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THE PREVALENCE OF CUTANEOUS LUPUS MANIFESTATIONS IN PATIENTS DIAGNOSED WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) ATTENDING THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL RHEUMATOLOGY OUTPATIENT CLINIC

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Submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree of Master of Medicine in Dermatology.

Johannesburg 2017

Declaration

I, Karen Koch declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Dermatology at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……..

…….day of……., 2017

Dedication

For my husband Roberto

Presentations arising from this work

Koch K, Tikly M, Pillay L. Cutaneous disease in South Africans with Systemic Lupus Erythematosus. Poster presentation. 10th European Lupus Meeting, Venice. October 2016

Abstract

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder. The skin is affected in up to 85% of cases.

Aims

The objective of this study was to determine the prevalence and spectrum of both specific and non-specific cutaneous findings in SLE patients attending Chris Hani Baragwanath Academic Hospital.

Methods

A retrospective record review of 298 patients meeting the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE. Cutaneous findings were divided into LE- specific disease (Cutaneous Lupus Erythematosus) and LE-non-specific findings. The Lupus Severity Index (LSI) was calculated according to the Bello *et al*.

Results

The mean (±SD) age at presentation was 35 years (11.8) and the female: male ratio was 13:1. Eighty-three percent of patients had cutaneous findings and CLE affected 76.1% of patients. Discoid Lupus Erythematosus (DLE) was the commonest form of CLE followed by Acute Cutaneous Lupus Erythematosus (ACLE). Patients with CLE had a significantly better Lupus Severity Index (LSI) (5.7 vs 6.1; p=0.001). Those patients with Chronic Cutaneous Lupus Erythematosus (CCLE) had a better LSI than

those with ACLE (6.07 vs 6.5; p=0.001).

Conclusion

The skin was the single most commonly affected organ system. DLE, both localised and generalised, was very common in patients with SLE, occurring more frequently than ACLE. Patients with CLE had a better LSI than those without.

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Abbreviations

ACLE	Acute cutaneous lupus erythematosus
ACR	American College of Rheumatology
ANA	Antinuclear factor antibodies
Anti-dsDNA	Anti-double stranded DNA antibodies
Anti-La Ab (SSA)	Anti-single stranded antibodies type A
Anti-RNP Ab	Anti ribonuclear protein antibodies
Anti-Ro Ab (SSB)	Anti-single stranded antibodies type B
Anti-Sm Ab	Anti-Smith Antigen antibodies
BILAG	British Isles Lupus Assessment Group Index
CCLE	Chronic cutaneous lupus erythematosus
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence interval
CLE	Cutaneous lupus erythematosus
Cum	Cumulative
DLE	Discoid lupus erythematosus
Katz SDI	Katz Severity Index of Disease
LE	Lupus erythematosus
LP	Lichen planus
LSI	Lupus severity index
N	Number
NOS	Not otherwise specified
NR	Not recorded
NS	Not significant
SCLE	Subacute cutaneous lupus erythematosus
SD	Standard deviation
SDI	Severity of Disease Index
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
TEN	Toxic epidermal necrolysis
TNF	Tumour necrosis factor

UK	United Kingdom
USA	Unites States of America
UV	Ultraviolet

Chapter One: Introduction and Review of the Literature

1.1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disease that occurs in all populations and has a particular predilection for women of childbearing age. SLE has a variety of systemic effects. Most commonly the joints are affected. Other organ systems that can be affected include the renal, neurological and haematologic system (Simmons *et al*., 2008). It is associated with the presence of multiple auto-antibodies, especially antinuclear antibodies (ANAs) (James *et al*. 2011; Walling *et al*., 2009).

Cutaneous lupus erythematosus is a chronic autoimmune skin disease with a broad spectrum of clinical manifestations and a variable course. It may occur in isolation or in conjunction with SLE (Walling *et al*., 2009). The relationship between SLE and CLE as envisage by Gillian and Sontheimer is depicted in Figure 1.

1.2. Background and History

'Lupus' means 'wolf' in Latin. It has been used as a descriptive term for both cutaneous tuberculosis (lupus vulgaris) and cutaneous lupus erythematosus since the tenth century. The term was most likely first used to describe skin disease by Herbernus of Tours in 916 AD, possibly mimicking the appearance of a wolf's bite (Smith *et al*., 1988; Barnett *et al*., 2016).

The frequency of cutaneous tuberculosis and varied presentations of cutaneous

lupus erythematosus made differentiating the two entities difficult without modern histological stains and laboratory testing. According to Rudolph Virchow, the use of the word ‘lupus’ throughout the Medieval and Renaissance period was used to loosely describe any process involving ulceration or necrosis (Smith, 1988).

The term ‘lupus vulgaris’ was first used in the early 19th century by the English physician Robert Willan (1757-1812) and his student Thomas Bateman. They identified lupus vulgaris as a separate clinical subtype of lupus. The discovery of tuberculosis by German scientist Roberto Koch in 1882 allowed lupus vulgaris to be clearly described as a form of cutaneous tuberculosis (Barnett *et al*., 2016; Wallace *et al*., 1997).

Laurent Theodore Blett of the Paris School of Dermatology is ascribed as the first physician to clearly describe lupus erythematosus as a distinct entity, using the term ‘erythema centrifugum.’ His student, Pierre Louis Alphee Cazenave published his findings in 1851, coining the term, ‘lupus erythematosus.’ Cazenava was also the first physician to associate lupus erythematosus with UV light exposure (Gronhagen *et al*., 2010; Smith *et al*., 1988).

Viennese pathologist Mortiz Kaposi, in 1872 subdivided lupus into the discoid and systemic forms, describing symptoms like arthritis, weight loss and fever in association with skin lesions and identifying an increased morbidity with the latter (Smith *et al*., 1988; Barnett *et al*., 2016). Jonathon Hutchinson in 1888 went on to accurately describe the photosensitive nature of LE and may have been the first to document annular Subacute cutaneous lupus erythematosus (SCLE) (Kuhn *et al*.,

2005).

In 1895 Canadian physician William Osler described a group of patients with lupus erythematosus and relapsing visceral diseases involving the heart, lungs and kidneys. He termed this condition ‘erythema exudativum multiforme’, later coining the term ‘Systemic Lupus Erythematosus’ (Barnett *et al*., 2016; Wallace *et al*., 1997).

In 1948 clinical haematologists Malcolm Hargraves and Robert Morton first described the LE cell (Hargraves *et al*., 1948). George Friou in 1958 developed the indirect immunofluorescence test using animal tissue as a substrate allowing for detection of antinuclear antibodies (Friou *et al*., 1967).

The further discovery of specific autoantibodies, including nuclear ribonucleoprotein (nRNP), Sm, Ro, La and anticardiolipin antibodies have further assisted in elucidation of lupus pathogenesis and clinical subtypes of disease (Norman, 2016).

The concept of a ‘disease spectrum’ in cutaneous lupus erythematosus was first described by Dubois and Tuffanelli in 1964 (Tuffanelli *et al*., 1964). James Gilliam and Richard Sontheimer in the 1970s further segregated cutaneous disease into clinical subtypes – a classification that remains largely unchanged to this day (Costner *et al*., 2004).

1.3. Classification Criteria for Systemic Lupus Erythematosus

There is, to date, no single diagnostic serological marker for SLE (Simmons *et al*.,

2008). The American College of Rheumatology (ACR) developed classification criteria for SLE, which include 11 criteria and a patient is classified as having SLE if at least 4 of the criteria are met. These criteria are mainly used for research purposes but are a useful guide for the practicing clinician (American College of Rheumatology, 1997). More recently these criteria have been updated in 2012 by the Systemic Lupus International Collaborating Clinics (SLICC). They include more clinical and laboratory criteria increasing the sensitivity of the criteria compared to the ACR criteria (Petri *et al*., 2012).

Table 1.1 SCLICC Classification Criteria for SLE	
Requirements: > 4 criteria (at least 1 clinical and 1 laboratory criteria) OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA	
Clinical Criteria	Immunologic Criteria
Acute Cutaneous Lupus	ANA
Chronic Cutaneous Lupus	Anti-DNA Ab
Oral or nasal ulcers	Anti-Sm Ab
Non-scarring alopecia	Antiphospholipid Ab
Arthritis	Low complement (C3, C4)
Serositis	Direct Coombs' test (do not count the presence of hemolytic anaemia)
Renal	
Neurologic	
Hemolytic anaemia	
Leukopaenia	

Thrombocytopaenia (<100,000/mm^2)	

CLINICAL CRITERIA

(1) Acute Cutaneous Lupus OR Subacute Cutaneous Lupus

Acute cutaneous lupus: lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash (in the absence of dermatomyositis)

Subacute cutaneous lupus: nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)

(2) Chronic Cutaneous Lupus

Classic discoid rash Localised (above the neck) or generalised (above and below the neck), hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chillblains lupus, discoid lupus/lichen planus overlap

(3) Oral Ulcers OR Nasal Ulcers

Oral: palate, buccal, tongue

Nasal ulcers

In the absence of other causes, such as vasculitis, Behcet's disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis, and acidic foods

(4) Nonscarring alopecia

Diffuse thinning or hair fragility with visible broken hairs, in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia

(5) Synovitis involving 2 or more joints

Charaterised by swelling or effusion

OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness

(6) Serositis

Typical pleurisy for more than 1 day OR pleural effusions OR pleural rub

Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography

In the absence of other causes, such as infection, uremia, and Dressler's pericarditis

(7) Renal

Urine protein–to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours OR red blood cell casts

(8) Neurologic

Seizures, psychosis, mononeuritis multiplex(in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)

(9) Hemolytic anaemia

(10) Leukopaenia (<4000/mm3) OR Lymphopenia (<1000/mm3)

Leucopenia at least once: In the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension.

Lymphopenia at least once: in the absence of other known causes such as corticosteroids, drugs, and infection

(11) Thrombocytopaenia (<100,000/mm3)

At least once in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura

IMMUNOLOGIC CRITERIA
(1) ANA level above laboratory reference range
(2) Anti-dsDNA antibody level above laboratory reference range (or 2-fold the reference range if tested by ELISA)
(3) Anti-Sm: presence of antibody to Sm nuclear antigen
(4) Antiphospholipid antibody positivity, as determined by
Positive test for lupus anticoagulant
False-positive test result for rapid plasma reagin
Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
Positive test result for anti–2-glycoprotein I (IgA, IgG, or IgM)
(5) Low complement (C3, C4, or CH50)
(6) Direct Coombs' test (in the absence of hemolytic anaemia)

The SLICC criteria are very specific regarding cutaneous findings and include a variety of findings such as acute cutaneous lupus erythematosus, chronic cutaneous lupus erythematosus, oral or nasal ulcers and non-scarring alopecia. Most academic institutions now follow the SLICC criteria (Petri *et al*., 2012).

1.4. Classification of Cutaneous Lupus Erythematosus

The classification of cutaneous lupus has remained an area of much debate due to the myriad of cutaneous findings and as well as the use of ambiguous terms to describe skin findings.

James Gilliam and Richard Sontheimer in the 1970s devised a nomenclature that encompassed the vast majority of mucocutaneous findings. They divided the findings of mucocutaneous SLE into Lupus Erythematosus (LE)-specific and LE-non-specific disease (Costner *et al*., 2004; Gilliam *et al*., 1981).

LE-specific phenomena are those which show the characteristic histopathology of lupus erythematosus and are further subdivided into acute, subacute and chronic forms. They are summarised in Table 1.2 (Gronhagen *et al*., 2011; Walling *et al*., 2009).

LE-non-specific lesions include a wide number of clinical signs and symptoms including Raynaud's phenomenon, palpable purpura, leukocytoclastic vasculitis (LCV), non-scarring alopecia and erythromelalgia amongst others which do not occur exclusively in the setting of SLE. They are summarised in Table 1.3 (Gronhagen, *et al*. 2011; Walling *et al*., 2009).

