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CORE TRAINING FOR DOCTORS



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# Cutaneous lupus erythematosus

Lupus erythematosus is an autoimmune disease with a wide spectrum of severity, from isolated cutaneous involvement through to systemic lupus erythematosus. This article focuses on cutaneous lupus erythematosus which can be divided into three main subtypes:

1. Acute cutaneous lupus erythematosus – characterized by erythema over light-exposed areas, classically causing a 'butterfly' rash of the face
2. Subacute cutaneous lupus erythematosus – comprising either annular (ring like) or papulosquamous (psoriasis like) eruptions
3. Chronic cutaneous lupus erythematosus – discoid lesions are most common and consist of well-defined erythematous scaly lesions that heal with scarring.

While this is a helpful framework for understanding cutaneous lupus erythematosus, there is considerable overlap, and clinical features of different subtypes may be seen in the same patient.

## Epidemiology

The annual incidence of cutaneous lupus erythematosus in western European populations is approximately 4.0 per 100 000 and has an overall female preponderance of 3:1, with a mean age of onset of 54 years (Grönhagen et al, 2011). Chronic cutaneous lupus erythematosus is the most common subtype and makes up approximately 80% of cases, in contrast to acute cutaneous lupus erythematosus which accounts for 6% of cases (Moghadam-Kia et al, 2009; Grönhagen et al, 2011). Cutaneous disease can occur in isolation or in association with systemic involvement. Acute cutaneous lupus erythematosus is almost exclusively associated with systemic lupus erythematosus (Koskenmies et al, 2008) while patients with chronic cutaneous lupus erythematosus rarely develop systemic lupus erythematosus.

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## Pathophysiology

The pathogenesis of cutaneous lupus erythematosus is complex and incompletely understood. It is thought that reduced clearance of apoptotic debris may result in antibody formation against nuclear antigen with subsequent immune complex deposition. Genetic, immunological and environmental factors are likely to play a role.

Each subtype of cutaneous lupus erythematosus has a number of genetic associations. Human leucocyte antigens (HLA), genes encoding cytokines such as IL-1 and IL-10, adhesion molecules such as ICAM 1 and E-selectin as well as the interferon pathway are associated and thought to be pathogenic (reviewed in Wenzel et al, 2010). Photosensitivity in subacute cutaneous lupus erythematosus is especially associated with HLA DR3 and B8 and the presence of anti SSA/Ro antibodies. Inherited complement deficiencies resulting in reduced clearance of immune complexes are highly associated with cutaneous lupus erythematosus. For example mutations leading to loss of function of C1Q, a key component of the classical complement pathway, results in systemic lupus erythematosus in 90% of cases (Botto et al, 2009). While this is informative from a pathogenic perspective, complement deficiencies are exceedingly rare and only found in a minority of patients with systemic lupus erythematosus.

Ultraviolet light is the most important exogenous trigger for cutaneous disease. Patients with cutaneous lupus erythematosus have increased numbers of apoptotic keratinocytes following ultraviolet exposure (Kuhn et al, 2006), and these cells secrete inflammatory cytokines and express nuclear antigens on their surface leading to the formation of anti-nuclear antibodies (ANA). Immune complexes consisting of

ANA and nuclear antigens are then thought to stimulate the secretion of interferon-α (IFN-α) by plasmacytoid dendritic cells in the skin, thereby potentiating the inflammatory cascade (Means et al, 2005).

Medication is another important exogenous cause. Drugs known to trigger cutaneous lupus erythematosus include angiotensin-converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs, statins, proton pump inhibitors and antihypertensive drugs.

**Table 1. Key components of the history when considering a diagnosis of cutaneous lupus erythematosus**

| | Important questions |
|---|---|
| Diagnosis | Acute or chronic onset |
| | Duration of lesions |
| | Site and spread |
| | Cutaneous scarring |
| | Associated alopecia and nail changes |
| Triggers | Ultraviolet exposure |
| | Drug history |
| | Occupational chemical exposure |
| Systemic involvement | Fever, weight loss, malaise |
| | Mouth ulcers, abdominal pain (splenomegaly) |
| | Arthralgia, myalgia |
| | Raynaud's phenomenon |
| | Bruising or bleeding |
| | Frequent infections |
| | Seizures and psychosis |
| | Abnormal sensation or weakness |
| | Shortness of breath or chest pain |
| | Orthopnoea, ankle swelling, reduced exercise tolerance |

## History

A careful history should be taken regarding the evolution of lesions as well as triggers and symptoms of systemic lupus erythematosus. Key components are summarized in *Table 1*.

