteroids are generally well-tolerated in reference to short-term utilization need to be taken into account in the form of first-line LSC therapy. Occlusive dressings might be utilized coupled with topical steroids; nevertheless, there is existence of occasional studies assessing their efficacious . A combination of topical steroids as well as salicylates further might be utilized for therapy (4). Based on the robustness of the disease, intralesional steroids, for instance triamcinolone acetonide, might further be taken into account[18]. Other non-steroidal avenues are inclusive of topical immunomodulators, for instance . i) tacrolimus in addition to ii) pimecrolimus, that barricade the liberation of a) inflammatory pruritic cytokines from T lymphocytes in the skin along with b) facilitate cutaneous host defences. Such topical immunomodulators result in avoidance of the inimical sequelae of long-term steroid use, for instance . i) atrophy, ii) irreversible striae, along with iii) telangiectasia, as well as need to be utilized in greater sensitive areas, for instance the vulva[19]. Nevertheless, they are capable of resulting in transient burning sensation, that need to be conveyed to patients[20]. Since LSC canonically result from habitual scratching; therefore, putting a break on the itch-scratch cycle is of pronounced significance in reference to therapy . Occlusion, generally utilized coupled with pharmacological therapy, for instance corticosteroids, possess the capacity of provision of a physical barricade which result in avoidance of further scratching, improves skin barricade injury as well as decreased pruritogenic stimuli besides escalating drug absorption. Certain frequently utilized occlusions in LSC are i) occlusive plastic film as well as ii) hydrocolloid dressings[21]. (iii) Menthol, which results in a cooling sensation through activation of TRP channels, in addition to iv) pramoxine, a local

anaesthetic, are capable of getting utilized in reference to regulating pruritus in such patients[18,22]. i) Noticeably, although capsaicin, ii) is frequently utilized anti-pruritic, over-the-counter iii) it has not been observed to be effective for the therapy of LSC pruritus[18]. i) Topical doxepin in the form of an adjuvant treatment to ii) topical steroids , along with iii) topical aspirin with iv) dicloromethane have further been illustrated to be efficacious in plethora of studies[23,24]. v) Topical analgesic mixture of ketamine-amitriptyline-lidocaine (KAL) in a lipoderm base has been observed to be efficacious further in reference to therapy of iv) patients with v) chronic pruritus, inclusive of the ones vi) with prurigo nodularis. vii) It is posited to act on c-fibre nerves via barricading of. i) N-methyl-D-aspartate receptor as well as ii) sodium channels[25]. i) Topical acetaminophen, that works along the ii) arachidonic pathway in addition to possessesiii) metabolites iv) which activate , along with sensitize TRPV channels, might attenuate chronic itch[26]. Further recently, Januskinase (JAK) hampering agents, for instance topical tofacitinib, have further been observed to reduce pruritus in patients with LSC as well as PN in a small case series[27]. As LSC is often localized, topical therapies are usually employed. Such compares with analogous , however greater widely organized, dermatological situations, for instance PN. Nevertheless, systemic therapies need to be taken into account in case of failure of topical therapies. One study documented 5 patients with severe LSC who responded to the anticonvulsant gabapentin, a neuroleptic agent that diminishes central neural hypersensitization, despite its precise anti-pruritic mechanistic modes continues to be uncharted [28]. Whereas i) aprepitant as well ii) naltrexone have been documented to attenuate other chronic pruritic diseases, there is existence of requirement of detection by investigations in case of such substances would be of value in treating patients withLSC[29]. Owing to the association amongst LSC as in addition to i) stress, ii) anxiety , along with iii) depression, certain clinicians point a plausible advantage of iv) anti-depressants in patients with comorbid anxiety or depression. Daytime scratching possess the capacity of be managed with selective serotonin reuptake hampering agents (SSRIs) in addition to night-time scratching with sedating antihistamines, along with tricyclics to assist in stimulating sleep[30]. Mirtazapine further diminishes night-time itch in LSC as well as allowing sleep [31]. A double-blind randomized control trial observed that treatment with chlorpheniramine or imipramine meaningfully diminished itch robustness in patients with LSC [32]. Methotrexate in addition to cyclosporine have been illustrated to be efficacious in PN, along with possess the plausibility of being efficacious in LSC, although there are no well- acknowledged studies regarding their effectiveness in LSC [33,34].