1.4.1. Cutaneous Lupus Erythematosus Specific Disease

Table 1.2 Gilliam and Sontheimer classification of specific cutaneous lupus erythematosus (Costner *et al*., 2004)	
Cutaneous Lupus	Subtype
Chronic cutaneous LE (CCLE)	I. Classic discoid LE (DLE) a. Localised DLE b. Generalised DLE II. Hypertrophic/verrucous DLE III. Lupus panniculitis/lupus profundus IV. LE tumidus/papulomucinous LE V. Chilblain LE VI. Lichenoid DLE (LE/lichen planus overlap)
Subacute cutaneous LE (SCLE)	VII. Annular SCLE VIII. Papulosquamous/psoriasiform IX. Drug-induced SCLE
Acute cutaneous LE (ACLE)	X. Localised ACLE (malar rash) XI. Generalised ACLE (morbilliform) XII. TEN-like ACLE
Other	XIII. Bullous SLE XIV. Rowell's syndrome (Erythema multiforme-like lesions)

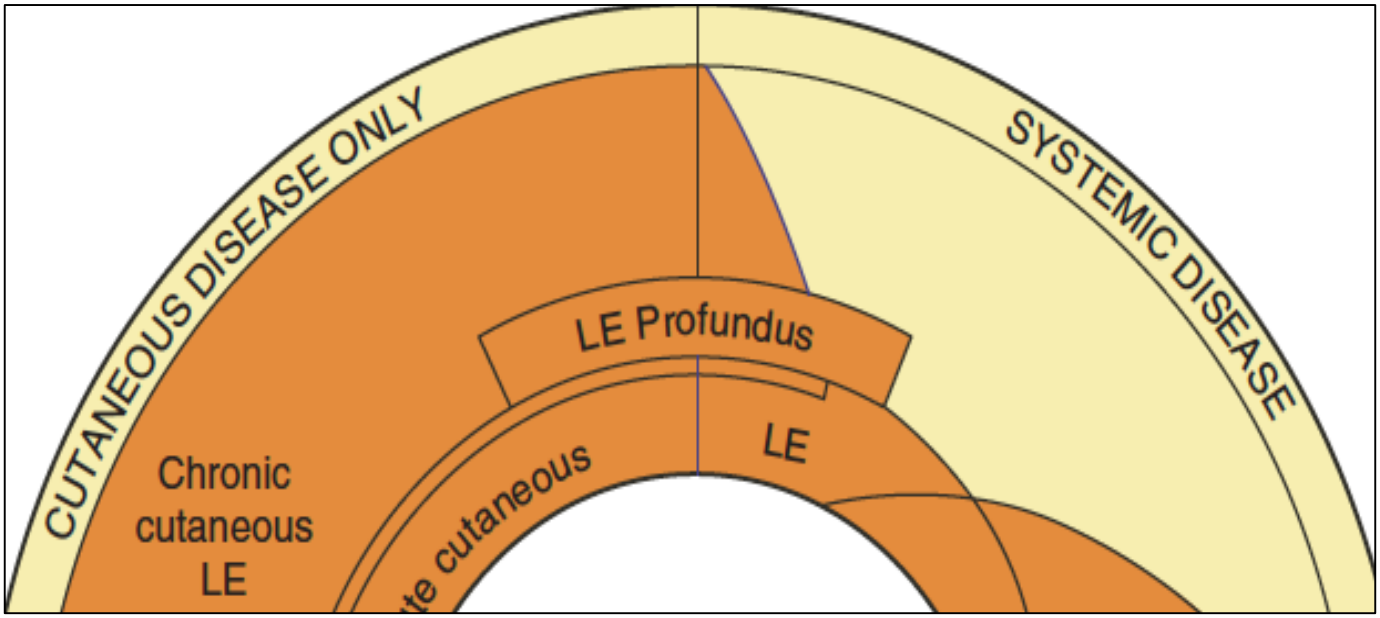

Figure 1: Gilliam and Sontheimer classification of the spectrum of Cutaneous Lupus Erythematosus and it's association with Systemic Lupus Erythematosus

1.4.1.1. Chronic cutaneous lupus erythematosus (CCLE)

The most common type of CCLE is discoid lupus erythematosus (DLE). Classic DLE may either be localised or generalised. Localised DLE is limited to the face (i.e. does not extend below the neck).

DLE lesions most commonly affect the face, scalp, ears, anterior neck and extensor arms. The lesions are indurated. They begin as an erythematous scaly macule or papule which develops central hypopigmentation and atrophy. The borders become hyperpigmented. Characteristic dilated hair follicles with central plugs are found. Destructive scarring leading to long-term pigmentation and hair loss is seen in half of all patients (Walling *et al*., 2009). Figures 2, 3 and 4 depict classic DLE.

Hypertrophic or verrucous DLE is a form of DLE with thickened keratotic plaques overlying classic DLE-type lesions. They are typically seen on the extensor arms, hands and face (Walling *et al*., 2009). They are often resistant to treatment (Kuhn *et al*., 2007).

Lupus panniculitis is a form of lupus affecting the subcutaneous fat – also known as the panniculus. These lesions present as painful subcutaneous plaques and nodules usually over the gluteal region, thighs and upper arms. When lesions arise with overlying DLE the condition is known as lupus profundus. Lupus panniculitis leads to deep scarring with lipoatrophy in the affected area sometimes accompanied by dystrophic calcification (Kuhn *et al*., 2007). Figure 5 depicts extensive lipoatrophy secondary to lupus panniculitis.

Lupus erythematosus tumidus (also known as papulomucinous lupus erythematosus) presents as oedematous erythematous urticarial-type plaques usually in photosensitive areas. Lesions heal without scarring (Walling *et al*., 2009).

Chilblain lupus erythematosus presents as painful violaceous plaques or nodules on areas of cold exposure. Ulceration may also occur. This lupus variant occurs more frequently in countries with a cooler climate (Walling *et al*., 2009; Kuhn *et al*., 2007).

Lichenoid DLE (LE/LP overlap) presents with features of both lupus and lichen planus. Cutaneous lesions mostly affect the distal arms, legs, face and trunk. Palmoplantar involvement is characteristic of this condition. Plaques are often painful, centrally atrophic, bluish-red to hypopigmented in colour, large, and scaly (Lospinoso *et al*., 2013).



Figure 2: Disseminated DLE



Figure 3: Localised DLE involving only the face



Figure 4: Localised DLE showing characteristic erythema, scaling and follicular plugging



Figure 5: Lupus panniculitis involving the face, arms and trunk

1.4.1.2. Subacute cutaneous lupus erythematosus (SCLE)

SCLE presents as a highly photosensitive eruption that may be annular or papulosquamous (psoriasiform) over the neck, chest, upper back, dorsal arms and hands but usually sparing the scalp and face.

SCLE lesions usually resolve without long-term scarring, however post inflammatory hyperpigmentation is common (Kuhn *et al*., 2007). SCLE is associated with SLE in 50% of cases. It is also strongly associated with anti-Ro (SSA) antibody (Gronhagen *et al*., 2014).

Annular SCLE consists of ring-like oval erythematous plaques with central clearing. Papulosquamous SCLE presents with scaling plaques reminiscent of psoriasis. Sometimes a mixed pattern may occur. About 15 to 20% of SCLE patients have other forms of CLE (Gronhagen *et al*., 2014)

Drug-induced SCLE is a well-described subtype of SCLE. The most common agents include terbinafine and TNF-alpha inhibitors. About one-third of all SCLE cases are thought to be drug-induced (Gronhagen *et al*., 2014).



Figure 6: Annular SCLE over the knee



Figure 7: Papulosquamous SCLE involving the back



Figure 8: Papulosquamous SCLE involving the dorsal hand and forearm

1.4.1.3. Acute cutaneous lupus erythematosus (ACLE)

Acute cutaneous lupus erythematosus may be localised or generalised. Localised ACLE is the classic 'butterfly rash' affecting the malar area of the cheeks. It consists of confluent symmetrical erythematous plaques on bilateral cheeks with sparing of the nasolabial folds. It may have a fine surface scale and be mistaken for sunburn. ACLE is inevitably associated with SLE. About 30-70% of SLE patients develop ACLE symptoms during the course of their disease. ANAs and anti-DS DNA antibodies are usually positive in 40-90% of cases (Walling *et al*., 2009).

Localised ACLE may present with oedema, blistering and bullae over the cheeks. The rash normally spontaneously resolves within a few hours to days without any scarring, however, post inflammatory hyperpigmentation may develop (Walling *et al*., 2009). Figure 9 is a classic example of ACLE occurring on a background of darker skin.

Generalised ACLE presents as a morbilliform or maculopapular rash which may be pruritic involving the whole body, but more pronounced in photosensitive areas. The rash may involve the palms and soles. On the dorsal hands there is typically sparing of the interphalangeal and metacarpal joints. The generalised form may have mucosal involvement of the mouth, nose, pharynx and genitalia. Lips may become crusted. Mucosal lesions of ACLE are usually painful (Gilliam *et al*., 1981; Costner *et al*., 2004).

Toxic epidermal necrolysis (TEN)-like ACLE is rare. It is a form of severe generalised ACLE presenting with extensive mucosal surface involvement (Kuhn *et al*., 2007).

1.4.1. 4. Other

Bullous lesions occur frequently in SLE, however the term 'Bullous lupus erythematosus' refers to a specific type of cutaneous disease in which auto-antibodies targeted at type VII collagen cause disruption of the dermo-epidermal junction resulting in extensive and deeply seated skin bullae.

Bullous lupus was not included in the original Gilliam and Sontheimer classification. Bullous LE is associated with severe SLE. It may appear as solitary or groups of vesicles or bullae. Severe ACLE or SCLE needs to be excluded. On histology a characteristic neutrophil-rich subepidermal vesicle is characteristic. On direct immunofluorescence immunoglobulin G deposits are found along the basement membrane zone. Auto-antibodies to type VII collagen are found on enzyme-linked immunosorbent assay (ELISA), immunoblotting or salt-split skin (Malcangi *et al*., 2003).

Rowell syndrome was first described by Rowell *et al* in 1963 and later redefined by Zeitouni *et al* in 2000 (Zeitouni *et al*., 2000; Rowell *et al*., 1963). Patients with SLE develop targetoid erythematous lesions. The diagnosis of Rowell syndrome requires the presence of all major criteria and at least one of the minor criteria. Major criteria include the coexistence of LE, typical erythema multiforme-like lesions, and a speckled pattern of antinuclear antibodies. Minor criteria include chilblains, positive anti-Ro (SS-A) or anti-La (SS-B) antibodies, and a reactive rheumatoid factor (Zeitouni *et al*., 2000).



Figure 9: ACLE with erythema and scaling involving the malar area, forehead and ears with sparing of the nasolabial folds

1.4.2. Non-specific cutaneous manifestations of SLE

Table 1.3 Gilliam and Sontheimer Classification of non-specific signs of cutaneous lupus erythematosus (Petri *et al*., 2012)	
Cutaneous vascular disease	XV. Small vessel cutaneous leukocytoclastic vasculitis secondary to LE a. Dependent palpable purpura b. Urticarial vasculitis XVI. Vasculopathy a. Degos' disease like lesions b. Secondary atrophie blanche XVII. Periungual telangiectasia XVIII. Livedo reticularis XIX. Thrombophlebitis XX. Raynaud's phenomenon XXI. Erythromelalgia
Non-scarring alopecia	
Sclerodactyly	
Calcinosis cutis	
Urticaria	
Papulonodular mucinosis	
Cutis laxa/anetoderma	
Acanthosis nigricans	
Leg ulcers	
Lichen planus	

1.4.2.1. Cutaneous vascular disease

Cutaneous vasculitis is the most common non-specific cutaneous finding associated with lupus. It typically presents as a small vessel **leukocytoclastic vasculitis** with palpable purpura on the peripheral limbs. Vasculitis has a highly variable prognosis depending on the size of the affected vessels (Gronhagen *et al*., 2011). Urticarial vasculitis is a subtype of small vessel vasculitis presenting clinically with urticarial lesions which last generally more than 24 hours and heal with hyper or hypopigmentation (James *et al*., 2011).

Periungual telangiectasia consists of dilated capillaries of the nailfolds. It is also a characteristic finding in other connective tissue disorders such as dermatomyositis and scleroderma. Nailfold telangiectasias in SLE patients has been associated with anti-U1RNP antibodies (Furtado *et al*., 2002). It is found more frequently in



Figure 10: Periungual erythema and melanonychia
Picture courtesy of Prof M Tikly

conjunction with SLE rather than CLE alone suggesting it may be a marker for systemic disease activity (Uva *et al*., 2012).

Livedo reticularis (as seen in Figure 13) presents as a mottled reticulated rash that appears as a lace-like purplish violaceous pattern most commonly on the buttocks and legs but which can affect any body part. It is caused by swelling of the medium veins in the skin, increasing their visibility. It is usually aggravated by exposure to cold (Uva *et al*., 2012).

Thrombophlebitis – which may be superficial or deep is a rare but well described complication of SLE, usually affecting the large subcutaneous venous vessels. It occurs more commonly in those patients with anticardiolipin or antiphospholipid antibodies (Cardinali *et al*., 2000).

Raynaud's phenomenon is an exaggerated vascular response to cold temperature or emotional stress. It can occur in otherwise healthy individuals or be associated with underlying disease, most commonly scleroderma. Other associated conditions include: mixed connective tissue disease, haematologic disorders, drugs, vibrational injury and arterial diseases. The classic changes consist of three stages. Initially the fingers turn white due to vasospasm. This is followed by bluish appearance due to reduced oxygenation and then pain and redness on reperfusion to the area (Uva *et al*., 2012).

Erythromelalgia is a rare disorder characterised by burning pain and erythema of the extremities on exposure to warmth. It typically affects the hands and feet. Secondary cold injuries from attempts to alleviate the burning pain with excessive cooling are characteristic (Gronhagen *et al*., 2014).