## Examination

Examination findings for acute, subacute and discoid lupus are summarized in *Table 2*.

### Acute cutaneous lupus erythematosus

The most common presentation is macular erythema in sun-exposed areas. This is classically seen as the 'butterfly rash' that is characterized by confluent macular erythema centred over the malar eminences but sparing the nasolabial folds (*Figure 1*). It can also be seen on the forehead, chin, neck, upper chest and extensor surfaces of the arms and hands with sparing over the knuckles. Healed lesions leave post-inflammatory hyperpigmentation but no scarring. Acute cutaneous lupus erythematosus is nearly always found in association with some degree of systemic organ involvement (*Table 3*).

## Subacute lupus erythematosus

Patients most commonly present with annular (ring-shaped) lesions (*Figure 2*) and/ or papulosquamous (scaly, psoriasis like) patches and plaques. This is the most photosensitive form of cutaneous lupus erythematosus and characteristically

***Figure 1. Characteristic butterfly rash of acute lupus erythematosus.***

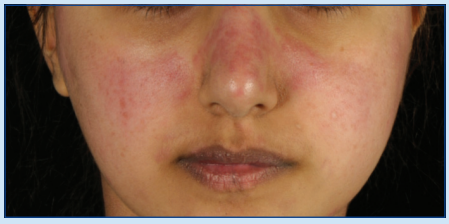


**Table 3. Pattern of organ involvement with systemic lupus erythematosus**

| System | Pattern of involvement |
|---|---|
| Musculoskeletal | Non-erosive arthritis of peripheral joints |
| | Capsular laxity or tendonitis can result in deformity (Jaccoud's arthropathy) |
| | Avascular bone necrosis |
| | Myositis |
| Renal | Glomerulonephritis |
| Cardiovascular | Pericarditis |
| | Myocarditis |
| | Libman–Sacks endocarditis |
| Respiratory | Pleuritis |
| | Interstitial lung disease |
| | Pulmonary hypertension |
| Neuropsychiatric | Seizures |
| | Psychosis |
| | Polyneuropathy |
| Haematology | Thrombocytopaenia |
| | Leucopaenia |
| | Haemolytic anaemia |
| Gastrointestinal | Oral ulceration |
| | Splenomegaly |

***Figure 2. Annular lesions on the right arm in keeping with subacute lupus erythematosus.***

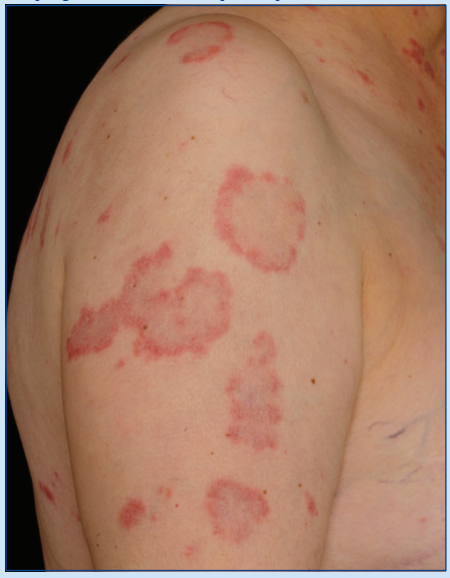


**Table 2. The clinical features of cutaneous lupus erythematosus**

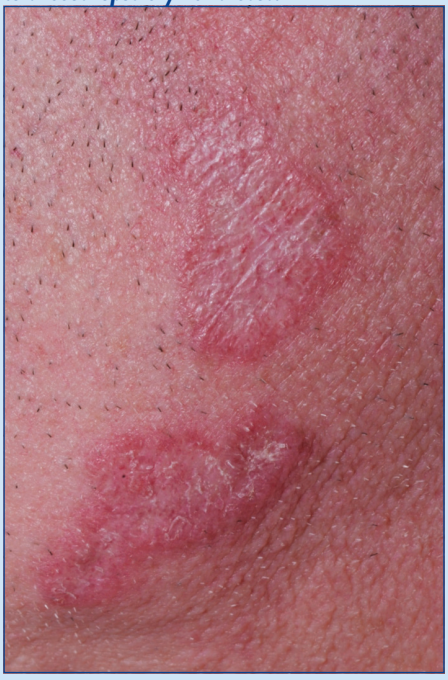
| | Acute cutaneous lupus erythematosus | Subacute cutaneous lupus erythematosus | Discoid lupus erythematosus |
|---|---|---|---|
| Typical presentation | Acute macular erythema in sun-exposed areas. Classically seen as a facial 'butterfly rash' | Subacute annular or papulosquamous lesions that heal without scarring but can leave pigmentary change | Erythematous scaly patches with atrophy and scarring |
| Classical distribution | Malar eminences (butterfly rash), forehead, neck, upper chest | Neck and upper chest | Localized to head and neck or disseminated |