A plethora of small studies have documented successful treatment of LSC with non- canonical therapies . Plethora of such have concentrated on the neuroimmune facets of the disease. One study that was inclusive of 26 patients with LSC observed that targeted narrow band UVB (NB-UVB)phototherapy was safe as well as efficacious, particularly in patients who were unreactive to topical therapies. Improvementof mean pruritus scores took place by 75%[35]. Transcutaneous electrical nerve stimulation (TENS), one more non-canonical

therapy, attenuates itch by sending pulsed electrical currents to hinder nociceptive A delta in addition to C fibres. Once employed in 22 patients with LSC nonreactiveness to topical corticosteroids, TENS efficaciously diminished itching by larger than 50% in 80% of patients[36]. Focused ultrasound treatment for the therapy of vulva possess the capacity of further facilitating reconstruction , along with growth of tissue impacted by LSC. A retrospective observational study illustrated 41 out of 85 patients attained full rectification of itch as well as restoration of skin elasticity[37]. There are plethora of innovative treatments that are attractive therapies for LSC, which might be utilized in greater recalcitrant, robust forms of LSC. Nemolizumab, amonoclonal antibody targeting the IL-31 receptor, was observed to be efficacious in diminishing pruritus as well as robustness of skin disfigurements in PN in a randomized clinical trial of 70 patients[38]. Plethora of clinical trials on the effectiveness of other biologic treatments, for instance dupilumab for PN, are presently ongoing in addition to might on therapeutic avenues for LSC be implementable to LSC [39]. Additionally, a present nonpublished phase 2 clinical trial on the effectiveness of vixarelimab, a completely -human monoclonal antibody which targets the oncostatin M receptor beta subunit (OSMRβ) of the IL-31 receptor, illustrates attractive outcomes in the beginning on the therapy of chronic pruritus, inclusive of amongst a small sample of patients with LSC[40]. Acknowledged the association of TRPV3 with itch signalling in keratinocytes, an innovative topical small molecular hampering agent of TRPV3 channel (KM001) is presently getting pursued in phase 2 trials for LSC [41]. Taken together, studies on existing , along with innovative opportunities for LSC therapy are restricted. A recent review of LSC therapies observed just 9 randomized clinical trials in the literature that were inclusive of greater than 25 patients (33). There is existence of requirement of greater severe along with novel investigations.

Conclusions

Previously we detailed A PCOS obese patient of atopic dermatitis (AD) who presented with robust pruritic lesions- which was misdiagnosed by dermatologist as fungal Infections &Illtreated with 3 anti fungals and steroid & exhaustively reviewed AD[42].Here we have further reviewed LSC as its differential diagnosis. Although, LSC delineates a considerably frequent as well as bothersome disease, historically, existence of miniscule knowledge was there regarding its etiological factors in addition to mechanistic modes lying beneath its etiology from perspective of its therapy. Canonically believed tobe a secondary dermatitis caused by chronic scratching in pruritic RNS situations, maximum of our insight of LSC comes from acquisition of insight in reference to itch along with its pathogenesis, that has considerably undergone meaningful recent advancements in this arena. Nevertheless, our in-depth insight of LSC as well as its therapy avenues are still restricted. There is existence of requirement of performance of greater exhaustive investigations regarding assessment in addition to provision of a thorough canvas of this recalcitrant, challenging disease, that

influences plethora of individuals globally. In milder cases use of emollients like N- palmitoylethanolamine,or with anaesthetic characteristics, for instance polidocanol, /Topical analgesic mixture of ketamine-amitriptyline-lidocaine (KAL) in a lipoderm basemight be of substantial help in contrast to need for systemic therapies in greater robust cases

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