Figure 11: Urticarial vasculitis affecting the face



Figure 12: Leukocytoclastic vasculitis with petechiae and bullous skin lesions

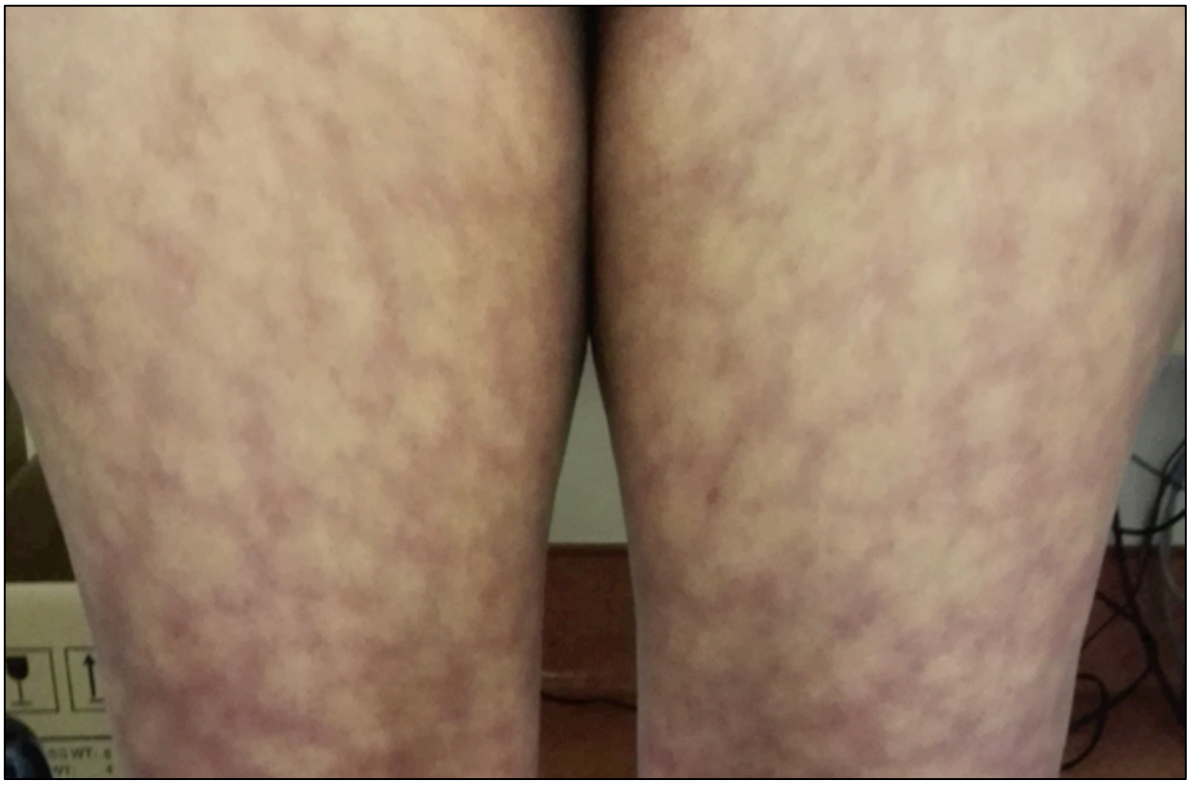

Figure 13: Livedo reticularis
Picture courtesy of Prof M Tikly

1.4.2.2. Non-scarring alopecia

Non-scarring alopecia is common affecting 40 to 80% of patients with SLE (Walling *et al*., 2009; Cardinali *et al*., 2000). It has been associated with more severe systemic illness. 'Lupus hair' is characterised by thin hair that easily fractures and varies in length. It usually occurs along the frontal hairline, is associated with disease activity, and grows back normally as the disease subsides (Cervera *et al*., 2012). Figure 14 shows a patient with extensive 'lupus hair'.

Telogen effluvium is condition of widespread hair loss due to excessive shedding of telogen hairs. It typically occurs 3 to 5 months after systemic disease. The premature conversion of anagen hairs to telogen hairs results in excessive hair shedding when these hairs reach the end of their natural hair cycle (James *et al*., 2011).

Drugs used to treat lupus, such as prednisone and immunosuppressive therapies, also may be responsible for reversible hair loss (Walling *et al*., 2009).



Figure 14: Non-scarring diffuse alopecia in a patient with SLE

1.4.2.3. Sclerodactyly

Tapering of the fingers typically occurs in scleroderma or scleroderma-like diseases however this is also a reported finding in SLE (Lee *et al*., 1977).

1.4.2.4. Calcinosis cutis

Calcinosis cutis is a well-known phenomenon occurring in a variety of rheumatic disorders particularly dermatomyositis and limited type scleroderma. Dystrophic calcification may occur in SLE particularly in lupus profundus (Walling *et al*., 2009).

1.4.2.5. Urticaria

Urticaria, also known as hives affects is charaterised by erythematous raised wheals on the skin associated with intense pruritus. Urticaria needs to be histologically differentiated from urticarial vasculitis (Yell *et al*., 1996).

1.4.2.6. Diffuse melanonychia

Melanonychia is a common general finding in the Black population. However, generalised blue-black discolouration of the whole nail or multiple dark bands is a non-specific cutaneous finding seen in certain medical conditions including SLE (Vaughn *et al*., 1990). Other causes of diffuse melanonychia include many medications (including antimalarials), vitamin deficiencies, HIV and several dermatoses (Vaughn *et al*., 1990). Images 15 and 16 depict examples of diffuse melanonychia see in our patients.



Figure 15: Diffuse melanonychia in a patient with SLE



Figure 16: Diffuse melanonychia in a patient with SLE and generalised DLE

1.5. Epidemiology

1.5.1. Cutaneous Lupus Erythematosus incidence and prevalence

There are few large population based studies providing epidemiological data regarding CLE. Gronhagen *et al* calculated the national incidence in Sweden to be 4 per 100,000 per year (Gronhagen *et al*., 2010). Durosaro *et al* in the US calculated an incidence of 4.3 per 100,000 per year over a 40-year period (Durosaro *et al*., 2009). Prevalence rates vary between 14 to 50 per 100,000 (Wallace *et al*., 1997).

ACLE has been reported in 20 to 60% of lupus cohorts and is more closely associated with SLE (Kuhn *et al*., 2006). Overall chronic cutaneous lupus erythematosus (CCLE) accounts for the majority of cutaneous disease. The most common subtype of CCLE is DLE which overall is responsible for 80% of all CLE (Gronhagen *et al*., 2010). SCLE is the most rare of the cutaneous groups accounting for only 4.5 to 6% of CLE (Gronhagen *et al*., 2011; Ng *et al*., 2000).

In those patients with isolated cutaneous disease, many have more than one specific subtype. Biazar *et al* found that 34.6% of patients with CLE had more than one subtype. ACLE occurred with DLE in 30.3% of cases and with SCLE in 13.8% of cases. DLE was associated with SCLE in 15.3% of cases. ACLE, DLE and SCLE occurred together in 11% of patients (Biazar *et al*., 2013).

1.5.2. Systemic Lupus Erythematosus incidence and prevalence

Systemic lupus erythematosus affects 0.9 to 8.7 per 100,000 people per year with wide variation between geographic area, climate and population. The tropical gradient proposed by Bae *et al* (1998) suggests a higher rate of SLE is likely to be seen in temperate regions compared to the tropics (Bae *et al*., 1998).

Table 1.4. Incidence of SLE in different countries

Study	Country	Year	No	Incidence*	Prevalence**
Iseki	Japan	1994	566	0.9	3.7
Gudmundsson	Iceland	1990	76	3.3	35.9
Hopkinson	UK	1993	147	4.0	24.6
Naleway	USA	2005	117	5.1	52.2
Vilar	Brazil	2002	43	8.7	-

*per 100,000 per year ** per 100,000

The prevalence of SLE similarly shows wide variability ranging from 3.7 per 100,000 (Iseki *et al*., 1994) to 52.2 per 100,000 (Naleway *et al*., 2005). The differences in prevalence may relate to differences in environmental, ethnic, sex and age related factors or due to differences in methods of study criteria, data capture and analysis (Wallace *et al*., 1997).

1.5.3. SLE incidence and prevalence South Africa

There is a paucity of epidemiologic studies of SLE in Africa. The contradiction remains that although the prevalence of SLE is commoner in those of African decent living in developed nations like the US, SLE in tropical Africa appears to be a rare disease (Tikly *et al*., 2008; Wadee *et al*., 2007)

An estimated 12.2 per 100,000 Black South Africans are affected and the disease has been widely reported in Black South Africans (Morrison *et al*., 1990). The largest South African cross-sectional study to date by Wadee *et al* showed 226 patients meeting ACR criteria for SLE over a 17 year period at CHBAH – a tertiary institute serving a population of approximately 3.5 million people (Baran *et al*., 2013).

Table 1.5. Selected studies from South Africa and Africa

Study	Year	Place	Period	No. of patients	Reference
Jessop	1973	Cape Town	11 years	130	(Jessop, 1973)
Seedat	1977	Durban	6 years	30	(Seedat, 1996)
Dessein	1988	Pretoria	12 years	30	(Dessein, 1988)
Wadee	2007	Johannesburg	17 years	226	(Wadee, 2007)
Adelowo	2009	Lagos	6 years	66	(Adelowo, 2009)
Ekwom	2013	Nairobi	3 years	13	(Ekwom, 2013)

1.5.4. Epidemiology of Cutaneous Lupus Eythematosus in Systemic Lupus Erythematosus

The skin is involved in up to 85% of systemic lupus erythematosus (SLE) cases and may be the only organ involved in cutaneous lupus erythematosus (CLE) (Health, 2014, Uva *et al*., 2012).

CLE may precede or follow SLE. Cutaneous manifestations are the second most common clinical sign following arthritis (Lin *et al*., 2007). The systemic manifestations of SLE precede the cutaneous findings in the majority of cases. However, cutaneous signs of lupus are the presenting manifestation of SLE in 20 to 25% of cases. These skin lesions may precede systemic symptoms by weeks to months (Gronhagen *et al*., 2011) .

In a large European review of CLE, Biazar *et al* found that only 27.1% of all patients fulfilled ACR criteria for SLE (Biazar *et al*., 2013). Cutaneous lupus occurs more frequently alone rather than in conjunction with SLE, however the risk of progression to systemic disease always remains a concern (Gronhagen *et al*., 2010).

1.5.4.1. Specific CLE

Specific CLE affects 23 to 85% of patients with SLE (Gronhagen *et al*., 2010; Zecevic *et al*., 2001). Gronhagen *et al* found more than one type of CLE was present in 4% of their patients with SLE and CLE (Gronhagen *et al*., 2010).

ACLE is most common form of CLE in SLE. Malar rash is included in the 2012

SLICC criteria as a form of localised ACLE (Walling *et al*., 2009; Gronhagen *et al*., 2010). Localised ACLE (malar rash) affects 30 to 70% of patients with SLE (Gilliam *et al*., 1981. Generalised ACLE affects up to one-third of patients with SLE (Cervera *et al*., 1993).

CCLE is the second most common form of CLE in SLE affecting 15 to 25% of patients with SLE (Gronhagen *et al*., 2010). Overall, localised DLE is more common than generalised DLE however in the setting of SLE, generalised DLE is more frequently encountered (Cardinali *et al*., 2000).

Cardenalli (2000) and Yell (1996) found localised DLE in 7.3% and 7% and patients and generalised DLE in 30% and 16% respectively (Cardinali *et al*., 2000; Yell *et al*., 1996). Other subtypes of CCLE which are less commonly encountered include lupus panniculitis, chilblain lupus, hypertrophic LE, lupus tumidus and LE/LP overlap syndrome (Gilliam *et al*., 1981; Gronhagen *et al*., 2010).

SCLE is found in 3.34 to 18.4% of SLE patients (Kole *et al*., 2009; Vitali *et al*., 1996). Studies are conflicting on the most common subtype of SCLE. Yell *et al* found psoriasiform (papulosquamous) SCLE in 7% of their patients and annular SCLE in only 1.3% whereas Cardanali *et al* found annular SCLE in 10.3% of their patients and psoriasiform SCLE in only 3.4% (Yell *et al*., 1996; Vitali *et al*., 1996).

1.5.4.2. Non-specific cutaneous manifestations of SLE

Non-specific cutaneous manifestations of SLE are common affecting 41 to 43% of

patients (Zecevic *et al*., 2001; Gronhagen *et al*., 2010). Non-specific cutaneous disease may be a marker of systemic disease activity, indicating systemic vasculitis and be associated with a poorer prognosis (Cardinali *et al*., 2000; Zecevic *et al*., 2001). Non-specific cutaneous findings are as follows:

- Cutaneous vasculitis is purported to affect 10 to 20% of patients with SLE. The most common subtype is leukocytoclastic vasculitis (Kuhn *et al*., 2007).
- Periungual telangiectasia is found in 10 to 15% of all SLE patients (Walling *et al*., 2009).
- Livedo reticularis affects 4 to 17% of patients with SLE (Cardinali *et al*., 2000; Rothfield *et al*., 2006). It is commoner in those patients with antiphospholipid syndrome. In one review 81% of patients with livedo reticularis had antiphospholipid antibodies (Yasue *et al*., 1986).
- Thrombophlebitis is found in 2.5 to 7.2% of SLE cases. It is considered to be an early sign of SLE and is especially prevalent in those patients with antiphospholipid syndrome (Cardinali *et al*., 2000).
- Raynaud's phenomenon is found in up to 60% of patients with SLE (Yell *et al*., 1996). Overall it is estimated that only 2 to 10% of patients with Raynaud's phenomenon have SLE (Provost *et al*., 2005).
- Non-scarring alopecia is common affecting 40 to 80% of patients with SLE (Walling *et al*., 2009; Cardinali *et al*., 2000).
- Sclerodactyly or sclerodermatous changes are rare but well described in SLE. It is commoner in patients with anti-U1RNP antibodies and is frequently associated with Raynaud's phenomenon (Provost *et al*., 2005). There are few

studies reporting the prevalence of this finding. Lee *et al* found sclerodactyly in 1.8% of patients with SLE (Lee *et al*., 1977).

