Review

Cutaneous Lupus Erythematosus

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Lupus erythematosus (LE) is a heterogeneous group of chronic autoimmune inflammatory diseases, ranging from solely cutaneous symptoms to systemic disease with extensive visceral involvement.[1] Lupus was first named in the Middle Ages, but evidence suggests that Hippocrates described it long before that time.[2] Its intricate pathogenesis makes lupus a mainstay in the world of dermatological research, especially since roughly 75% of affected individuals experience cutaneous symptoms at some point during the course of the disease.[3] As a result, thorough knowledge of cutaneous lupus erythematosus (CLE) is integral to successful management of affected patients.

Epidemiology of LE

The prevalence of systemic lupus erythematosus (SLE) is 17-48 per 100,000 worldwide.[3-4] Although it was once believed that CLE was 2-3 times more common than SLE,[5] emerging evidence suggests that the incidence rates are comparable. Typically, patients with LE are between the ages of 20-40 with a female predominance that varies according to subtype.[1] Patients with African ancestry have been found to be slightly more susceptible.[1]

As previously mentioned, cutaneous manifestations are one of the most common clinical complaints of patients with LE, and are the second most common presenting symptom after joint involvement.[3] Although CLE is rarely life-threatening, it contributes disproportionately to disease burden through vocational disability and effects on personal and social well-being, in addition to significant medical and social costs.[7]

Although CLE typically occurs in conjunction with systemic involvement, it is important to clarify that it may exist independently of extracutaneous symptoms.[3] This distinction is important - it is crucial to identify the specific subtype of CLE, since it functions as an indicator of the extent of systemic disease, in addition to directing the management plan and affecting the patient's prognosis.[8]

Pathogenesis of CLE

The pathogenesis of CLE is complicated and has not yet been fully elucidated. The mechanisms involved in the development of the disease continue to be an area of active investigation.

Patients with CLE have dysregulated apoptosis, as well as decreased apoptotic cell clearance. Research shows that UV light induces apoptosis of keratinocytes through IL-1 & TNF-α, and occasionally, at very high doses, leads to necrosis.[9-10] There is also increased antibody binding to keratinocytes following UV exposure, which could be a result of UV-induced translocation of antigens to the cell surface or UV-induced alteration of antigen properties. UV light induces apoptosis of keratinocytes, and apoptotic blebs may be presented to lymphocytes, resulting in the stimulation of an immune response.[9-10]

It is believed that patients with CLE have upregulated interferon-α inducible genes.[9-10] Local production of type 1 interferons leads to recruitment of chemokines and T lymphocytes to the skin, which results in Th1-biased inflammation. It has been thought that B cells may not be as important in the pathogenesis of CLE, compared to SLE, since anti-B cell therapy is not a particularly effective treatment of CLE.[9-10]

Classification: Clinical, Histopathological & Immunological Diagnostic Features

The classification of CLE consists of a tiered system of divisions based on histopathologic examination and cutaneous lesion morphology. CLE is first classified as either LE-specific or LE-nonspecific. LE-specific cutaneous manifestations are further classified as chronic (CCLE), subacute (SCLE) or acute (ACLE), each of which consists of a variety of different subtypes.[8] In a prospective study completed in a tertiary care dermatological reference center, the frequency distribution for CLE was found to be: 67.5% for Discoid LE (the most common form of CCLE), 18.4% for SCLE, 6.1% for ACLE and 6.1% for LE-nonspecific CLE.[11] However, it is not uncommon to have difficulty identifying a single subtype of CLE since overlapping features are prominent on the disease continuum.[12] In patients with SLE, the presence of more than one LE-specific subtype is especially prevalent.[1]

LE is regarded as the great imitator, so confidence in classification is essential for prompt and proper diagnosis and effective management, which varies according to subtype.

LE-Nonspecific CLE versus LE-Specific CLE
LE-nonspecific CLE and LE-specific CLE are distinguished on the basis of histopathological characteristics described originally by the Gilliam and Sontheimer classification of LE-associated skin lesions. It is based on the presence of interface dermatitis-inflammation at the basal membrane zone of the interfollicular epidermis.[7] The following hallmarks of lichenoid tissue reaction are common amongst LE-specific cutaneous lesions: hyperkeratosis; epidermal atrophy; liquefactive degeneration of the epidermal basal-cell layer; a mononuclear cell infiltrate focused at the dermo-epidermal junction, perivascular areas and perifollicular areas; thickening of the basal membrane; and melanin pigment incontinence.[12] In contrast, LE-nonspecific lesions may be seen as part of another disease process – their histology is not distinct for LE.[4]

