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UPDATE ON THE CLASSIFICATION AND MANAGEMENT OF CUTANEOUS LUPUS ERYTHEMATOSUS

Introduction

Lupus erythematosus (LE) is an immune-mediated, chronic, complex disease that can affect anyone. It occurs most commonly in middle-aged women; however, it can also affect men, and individuals of all ages.[1] The skin is one of the most commonly affected organs in systemic lupus erythematosus (SLE). Cutaneous involvement and skin manifestations are known to occur in 60% to 85% of patients over the course of the disease. Skin manifestations are the first type of presentation in virtually 20%-25% of patients.[1]

Disease Classifications and Criteria

Various classifications and criteria exist for the diagnosis of SLE.[2-4] These include the following criteria: 1997 American College of Rheumatology (ACR) **(Table 1)**; 2012 Systemic Lupus International Collaborating Clinics (SLICC); and 2019 joint European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) criteria **(Table 2A-B)**.

Four of the eleven 1997 ACR criteria are skin manifestations (e.g., photosensitivity, malar rash, discoid lesions, and oral ulcers). However, photosensitivity and oral ulcers are not specific for SLE. Furthermore, a patient with discoid lesions, photosensitivity, and positive antinuclear antibody (ANA) with concomitant oral ulcers related to condition other than SLE meet the criteria for SLE. However, the diagnosis might actually be cutaneous lupus erythematosus (CLE). Therefore, the updated 2019 EULAR/ACR classification requires a positive ANA (titer of at least 1:80) plus 10 or more cumulative points from 22 "additive weighted" criteria comprising seven clinical domains and three immunologic domains **(Table 2A-B)**. Each criterion is assigned points ranging from 2 to 10. One of the clinical domains in the EULAR/ACR criteria is mucocutaneous, and includes 2 points for oral ulcers; 2 points for non-scarring alopecia; 4 points for subacute cutaneous lupus erythematosus (SCLE) or chronic cutaneous lupus erythematosus (CCLE) including discoid lupus erythematosus (DLE); and 6 points for acute cutaneous lupus erythematosus (ACLE).[3,4]

Few classifications exist for CLE, however, the Gilliam and Sontheimer classification remains the most commonly used criteria.[4-6] In this criteria, CLE is divided into specific and non-specific manifestations.

The specific skin manifestations include ACLE, SCLE and CCLE **(Table 3)**.

Clinical Manifestations

ACLE typically appears as a butterfly-shaped malar erythema over the cheeks and nasal bridge sparing the nasolabial folds. The generalized form of ACLE often covers large areas of the body and is more intense on the photo-exposed areas. Interestingly, this form of the disease tends to spare the metacarpophalangeal and interphalangeal. In excess of 90%-95% of ACLE patients have positive ANA. Systemic involvement is extremely high in ACLE and, in fact, ACLE activity often occurs in parallel with systemic disease activity.[1,7]

SCLE is characterized by highly photosensitive annular or papulosquamous (psoriasiform) plaques on the arms, shoulders, chest, upper back, and sides of the face **(Figure 1)**. These lesions rarely extend below the waist and rarely scar. Approximately 70%-80% and 20% of patients with SCLE are SSA- and/or SSB-positive, respectively.[1,7]

CCLE has subtypes of which DLE is the most common. This type is characterized by erythematous papules and plaques on the head and neck (localized form) or the trunk (disseminated form). These lesions progress to have central atrophy, hypopigmentation, and peripheral raised hyperpigmentation.[1,7] These lesions generally heal with scarring **(Figure 2)**. Only 10%-15% of patients have positive ANA. Subcutaneous LE is a form of panniculitis. It is characterized by tethered, indurated plaques in areas with high adipose tissue such as the upper arms, thighs, and breast. Lupus erythematosus tumidus (LET) is characterized by recurrent, photosensitive, raised erythematous, non-scaly, urticarial-like papules or plaques on the face or upper trunk **(Figure 3)**. This subtype of the disease is rarely ANA positive. Chilblain lupus is characterized by recurrent, itchy or painful erythematous-violaceous papules and plaques in the distal acral areas such as the fingers, toes, ears and nose. They generally are triggered by exposure to cold temperature, however, they can occur spontaneously **(Figure 4)**. Other rare types of CCLE include the oral and mucosal, hypertrophic, and verrucous forms.[1,7]

Management of Cutaneous Lupus Erythematosus

Management of CLE involves a combination of lifestyle modification and preventive measures, in addition to topical therapy and systemic and/or biologic agents. **Table 4** summarizes general recommendations and lifestyle modifications for CLE management.

Few guidelines exist for the treatment of CLE; currently, there is no FDA or Health Canada approved drug for its treatment.

Topical corticosteroid agents remain effective first-line treatment of all types of CLE.[8-11] Determining the potency of the corticosteroid agent depends on several factors including the severity of the disease, age of the patient, thickness of the lesions, and the sites affected. As a general rule, these agents should be applied for a short time period of time or intermittently to avoid adverse effects such as steroid-induced skin atrophy, telangiectasia, and steroid-induced dermatoses including acne, rosacea, and folliculitis. An exception allowing for the prolonged use of topical corticosteroids in CLE lesions is thick DLE on the scalp, in which case prolonged yet intermittent use may be necessary. In these cases, intra-lesional injection of corticosteroids such as triamcinolone on the scalp or other areas with localized refractory DLE lesions may also be extremely helpful.[8-11]

Topical calcineurin inhibitors (TCIs) such as tacrolimus 0.03% and 0.1% ointment and pimecrolimus cream can be used off label as well, although few clinical studies have demonstrated their efficacy in treating CLE. These agents have a favourable overall safety profile vs TCS, but they may not be as effective, particularly in thick lesions.[12,13]

Only few anecdotal reports exist on the use of topical retinoids for the treatment of CLE, particularly in the hypertrophic subtype. In these reports, patients who had failed to respond to topical corticosteroids were successfully treated by topical retinoids.[14-16]

Recently, Park et al reported a case of an SLE patient with skin and scalp involvement who had previously failed belimumab and hydroxychloroquine (HCQ) improved significantly following two months of topical ruxolitinib 1.5% cream daily.[17] Topical ruxolitinib demonstrated favourable results in a case of chilblain lupus as well.[18]

Antimalarial drugs remain the first-line systemic treatment for all types of CLE. Three agents can be used, including HCQ, chloroquine (CQ) and quinacrine. There is also ample evidence for beneficial effects of HCQ in SLE with skin manifestations.[19] Yokogawa et al evaluated the efficacy of HCQ for CLE in a double-blinded, randomized, placebo-controlled, Phase 3 trial. After 16-weeks, the HCQ treated group showed a significantly greater proportion of "improved" and "remarkably improved" subjects compared vs the placebo group (51.4% versus 8.7%, respectively).[20]

Several theories have been proposed about the mechanisms of antimalarials in the treatment of CLE and LE including interference with antigen processing, inhibition of nuclear material traffic, and indirect reduction of interferon-alpha (IFN-α). However, the exact mechanism remains elusive.[21,22]

To minimize the risk of retinopathy, antimalarial doses should be calculated based on body weight with a maximum daily dose of ≤5 mg/kg of real body weight for HCQ and ≤2.3 mg/kg of real body weight for CQ.[23]

In addition, it is recommended for patients to undergo an examination with an ophthalmologist at baseline and annually following five years of initial treatment with HCQ or CQ. Patients with underlying risk factors for retinopathy should undergo an annual examination even after five years of treatment.[24]

In light of the fact that LE, including CLE, is primarily a disease that occurs in middle-aged women of childbearing age, pregnancy is a challenge throughout the course of the disease. Several studies and meta-analyses have not shown a higher incidence of premature births, congenital defects or spontaneous abortions in women treated with HCQ.[25,26] Therefore, HCQ is considered one of the safest drugs for use during pregnancy.

Systemic corticosteroids are also recommended as first-line treatment largely because of their quick onset in improving severe CLE. However, systemic corticosteroids should be used for short periods only and not as maintenance therapy due to their potential side effects. In a multicentre study, systemic corticosteroids showed extremely high efficacy in the treatment of CLE vs all other systemic agents.[27] Prednisone at a dose of 0.5-1 mg/kg/day can be used with a tapering course over few weeks until a steroid sparing immunosuppressant has been initiated.[28-30]

Oral or subcutaneous methotrexate (MTX) is considered a second-line treatment for CLE. MTX can be used as monotherapy or concomitantly with an antimalarial agent. Although primarily retrospective, several studies have demonstrated favourable efficacy of MTX in the treatment of CLE.[31-34]

Many patients with CLE remain unresponsive and refractory to antimalarial agents and MTX. Thalidomide is an immunomodulatory, anti-inflammatory and anti-angiogenic drug that is considered as a second-line treatment for refractory CLE. The most widely-used dose for thalidomide in CLE is 100 mg daily, although 50 mg daily has also been shown to be effective.[35-37] However, thalidomide is associated with severe potential adverse effects, particularly peripheral polyneuropathy and teratogenicity. These side effects are associated with high rates of treatment discontinuation.[38-40]

Dapsone is considered a first-line treatment for bullous LE. It can also be used as second-line monotherapy or in combination with antimalarial agents for refractory CLE. The efficacy of dapsone in CLE has been reported in several respective studies.[41-47] Patient levels of glucose 6-phosphate dehydrogenase (G6PD) should be tested initially. The recommended dose for dapsone is 50 mg-150 mg daily.

Systemic retinoids acitretin and isotretinoin have been used with success in CLE, particularly in hyperkeratotic lesions and verrucous LE. While few reports have shown high rates of efficacy when used as monotherapy, it is preferable to use these in combination with antimalarial drugs.[48-51] The recommended daily dose of acitretin for the treatment of CLE is 25-50 mg daily. As LE is a disease that occurs primarily in middle-aged women, retinoids should be used very carefully due to their teratogenicity. Female patients exposed to acitretin should not conceive for three years following discontinuation of the drug.

Anecdotal reports support the use of other systemic agents such as mycophenolate mofetil, azathioprine, cyclosporine, cyclophosphamide, belimumab, rituximab, and oral Janus kinase (JAK) inhibitors. However, their efficacy has not been established in large case reports or randomized clinical trials.[24,52]

JAK inhibitors have great potential in the treatment of LE. Skin involvement in LE and in connective tissue diseases is believed to be due to increased expression and activation of type I interferons. This type of interferons is mediated primarily via JAK1. Therefore, the inhibition of JAK1 might be a promising therapy for all types CLE.[53,54]

Conclusion

CLE has various cutaneous manifestations that can have tremendous psychosocial impact and burden on affected patients. Currently, there are no agents approved specifically for this condition. Topical and oral corticosteroids, antimalarial drugs, and MTX remain the most widely-used agents in its management. Other immunosuppressive and immunomodulatory agents are reserved for refractory cases and should be used preferably in consultation with a rheumatologist. Future large clinical trials and robust prospective studies are needed to evaluate the efficacy of additional agents including emerging therapies such as topical and oral JAK inhibitors.

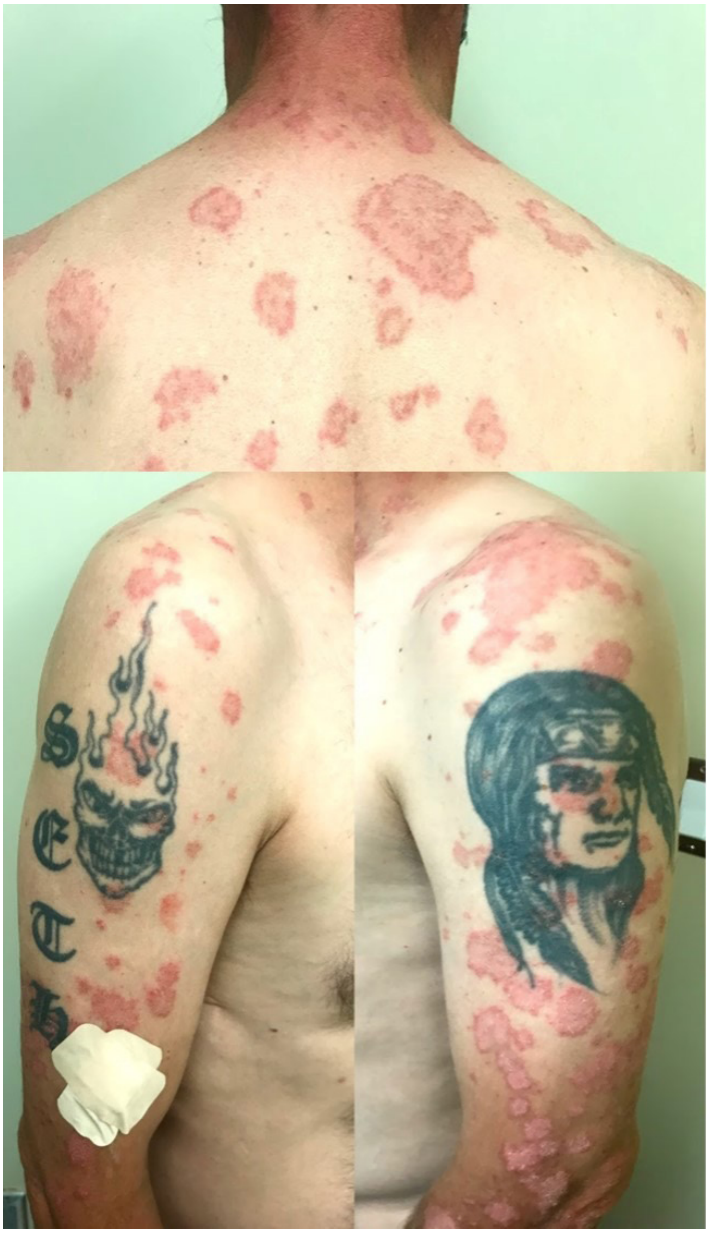

Figure 1. *A case of SCLE with annular scaly plaques on the upper back and arms; photo courtesy of Mohannad Abu-Hilal, MD*

Figure 2. *A case of DLE; photo courtesy of Mohannad Abu-Hilal, MD*

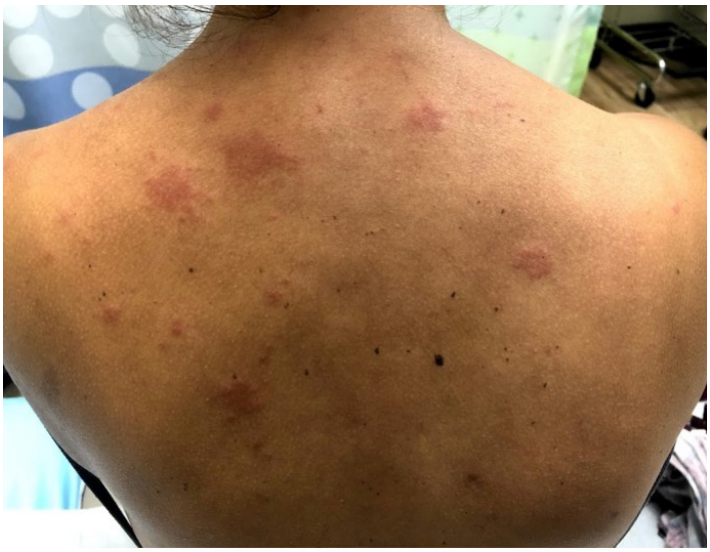

Figure 3. *A case of LET with non-scaly erythematous papules and plaques on upper back; photo courtesy of Mohannad Abu-Hilal, MD*