- Calcinosis cutis occurs more commonly in association with scleroderma and dermatomyositis, however it does rarely occur in the context of SLE. It is estimated to occur in less than 2% of SLE patients (Cardinali *et al*., 2000).
- In a recent review of the 42 studies by Kolkhir *et a*l, chronic spontaneous urticaria was found in up to 21.9% of SLE patients (Kolkhir *et al*., 2016).
- Diffuse melanonychia was reported by Vaughn *et al* in 37% of their patients with SLE and 52% of Black patients with SLE (Vaughn *et al*., 1990).
- Erythromelalgia is extremely rare. It was initially reviewed as a non-specific complication of SLE by Alarcon-Segovia *el in* 1963 (Alarcon-Segovia *et al*., 1963). Viguier *et al* in 2001 reviewed a series of patients with chilblain lupus and found 3 of 22 had erythromelalgia (Viguier *et al*., 2001).

Table 1.6. Cutaneous manifestations of SLE - International Studies						
	Vitali (Multicentre)	Yell (UK)	Cardenalli (Italy)	Cervera (Europe)	Kole (India)	Gronhagen (Sweden)
Year	1996	1996	2000	2009	2009	2011
Number	61	73	58	1000	150	260
Any cutaneous involvement	-	100%	-	78%	100%	87%
ACLE	-	51%	46.5%	31.1%	26.67%	57%
DLE (localised & generalised)	17.2%	25%	32.6%	7.8%	20%	11%
Lupus panniculitis	-	1%	-	-	3.34%	0.4%
Chilblain LE		20.5%	10.3%	-	-	-
SCLE	18.4%	7%	13.8%	6.7%	3.34%	8%
Malar rash	40%	51%	46.5%	31.1%	80%	53%
Photosensitivity	-	63%	-	22.9%	50%	-
Raynaud's phenomenon	-	60%	39.6%	34%	6.67%	25%
Cutaneous vasculitis	18.6%	11%	13.7%	-	33.34%	8%
Non-scarring alopecia	24.1%	40%	31%	-	86.67	9%
Livedo reticularis	16.7%	4%	8.6%	7%	-	3%
Periungual telangiectasia	-	-	20.6%	-	1.34%	-
Urticaria	6.3%	44%	-	-	6.67%	7%

1.5.5. Epidemiology of CLE in South Africa

Overall, South African SLE studies indicate that mucocutaneous disease affects 60 to 87% of all patients with SLE (Jessop *et al*., 1973; Dessein *et al*., 1988; Seedat *et al*., 1996; Jacyk *et al*., 1996; Wadee *et al*., 2007; Simmons *et al*., 2008; Tikly *et al*., 1996). The cutaneous features are summarised in Table 1.8.

Unfortunately there are no South African studies that document all the subtypes of CLE-specific disease either alone or as a finding of SLE.

Clinical studies by Jessop (1973), Seedat (1977), Dessein (1988), Jacyk (1996), Tikly (1996), Wadee (2007) and most recently Simmons (2008) have included cutaneous lupus as a finding in the ACR criteria as well as certain other cutaneous manifestations. A single case series by Jacyk in 2006 reviewed 10 cases of lupus erythematosus profundus – a subtype of CCLE (Jacyk *et al*., 2006).

Using the ACR criteria to deduce the cutaneous manifestations of SLE is limiting as many cutaneous lesions including SCLE, generalised ACLE, bullous ACLE, non-scarring alopecia, lupus panniculitis, chilblain lupus or LE/LP overlap are not included. Furthermore the criteria also do not distinguish between localised or generalised DLE.

Both Jessop and Seedat found a ‘non-specific rash’ as the most common cutaneous finding, the exact prevalence of which was not specified (Jessop *et al*., 1973; Seedat *et al*., 1996).

Localised ACLE (malar rash) affects 29.2 to 69.7% of all patients with SLE (Jessop, 1973 #95;Simmons, 2008). Jacyk *et al* found Black patients to have a lower risk of photosensitivity and malar rash (Jacyk *et al*., 1996).

Discoid lesions, a subtype of CCLE has been reported in 10.8 to 52% of patients which is more frequent than found internationally, but in keeping with the largely Black cohort of patients included in South African studies (Jessop *et al*., 1973; Seedat *et al*., 1996; Jacyk *et al*., 1996).

There is no data relating to the frequency of SCLE in South Africa.

The most common non-specific finding reported is vasculitis affecting 17 to 54.4% of patients. Tikly *et al* reported a high prevalence of cutaneous vasculitis which was associated with high anti-DS DNA antibody titres (Tikly *et al*., 1996).

Raynaud's phenomenon is the second most common non-specific cutaneous finding of SLE affecting 13.3 to 36.9% of patients (Seedat *et al*., 1996; Tikly *et al*., 1996). Tikly *et al* found a correlation between Raynaud's phenomenon and anti-La antibody positivity (Tikly *et al*., 1996).

Alopecia (both scarring and non-scarring) is relatively rare in South Africa reported in only 3 to 23.2% of patients with SLE (Seedat *et al*., 1996; Sutej *et al*., 1989). This is in contrast to international studies where alopecia affects 40 to 80% of patients with SLE (Walling *et al*., 2009; Cardinali *et al*., 2000).

Table 1.7. Cutaneous manifestations of SLE in South Africa							
	Jessop (Cape Town)	Seedat (Durban)	Dessein (Pretoria)	Jacyk (Pretoria)	Tikly (Johannesburg)	Wadee (Johannesburg)	Simmons (Bloemfontein)
Year	1973	1977	1988	1996	1996	2007	2008
Number	130	30	30	40	111	228	76
Any cutaneous involvement	78%	73%	60%	NR	NR	NR	86.9%
Photosensitivity	NR	NR	NR	NR	33.3%	38.9%	53.9%
Malar rash	29.2%	43%	30%	53%	55%	46.5%	69.7%
Discoid rash	10.8%	NR	27%	52%	28.8%	35%	NR
Oral ulcers	NR	NR	23%	30%	21.6%	22.1%	47.4%
Alopecia	10.8%	3%	NR	13%	23.2%	NR	NR
Raynaud's phenomenon	23.8%	13.3%	30%	NR	36.9%	NR	30.3%
Vasculitis	NR	17%	NR	23%	54.4%	NR	19.7%

1.5.6. Gender

Female sex has been consistently associated with SLE. More than 90% of patients with SLE are female (Wallace *et al*., 1997).

Cutaneous lupus erythematosus, on the other hand, is considered to occur more frequently in men than SLE. Gronhagen *et al* showed a female-to-male ratio of 3:1 whilst Biazar *et al* demonstrated a ratio of 5.3:1 (Gronhagen *et al*., 2011; Biazar *et al*., 2013).

Widespread DLE and papular and nodular mucinosis occur more frequently in men than women with SLE (Kanda *et al*., 1996). Other studies have shown no significant gender differences in CLE manifestations in SLE (Kaufman *et al*., 1989).

South African SLE statistics vary with a marked female preponderance ranging from 6:1 (Jacyk *et al*., 1996) to 18:1 (Wadee *et al*., 2007). Table 1.8 shows some epidemiologic data from South African studies (Jessop *et al*., 1973; Dessein *et al*., 1988; Seedat *et al*., 1996; Jacyk *et al*., 1996; Wadee *et al*., 2007; Simmons *et al*., 2008).

1.5.7. Race

SLE is known to be more common in African Americans with incidence rates being three to four times higher in those of African descent (Gilkeson *et al*., 2011).

Cutaneous lupus erythematosus LE demonstrates variation in different racial groups.

DLE is reported more frequently in Black patients across the globe (Adelowo *et al*., 2009). Photosensitivity and malar rash have been reported less frequently in Black South Africans than in Caucasians (Sutej *et al*., 1989; Jacyk *et al*., 1996). However Black patients have been shown to have an increased risk of small vessel vasculitis, alopecia and urticarial vasculitis (Jacyk *et al*., 1996).

Studies from all areas other than Cape Town have shown a marked preponderance of SLE in Black patients. In Cape Town the majority of patients were of mixed ancestry which may reflect the local population epidemiology rather than true disease incidence (Jessop *et al*., 1973).

It is thought that genetic differences may play a role in the development of SLE and several HLA subtypes affecting Black patients with SLE have been identified.

Furthermore the increased risk of SLE amongst Black patients living outside the tropics, as well as overall poorer prognosis, raises an important conundrum in lupus pathogenesis – the so-called 'tropical gradient' (Bae *et al*., 1998).

The current hypothesis postulates that tropical infections such as malaria may suppress the immune response leading to a reduced incidence of autoimmune diseases such as lupus (Greenwood *et al*., 1968). It is also likely that SLE is more common in central and Sub-Saharan Africa than previously reported – most likely due to poor access to healthcare and a paucity of epidemiologic studies from these areas (Bae *et al*., 1998; Adelowo *et al*., 2009).

Table 1.8. Epidemiology of SLE in South Africa						
	Jessop (Cape Town)	Seedat (Durban)	Dessein (Pretoria)	Jacyk (Pretoria)	Wadee (Johannesburg)	Simmons (Bloemfontein)
Year	1973	1977	1988	1996	2007	2008
Number	130	30	30	40	228	76
Female: Male ratio	11:1	14:1	29:1	6:1	18:1	14:1
Ethnicity						
Black	6%	56%	100%	100%	93%	61%
Mixed	66%	0	0	0	3%	3%
White	28%	0	0	0	1%	34%
Asian	0	44%	0	0	3%	1.6%

1.6. Aetiopathogenesis of Lupus Erythematosus

Cutaneous lupus erythematosus and SLE result from a complex interplay between genetic factors, hormones, autoantibodies and environmental factors. Tissue damage and inflammation in SLE results from antibody and complement-fixing immune complex deposition. It is characterised by immunologically mediated, clinical and serological phenomena. It may resemble any of a variety of infectious, inflammatory, nutritional, malignant and metabolic disorders (Rahman *et al*., 2008).

Ultraviolet (UV) light is an important factor in the pathogenesis of CLE and, to some extent, SLE. UV irradiation is thought to induce keratinocyte apoptosis leading to autoantigen presentation and promotion of the production of pro-inflammatory cytokines. SLE is also believed to be triggered and aggravated by UV exposure, patients often noticing a flare in symptoms following sun exposure (Achtman *et al*., 2015).

Genetics are thought to play an important role in the development of both SLE and CLE. Siblings of patients with SLE are 30 times more likely to develop SLE themselves. Genes commonly affected are those associated with immune response and inflammation (Cervera *et al*., 2012).

Some of the genetic associations found in CLE include:

- HLA-DR2, –DR3 and HLA DRB1*03 is associated with SLE, anti-Ro (SSB) and anti-La (SSA) antibodies and SCLE (Gilkeson *et al*., 2011). HLA-DR2 has

been demonstrated to be of significance in African patients (Osmola *et al*., 2004; Kachru, 1984).

- HLA-DQA1 and DRB1 has been associated with DLE (Osmola *et al*., 2004)
- TNFa polymorphism -308A is associated with SCLE and HLA-DR3 (Werth, 2000)
- TYK2, CTLA4 and IRF5 are all associated with DLE (Jarvinen *et al*., 2010)
- TREX1 is associated with familial chilblain lupus (Lee-Kirsch *et al*., 2007)
- Complement deficiencies and c1-esterase inhibitor deficiency has been associated with SCLE and DLE (Asghar *et al*., 1991)

Drug related causes are particularly relevant for SCLE. A Swedish population-based matched case-control matched study that included all patients with SCLE from 2006 to 2009 found exposure to terbinafine and TNF-alpha inhibitors to be significantly associated with an increased risk of SCLE (Gronhagen *et al*., 2012).

1.7. Systemic features

SLE has a variety of systemic effects. Most commonly the joints are affected. Other organ systems that can be affected include the renal, neurological and haematologic system (Simmons *et al*., 2008).

Systemic disease complications and autoantibody profiles vary between individuals and populations. The main clinical manifestations of SLE found in South Africans as well as selected international studies are summarised in Table 1.9 (Jessop *et al*., 1973; Seedat *et al*., 1996; Jacyk *et al*., 1996; Wadee *et al*., 2007; Simmons *et al*., 2008; Wadee *et al*., 2007; Cervera *et al*., 2012; Houman *et al*., 2004; Cervera *et al*.,

2003).

1.7.1. Arthritis

Arthritis or arthralgia is the most common clinical finding of SLE ranges in frequency in South Africa from 70.5% (Wadee *et al*., 2007) to 97% (Seedat *et al*., 1996). This is in keeping with international studies (Somers *et al*., 2014; Houman *et al*., 2004).

1.7.2. Renal disease

Several studies have shown an increased risk of nephritis in Black patients (Petri, 2012; Wadee, 2007; Somers, 2014). Certainly renal involvement is not uncommon amongst South Africans with SLE ranging from 43.8 to 90% (Wadee *et al*., 2007; Seedat *et al*., 1996). Wadee *et al* found that nephritis was associated with a poorer outcome for patients with SLE (Wadee *et al*., 2007).

1.7.3. Other systemic features

Haematological abnormalities have been reported to affect 40 to 70% (Jacyk *et al*., 1996; Dessein *et al*., 1988) of South African patients with SLE. Leukopaenia is the most common haematological finding, followed by thrombocytopaenia. Haemolytic anaemia is relatively rare affecting only 5 to 14.5% (Jacyk *et al*., 1996; Jessop *et al*., 1973) of patients.

Jacyk *et al* found Black patients to be less likely to have malar rash, photosensitivity, low complement and haematological abnormalities than their White counterparts

(Jacyk *et al*., 1996).