LE-Nonspecific Lesions
LE-nonspecific lesions are extremely prevalent in patients with SLE and, therefore, manifestations such as oral ulcers and photosensitivity are included as part of the ACR diagnostic criteria for SLE.[1] Furthermore, the presence of LE-nonspecific lesions may be used as an indicator of underlying SLE activity. Research has revealed that the presence of such lesions is associated with higher activity scores than the presence of only LE-specific lesions or a combination of both types of lesions.[1,4,13] Likewise, the number of different skin lesion types has also been found to correlate with disease activity. Patients with three or more different lesion types (specific or nonspecific) were found to have higher disease activity scores.[13] Photosensitivity in particular is a markedly sensitive indicator of SLE. It is estimated that 50-93% of SLE patients experience photosensitivity.[1]

Generally speaking, LE nonspecific lesions may be divided into three main groups: cutaneous vascular disease, non-scarring alopecia, and other dermatologic conditions.

Cutaneous vascular conditions are often indicators of underlying systemic vascular pathology. As a result, recognition of such conditions in patients with SLE is extremely important. Raynaud's phenomenon is the most common vascular reaction in patients with SLE, occurring in an estimated 40% of affected patients.[14] The presence of this phenomenon is associated with higher disease activity scores and poorer prognosis.[15-16]

LE-nonspecific vasculopathy occurs generally as a vasculitis in patients with SLE as a result of antiphospholipid antibodies. In such cases, it is important to investigate the possibility of vasculopathy due to thromboembolism, since clinical findings would be similar.[1]

Urticaria is also not uncommon in patients with SLE and is speculated to be a result of immune dysregulation. In one study, it was found that 44-73% of SLE patients had chronic urticaria.[17]

Other LE-nonspecific cutaneous conditions include: cutaneous vascular disease (periungal telangiectasia, livedo reticularis, thromophelitis, erythromelalgia), non-scarring alopecia ("lupus hair," telogen effluvium, alopecia areata), and other dermatologic conditions (sclerodactyly, rheumatoid nodules, calcinosis cuti, LE-nonspecific bullous lesions, papulonodular mucinosis, cutis laxa/anetoderma, acanthosis nigricans, erythema multiforme, leg ulcers, lichen planus).[1]

LE-Specific Lesions
ACLE
Important Points:
ACLE occurs almost exclusively in patients with SLE. Patients with ACLE have almost 100% chance of having clinically significant systemic manifestations.[7] Photosensitive distribution with severity that flucates with sun exposure and SLE severity.[8] Post-inflammatory pigmentary changes may occur, but scarring is rare.[1]

Clinical Presentation:
LOCALIZED: Classic "butterfly" rash – confluent, erythematous, edematous rash located on the nasal ridge and malar eminences. May extend to forehead, chin or V-area of the neck. Spares the nasolabial folds.[1]
GENERALIZED: Pruritic, maculopapular rash typically located on extensor aspects of the arms and hands but sparing the knuckles.[1,8]

Associated Findings:
Diffuse hair thinning, receding hairline, telangectasias and erythema of the proximal nail fold.[3,7]

Histological Findings:
Interface dermatitis with basal layer vacuolization, edema in the upper dermis, focal liquefactive degeneration or the basal cell layer and lymphocytic dermal infiltrates.[7,8,18]

Immunological Findings:
Lupus band test identifies granular deposits of immunoglobulin and complement at the dermo-epidermal junction. It is useful for distinguishing between SLE and CLE, because it is positive for both affected and unaffected areas in SLE but only in affected areas in CLE. Other conditions, as well as healthy sun exposed skin, may produce positive results.[7,19]

Serological Findings:
Typically ANA and anti-dsDNA positive and have low complement. Anti-Sm antibodies have a strong specificity for SLE and are used to determine underlying systemic disease.[18]

SCLE
Important Points:
Associated with mild systemic symptoms, most commonly musculoskeletal.[20] Lesions are trauma-induced and photo-aggravated. Many drugs have also been linked to the onset and exacerbation of symptoms.[20] SCLE commonly heals without scarring or dermal atrophy, however telangectasias and post-inflammatory hypopigmentation are common.[8] Papulosquamous type, leukopenia and high titers of ANA and anti-dsDNA antibodies have all been linked to increased risk of developing SLE.[1]

Clinical Presentation:
Characterized by recurring, non-scarring symmetrical lesions occurring in a photosensitive distribution. Lesions begin as erythematous macules and/or papules and progress to hyperkeratotic plaques.[1,8,20]