affects the neck, upper chest, extensor surfaces of the arms and the upper back. The malar areas of the face are less commonly affected than in acute cutaneous lupus erythematosus. Lesions heal without scarring but may leave some pigmentary change.

### Chronic cutaneous lupus erythematosus

There are many subsets of chronic cutaneous lupus erythematosus, although discoid lupus erythematosus is by far the most common and accounts for over 90% of cases. Discoid lupus erythematosus is characterized by well-defined red scaly patches that heal with scarring, atrophy and pigmentary change (*Figure 3*). The disease can be limited to the head and neck (localized discoid lupus erythematosus) in 80% of cases or more widespread (disseminated discoid lupus erythematosus) in 20% of cases. The face is the most commonly affected site (*Figure 4*) and one third of patients have associated alopecia. Other features include follicular plugging, hyperkeratotic (scaly) nails, ulcerating mucosal lesions (can resemble leukoplakia) and conjunctival involvement. Other subsets of chronic cutaneous lupus erythematosus include lupus erythematosus panniculitis, lupus erythematosus tumidus and chilblain lupus.

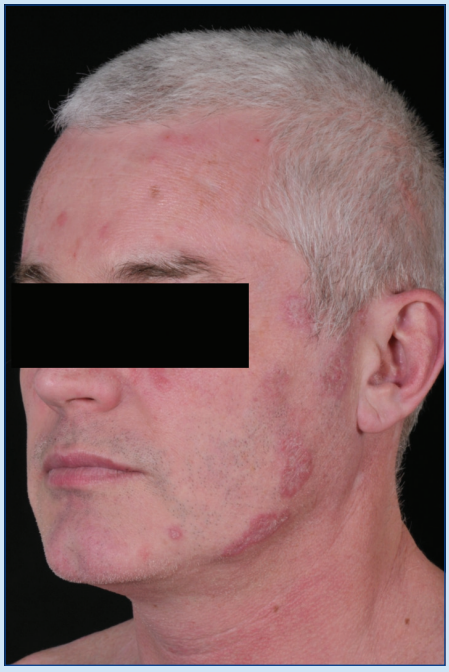
***Figure 3. Characteristic discoid lesions of chronic cutaneous lupus erythematosus.***



## Investigations

Investigations should focus on diagnosing cutaneous disease and identifying the extent of systemic organ involvement. In terms of laboratory investigations, acute cutaneous lupus erythematosus has similar markers of disease to systemic lupus erythematosus. The frequencies with which different autoantibodies are detected in each subtype of cutaneous lupus erythematosus are summarized in *Table 4*. Anti-double stranded DNA (dsDNA) and anti-Smith (Sm) are highly disease specific. Subacute cutaneous lupus erythematosus is highly associated with anti-Ro/SSA antibody and their presence is also associated with photosensitivity (Kuhn and Beissert, 2005). Discoid lupus erythematosus is associated with positive ANA titres in 10–30% of cases (Wenzel et al, 2000), but when present they may predict progression to systemic lupus erythematosus. Other laboratory abnormalities associated with cutaneous lupus erythematosus include anaemia, leucopaenia, thrombocytopaenia and a raised erythrocyte sedimentation rate, although the C-reactive protein level is usually normal especially in systemic lupus erythematosus. Investigations for renal, neurological, cardiac or pulmonary involvement may also be necessary if systemic involvement is suspected.

***Figure 4. Characteristic facial discoid lesions of chronic cutaneous lupus erythematosus.***



Skin biopsy of lesions can be helpful in the diagnosis of cutaneous lupus erythematosus but it can be difficult to distinguish subtypes of the disease on histological appearances alone. Shared histological features of all subtypes of cutaneous lupus erythematosus include hyperkeratosis, epidermal atrophy, basement membrane thickening and a dermal mononuclear infiltrate found perivascularly, perifollicularly and at the dermoepidermal junction. Direct immunofluorescence analysis of skin biopsies reveals deposition of IgG, IgM and rarely IgA antibiodies along with C3 at the dermoepidermal junction. However, these findings are non-specific, as they can be found in sun-exposed skin as well as other inflammatory dermatoses.

## Treatment and prognosis

Treatment of cutaneous disease can be topical or systemic. Ultraviolet light initiates and potentiates the inflammatory

**Table 4. Autoantibody frequencies in patients with cutaneous lupus erythematosus**

| | Type of lupus erythematosus | | |
|---|---|---|---|
| | Systemic | Subacute | Discoid |
| Antinuclear antibody | 96.1% | 83.6% | 28.6% |
| Extractable nuclear antigen | 64.0% | 83.6% | 27.6% |
| Ro/SS-A antibody | 61.8% | 82.9% | 26.1% |
| La/SS-B antibody | 23.6% | 43.9% | 3.6% |
| RNP antibody | 22.7% | 9.1% | 4.6% |
| Sm antibody | 12.0% | 0% | 0.6% |
| DsDNA | 44.2% | 5.6% | 8.6% |

From Koskenmies et al (2008)

response, therefore minimizing sun exposure and frequent application of sunscreen is an essential preventative approach. A careful review of the patient's medication is also important, with the removal of possible drug triggers. Topical steroids and calcineurin inhibitors are effective treatments for cutaneous lupus erythematosus (Lee and Sinha, 2006; Sticherling, 2011). Potent topical steroids such as clobetasol propionate or mometasone furoate can be used for lesions on the scalp, trunk and limbs but patients should be warned of the risk of steroid-induced skin atrophy with prolonged use. Generally mild to moderate potency topical steroids such as 1% hydrocortisone or clobetasone butyrate should be used on the face, although some dermatologists use more potent steroids on the face for short durations. Topical calcineurin inhibitors such as tacrolimus are steroid-sparing agents and are therefore especially useful for sensitive areas such as the face.

Hydroxychloroquine is first line for systemic therapy because of its efficacy and infrequent side effects (reviewed in Winkelmann et al, 2013). The addition of mepacrine to hydroxychloroquine can also augment its clinical efficacy. Other systemic agents that can be used to treat resistant cases include oral glucocorticoids, azathioprine, mycophenolate mofetil and methotrexate. These are less frequently prescribed but are often needed for treatment refractory cases.

There is also a role for biologic agents such as rituximab and intravenous immunoglobulin (Winkelmann et al, 2013). Belimumab is a monoclonal antibody that binds soluble B lymphocyte stimulator (BLyS) and reduces the differentiation of B cells into antibody producing plasma cells. It is used in the treatment of mucocutaneous and musculoskeletal involvement in systemic lupus erythematosus (Manzi et al, 2012), but is not licensed for the treatment of cutaneous disease and its use is limited to a small number of specialist centres.

The prognosis of cutaneous lupus erythematosus is determined by the pattern and extent of systemic involvement. Chronic cutaneous lupus erythematosus rarely progresses to systemic lupus erythematosus and while chronically active, skin disease is usually well controlled with treatment. Subacute cutaneous lupus erythematosus carries a good prognosis if uncomplicated by systemic lupus erythematosus and cutaneous disease is characterized by chronically active lesions with episodes of remission. Acute cutaneous lupus erythematosus, like systemic lupus erythematosus, carries a 10-year survival of approximately 90% (Lerang et al, 2014). Women with subacute cutaneous lupus erythematosus who are positive for anti SSA/Ro antibodies should be counselled about the risk of neonatal lupus syndrome including congenital heart block. The risk of this complication is reduced by the use of hydroxychloroquine in pregnancy (Izmirly et al, 2012). BJHM

*Conflict of interest: none.*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## KEY POINTS

- Subtypes of cutaneous lupus erythematosus are acute, subacute or chronic.
- Acute cutaneous lupus is usually associated with systemic lupus erythematosus and results in macular erythema on sun-exposed sites.
- Subacute cutaneous lupus is characterized by annular or papulosquamous eruptions and is commonly photosensitive.
- Discoid lupus erythematosus makes up the majority of cases of chronic cutaneous lupus erythematosus and is characterized by scarring plaques, usually confined to the head and neck. It is rarely associated with systemic lupus erythematosus.
- Treatments can be topical steroids or calcineurin inhibitors or systemic agents such as hydroxychloroquine. Rituximab and belimumab are biologic agents that are used to treat systemic lupus erythematosus but may result in improvement of cutaneous disease.