Dessein *et al*, on the other hand, who exclusively reviewed Black South Africans with SLE, found haematological abnormalities to be on par with international reported literature (Dessein *et al*., 1988).

Zhao *et al* retrospectively reviewed the clinical implications of thrombocytopaenia in patients with SLE finding those with thrombocytopaenia to have a higher disease activity index, greater association with renal failure and less likely to have cutaneous involvement. Thrombocytopaenia is considered to be a poor prognostic marker in SLE (Zhao *et al*., 2010).

Hochberg *et al* observed that Black patients with SLE had a significantly increased risk of pneumonitis, complement abnormalities and hypergammaglobulinaemia (Hochberg *et al*., 1985).

The prevalence of serositis and neuropsychiatric disease in SLE appears to be similar in South Africans compared to other countries (Jessop *et al*., 1973; Seedat *et al*., 1996; Jacyk *et al*., 1996; Wadee *et al*., 2007; Simmons *et al*., 2008; Wadee *et al*., 2007; Cervera *et al*., 2012; Houman *et al*., 2004; Cervera *et al*., 2003).

Table 1.8. Systemic manifestations of SLE in selected countries								
	South Africa					International		
Study	Jessop (Cape Town)	Seedat (Durban)	Dessein (Pretoria)	Jacyk (Pretoria)	Wadee (Johannesburg)	Houman (Tunisia)	Cervera (Europe)	Somers (US)
Year	1973	1976	1988	1996	2007	2004	2009	2014
Number	130	30	30	40	224	100	1000	2139
Arthritis/ arthralgia	74%	97%	90%	72%	70.4%	78%	48.1%	70.8%
Renal involvement	58.5%	90%	60%	58%	43.8%	43%	27.9%	31.9%
Serositis	46.1%	23%	17%	12%	18.1%	45%	12.9%	43.9%
Neuropsychiatric disease	25%	14%	17%	18%	15.9%	25%	13.6%	18.4%
Haematological abnormalities	63%	57%	70%	40%	52.2%	81%	18.2%	66%
Leukopaenia	22.8%	12%	63%	32%	-	50%	-	-
Haemolytic anaemia	14.5%	-	-	5%	-	6%	4.8%	-
Thrombocytopaenia	17.7%	3%	10%	10%	12.8%	12%	13.4%	-
Hypocomplementaemia	NR	46%	-	-	65%	48%	-	-

1.8. Autoantibodies

The main autoantibody findings are summarised in Table 1.10 ((Jessop *et al*., 1973; Seedat *et al*., 1996; Jacyk *et al*., 1996; Wadee *et al*., 2007; Simmons *et al*., 2008; Wadee *et al*., 2007; Cervera *et al*., 2012; Houman *et al*., 2004; Cervera *et al*., 2003).

Tikly *et al* found clinic-serological associations between anti-DS DNA antibodies with cutaneous vasculitis, anti-Smith antibodies with psychosis, anti-RNP antibodies with Raynaud's phenomenon and anti-Ro antibodies with renal disease, malar rash and psychosis. They also found the combination of anti-DS DNA and low complement to be associated with renal disease (Tikly *et al*., 1996).

Anti-nuclear antibodies (ANA) are sensitive but not specific markers of SLE and are found in up to 96% of patients with SLE and 4 to 63% of patients with CLE (Cervera *et al*., 2012; Kuhn *et al*., 2007). Low ANA titres are seen in up to 5% of the general population (Tan *et al*., 1997).

Anti-DS DNA antibodies are found in up to 70% of SLE patients and are one of the most specific markers of disease activity (Cervera *et al*., 2003). In South Africa it has been found in 30 to 55.4% of patients (Jacyk *et al*., 1996). Anti-DS DNA is generally negative in patients with lupus panniculitis and is less commonly positive in the context of isolated cutaneous disease (Kuhn *et al*., 2007).

Anti-Ro (SSA) antibodies, often accompanied by anti-La (SSB), are found in SLE with a prevalence varying between 20 and 30% (Jacyk *et al*., 1996; Cervera *et al*.,

2012; Simmons *et al*., 2008). Both anti-Ro (SSB) and anti-La (SSA) antibodies have been associated with an increased risk of SCLE. Anti-La antibodies have also been associated with malar rash, photosensitivity, arthritis, serositis and thrombosis in the Euro-lupus cohort (Cervera *et al*., 2003). Simmons-O'Brien *et al* found an association between Raynaud's phenomenon and both anti-Ro (SSB) and anti-La (SSA) antibodies (Simmons-O'Brien *et al*., 1995).

Anti-Sm antibodies have been found in 40-67% of South African patients and 10% of patients internationally (Wadee *et al*., 2007; Jacyk *et al*., 1996; Cervera *et al*., 2012; Cervera *et al*., 2003). Jacyk *et al,* found that Black patients are more likely to have anti-Sm antibodies (Jacyk *et al*., 1996). Anti-Sm antibodies are associated with SLE-related renal disease (Alba *et al*., 2003).

Ward and Studenski in a large case series also noted that Black patients were more likely to have Anti-RNP antibodies (Ward *et al*., 1990).

Table 1.10. Autoantibodies associated with SLE in selected countries						
	South Africa				International	
Study	Jessop (Cape Town)	Jacyk (Pretoria)	Wadee (Johannesburg)	Simmons (Bloemfontein)	Houman (Tunisia)	Cervera (Europe)
Year	1973	1988	2007	2008	2004	2009
Number	130	40	224	76	100	1000
ANA	-	100%	99.1%	88.2%	100%	96%
Anti-Sm Antibody	-	67%	40.7%	42.1%	61%	10%
Anti-DS DNA	-	30%	55.3%	40.8%	56%	78%
Antiphospholipid Ab	-	-	27%	-	62%	15%
Anti-La Ab (SSA)	-	30%	-	46.1%	-	19%
Anti-Ro Ab (SSB)	-	68%	-	48.7%	-	25%
Anti-RNP Ab	-	75%	-	48.7%	23%	13%

1.9. Prognosis of Cutaneous Lupus Erythematosus

Cutaneous lupus erythematosus LE is generally regarded as having a better prognosis than SLE (Tebbe *et al.*, 2005). ACLE has a poorer prognosis than DLE or SCLE due to its frequent association with SLE (Walling *et al*., 2009). The onset of ACLE is often accompanied by renal dysfunction (Zecevic *et al*., 2001).

DLE is the most common subtype of CLE and has the least association with progression to SLE (Healy *et al*., 1995). However, Watanabe and Tsuchida reported more severe systemic complications in association with disseminated DLE (Watanabe *et al*., 1995).

SCLE is less likely to be associated with systemic disease. When systemic disease was present SCLE patients frequently had a milder disease course characterised by musculoskeletal complaints without renal or CNS involvement (Gilliam *et al*., 1981).

Zecevic *et a*l noted that non-specific skin lesions are associated with a higher disease activity index (Zecevic *et al*., 2001). Diffuse alopecia and urticaria both positively correlate independently with disease activity (Tuffanelli *et al*., 1964; Wysenbeek *et al*., 1991). Parodi *et al* found that Raynaud's phenomenon was also associated with a poorer prognosis (Parodi *et al*., 2000).

CLE in SLE is associated with a milder disease course, however the severity of SLE worsens with increasing number of cutaneous findings (Zecevic *et al*., 2001).

In particular livedo reticularis may indicate a potentially serious underlying complications in SLE (Biazar *et al*., 2013).

1.10. Assessing disease activity, damage and severity in Systemic Lupus Erythematosus

SLE has a broad range of systemic symptoms. The involvement of certain systems (neurological and renal) is associated with a higher mortality. Different classification systems are used to assess the burden of disease. Some systems are more useful in the clinical setting whilst others are most often used in clinical trials and research. In general these scoring systems are used to assess three broad spheres, namely disease activity, disease damage and disease severity.

1.10.1. Disease activity scores

SLE is a generally a chronic relapsing autoimmune disease. Ongoing disease activity is therefore part of the course of the illness. The history, examination and laboratory investigations are all used in monitoring disease activity.

There are a variety of tools used for the assessment of disease activity. The two most commonly used are the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Gladman *et al*., 1992) and the British Isles Lupus Assessment Group (BILAG) Index (Hay *et al*., 1993).

The SLEDAI includes 24 criteria each with a score weighting ranging from 2 to 8. The maximum score is 105 (Gladman *et al*., 1992).

The BILAG index includes many more symptoms than the SLEDAI and is therefore more comprehensive. It is also more time consuming to calculate and is most often used in the setting of clinical research or trials (Lam *et al*., 2005). The BILAG index is based on clinical disease activity in 8 different organ systems. Disease activity is categorised according to an alphabetical score of A (most active), B (moderate activity), C (minor activity), D (stable) or E (never present) that can be converted to a numerical disease index with a maximum potential score of 72(Hay *et al*., 1993).

1.10.2. Disease damage score

The Systemic Lupus International Collaborating Clinics (SLICC)/ American College of Rheumatology (ACR) damage index is a validated tool used to assist in the assessment of the extent of systemic organ involvement (Gladman *et al.,* 1996).

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The damage index is based on the involvement of 12 organs or systems over a period of 6 or more months. The maximum score is 47 (Gladman *et al.,* 1996). Early organ system involvement is generally associated with a poorer disease outcome. The limitation of this index is that it does not include the deleterious effects of medications (Cervera *et al*., 2012).

1.10.3. Lupus severity score

The first SLE severity score index was introduced by Katz *et a*l in 1993 (Katz *et al*., 1993). The Katz Severity Index of Disease (Katz SDI), also known as the Lupus Severity of Disease Index (Lupus SDI) was based on literature review and included

the clinical manifestations of SLE associated with a higher morbidity. Subsequently different grading systems have been used.

Most recently Bello *et al* have devised the Lupus Severity Index (LSI) based on a statistical risk model using the components of the ACR criteria to assess the burden of disease in SLE subsets. This scoring system is useful in assessing the relative risk for individual patients diagnosed with SLE as well as in research regarding SLE (Bello *et al*., 2016).

1.11. Aims and Objectives

In view of the paucity of data regarding cutaneous disease in SLE, especially regarding specific subtypes of cutaneous lupus erythematosus in South Africa, we undertook a retrospective study of mostly Black patients attending Chris Hani Baragwanath Academic Hospital, a major tertiary referral centre that serves the people of Soweto and surrounding southern Gauteng.

Chapter Two: Patients and Methods

2.1. Study design

A retrospective review of available clinical records of all patients attending CHBAH rheumatology lupus outpatient clinic between 1 March 1992 and 30 June 2014 was performed. In total 362 records were reviewed.

CHBAH is a tertiary referral hospital servicing the largely black, unemployed population of Soweto and surrounding areas.

2.2. Patients

2.2.1. Inclusion criteria

1. Patients with a confirmed diagnosis of SLE according to the 2012 SLICC Classification criteria.
2. Patient files dating from 1 March 1992 to 30 June 2014.
3. Patients must have attended the clinic on at least 2 separate occasions and for a total consecutive period of no less than 6 months

2.2.2. Exclusion criteria:

1. Patients with more than one autoimmune disease (e.g. mixed connective tissue disease)

2.3. Methods of data abstraction

Demographic, clinical and serological data was abstracted from the clinic records. A data capture sheet was used for each patient. Appendix 2 is an example of the form used to record data.

The clinical and laboratory criteria relating to the SLICC criteria for SLE were recorded. Clinical features captured according to cutaneous lupus erythematosus subtype and the clinical variants thereof.

Non-cutaneous features of SLE were similarly documented. Data was stratified according to whether it was present at the time of diagnosis (or within one month of presentation) or developed subsequently.

Serological tests that were captured include the anti-nuclear antibody (ANA) test, antibodies to the extractable nuclear antigens RNP, SM, Ro and La, Anti-dsDNA antibodies, Coomb's test and antiphospholipid antibodies (either a positive IgG or IgM anticardiolipin antibody test or a positive test for lupus anticoagulant). The highest titre of ANA was recorded for each patient. The presence of thrombocytopaenia, anaemia, hypocomplementenenia and lymphopaenia was recorded.

Using the latex test for indirect immunofluorescence, the ANA and Anti-dsDNA antibodies were detected. ELISA testing was done to detect the presence of Anti-Sm

antibody (Smith), anti-RNP antibodies (ribonuclear protein), anti-Ro and anti-La antibodies.

The Lupus Severity Index was calculated according to Bello *et al.* We were not able to include photosensitivity in our calculation (Bello *et al*., 2016).

2.4. Statistical methods

The patients were broadly divided into two groups: those with CLE and those without CLE. Descriptive statistics on general characteristics/demographics of the patients such as age, gender and ethnic group were collated. Numerical variables were described using mean and standard deviations. Associations between pairs of categorical variables were determined using Pearson's Chi-Square test and, where applicable, Fisher's exact test and Mann-Whitney U test was used.

To test for association with continuous variables like disease duration, the unpaired T-test was used. Statistical significance was ascertained at the 5% level, thus a p-value of less than 0.05 was significant. Where the p-value ranged from 0.051-0.1 the odds ratio and confidence interval was calculated.

Patients were divided into two groups – those who had CLE (n=227) and those who had no CLE (n=71). Those who had CLE were further subdivided into those with CCLE (n=161), ACLE (n=90) or SCLE (n=10).