Histological Findings:
Compared to ACLE, SCLE has more prominent vacuolization on the basal layer, marked atrophy of the epidermal/adnexal epithelium and denser lymphocytic infiltrate.[7] Compared to DLE, SCLE tends to have less hyperkeratosis, follicular plugging, adnexal infiltrates and dermal melanophages.[20]

Immunological Findings:
Often characterized by a pattern of "dust-like" particles of IgG that are visible upon direct immunofluorescence and are associated with the presence of Ro/SSA autoantibodies. Unique to SCLE, but low diagnostic sensitivity.[3,7]

Serological Findings:
Anti-Ro/SSA is most important and is found in 70-90% of cases. Anti-La/SSB is found in 35-70% of cases. Transplacental passage of anti-Ro and/or anti-La antibodies can react with fetal antigens and result in neonatal lupus erythematosus.[7]

CCLE
Important Points:
Occurs in patients with long term, low-grade illness. Discoid type is most common.[3,8] Classified as localized, (70%) or generalized (30%).[8] Localized lesions typically occur above the neck, whereas generalized lesions occur above and below the neck.[1,20] Trauma induced and exacerbated by sun, but less so than ACLE and SCLE.[1,8] Generally resolves with atrophy, irreversible scarring, pigmentary changes, telangectasias and permanent-scarring alopecia.[1,7]

Clinical Presentation:
One or more clearly demarcated, erythematous, disc-shaped papules or plaques with adherent hyperkeratotic scale extending into surrounding pilosebaceous follicles (follicular plugging). Removal of the scale is quite painful and may result in the "carpet tack sign."[1,7] Nail findings may include nail plate dystrophy, pitting, ridging, leukonychia striata, onycholysis, clubbing, nail bed erythema and telangectasias.[1,7,20]

Histological Findings:
Hyperkeratosis of the epidermis, keratotic follicular plugging, vacuolar degeneration of basal keratinocytes and dermal mononuclear cellular infiltrate (infiltrate extends deeper than in ACLE and SCLE).[8,20]

Immunological Findings:
Direct immunofluorescence reveals immunoglobulins and complement in a granular band along the dermo-epidermal junction.[7-8] Lupus band test is positive in 90% when performed on lesional skin and in 10-20% when performed on non-lesional skin.[8]

Serological Findings:
Only 1/3 of patients are ANA positive. Positive serology tends to be more common in patients with generalized disease, those who have had DLE for a long time and elderly patients. Serology should be monitored to track disease progression.[7-8]

Treatment of CLE and Associated Adverse Effects

Although CLE has several different forms, treatment regimens remain similar across the board, with the goal to prevent lesion progression and enhance patient appearance.[3]

Initial management focuses on patient education. It is essential to identify provocative agents and develop strategies to deal with these precipitating factors. Heat,

certain drugs, and most importantly, sunlight should all be avoided. Sunscreen and sun avoidance is the cornerstone of CLE treatment.[21] It is recommended that patients photo-protect, both physically, through tightly woven clothing and hats and chemically, through sunscreens of at least SPF 30 with both UVB and UVA protection.[20] This is especially important in patients with SCLE, since 64% will develop skin lesions after one week of irradiation. However, it is not to be neglected in other patients, considering many who report no photosensitivity actually produce abnormal photo-provocative test results, which is likely accounted for by a delayed reaction following sun exposure.[21]

Initial therapy often also includes a medium potency topical corticosteroid, applied daily to lesional skin.[20] High potency steroids may be used, but are typically reserved for thicker skin. Once improvement occurs, patients are instructed to taper corticosteroid potency.[21] Generally, however, topical corticosteroids alone do not result in adequate improvement. For localized lesions, intralesional corticosteroid injections are an option. However, side effects include subcutaneous atrophy and leukoderma at the site of injection.[20] Oral corticosteroid therapy is avoided when possible, though can be useful in short courses while waiting for slow-acting agents to take effect.[3,20] Nonetheless, it is important to note that LE patients are at increased risk of avascular necrosis and thromboembolism.[21]

Antimalarial agents have been used for decades as treatment for LE and continue to play a major role in successful treatment of these conditions. Roughly 75% of patients with SCLE will respond to mono or combination antimalarial therapy.[20] Hydroxychloroquine, chloroquine and quinacrine are all used in practice,[21] with the former two being used most frequently due to less serious adverse effects.[22]

Antimalarials have more than one mechanism of action. They increase vacuolar pH, which decreases the immune response to autoantigens due to alteration in antigen processing and presentation. However, they also inhibit the release of pro-inflammatory cytokines. In addition, there is evidence that antimalarials inhibit granulocyte migration and phospholipase A2 activity, which may be implicated in their effectiveness in treating LE.[21]