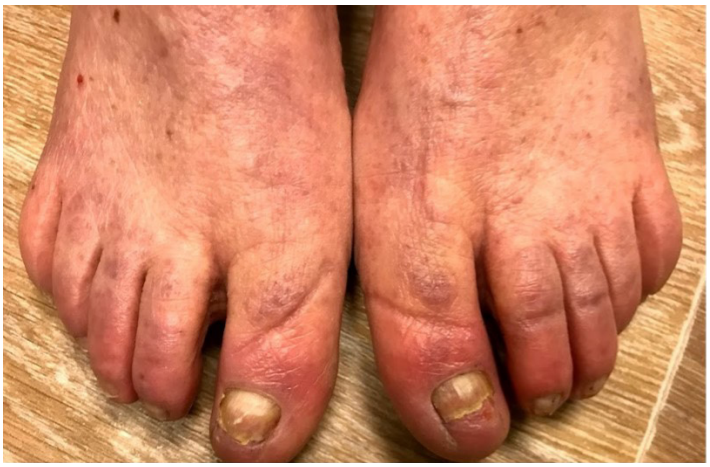

Figure 4. *A case of chilblain lupus with erythematous papules on distal parts of the toes; photo courtesy of Mohannad Abu-Hilal, MD*

Photosensitivity	Erythematous changes in reaction to exposure to sunlight
Discoid rash	Erythematosus papules and plaques with keratotic scaling and follicular plugging, and sometimes central atrophy or scarring
Malar rash	Persistent erythema over the malar area and the nose; typically spares the nasolabial folds
Oral ulcers	Recurrent, often painless oral ulcers observed by a clinician
Arthritis	Non-erosive arthritis involving two or more peripheral joints
Serositis	Pleuritis or pericarditis
Renal disorder	Cellular casts or persistent proteinuria greater >0.5 g/24 hours
Neurologic disorder	Seizures or psychosis
Hematologic disorder	Hemolytic anemia – With reticulocytosis OR Leukopenia – <4000/mm^3 total on two or more occasions OR Lymphopenia – <1500/mm^3 on two or more occasions OR Thrombocytopenia – <100,000/mm^3 (in the absence of offending drugs)

Table 1. *The 1997 American College of Rheumatology revised criteria for the classification of SLE.*[4]

Domain	Criteria	Points
Antiphospholipid antibodies	Anti-cardiolipin antibodies or Anti-β2GP1 antibodies or Lupus anticoagulant	2
Complement system	Low C3 or low C4 Both Low C3 and low C4	3 4
SLE-specific antibodies	Anti-dsDNA or Anti-Smith antibody	6

Table 2A. Immunologic domains, criteria and points for SLE per the 2019 joint EULAR and ACR criteria.[3]

Domain	Criteria	Points
Constitutional	Fever	2
Hematologic	Leukopenia Thrombocytopenia Hemolysis	3 4 4
Neuropsychiatric	Delirium Psychosis Seizure	2 3 5
Mucocutaneous	Oral ulcers Non-scarring alopecia Subacute cutaneous or discoid lupus Acute cutaneous lupus	2 2 4 6
Serosal	Pleural and/or pericardial effusion Pericarditis	5 6
Musculoskeletal	Joint involvement	6
Renal	Proteinuria >0.5 g/24 h Kidney biopsy class II or V lupus nephritis Kidney biopsy class III or IV lupus nephritis	4 8 10

Table 2B. *Clinical domains, criteria and points for SLE per the 2019 joint EULAR and ACR criteria.*[3]

Specific CLE
Acute cutaneous lupus erythematosus (ACLE) Subacute cutaneous lupus erythematosus (SCLE) Chronic cutaneous lupus erythematosus (CCLE) • Discoid lupus erythematosus (DLE) • Lupus erythematosus tumidus (LET) • Subcutaneous lupus erythematosus • Chilblain lupus
Non-specific CLE
Raynaud's phenomenon Peri-ungual erythema and telangiectasia Livedo reticularis Thrombophlebitis Non-scarring alopecia Oral ulcers

Table 3. *Classification of CLE.*[4-6]

Sun protection practices (i.e., use of broad-spectrum chemical sunscreen, wearing long-sleeved garments and wide-brim hats)
Smoking cessation
Vitamin D supplementation in patients using long-term sun protection
Avoidance of photosensitizing drugs
Avoidance of drugs that may cause drug-induced lupus

Table 4. *General recommendations and lifestyle modification for patients with CLE.*

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