Chapter Three: Results

3.1. Demographics and Clinical Characteristics of overall cohort

Of the 298 patients, 262 were black, 11 were of mixed ancestry, 12 were Indian and 13 were white. Ages ranged from 12 to 80 years of age and the mean (S.D.) age at presentation was 35 (11.8) years.

Most patients were black African females (242; 81.5%). The female (n=277) to male (n=21) ratio ratio was 13: 1. The average follow-up period was 8.03 (S.D. 5.9) years.

In males with SLE, the mean age of presentation was 33.9 years which was not significantly different from females (35.3 years). Average duration of follow-up was 8.04 years in females and 7.9 years in males.

Clinical and laboratory characteristics according to the 2012 SLICC criteria are summarised in Table 3.1 The mean cumulative number of SLICC criteria was 7.25 (range: 2-16) whilst the mean Lupus Severity Index was 6.36 (range: 4.76-9.2).

Only 9% of patients were HIV positive.

Table 3.1: Overview of demographic and clinical features of 298 SLE patients	
Demographic data (n=298)	
Age at initial presentation (±SD) (years)	35 (11.8)
Female: Male ratio	277:21 (13:1)
Duration of follow-up (±SD) (years)	8.03 (5.9)
Ethnicity	
	N (%)
Black	262 (93.6)
Mixed ancestry	11 (3.7)
Indian	12 (4)
White	13 (4.3)
SLICC Clinical	
ACLE	90 (30.2)
CCLE	161 (54)
Oral or nasal ulcers	129 (43.2)
Alopecia (non-scarring)	65 (21.8)
Arthritis	199 (66.7)
Serositis	74 (24.8)
Renal disease	105 (35.2)
Neurologic disease	65 (21.8)
Haemolytic anaemia	6 (2)
Thrombocytopaenia	149 (50)
Lymphopaenia	60 (20.1)
SLICC Immunological	
ANA	296 (99.3)
Anti-dsDNA Ab	118 (39.6)
Anti-Sm Ab	183 (61.4)
Low complement	165 (55.3)
Antiphospholipid Ab	143 (47.5)
Direct Coombs' test	136 (45.6)
Disease severity	
Lupus severity index (range)	6.34 (4.76-9.2)
SLICC criteria total (range)	7.25 (2-16)
HIV status	
HIV positive	27 (9)
HIV negative	263 (88.2)
HIV status unknown	7 (2.8)

3.2. Cutaneous findings

3.2.1. Cutaneous findings: Overview

Cutaneous findings of any form affected 248 (83.2%) patients while cutaneous lupus erythematosus (CLE) affected 227 (76.1%) patients.

Of the 227 patients with CLE, 178 (78.4%) had CLE at the time of initial presentation.

Non-specific cutaneous findings were found in 180 (79.3%) of 227 patients with CLE and 21 (29.6%) of patients without CLE.

The most common cutaneous finding was CCLE (54%), Raynaud's phenomenon (42.6%), melanonychia (39.9%), ACLE (30.2%) and non-scarring alopecia (21.8%).

Less common cutaneous findings included: Periungual telangiectasia (11.1%), livedo reticularis (9%), leukocytoclastic vasculitis (6.3%), SCLE (3.4%) and sclerodactyly (3.3%).

The most common cutaneous features at the time of presentation was CCLE (48.3%) and melanonychia (39.9%).

The cutaneous findings of SLE are listed in Table 3.2

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Table 3.2: Overview of all cutaneous findings		
Cutaneous Lupus Erythematosus (n=298)		
	N (%)	N (%)
	At presentation	Cumulative
CCLE	144 (48.3)	161 (54)
SCLE	8 (2.6)	10 (3.4)
ACLE	84 (28)	90 (30.2)
Non-specific cutaneous features in SLE		
	At presentation	Cumulative
Raynaud's phenomenon	117 (39.2)	127 (42.7)
Oral or nasal ulcers	38 (12.8)	129 (43.4)
Melanonychia	119 (39.9)	119 (39.9)
Alopecia (non-scarring)	23 (7.7)	65 (21.8)
Sicca	36 (12.1)	48 (16.1)
Periungual telangectasia	28 (9.4)	33 (11.1)
Livedo reticularis	17 (5.7)	27 (9)
Alopecia (scarring)	16 (5.4)	22 (7.4)
Leukocytoclastic vasculitis	13 (4.4)	19 (6.3)
Sclerodactyly	8 (2.7)	10 (3.3)
Calcinosis cutis	3 (1)	6 (2)
Leg ulcers	2 (0.6)	2 (0.6)
Erythromelalgia	1 (0.3)	1 (0.3)

3.2.2. Subtypes of CLE

CCLE was the most common type of CLE (54%). Localised DLE (26.9%) was more common than generalised DLE (25.2%). Lupus panniculitis (profundus) affected 5.7% of patients. No lupus tumidus, chilblain lupus or lichenoid DLE was found in this study.

ACLE (30.2%) was less commonly found than CCLE (54%). Localised ACLE (19.5%) occurred more frequently than generalised ACLE (8.4%).

SCLE was rare, found in only 3.4% of patients. Annular type SCLE (2.7%) was more common than papulosquamous (psoriasiform) type (0.6%).

Localised DLE (24.5%) was the most common presenting form of CLE occurring more frequently than the typical malar rash of ACLE (18.5%).

A complete breakdown of CLE subtypes are listed in table 3.3.

Table 3.3: Cutaneous Lupus Erythematosus Subtypes N=298		
	At presentation	Cumulative
	N (%)	N (%)
Chronic cutaneous lupus erythematosus (CCLE)		
Localised DLE	73 (24.5)	80 (26.9)
Generalised DLE	65 (21.8)	75 (25.2)
Hypertrophic/ verrucous DLE	1 (0.3)	1 (0.3)
Lupus panniculitis/ lupus profundus	8 (2.6)	17 (5.7)
LE tumidus	0	0
Chilblain LE	0	1 (0.3)
Lichenoid DLE	0	0
Subacute cutaneous lupus erythematosus (SCLE**)**		
Annular SCLE	6 (2)	8 (2.7)
Papulosquamous SCLE	0	2 (0.6)
Acute cutaneous lupus erythematosus (ACLE)		
Localised ACLE (malar rash)	55 (18.5)	58 (19.5)
Generalised ACLE (morbilliform)	21 (7)	25 (8.4)
TEN-like ACLE	4 (1.3)	8 (2.7)

3.2.3. Overlapping of CLE subtypes

Of 227 patients with CLE, 189 (83.2%) patients had a single type of CLE while 38 (17.8%) had more than one subtype.

Isolated CCLE was found in 136 (59.9%) patients whilst isolated ACLE occurred in 53 (23.3%) patients.

Of those patients with more than one type of CLE the most common combination was ACLE with CCLE (28).

All of the patients with SCLE had either CCLE (1.4%) or ACLE (1.3%) and 11 of 18 (61%) patients with lupus profundus had either localised or generalised DLE. Two patients had ACLE, CCLE and SCLE.

Table 3.4: Overlapping subtypes of CLE

N=298

CLE Subtype	Number of patients
	N (%)
CCLE	136 (45.6)
ACLE	53 (17.8)
CCLE + ACLE	28 (9.4)
CCLE + SCLE	4 (1.3)
ACLE + SCLE	4 (1.3)
CCLE + ACLE + SCLE	2 (0.6)

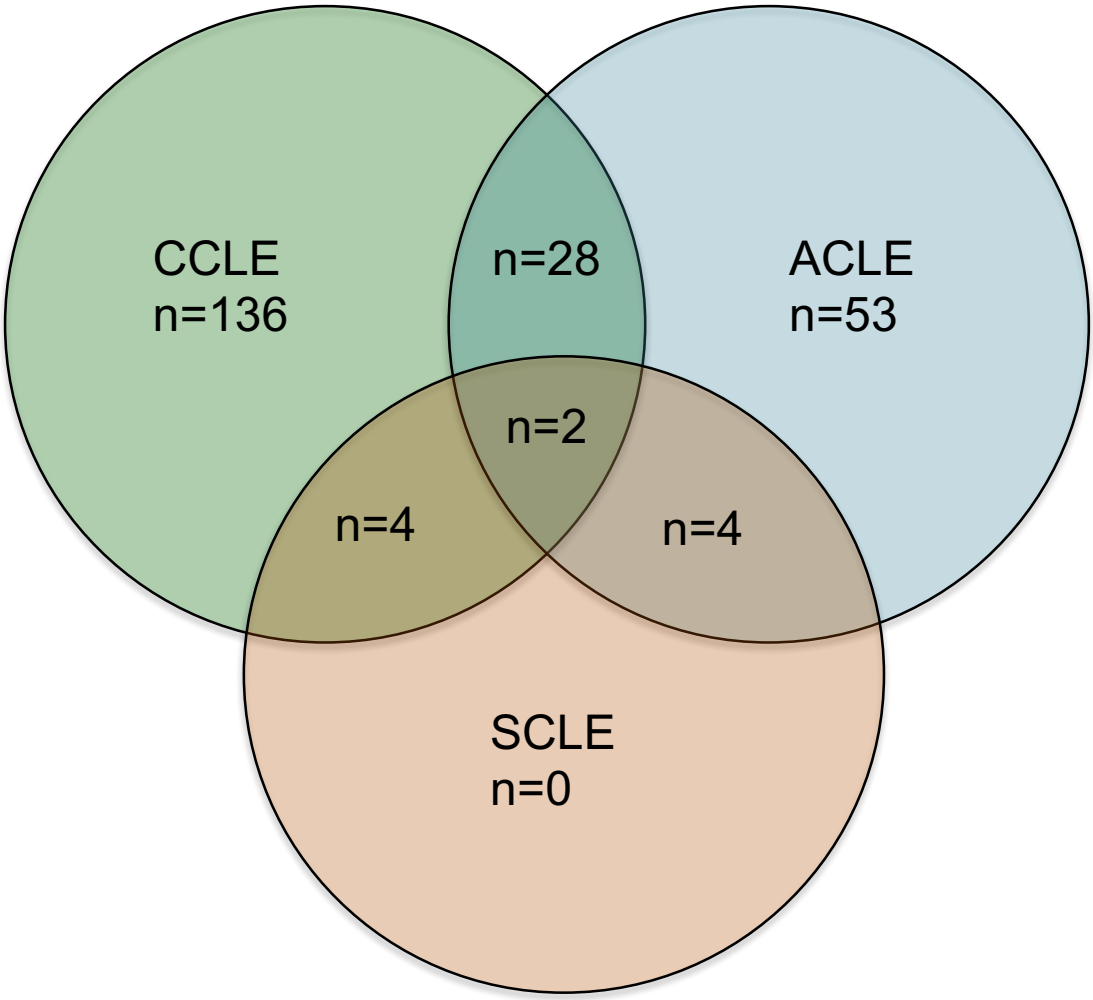

Figure 17: Cutaneous Lupus Erythematosus

3.2.4. CLE subtypes epidemiology and disease severity

Of all 298 patients in this study, isolated CCLE was found in 136 (45.6%) of patients whilst isolated ACLE was found in 53 (17.8%).

Females outnumbered males more frequently in patients with CCLE compared to ACLE, but this finding was not significant.

Patients with ACLE had an overall lower number of SLICC criteria but a significantly worse LSI compared to those patients with CCLE ($p<0.001$).

Table 3.5: Differences in epidemiology and disease severity in those patients with isolated CCLE compared to those with isolated ACLE

	Overall (n=227)	CCLE (n=136)	ACLE (n=53)	P-value
Female: male ratio	17:1	26:1 131:5	11:1 49:4	0.0841 Fischer's exact
Mean age (±SD) age (years) at initial presentation	34.8 (12.1)	35.6 (12)	34 (12.3)	0.2414
Median (range) disease duration (years)	8.2 (1-33)	7.9 (6)	8.9 (6.1)	0.5164 Mann-Whitney
Number of SLICC criteria (range)	7.4 (3-16)	8.0 (3-15)	7.64 (4-15)	0.0286
Lupus severity index Median (range)	5.8 (4.76-9.1)	6.07 (4.76-9.1)	6.5 (4.76-9.1)	**<0.001**

3.2.5. Non-specific cutaneous findings

Non-specific cutaneous features were a common finding affecting 230 (77.2%) of all patients.

Non-specific cutaneous findings, excluding oral or nasal ulcers, were found in 180 (79.3%) of 227 patients with CLE and 21 (29.6%) of patients without CLE.

Oral ulcers were the most common non-specific mucocutaneous finding (43.2%), Raynaud's phenomenon (42.6%), melanonychia (39.9%) and non-scarring alopecia (21.8%).

The most common cutaneous features at the time of presentation were CCLE (48.3%) and melanonychia (39.9%).

Table 3.6: Non-specific cutaneous features N= 298		
	At presentation	Cumulative
	N (%)	N (%)
Oral or nasal ulcers	38 (12.8)	129 (43.4)
Raynaud's phenomenon	117 (39.3)	127 (42.7)
Melanonychia	119 (39.9)	119 (40)
Alopecia (non-scarring)	23 (7.7)	65 (21.8)
Sicca	36 (12.1)	48 (16.1)
Periungual telangectasia	28 (9.4)	33 (11.1)
Livedo reticularis	17 (5.7)	27 (9)
Alopecia (scarring)	16 (5.4)	22 (7.4)
Leukocytoclastic vasculitis	13 (4.4)	19 (6.3)
Sclerodactyly	8 (2.7)	10 (3.3)
Calcinosis cutis	3 (1)	6 (2)
Leg ulcers	2 (0.6)	2 (0.6)
Erythromelalgia	1 (0.3)	1 (0.3)

3.3 Patients with CLE compared with isolated SLE

3.3.1. Patients with CLE compared with isolated SLE: Overview

Of the 298 patients, 227 (76.2%) had CLE while 71 (23.8%) had no CLE.