Typically, patients are started on 200mg once daily of hydroxychloroquine to determine gastrointestinal tolerance and, in the absence of any issues, the dose is increased to 200mg twice daily.[21-22] It often takes roughly two months for effects to become apparent.[22] If monotherapy proves unsuccessful, quinacrine 100mg once daily may be added to the regimen. It has been found that hydroxychloroquine and quinacrine combination therapy is effective in treating patients for which hydroxychloroquine monotherapy has proved ineffective. If combination therapy continues to be ineffective after approximately six weeks, hydroxychloroquine may be replaced with chloroquine in a dose of 250-500mg once daily.[20-21] However, hydroxychloroquine and chloroquine should never be used in combination due to the increased risk of retinopathy.[3] It is recommended that patients remain on antimalarial therapy for one to two years to fully suppress cutaneous LE activity.[20]

In addition to being an effective treatment for LE, antimalarial therapy has a variety of other benefits including improvement of fatigue, headache, fever, arthralgias, arthritis, pleuritis, and pericardial inflammation.[3,21] In addition to these benefits, hydroxychloroquine has antithrombotic effects and will also lower cholesterol.[3,21] However, like any treatment, antimalarials are not without adverse effects; fortunately, side effects generally occur in less than 10% of patients.[23] Gastrointestinal complaints are the most common adverse event for all types of antimalarials, but are typically evanescent, and can be ameliorated by decreasing drug dose.[22] The most serious complication of hydroxychloroquine/chloroquine treatment is irreversible retinal toxicity. Patients taking this therapy should be followed closely by an ophthalmologist – every six months for hydroxychloroquine and every four months for chloroquine.[3,22] Other less common symptoms associated with hydroxychloroquine/chloroquine include blue-grey hyperpigmentation, urticaria, MSK flu-like symptoms, headache, nervousness, insomnia, psychosis, and seizures. Hematologic and hepatic effects have also been reported, but are exceptionally rare. There are also several case reports of cholorquine being associated with cardiac conduction issues, which should be considered in patients with a pre-existing conduction defect.[24] In patients taking quinacrine, adverse effects include GI symptoms, discoloration of the skin and bodily secretions, eczematous skin lesions, exfoliative skin lesions, headache, and dizziness. Retinal toxicity is not an issue.[3,21]

Although the mechanism is unclear, there is evidence to suggest that smoking interferes with the effectiveness of antimalarials. One study of patients with DLE and patients with SCLE found that cutaneous lesions were responsive to antimalarials in 91% of non-smoking patients, but only 40% of smokers.[25] Furthermore, it has

been suggested that smoking also directly exacerbates cutaneous LE lesions.[20] Therefore, smoking cessation plays a key role in successful management of LE through antimalarial treatment.

Another issue that arises with the use of antimalarials is safety in pregnancy. Initially, withdrawal of antimalarial therapy was recommended in pregnant patients with LE. However, since hydroxychloroquine and chloroquine have a high affinity for binding in tissue, it takes several months for them to be cleared from the system. As a result, stopping therapy at the first sign of pregnancy does not eliminate fetal drug exposure.[21] Evidence has since indicated that antimalarials have a good safety profile and prove quite useful in suppressing LE flares that may occur during pregnancy.[26-28] One study revealed lower frequency of LE flares during pregnancy, as well as absence of teratogenic effects in children after a three-year follow-up.[27] Generally, hydoxychloroquine is considered safer than chloroquine since it is less toxic, binds less readily to tissues, and is less able to cross the placenta.[27] Safety of these drugs in breastfeeding mothers has not yet been established.[22]

Dapsone and retinoids, although less effective than antimalarials, are also a treatment option for patients with CLE. Dapsone has been found to successfully treat patients with bullous LE, SCLE and DLE.[29-31] It is also a good choice for patients with LE who also have vasculitis. Retinoids have proved useful in the treatment of hypertrophic DLE.[32]

Thalidomide has been well publicized for its teratogenic effects; however, despite its generally bad reputation it is extremely effective in the treatment of CLE. Research shows that on average, thalidomide produces therapeutic benefit in 90% of patients with CLE.[33] The therapeutic effects of thalidomide are thought to be a result of decreased TNF-α activity and inhibited angiogenesis.[3] Careful patient selection and vigilant drug monitoring are crucial when using thalidomide therapy. Patients should be extensively counseled about the drug . Female patients of childbearing age are required to use two effective forms of contraception one month prior to starting therapy, during therapy, and one month after the completion of therapy.[33] In terms of potential adverse effects, the most commonly reported are mild, and include constipation, weight gain and sedation.[3] Thalidomide-induced peripheral neuropathy is a significant concern as it has been reported to occur in up to 50% of patients in some series and is potentially irreversible. Therefore, neurological testing of patients on thalidomide is mandatory. Other less common but serious effects include teratogenicity, ovarian failure, and thrombosis.[33]

Refractory CLE is defined as a disease that does not respond to systemic antimalarial and corticosteroid therapy added to topical therapy, and with which concomitant pathogenic processes have been excluded.[34] First, when assessing refractory disease, consideration should be given to modifiable factors such as sun-exposure, smoking and drugs that are known to exacerbate CLE. Although there are no universal guidelines for the treatment of refractory CLE, some medications have been identified as more effective than others. Thalidomide and methotrexate have shown impressive results with patient response rates of over 90%.[34]

Prognosis and Quality of Life

An outcome measurement for CLE has recently been developed in the form of CLASI (Cutaneous Lupus erythematosus disease Area and Severity Index). CLASI has two scores, one for disease activity and one for damage as a result of the disease. Activity is a summative score of erythema, scale/hypertrophy, mucous membrane involvement, acute hair loss or non-scarring alopecia. Damage is a summative score of dyspigmentation or scarring, including scarring alopecia.[35-36] The availability of such a scale, although not a perfect representation of such a multidimensional disease, can help quantify a patient's condition, which is helpful in clinical practice, and is useful for clinical trials.[36]

Prognosis for patients with CLE is strongly connected to severity and extent of systemic involvement. Presently, prognosis is favourable, with 10-year survival exceeding 80%. Most fatalities associated with LE occur as a result of systemic involvement, especially renal and CNS and infections.[5] Therefore, this is of particular concern in patients with ACLE since it is almost exclusively associated with SLE.

Quality of life is a major concern in patients with dermatologic conditions. Psychiatric morbidity is higher in the dermatologic population than the general population – with prevalence ranges of 20-40% and 11-30%, respectively.[37] It is no surprise that patients with CLE are at risk for mental health issues as a result of poor quality of life associated with their illness.[38] Researchers have shown that presence of cutaneous disease has a clear effect on patients' quality of life, and that this effect is most significant for those with generalized DLE.[38] Evidence suggests that factors related to poor quality of life include female gender, young

age, severe or generalized lesions, and distribution of lesions, particularly on the face.[37] Mental health is crucial to overall health, and practitioners should be aware of the potential serious effects CLE can have on quality of life and patient well-being.

Transition of Cutaneous LE into Systemic LE

It is important for practitioners to recognize the potential for CLE to progress to more widespread systemic disease. ACLE is exclusively associated with SLE, thus this is applicable mainly to patients with SCLE and CCLE. It is difficult to predict disease course, however, a prospective multicenter study found that patients with signs of nephropathy, arthralgias and elevated ANA titers were at increased risk of developing extracutaneous LE symptoms, and that risk increased with the number of positive variables.[39] Therefore, it may be beneficial to monitor such patients closely and tailor treatment accordingly.[5] In terms of slowing the progression of CLE to SLE, research is limited. One study of military recruits, however, demonstrated an association between the use of antimalarial therapy and an increased lag time between first systemic symptom to fully developed SLE.[38]

Approximately 5-10% of patients with CDLE and 50-60% of patients with SCLE will develop extracutaneous involvement and progress to SLE during the course of their disease.[5,40]

CLE and Malignancy

Patients with LE are at an increased risk for the development of malignant neoplasms, particularly lymphoma and carcinoma of the skin. The frequency of malignancy in patients with SLE has been reported to be between 2.4 and 13.8%.[41] Researchers are unsure of the exact mechanism. It has been speculated that malignant transformation may be linked to the disease process itself, or that it occurs as a result of immunosuppressive therapy that is often used in patients with LE.[42] It has also been suggested, however, that antimalarials may serve as a protector against malignant transformation through mutation prevention, inhibition of telomerase, increased synthesis of p53 and improvement of DNA cell repair.[42] Regardless, it is important to be aware of the possibility of neoplasm development when managing patients with CLE.

Conclusion

Accurate diagnosis of CLE is crucial, as it signifies the extent of systemic disease, directs the management plan, and indicates patient prognosis. CLE is the second most common presenting symptom and one of the most common patient complaints of individuals with LE. It also contributes disproportionately to vocational disability. Therefore, regardless of the field of medicine, an awareness of CLE is imperative to comprhensive patient care.

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