Females outnumbered males in both groups, however there was a significantly ($p<0.032$) higher female-to-male ratio in those patients with CLE.

The duration of disease follow up was marginally higher in those patients with CLE as listed in Table 3.7.

Patients with CLE had a significantly higher number of cumulative SLICC criteria ($p<0.001$) but a lower Lupus Severity Index ($p<0.001$).

Table 3.7: Overview of differences between those patients with CLE and those with isolated SLE

	Overall (n=298)	SLE with CLE (n=227)	SLE without CLE (n=71)	P-value
Female: male ratio	13:1	17:1	6.9:1	**0.032**
Mean age (±SD) age (years) at initial presentation	35.04 (11.8)	34.8 (12.1)	36.3 (11.9)	0.6115 Unpaired t-test
Median (range) disease duration (years)	8.03 (5.9)	8.2 (1-33)	7.3 (1-23)	0.2526 Mann-Whitney
Number of SLICC criteria (range)	7.25 (2-16)	7.4 (3-16)	5.9 (2-11)	**<0.001**
Lupus severity index Median (range)	6.3 (4.76-9.2)	5.7 (4.76-9.1)	6.1 (5.2-9.2)	**<0.001**

3.3.2. Association with systemic disease between groups

Arthritis was the second most common organ involved following the skin, affecting 199 (66.7%) of all patients. Arthritis occurred more frequently in those patients with CLE (69.8%) compared to those patients with isolated SLE (57.7%) but the difference was not significant.

Renal diseases was the third most common systemic finding in both groups, affecting 105 (35.2%) of patients. There were no significant differences in systemic organ disease when comparing those patients with and without CLE.

Table 3.8: Differences in systemic illness in those patients with CLE and those patients with isolated SLE

	Total (n=298)	SLE with CLE (n=227)	SLE without CLE (n=71)	P-value	Odds ratio 95%CI
	N (%)	N (%)	N (%)		
Arthritis	199 (66.7)	158 (69.6%)	41 (57.7)	NS 0.083	1.67 0.967 – 2.9
Renal disease	105 (35.2)	77 (33.9%)	28 (39.4)	NS 0.3152	-
Serositis	74 (24.8)	52 (22.9%)	22 (31)	NS 0.2075	-
Neuropsychiatric disease	65 (21.8)	53 (23.3%)	12 (16.9)	NS 0.3232	-
Venous thromboembolism	24 (8)	15 (6.6%)	9 (12.7)	NS 0.400	-
Stroke	13 (4.4)	8 (3.5%)	5 (7)	NS 0.2464	-
Recurrent miscarriage	12 (4)	11 (4.8%)	1 (1.4)	NS 0.2062	-

3.3.3. Association with haematological disease between groups

Haematological disorders were common in this study affecting 53.4% of all patients. Hypocomplementaemia was the most frequently observed serological abnormality with a slight preponderance in patients with CLE.

Haemolytic anaemia was rare but significantly more common those patients without CLE ($p<0.03$). Thrombocytopaenia similarly occurred more frequently in patients without CLE approaching significance. All haematological findings are outlines in Table 3.9.

Table 3.9: Differences in haematological disorders in those patients with CLE and those patients with isolated SLE

	Total (n=298)	SLE with CLE (n=227)	SLE without CLE (n=71)	P-value	Odds ratio 95%CI
	N (%)	N (%)	N (%)		
Hypocomplementaemia	165 (55.3)	130 (57.3)	35 (49.3)	NS 0.2743	-
Haematological abnormalities	159 (53.4)	118 (51.9)	41 (57.8)	NS	-
Leukopaenia	149 (50)	116 (51.1)	33 (46.5)	NS 0.5867	-
Thrombocytopaenia	60 (20.1)	40 (17.6)	20 (28.2)	NS 0.062	0.5455 0.294 - 1.013
Haemolytic anaemia	9 (3)	5 (2.2)	4 (5.6)	**0.031**	-

3.3.4. Association with autoantibodies between groups

All patients without CLE had antinuclear autoantibodies (ANA). However those patients with CLE who did have positive ANA were significantly more likely to have a titre above 1:640 ($p<0.0001$).

The most common autoantibodies associated with both groups was ANA, Anti-RNP antibody and Anti-Sm antibody. All antibody findings are outlined in table 3.10.

Table 3.10: Differences in autoantobodies in those patients with CLE and those patients with isolated SLE

	Total (n=298)	SLE with CLE (n=227)	SLE without CLE (n=71)	P-value
	N (%)	N (%)	N (%)	
ANA	296 (99.3)	225 (99.1)	71 (100)	0.6976
ANA 1:640 or more	76 (25.5)	72 (31.7)	4 (5.6)	**<0.001**
Anti-RNP Ab	233 (78.2)	175 (77.1)	58 (81.7)	0.4129
Anti-Sm Ab	183 (61.4)	143 (63)	40 (56.3)	0.3145
Anti-Ro Ab (SSB)	176 (59.1)	130 (57.3)	46 (64.8)	0.2607
Antiphospholipid Ab	143 (48)	108 (47.6)	35 (49.3)	0.8003
Direct Coombs' test	136 (45.6)	99 (43.6)	37 (52.1)	0.6867
Anti-La Ab (SSA)	119 (39.9)	91 (40.1)	28 (39.4)	0.9221

3.3.5. Non-specific cutaneous findings between groups

As previously mentioned non-specific cutaneous findings were commonly found in this study, affecting 230 (77.2%) of all patients.

Oral ulcers were another common systemic finding and were significantly ($p=0.003$) more frequently found in patients with CLE.

Raynaud's phenomenon was the most common non-specific cutaneous finding in patients with isolated CLE (44.9%) while non-scarring alopecia was the most common non-specific finding in patients with isolated SLE. Non-scarring alopecia occurred significantly more often in patients without CLE ($p<0.0001$) affecting 67.6% of this group.

Both livedo reticularis ($p<0.01$) and scarring alopecia ($p=0.006$) were found more frequently in patients with CLE. Melanonychia was a common finding in both groups affecting 42.7% of patients with CLE and 31% of patients with no CLE.

Melanonychia was the most common non-specific cutaneous finding at presentation in both groups.

Table 3.11: Differences in non-specific cutaneous findings in those patients with CLE and those patients with isolated SLE				
	Total (n=298)	SLE with CLE (n=227)	SLE without CLE (n=71)	P-value
	N (%)	N (%)	N (%)	
Any non-specific finding	230 (77.2)	180 (79.3)	21 (29.6)	**<0.001**
Oral or nasal ulcers	111 (43.2)	95 (41.8)	16 (22.5)	**0.003**
Raynaud's phenomenon	127 (42.6)	102 (44.9)	25 (35.2)	0.1482
Melanonychia	119 (39.9)	97 (42.7)	22 (31)	0.0778
Alopecia (non-scarring)	65 (21.8)	17 (7.5)	48 (67.6)	**<0.001**
Periungual telangectasia	33 (11.1)	28 (12.3)	5 (7)	0.2149
Livedo reticularis	27 (9)	26 (11.5)	1 (1.4)	**0.01**
Alopecia (scarring)	22 (7.4)	22 (9.7)	0	**0.006**
Leukocytoclastic vasculitis	19 (6.3)	14 (6.2)	5 (7)	0.2149
Sclerodactyly	10 (3.3)	7 (3.1)	3 (4.2)	0.6411
Calcinosis cutis	6 (2)	6 (2.6)	0	0.5488
Leg ulcers	2 (0.6)	1 (0.4)	1 (1.4)	0.3833
Erythromelalgia	1 (0.3)	1 (0.4)	0	0.3833

Chapter Four: Discussion

In this retrospective review of patients with SLE at Chris Hani Baragwanath Academic Hospital Soweto Gauteng we describe the prevalence of cutaneous findings in 298 patients meeting the 2012 SLICC criteria for SLE. We have compared those patients with CLE to those without CLE.

The demographics of study are in keeping with both local and international studies with an overwhelming female predominance (13:1). Only 21 patients were male.

The female-to-male ratio is markedly higher in those patients with CLE (17:1) but this is still well within the reported range of female predominance in South Africa (Wadee *et al*., 2007; Dessein *et al*., 1988). This does, however differ from international reports where the female predominance tends to be less marked in patients with CLE (Biazar *et al*., 2013; Gronhagen *et al*., 2011).

The reason for this is not clear but may reflect differences in healthcare seeking behaviour between genders, an overall higher number of females in our population or potentially highlight an important difference in the cutaneous findings in SLE in Black Africans.

Cutaneous findings of any kind (CLE and non-specific findings) were present in 83.2% of our population. This is in keeping with findings by Gronhagen *et al* (2011) and Cervera *et al* (2009) who reported 87% and 78% overall cutaneous involvement respectively (Gronhagen *et al*., 2010; Cervera *et al*., 2012).

CLE affected 76.2% of our patients and the majority (78%) of those with CLE had cutaneous disease at the time of presentation.

Non-specific cutaneous symptoms of SLE affected 77.2% of our patients – a much higher figure compared to international studies (Gronhagen *et al*., 2010). Unfortunately there is no data with which to compare this figure in South Africa.

All cutaneous findings in this study were reported in a specialist rheumatology clinic. According to Yell *et al* when dealing with the same patient population dermatologists tend to diagnose cutaneous disease, in particular CCLE, more frequently than rheumatologists suggesting that if anything these results reflect under rather than overestimation of the burden of cutaneous disease (Yell *et al*., 1996).

Histological confirmation of every case of CLE is the only objective way to accurately determine the burden of CLE but is unfortunately not possible in our setting.

CLE affected 76.2% of our patients and was present at the time of diagnosis in the majority of cases.

Contrary to findings in industrialised nations and in keeping with local trends, DLE was far more common than ACLE in our patients with SLE. DLE affected 51.7% of our patients. This finding is higher than those previously reported in South African studies (Wadee *et al*., 2007; Tikly *et al*., 1996).

The localised malar rash of ACLE was only present in 19.5% of our patients. This is remarkably lower than findings from European studies that report malar rash in 31.1 to 57% of SLE patients (Cervera *et al*., 2003; Gronhagen *et al*., 2010).

DLE was present at the time of diagnosis in 46.3% of patients while ACLE was only present in 28%.

These findings may also indicate that patients with a fluctuating malar rash are not being referred to this tertiary institution. DLE lesions cause significant scarring and hyperpigmentation, persisting for longer periods than ACLE making it a more recognisable cutaneous finding. Erythema is also a more difficult feature to assess in patients with darker skin tones making the diagnosis of a subtle malar rash more challenging. Furthermore, patients with DLE are perhaps more likely to notice their cutaneous findings are and seek medical assistance.

This finding may also represent subjective bias when clinically assessing a patient for the malar rash of localised ACLE. Gronhagen *et al* found that when patients were examined by both rheumatologists and dermatologists there was consensus in the diagnosis of malar rash in only 60% of patients (Gronhagen *et al*., 2010).

The term ‘malar rash’ is not favoured amongst dermatologists as the differential diagnosis is broad including conditions like eczema, rosacea and polymorphous light eruption (Gronhagen *et al*., 2014). In the future this clinical assessment bias may be reduced by use of the 2012 SLICC criteria that are more specific in detailing the definition of malar rash, including it as only one aspect of ACLE.

DLE was approximately two- to five-times more common in our population than in European studies (Gronhagen *et al*., 2010; Cardinali *et al*., 2000), the overall percentage of patients with generalised DLE (25.2%) was similar to those findings by Cardenalli (2000) and Yell (1996).

Generalised DLE has always been associated with a higher risk of progression to SLE making it logically a more common finding in a group of patients with SLE (Watanabe *et al*., 1995).

What is unusual in this study is the fact that 26.9% of our patients had localised DLE. According to international literature localised DLE has a much lower risk of progression to SLE and has been reported in only 7 to 7.3% of patients with SLE (Yell *et al*., 1996; Cardinali *et al*., 2000; Healy *et al*., 1995).

While this finding may simply be indicative of an extremely high prevalence of localised DLE and therefore be incidental, it may also suggest that localised DLE carries a higher overall risk of progression to SLE within our population and is not as ‘benign’ as international literature suggests.

Nonetheless, the Lupus Severity Index was significantly higher in those patients with ACLE compared to those with CCLE suggesting that where ACLE is present it is associated with more marked disease activity. Studies involving long-term follow-up of patients with CLE would be required to confirm this.

SCLE is a relatively uncommon form of CLE worldwide, however it was a particularly rare finding in our study affecting only 3.4% of patients. All patients with SCLE had another form of CLE. This finding may reflect the more benign course of SCLE, making patients less likely to develop systemic symptoms requiring specialist rheumatologic assistance.

It may also indicate that the SCLE is simply being underdiagnosed in our general population. SCLE clinically mimics multiple skin conditions necessitating skin punch biopsy for tissue confirmation. With limited access to dermatological services in South Africa many patients with SCLE may be clinically misdiagnosed.

The overlap of CLE subtypes in our study was higher than reported by Gronhagen *et al* (2011). Zecevic *et al* (2001) showed that an increasing number of overlapping CLE subtypes in patients with SLE indicates an overall poorer prognosis. Unfortunately, the small number of patients with overlapping cutaneous features in this study made it difficult to draw any real conclusions in this regard (Zecevic *et al*., 2001).

Biazar *et al* reported a higher number of overlapping CLE subtypes but included patients without SLE in their study, perhaps making their data not ideal to compare to our own (Biazar *et al*., 2013).

Non-specific cutaneous features, excluding oral ulcers, were very common affecting 77.2% of our patients.

Zecevic *et al* noted that non-specific cutaneous features are associated with a higher disease activity index (Zecevic *et al*., 2001). Cardinali *et al* proposed that non-specific cutaneous findings are important markers of disease activity (Cardinali *et al*., 2000). Most likely our common finding of non-specific cutaneous features reflects the higher likelihood of disease activity in our patient population.

We know that South African patients with SLE tend to have a high disease activity index and lupus nephritis in particular is a poor prognostic marker of disease (Wadee *et al*., 2007). Non-specific cutaneous features may be representative of this fact.

Oral and/or nasal ulcers were the most common non-specific mucocutaneous finding of SLE and reported more frequently than in other South African studies (Wadee *et al*., 2007; Tikly *et al*., 1996). This may be due to the fact that all patients in this study were attending a specialist rheumatology clinic and had therefore most likely been questioned specifically regarding the presence of ulcers. Without direct questioning oral or nasal ulcers may be easily overlooked.

Non-scarring alopecia affected 21.8% of patients similar to those findings by Tikly *et al* (1996) (Tikly *et al*., 1996). Interestingly, non-scarring alopecia was significantly more common in those patients with isolated SLE. This group of patients also had a significantly higher overall Lupus Severity Index. These findings are in keeping with those by Zecevic *et al* who suggested a direct correlation between disease activity and non-scarring alopecia (Zecevic *et al*., 2001).

Diffuse melanonychia is an unusual finding which Vaughn *et al* (1990) reported in

52% of their Black patients with SLE (Vaughn *et al*., 1990). We found diffuse melanonychia in 39.9% of our patients and in all cases it was present at the time of initial presentation. Diffuse melanonychia was the most common non-specific cutaneous finding on presentation in this study.

The exact cause of diffuse melanonychia is not known. Like Vaughn *et al* we surmise that the increased pigment is likely due to increased melanin deposition in the nail plate, but further studies with nail biopsy conformation would be required to confirm this (Vaughn *et al*., 1990).

Melanin in the nail plates is composed of granules derived from the matrix melanocytes. In the general population isolated longitudinal bands of melanonychia are very common amongst patients of African descent. 77% of Black people will have melanonychia by the age of 20 and almost 100% by the age of 50 (Baran *et al*., 2012).

Diffuse melanonychia or melanonychia comprised of several bands of discolouration is rarer. It may occur as a result of many medications (including antimalarials), vitamin deficiencies, HIV and several dermatoses (Vaughn *et al*., 1990).

The mechanism of nail melanocytes activation is not fully known but it is believed to be partly due to over expression of alpha-melanocyte-stimulating hormone and adrenocorticotropic hormone activity as well as ultraviolet light (Ehsanzadeh-Cheemeh *et al*., 2011). In dermatologic disorders such as lichen planus pigmentation is thought to be caused by inflammatory activation of melanocytes in

the nail matrix (Jefferson *et al*., 2012).

Ehsanzadeh-Cheemeh *et al* found that Black patients with HIV were more likely to have melanonychia regardless of their antiretroviral regimen (Ehsanzadeh-Cheemeh *et al*., 2011). While the exact cause in these patients also remains unclear it's possible that there is a link between generalised inflammation and increased melanin production (Ehsanzadeh-Cheemeh *et al*., 2011).

Raynaud's phenomenon was present in 42.7% of patients, a finding consistent with other South African studies (Simmons *et al*., 2008; Wadee *et al*., 2007; Tikly *et al*., 1996). The prevalence of Raynaud's phenomenon in SLE varies widely in international literature ranging from 6.67% to 60% (Kole *et al*., 2009; Cardinali *et al*., 2000).

Unlike global literature, arthritis was the second most common systemic, occurring less frequently than the skin and found in 66.7% of patients. It was present at the time of diagnosis in 63.1% of patients.

Arthritis occurred more frequently in those patients with CLE (69.8%) compared to those patients with isolated SLE (57.7%) but the difference was not significant.

Renal disease is a commonly reported complication of SLE in South Africa and associated with a poorer overall prognosis (Wadee *et al*., 2007). Renal dysfunction was found in 35.2% of our patients and in the majority (22.5%) it was present at the time of diagnosis. CLE was present in 62.7% of patients presenting with renal

dysfunction and there was significant association of renal disease with ACLE, a finding also reported by Zecevic *et al (*Zecevic *et al*., 2001*).*

While these renal findings are lower than those reported by Seedat *et al* (Seedat *et al*., 1996) and Jessop *et al* (Jessop *et al*., 1973) the aforementioned studies were based on inpatient records, possibly resulting in selection bias and therefore overestimation in the prevalence of renal disease in the overall population of patients with SLE.

There was no significant difference in the prevalence of serositis, neuropsychiatric disease, stroke or other systemic disease between those patients with and without CLE in this study.

Despite this lack in obvious differences in systemic organ involvement between our two groups, the Lupus Severity Index was significantly higher in those patients without CLE suggesting a more aggressive disease course and poorer overall prognosis.

Haematological disorders were common in this study affecting 53.4% of all patients - similar to other South African reviews and supporting findings by Dessein *et al* who showed no difference in haematological abnormalities in Black patients compared to other racial groups (Dessein *et al*., 1988).

Haemolytic anaemia was rare but significantly more common those patients without CLE ($p<0.03$). Thrombocytopaenia similarly occurred more frequently in patients

without CLE approaching significance. Thrombocytopaenia is a known poor prognostic marker for SLE and has been shown in other studies to have an inverse relationship with cutaneous disease (Zhao *et al*., 2010).

As with Wadee *et al*, hypocomplementaemia was the most frequently observed haematological abnormality (Wadee *et al*., 2007). In our study we found a slight but not significant risk of hypocomplementenaemia in patients with CLE.

Interestingly, unlike Gronhagen *et al* our research showed no real differences in autoantibody profiles between those patients with and without CLE (Gronhagen *et al*., 2010). Specifically we found no increase in the presence of Anti-Ro antibodies in those patients with CLE, a finding reported elsewhere in the literature (Tikly *et al*., 1996).

While ANA positivity was only marginally higher in patients without CLE, an ANA titre above 1:640 was more likely to occur in those patients with CLE. This finding is counterintuitive since a higher ANA titre is traditionally associated with a poorer disease prognosis.

Further research is needed to better understand the subtypes of CLE and their autoantibody associations in South Africa.

Limitations

As with all retrospective studies we were limited by the data recorded in outpatient files. Missing data, inconsistencies in data recording by different clinicians and differences in interpretation of cutaneous signs may lead to under or over reporting of cutaneous findings.

Certain cutaneous findings, particularly ACLE may be more difficult to assess in Black patients.

Ideally all patients should be evaluated by both a dermatologist and rheumatologist to increase the accuracy of cutaneous findings. This is unfortunately not possible in a retrospective review. The gold standard of diagnosis however would be histological confirmation of the diagnosis of Cutaneous lupus erythematosus.

Data regarding photosensitivity was not included in this study as we used the 2012 SLICC criteria for inclusion of a diagnosis of SLE. Photosensitivity is a cutaneous symptom particularly open to interpretation. Unfortunately this also means that the Lupus Severity Index Score (LSI) calculated here did not include photosensitivity and therefore represents an overestimation of true LSI values in our population.

This review may also be prone to statistical error. Certain subcategories which were analysed contained overall small numbers leading to less statistical accuracy.

Chapter Five: Conclusion

Some important conclusions that have been drawn from this study despite the above limitations are:

- Cutaneous Lupus Erythematosus (CLE) was the most common single organ system finding in patients with SLE occurring more frequently than arthritis;
- Non-specific cutaneous findings were more common than CLE;
- DLE, both localised and generalised, is very common in patients with SLE, occurring more frequently than ACLE in this study;
- Localised DLE was more likely to be present at the time of initial presentation than localised ACLE making the malar rash of SLE a less helpful distinguishing feature of SLE in our population;
- Patients with DLE were as likely to have systemic organ disease including arthritis, nephritis and serositis as those with other forms of CLE, suggesting that DLE is not necessarily a benign cutaneous finding in our population;
- Patients with CLE are more likely to be female and have a lower Lupus Severity Index compared to those without CLE;
- Non-scarring alopecia is a common non-specific cutaneous finding and is more frequently found in patients with isolated SLE. It may be a useful surrogate marker of disease activity;
- Diffuse melanonychia is a common and unusual finding reported in this study. It was found in all affected cases at the time of initial presentation.

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Appendices

Appendix 1

DEMOGRAPHIC DATA					
Study number:					
Age of onset:					
Duration of disease:					
Gender:	Male		Female		
Race:	Black	White	Indian	Coloured	Other
HIV status	Positive	Negative	Unknown	HAART+	HAART-

SCLICC CRITERIA	
Clinical Criteria	> 4 criteria (at least 1 clinical and 1 laboratory criteria)
Index	Where 0 = not at all, 1 = yes at diagnosis
Acute Cutaneous Lupus	
Chronic Cutaneous Lupus	
Oral or nasal ulcers	
Non-scarring alopecia	
Arthritis	
Serositis	
Renal	
Neurologic	
Hemolytic anemia	
Leukopenia (<4000/mm3)	
Thrombocytopenia (<100,000/mm2)	
Immunologic Criteria	
ANA	
Anti-DNA	
Anti-Sm	
Antiphospholipid Ab	
Low complement (C3, C4)	

Direct Coombs' test (do not count the presence of hemolytic anemia)	

CUTANEOUS SIGNS		
Index		Where 0 = not at all, 1 = at baseline and 2 = during the course of disease
LE-specific cutaneous symptoms		
CCLE	Localized DLE (above neck)	
	Generalized DLE	
	Hypertrophic/verrucous DLE	
	Mucosal DLE (Oral, nasal, genital)	
	LE tumidus/papulomucinous LE	
	Chilblain LE	
	Lichenoid DLE (LE/LP overlap)	
	Lupus panniculitis/lupus profundus	
SCLE	Annular SCLE	
	Papulosquamous/psoriasiform	
	TEN-like SCLE	
ACLE	Localized ACLE (malar rash)	
	Generalized ACLE (morbiliform)	
	TEN-like ACLE	
LE non-specific cutaneous symptoms		
LCV		
Periungual telangiectasia		
Livedo reticularis		
Raynaud's phenomenon		
Erythromelalgia		
Non-scarring alopecia		
Scarring alopecia		

Sclerodactyly	
Rheumatoid nodules	
Calcinosis cutis	
LE-nonspecific bullous lesions (bullous SLE)	
Papulonodular mucinosis	
Acanthosis nigricans	
Erythema multiforme	
Leg ulcers	
Melanonychia	

SYSTEMIC INVOLVEMENT		
Index: Where 0 = not at all, 1 = at baseline and 2 = during the course of disease		
Inflammatory arthritis		
Pleuritis		
Pericarditis		
Renal disorders		
(Subtype)	Minimal mesangial lupus nephritis (class I)	
	Mesangial proliferative lupus nephritis (class II)	
	Focal lupus nephritis (class III)	
	Diffuse lupus nephritis (class IV)	
	Membranous lupus nephritis (class V)	
	Advanced sclerosing lupus nephritis (class VI)	
	Overlap of lupus and ANCA glomerulonephritis	
	Not specified (NOS)	
Neurologic disorders	Seizures	
	Psychosis	
	Mononeuritis multiplex	

	Myelitis	
	Peripheral or cranial neuropathy	
	Acute confusional episode	
Venous or arterial thrombosis	Venous thromboembolism	
	Cerebrovascular accident (obstructive)	
Pregnancy loss (recurrent miscarriage)		
Sicca syndrome		

SEROLOGICAL FEATURES			
Index:		Where 0 = not at all, 1 = at baseline and 2 = during the course of disease	
			Highest titre reached
Hemolytic anemia			
Leukopenia (<4000/mm3)			
Lymphopenia (<1000/mm3)			
Thrombocytopenia	>100,000/mm3 (Low platelets)		
	<100,000/mm3 (ITP)		
ANA level (>1:80)			
Anti-dsDNA antibody positivity			
Anti-Sm antibody positivity			
Antiphospholipid antibody positivity			
Low complement (Decreased C3, C4)			
Direct Coombs' test			
Rheumatoid factor (only if titre >1:40)			
Anti-Ro Antibody			
Anti-La Antibody			

Appendix 2

R14/49 Dr Karen Koch

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140942

NAME: (Principal Investigator)	Dr Karen Koch
DEPARTMENT:	Dermatology Rheumatology Chris Hani Baragwanath Acedemic Hospital
PROJECT TITLE:	The Prevalence of Cutaneous Lupus Manifestations in Patients Diagnosed with Systematic Lupus Erythematous (SLE) Attending the Chris Hani Baragwanath Academic Hospital Rheumatology Outpatient Clinic
DATE CONSIDERED:	03/10/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Lushen Pillay
APPROVED BY:	pp Professor C Feldman Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/01/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES