

**THE SPECTRUM OF DERMATOLOGICAL DISORDERS FOUND IN PATIENTS
WITH SARCOIDOSIS PRESENTING TO THE DERMATOLOGY OUTPATIENT
CLINIC AT THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL**

BABALWA PHINDISWA ZINZISWA MBUQE-LIMBA

Student no. 589938

A research report submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of
Master of Medicine in the branch of Internal Medicine (Dermatology)

Johannesburg 2017

DECLARATION

I, Babalwa Phindiswa Zinziswa Mbuqe-Limba hereby declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine (Dermatology) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

.....

DR BPZ Mbuqe-Limba, MBChB (WSU), FCDerm (SA).

..... day of.....2017

DEDICATION

This research is dedicated to my four children; Xola, Liyema, Alwande and Cwambu, and their father Lunga, for their encouragement, support and believing in me.

ABSTRACT

Backgrounds

There is a paucity of studies on cutaneous sarcoidosis in the South African setting, with the last study published 18 years ago. More studies are needed to explore these gaps to inform referral policy and guidelines for early diagnosis and management of cutaneous sarcoidosis in the country.

Objectives

The study focuses on the patterns of cutaneous sarcoidosis, demographic features, and histological associations with the clinical patterns of skin sarcoidosis found in patients with sarcoidosis presenting to the dermatology outpatient clinic at the Chris Hani Baragwanath Academic hospital. In addition, the pattern, chronicity and severity of the cutaneous manifestations were described. Furthermore, the co-existence of HIV/AIDS and sarcoidosis was also examined.

Methods

A retrospective descriptive study that spans from 1991 to 2015, was carried out which included cases that had a definitive diagnosis of sarcoidosis. One hundred case records of patients with cutaneous sarcoidosis that attended the Dermatology Outpatient Clinic, from the study site in Soweto, in the south of Johannesburg, were collected and transferred to a collection data sheet.

Results

In this predominantly Black African population, women above 45 years old (70%), were most commonly affected. Papules (68.8%) and plaques (27.1%) were the most frequent skin findings in Black Africans. The most frequent extra-cutaneous organ affected was the lung (53%). Subcutaneous lesions were found to be significantly associated (p-value <0.012) with Scadding stage 0 and stage 4 lung involvement. On histology 70% of the cases had clean granulomas, frequently associated with papules clinically. HIV seropositive and sarcoidosis cases demonstrated an inversely proportional association with the CD4 count, with disease progression noted with CD4 increments after initiation of therapy.

Conclusion

The variations in the patterns of presentation revealed in this study can improve our knowledge of cutaneous patterns of sarcoidosis in this study population and assist with the development of prompt diagnosis and early treatment intervention.

ACKNOWLEDGEMENTS

The assistance and guidance of my supervisors Professor Michelle Wong and Professor Colin Menezes is greatly appreciated. Special thanks to Mr. Ajayi Anthony for assisting with the statistical analysis and providing intellectual contribution towards the successful completion of this research report.

The Division of Pulmonology at Chris Hani Baragwanath Academic Hospital and the nursing staff were generous with their time and support during the period of the data collection. The National Health Laboratory Services gave access for the collection of data from patients' histology records.

I am indebted to my colleagues and friends; Dr. Sli Sibisi Shange and Dr. Mpumi Sotobe Mose for believing in me and with their zealous encouragement. Finally, I am grateful to Dr. Vincent Adeniyi, for his mentorship and guidance with the research report.

Table of Contents

DECLARATION	ii
DEDICATION	iii
ABSTRACT.....	iv
ACKNOWLEDGEMENTS	v
LIST OF FIGURES	ix
LIST OF TABLES.....	ix
DEFINITION OF KEY CONCEPTS	xi
LIST OF ABBREVIATIONS	xii
CHAPTER ONE	1
1.1INTRODUCTION	1
1.1.1Historical background	1
1.1.2 Sarcoidosis.....	2
1.1.3 Cutaneous sarcoidosis	2
1.1.4 Problem Statement.....	3
1.1.5 Significance of the study	4
1.1.6 Aim of the study	4
1.1.7 Objectives.....	5
1.1.8 Research Questions	5
1.1.9. Chapter layout	5
1.1.10. Conclusion.....	6
1.2 LITERATURE REVIEW	7
1.2.1. Introduction	7
1.2.2. Literature Search Strategy	7
1.2.3. Clinical manifestations and trends in the epidemiology.....	7
1.2.4. Aetiopathogenesis.....	10

1.2.5. Immunology	11
1.2.6. Diagnosis	11
1.2.7 The impact of HIV/AIDS pandemic on the clinical manifestation of cutaneous sarcoidosis	13
1.2.8 Management	13
1.2.9. Conclusion	15
CHAPTER TWO.....	16
METHODOLOGY	16
2.1 Introduction.....	16
2.2 17 Design	16
2.3 Study setting	16
2.4 Study population.....	16
2.5 Selection criteriaand sample size	17
2.6 Data collection (see Appendix A for the data collection sheet).....	17
2.6.1 Measurements.....	18
2.8 Data entry.....	19
2.9 Data analysis	19
2.10 Ethical approval and other considerations	20
2.11 Conclusion	20
CHAPTER THREE.....	21
RESULTS.....	21
3.1Introduction.....	21
3.2 Demographic characteristics.....	21
3.3 Distribution of patients with sarcoidosis by occupation.....	21
3.4 Demographic characteristics of patients and clinical cutaneous manifestations	22
3.5 Extracutaneous organ involvement.....	23
3.5.1 Number of organ involvement.....	24

3.5.2 Patients with four and five organs involved	25
3.5.3 Association of demographical characteristics and number of organ involvement	26
3.5.6 Extracutaneous organ involvement by specific type lesion.....	27
3.6 Clinical patterns of cutaneous sarcoidosis and the chest X-ray findings.....	29
3.7 Chronicity of cutaneous sarcoidosis	30
3.8 Treatment	33
3.9 Histology findings	34
3.10 Sarcoidosis in people living with HIV	36
3.11 Summary.....	37
CHAPTER FOUR	38
SUMMARY OF FINDINGS, DISCUSSION, CONCLUSION	38
4.1 Introduction.....	38
4.2 Summary of findings	38
4.3 Discussion of results.....	39
4.3.1 Where are we today?	39
4.3.2 Correlations between demographic characteristics and patterns of cutaneous sarcoidosis .	40
4.3.3 Patterns, severity and chronicity of cutaneous manifestations of sarcoidosis in patients....	41
4.3.4 Histopathological findings of biopsy specimens of cutaneous lesions of sarcoidosis.....	42
4.3.5 Association between HIV and cutaneous or systemic sarcoidosis	43
4.4 Limitations.....	44
4.5 Conclusion	44
APPENDIX A (Data collection sheet).....	52
APPENDIX B (Ethics Certificate)	58
APPENDIX B (Ethics Certificate continued)	59

LIST OF FIGURES

Figure 1.1: Step-wise approach to diagnosis of sarcoidosis.....	12
Figure 1.2: A proposed therapeutic ladder for the treatment of skin sarcoidosis.....	15
Figure 2.1: Map showing the study area.....	17
Figure 3.1: Proportion of patients with sarcoidosis by age and sex.....	21
Figure 3.2: Types of cutaneous lesions by age	21
Figure 3.3: Extra-cutaneous organ involvement	24
Figure 3.4: Number of organ involvement	25

LIST OF TABLES

Table 1.1: Systemic manifestations of sarcoidosis.....	1
Table 1.2: Cutaneous manifestations of sarcoidosis.....	8
Table 1.3: Cutaneous sarcoidosis treatment.....	14
Table 3.1: Types of cutaneous lesions by gender and race.....	22
Table 3.3: Patients with three organ involvement.....	25
Table 3.4: Number of organ involvement by age, gender and race.....	26
Table 3.5: Organ involvement by specific type lesion.....	28
Table 3.6: Severity by pattern of clinical presentation.....	29
Table 3.7: Clinical outcomes of sarcoidosis patients according to patterns of presentation.....	31
Table 3.8: Clinical outcomes of sarcoidosis patients based on the number of organs involved.....	32
Table 3.9: Clinical outcomes of sarcoidosis patients based on number of morphologies on	

presentation.....	33
Table 3.10: Treatment combinations administered to patients.....	34
Table 3.11: Site of biopsy.....	35
Table 3.12: Frequency distribution of granulomatous reaction patterns.....	35
Table 3.13: Pattern of presentation versus histological results of patients.....	36

DEFINITION OF KEY CONCEPTS

The terms and concepts identified as being central to the research topic are defined below:

- **Sarcoidosis:** In Greek, sarco means "flesh," eidos means "like," and osis means "condition"; thus, flesh-like condition (72).
- **Cutaneous sarcoidosis lesions:** Eruptions caused by sarcoidosis are classified as "specific" (non-caseating granulomas are present in biopsy specimens) or "non-specific" (lesions develop as a result of a reactive process without the formation of granuloma) (32)
- **ACCESS:** A Case Control Etiological Study Of Sarcoidosis was designed by Baughman and his colleagues to study the aetiology of sarcoidosis. Judson and colleagues later updated the instrument used to define the diagnostic criteria for sarcoidosis, in 2014 (WASOG sarcoidosis organ assessment instrument).
According to this instrument, prerequisites for the acceptance that an organ is involved by sarcoidosis were (1) histological features of granulomatous inflammation without a known cause in another organ; (2) exclusion of other causes for the clinical manifestations. These clinical manifestations were further classified as being due to sarcoidosis according to the following definitions: (i) highly probable ($\geq 90\%$ likelihood), (ii) probable (50 - 90% likelihood), (iii) possible ($< 50\%$ likelihood).
- **HIV infection:** infection by the Human Immunodeficiency Virus as diagnosed by a positive HIV antibody test, confirmed by a second HIV antibody test.
- **HAART:** highly active anti-retroviral therapy is defined as treatment with three or more antiretroviral agents, including a protease inhibitor.

LIST OF ABBREVIATIONS

ACCESS	A Case Control Etiologic Study Of Sarcoidosis
ACE	Angiotensin converting enzyme
AIDS	Acquired immunodeficiency syndrome
ATS	American Thoracic Society
Ca2	Calcium
CHBH	Chris Hani Baragwanath Academic Hospital
CXR	Chest X-ray
HAART	High active anti-retroviral therapy
HIV	Human immunodeficiency virus
HRCT	High resolution computerized tomography
HXR	Hand X-ray
WASOG	World Association of Sarcoidosis and Other Granulomatous Disorders

CHAPTER ONE

1.1 INTRODUCTION

1.1.1 Historical background

The first dermatological presentation of sarcoidosis was described in the 19th century in 1875 by Hutchinson, a physician of English descent. The clinical pattern he described was that of a patient who presented with multiple, raised, purplish skin patches which had appeared over a two year period. In 1899, Caesar Boeck, a nephew to a Norwegian dermatologist, reported the cutaneous histology of these lesions. The skin lesions resembled a sarcoma but they were benign clinically and histologically. Boeck then coined the term ‘sarkoid’ and the word sarcoidosis stemmed from this report (1, 2). It was previously considered as an isolated skin disease entity, but over the past two centuries, it became clear that sarcoidosis affects multiple organs (3-5). Table 1.1 shows the systems involved in order of frequency.

Table 1.1 Systemic manifestations of sarcoidosis (adapted from Haimovic *et al.* 2012 (71))

Extra-cutaneous organ involvement	Frequency (%)	Comment
Respiratory system	95%	Most commonly involved organ
Cutaneous	15 -25	Erythema nodosum, plaques subcutaneous nodules, lupus pernio
Lymph nodes	15 -30 (hilar 90%)	Firm non-tender
Ophthalmic system	12	65% anterior uveitis
Hepatic	12	Granulomas in 40 – 70%
Neurological system	5 -10	Facial nerve palsy most common
Bone marrow	4 – 20	Anaemia and leukopaenia
Metabolic	4 -11	Hypercalciuria 40%, renal stones 10%
Cardiac	5- 10	75% diagnosed at autopsy
Bone/joint	0.5	Joint 25 -40%
Muscle	0.4	

1.1.2 Sarcoidosis

Sarcoidosis is a multi-systemic granulomatous disorder of unknown aetiology (6). It is characterised by heterogeneous clinical features of which the respiratory system is commonly affected with an estimated frequency of 95%, followed by cutaneous involvement in up to 25% of cases (6-8). According to Baughman *et al.*, African American patients have an increased incidence of cutaneous sarcoidosis compared to the Caucasian population, and a higher prevalence of skin manifestations of sarcoidosis occurs in females (9-11).

There has been a change in the age of diagnosis demonstrated in recent epidemiologic studies, with the investigators finding a shift in the peak incidence to 40 – 59 years (13, 14). A study conducted over three decades at Groote Schuur Hospital in Cape Town demonstrated a prevalence rate of sarcoidosis of 17/100000 in the Coloured population, 27/100000 in the Black and 6/100000 in White population (15). Many studies have reported a higher incidence of sarcoidosis in females (13, 15-17). However, a few reports did not find any gender preference (13, 18). A South African study of 110 cases conducted in Cape Town over a 7 year period with 71 Coloured, 25 Black African, and 14 Caucasians described a discrepancy in gender distribution with 2:1 female to male ratio in the Coloured population contrary to the other racial groups (1:1 in both Black African and White populations) (19). The findings were attributed to demographic bias, as the population of the Cape Peninsula at that time consisted of 610 215 Coloureds, 378 505 Whites and 107 877 Black Africans. A familial tendency was observed among the African American population with cutaneous sarcoidosis (9, 20).

1.1.3 Cutaneous sarcoidosis

Overall, skin manifestations occur in 20-35% of the patients diagnosed with sarcoidosis, and occur mainly at the onset of the disease (12). Isolated cutaneous lesions have been reported in about a third of the patients with sarcoidosis (3, 12), which are subsequently followed by extra-cutaneous systemic involvement over a period of four weeks to twelve months (3). Skin manifestations of sarcoidosis may appear at any age with peaks observed between ages 20 to 40 years (10). Studies on cutaneous sarcoidosis in South Africa are limited.

Having worked as a registrar at the CHBH, in Soweto, Johannesburg, the researcher noticed the lack of guidelines and protocols to assist with the diagnosis of cutaneous sarcoidosis and treatment options. Because the disease has no specific aetiological source and presents with variable clinical patterns and an unpredictable course, it is difficult to define a specific management strategy. It is important to conduct a study to review the clinical spectrum of cutaneous sarcoidosis in the African context so as to improve on the identification of specific clinical patterns reported on in Africa and enhance treatment interventions.

1.1.4 Problem Statement

Sarcoidosis is a multi-organ disorder characterized by non-caseating granulomas of unknown aetiology (6). Cutaneous manifestations occur in 20-35% of cases of sarcoidosis (12, 21-24). Cutaneous sarcoidosis often develops as an isolated organ involvement (3) or in combination with multi-organ involvement (12, 25).

Although female predominance of cutaneous sarcoidosis appears to be consistent across ethnic groups, some variations in the gender ratio of cases across ethnic groups have been observed. Percentages of female patients with sarcoidosis reported in different continents are listed as follows: 68% in America; 74% in Northern Europe; 77% in Southern Europe; 81% in Northern Asia and 83% in sub-Saharan Africa (12, 17, 21, 22, 24). Other authors reported no gender preference (13, 18). The African American/ Black African female population, is the racial group mostly affected by cutaneous sarcoidosis (12, 17, 21, 22, 24). an American author conducted a study on a military veteran population which was racially heterogeneous and found the highest incidence of cutaneous sarcoidosis in female African Americans (29 versus 12 Caucasian females) (9, 19). Differences in recruitment of study populations may influence reported gender demographics.

The impact of HIV/AIDS on patterns of presentation of cutaneous sarcoidosis and the influence of demographics is an additional goal of this study. With a period of 18 years where no reviews of the condition were done in South Africa, there is justification for a new study to further understand the pattern of presentation, severity, and histopathology of cutaneous sarcoidosis. Access to medical care, which was easily open to the White population in the past and less so to Black South Africans, might have had a significant influence on the apparent incidence, the clinical spectrum of cutaneous sarcoidosis and the subsequent severity and chronicity described in the South African literature. This lack of access could have

contributed to the reported late presentation and advanced nature of cutaneous sarcoidosis in the Black Africans, hence giving rise to the notion that the spectrum of cutaneous sarcoidosis is more florid amongst African Americans and Black Africans (17). Interestingly Rybicki, an American author, conducted a series of studies to determine the familial and probable genetic link of cutaneous sarcoidosis in African American and /or Black African race (9, 20). Together with his colleagues, Rybicki attempted to confirm reports of sarcoidosis in first-degree relatives of cases and controls by personal interviews, concluding that familial associations were a risk factor for cutaneous sarcoidosis. He also concluded from his findings that increased surveillance of relatives for cases of sarcoidosis cases is probably not warranted, given the small percentage (1%) in whom it will eventually develop (20).

Dermatologists are often the first clinicians to examine and define skin lesions, but thoracic physicians or rheumatologists publish many reports on cutaneous sarcoidosis, especially in poorly resourced countries.

Florid and nonspecific atypical cutaneous manifestations of sarcoidosis (e.g. hypo-pigmented and ichthyosiform lesions, mutilating disfiguring chronic lesions) are associated more commonly with non-Caucasians (11, 26). In South Africa, there is a paucity of literature examining the spectrum and the management of cutaneous sarcoidosis. This study prompts a fresh review of this topic amongst Black South Africans.

1.1.5 Significance of the study

Epidemiological data on the incidence, trends, presentations, severity and treatment outcomes could inform the development of protocols for prompt diagnosis and early management intervention at the Dermatology Outpatient Clinic at Chris Hani Baragwanath Academic Hospital. Findings from this study will add to the limited knowledge of cutaneous sarcoidosis in South Africa.

1.1.6 Aim of the study

The overall aim of the study was to evaluate the spectrum of cutaneous manifestations of sarcoidosis at Chris Hani Baragwanath Academic Hospital Dermatology outpatient clinic.

1.1.7 Objectives

In order to provide direction for the study, the following objectives were formulated:

- i. To examine the correlations between demographic characteristics and cutaneous manifestations of sarcoidosis.
- ii. To describe the pattern, severity and chronicity of cutaneous manifestations of sarcoidosis in patients attending the Dermatology outpatient clinic at the Chris Hani Baragwanath Academic Hospital.
- iii. To describe the histopathological findings of biopsy specimens of cutaneous lesions of sarcoidosis in the cohort.
- iv. To identify any association between HIV and cutaneous or systemic sarcoidosis.

1.1.8 Research Questions

The study will address the following questions:

- i. Are there correlations between demographic characteristics and cutaneous manifestations of sarcoidosis in patients managed at Chris Hani Baragwanath Academic Hospital?
- ii. What are the patterns, severity and chronicity of cutaneous manifestations of sarcoidosis in patients attending the outpatient clinic at Chris Hani Baragwanath Academic Hospital?
- iii. What are the histopathological findings of biopsy specimens of cutaneous lesions of sarcoidosis in the cohort?
- iv. Is there any association between HIV and cutaneous or systemic sarcoidosis?

1.1.9. Chapter layout

Chapter 1: This chapter covers the protocol for the study and also provides in-depth literature review on cutaneous sarcoidosis, and an appraisal of studies done globally, in sub-Saharan Africa and South Africa. The existing gaps in the literature are identified, thus, providing appropriate context for the new study.

Chapter 2: This chapter highlights the methodology employed in carrying out the study.

Chapter 3: This chapter provides the results, using tables, flow diagrams and graphs.

Chapter 4: This chapter discusses the findings of the study, limitations of the study and conclusion.

1.1.10. Conclusion

Cutaneous sarcoidosis with its protean clinical manifestations has an unpredictable natural course (2). Review of the literature has revealed a paucity of studies examining the spectrum and management of cutaneous sarcoidosis in South Africa. More studies are needed to explore these gaps to inform referral policy and guidelines for early diagnosis and management of cutaneous sarcoidosis in the country. The next chapter appraises the existing literature on cutaneous sarcoidosis globally, regionally and in South Africa.

1.2 LITERATURE REVIEW

1.2.1. Introduction

This section is designed to provide a review of what is currently known about the research topic and areas surrounding it. An overview of the current global trends of sarcoidosis and the cutaneous patterns of presentation with particular emphasis on the South African context will be presented. The factors that may have an influence on the cutaneous sarcoidosis spectrum in South Africa are discussed. The last review of this topic was published in 1999, and prompted the author's review. A commentary on the co-existence of HIV/AIDS and cutaneous sarcoidosis is also included.

1.2.2. Literature Search Strategy

A search of published literature was conducted using PubMed, Clinical Key, Scopus, South African ePublications and Google Scholar. Keywords used in a variety of combinations were: Cutaneous Sarcoidosis, Clinical patterns of cutaneous sarcoidosis; cutaneous sarcoidosis in sub-Saharan Africa; co-existence of HIV/AIDS and sarcoidosis. The websites of the National Health Laboratory Service (NHLS) and Statistics South Africa (Stats SA) were also searched for relevant information. Electronic journals were accessed using the University of the Witwatersrand and the Walter Sisulu University online facility. All the articles retrieved were in English.

1.2.3. Clinical manifestations and Trends in the epidemiology

i. Definition

Sarcoidosis is a multi-organ granulomatous disorder with no known cause (6). This disease has variable clinical manifestations, with the skin as the second most frequently affected organ (20 - 35% of the cases on average) (3), preceded only by the respiratory system (3, 14, 27). A table (Table 1.1) highlights a list of other organs affected in order of frequency. The skin manifestations of sarcoidosis are categorized as "specific" (non-caseating granuloma present in biopsy specimen of tissue) or "nonspecific" (lesions develop as a result of a reactive process) (Table 1.2) (4). Race, age and gender have an influence on the manifestations of sarcoidosis, resulting in variations in incidence (28, 29). A number of studies show that the presence or absence of granulomatous cutaneous involvement has no prognostic significance (30, 21).

Table 1.2 Cutaneous Manifestations Of Sarcoidosis (adapted from Heath *et al.* 2012 (11))

Specific skin lesions		Non-specific skin lesions
Distinct lesions	Non-distinct lesions	<u>Erythema nodosum</u>
Papules	Subcutaneous nodules	Calcification
Plaques	Hypopigmented macules	Prurigo
Lupus pernio	Ulcerative sarcoidosis	Dactylitis
Scar sarcoidosis	Psoriasiform lesions	
	Alopecia and nail sarcoidosis	
	Ichthyosiform presentation	
	Erythrodermic presentation	

The most common specific cutaneous lesions are maculo-papules, plaques, subcutaneous nodules, lupus pernio and scarsarcoidosis (4). The site of predilection for maculo-papular eruptions is the face, anterior chest, extremities, and the mucosa. Erythema nodosum (EN) is the most frequent non-specific cutaneous presentation and is associated with an acute presentation, good prognosis and spontaneous resolution (31, 22). This presentation consists of a painful, red and elevated subcutaneous nodule, characteristically on the anterior aspect of the legs. As the nodules involute, residual post-inflammatory hyperpigmentation is seen. There is an ethnic difference as these lesions are seen less frequent in Blacks and Asians. EN and bilateral hilar lymphadenopathy on the chest x-ray are a constellation of features that is termed Löfgren's syndrome.

Papular lesions and subcutaneous nodules are more often associated with remission of extra-cutaneous disease at twenty four months, while plaques and, mainly, lupus pernio are considered predictive features of chronicity (33, 22). The majority of cutaneous lesions of sarcoidosis are mild and treatment may not be required. However, lupus pernio (LP) is a chronic, disfiguring skin lesion and can have a strong psychosocial impact (4, 31, 32). LP is frequently associated with upper respiratory involvement and pulmonary fibrosis. The primary pattern arises *de novo* or from established sarcoid-specific lesions. This characteristic

primary pattern of presentation occurs with a raised erythematous or violaceous infiltrate, with the site of predilection being the head and face (33).

Skin sarcoidosis has an unpredictable natural course (2).

ii. Epidemiology

• Global trends

An increase in reports on case series of sarcoidosis led to better definitions and diagnostic tools, improving the determination of incidence and outcome of the disease (12,17, 21, 22, 24). Sarcoidosis may appear at any age, with bimodal peaks at age 20 - 40 years and 40 - 59 years (18). African American patients have an increased incidence of 4:1 compared to the White population, with a female predominance (8, 10, 14). Rybicki and colleagues conducted a study on a military veteran population which was racially heterogeneous, and found the highest incidence in female African Americans compared to Caucasian females (29 versus 12 per million) (13). There is an increased familial prevalence, particularly in African American patients (34) but genetic associations remain unknown (20).

Skin involvement occurs mainly at the onset of disease. A study reviewing specific cutaneous lesions in southern Europe reported that skin lesions manifest in 30% of patients with sarcoidosis and are subsequently followed by systemic involvement in a period of one month to a year (4). The risk of progression from primarily isolated skin lesions to systemic involvement is not known.

• Sub-saharan African Cutaneous Sarcoidosis trends

Studies on the cutaneous manifestations of sarcoidosis are limited in Africa. The profile of sarcoidosis has been studied in Nigeria and Ethiopia. The most common clinical picture reported was that of sarcoidal infiltration of scarification marks. Facial maculo-papular lesions also were frequently present (23, 35, 36).

• South Africa

The frequency of the skin types described by Jacyk (17) in Black South Africans showed similarities to those in the general population with sarcoidosis. A comparative study of

sarcoidosis (19) conducted among the racial groups in South Africa found an increase in frequency and much more florid cutaneous manifestations of sarcoidosis amongst the non-White population. In addition, a more atypical nonspecific spectrum is reported, including hypopigmented, ichthyosiform, mutilating, ulcerative chronic and severe lesions. In contrast, EN (nonspecific) was reported to be the most frequent finding amongst the White population in South Africa, as in the European population. Lupus pernio associated with systemic involvement, together with subcutaneous lesions, was amongst the least common in the non-White community (19). Studies done in South Africa on the cutaneous spectrum of sarcoidosis have been case reports (37, 38) and a small case series (39) describing a subset in the spectrum of cutaneous sarcoidosis. The last cohort study was concluded almost two decades ago (17). The pattern of presentation in the Black Africans described as florid and disfiguring is an unusual manifestation of cutaneous sarcoidosis (15). One may argue that there is no statistical significance of the findings in the South African literature as these were single case reports (38) or small case series (37, 39) over a short-term follow-up period. However, these associations are important to study further and may represent opportunities for further research.

Sarcoidosis was ranked the 50th most common dermatological disease in 2003 in Johannesburg in a survey of dermatological outpatients in the five academic hospitals serving the public sector in the Johannesburg area (40). Other studies on cutaneous sarcoidosis done in South Africa demonstrated differences in the disease pattern, frequency, degree and laboratory findings (17, 19, 41). However, the paucity of recent epidemiologic studies limits the true incidence and prevalence of this disease in South Africa.

1.2.4. Aetiopathogenesis

Various trigger factors have been implicated as promoting this granulomatous inflammatory response. Recently, mycobacteria and propionibacteria, which demonstrate a similar histopathological granulomatous process, have been implicated (31). However, as the microbiology techniques that yield mycobacteria have become more widely available to diagnose tuberculosis, it is now clear that tuberculosis is not a variant of sarcoidosis (6). The granulomas formed include oligoclonal CD4 T cells that have been stimulated by an unknown sarcoidal antigen, giving the characteristic histologic feature of non-caseating granulomas in multiple organ systems (5). The core, highly organized granuloma, comprises macrophages and epithelioid cells in 100% of the cases, surrounded by giant cells in 97%, and scanty lymphocytes, which are predominantly CD4 positive, in 71% of the cases. Other cellular

types include neutrophils associated with necrosis. Asteroid bodies and Schaumann bodies are seen in a minority of cases. These changes are less sensitive and are nonspecific markers of sarcoidosis (42, 43). Rarely, varying degrees of necrotic changes are found in the histopathological specimen (44, 45). Of note, there are no significant histopathological differences found between cutaneous sarcoidosis and extra-cutaneous sarcoidosis (42).

1.2.5. Immunology

The pathogenesis of sarcoidosis involves the contribution of a wide range of cellular components of the immune system, including lymphocytes, macrophages and antigen-presenting cells. A cascade of reactions mediated and co-ordinated by various cytokines and chemokines are implicated in the disease process. Data suggests that a pro-inflammatory cytokine, tumour necrosis factor-alpha (TNF- α) in particular, is not only required to stimulate the formation of a granuloma in response to an antigen, but sustains the existence of the granulomatous process (46, 47). This observation is an important consideration in the light of the commercially available monoclonal antibodies against TNF- α as a therapeutic option (46, 48).

1.2.6 Diagnosis

In the early seventies, very few diagnostic indicators were used, i.e., a suspicious lesion, a suspicious chest X-ray (CXR) or hand X-ray (HXR), or a granulomatous histological specimen which did not exclude other granulomatous aetiological agents (19). These methods opened gaps for misdiagnosis of cutaneous sarcoidosis. How the diagnosis is made and how it relates to the treatment of choice in the 21st century needs further exploration.

The diagnostic process of sarcoidosis is complex; therefore a correct diagnostic workup which includes clinical, radiologic, and histopathological evaluation needs to be done. Histology of sarcoidal lesions demonstrates a granulomatous reaction pattern characterized by multiple discrete, predominantly epithelioid, granulomas without necrosis, the so-called “naked” granulomas, which are surrounded by sparse lymphocytic infiltrate and mild fibrosis (44, 45).

The definitive diagnosis of cutaneous sarcoidosis has to include: compatible skin and clinical or radiological features, together with one or more biopsy specimens that demonstrates non-caseating granulomas, as well as exclusion of other aetiologies of granulomatous diseases

such as tuberculosis or deep fungal infections (6, 10, 22, 28,49). American authors Sanchez *et al.*, developed a simple step ladder approach towards the diagnosis of sarcoidosis (32). This approach is easy to use, assists towards making a focused diagnosis, and provides guidance that will eliminate unnecessary delays towards a definitive diagnosis. **Figure 1.1** elaborates on the step-wise approach to diagnosis of sarcoidosis.

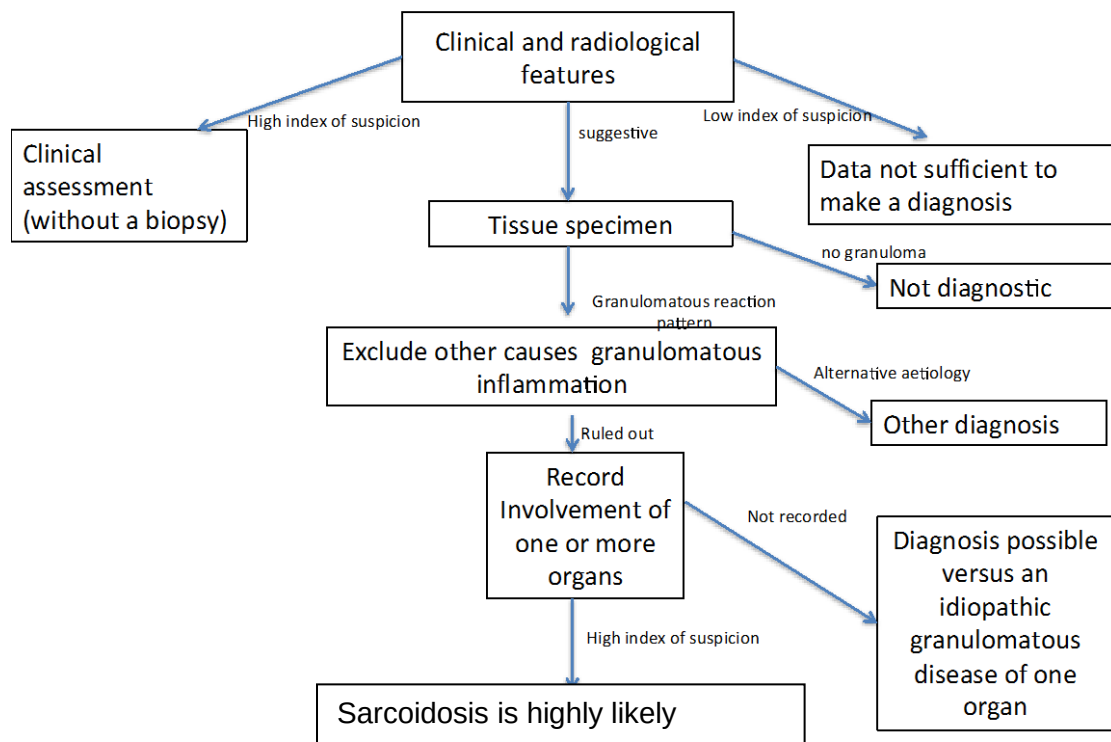


Figure 1.1 Step-wise approach to diagnosis of sarcoidosis (adapted from Haimovic A.*et al.* 2012 (71))

Genetic aspects of sarcoidosis supporting the familial predisposition in the context of case control study designs address a component of genetic epidemiology of quantifying the familial risk (20). Harrington *et al.* described 19% of the African American population and 86% of Caucasians with a positive family history of sarcoidosis (50). Even with the current advances in the study of genetic components associated with sarcoidosis, the data remains elusive.

1.2.7 The impact of HIV/AIDS pandemic on the clinical manifestation of cutaneous sarcoidosis

Anecdotal reports in recent international literature of the co-existence of sarcoidosis and HIV/AIDS describe the relationship of the clinical manifestations of sarcoidosis being inversely proportional to the CD4 count (51-53). However reports fail to demonstrate any correlation with the pattern, severity or chronicity of this disease in this population.

The granulomatous reaction pattern of sarcoidosis has been implicated to depend on CD4 T-helper lymphocytes, but infection with HIV depletes these cells and attenuates the expression of sarcoidosis. Morris *et al.*, American authors, conducted one of the largest studies of HIV seropositive cases with sarcoidosis in 2003. The findings strongly suggest that a raised level of cellular immunity is needed for HIV seropositive individuals to manifest the granulomatous response to the sarcoid agent, unlike mycobacteria or chronic infection (54, 55). The clinical manifestations of sarcoidosis occur either coincidently with, or following, a diagnosis of HIV seropositivity. The CD4 lymphocyte count was recorded as more than 200 cells/ μ L at the time of the clinical presentation with granulomatous inflammation.

In about 50% of cases initiated on HAART, there is manifestation of an immune reconstitution inflammatory syndrome (IRIS) phenomenon (56, 57). Although rare, clinicians should be aware of the appearance of sarcoidosis lesions in HIV-infected individuals whose immune systems have improved with the initiation of HAART (51, 53, 58). The clinical, radiographic, and pathologic features of sarcoidosis in the context of pre-existing HIV infection are reported to be similar to the well-known features of sarcoidosis in non-HIV-infected individuals (54).

- **South Africa**

More studies are necessary to elucidate the relationship of HIV and cutaneous sarcoidosis especially in the South African setting, where 7.1 million people currently live with HIV (70).

1.2.8 Management

With the available treatment options, patients can go into remission for long periods, but treatment of sarcoidosis still remains a challenge (39). The decision to initiate therapy in an individual with cutaneous sarcoidosis is determined by how extensive or disfiguring the

presentation is. It can also be limited by other co-existing disease entities such as hypertension, diabetes and renal insufficiency, that increase the side-effect profile of the drug used or exacerbate the existing co-morbid condition (e.g. the use of systemic steroids can cause hypertension and hyperglycaemia; methotrexate can cause renal toxicity (Table 1.3)). A multidisciplinary approach is crucial for optimal management. There is a paucity of double-blinded randomized control studies. However, the first-line standard therapy for mild to severe skin lesions includes topical, intra-lesional and systemic corticosteroids. Topical steroids or intra-lesional steroids are first-line therapeutics for an isolated or non-threatening sarcoidal lesion (59, 60). Oral corticosteroids are the therapeutic agents that are preferred for rapidly progressive cutaneous sarcoidosis eruptions, in combination with topical therapy for poorly responsive lesions (30, 61). Other anti-inflammatory and immunosuppressive agents may be prescribed as monotherapy or as adjuvant to slowly reduce the dose of corticosteroids (34). The table (**Table1.3**) below highlights the current therapeutic agents available for use.

Table1.3 Cutaneous sarcoidosis treatment (adapted from Heath CR. *et al.* 2012 (11))

Drug therapy	Evidence based category	Side effects
Topical corticosteroids	2	Hypopigmentation, thinning of the skin
Intra-lesional corticosteroids	2	Hypopigmentation, thinning of the skin
Systemic corticosteroids	2	Short term: Gastric irritation, increased appetite, mood disturbances. Long term: osteoporosis, hypertension, acne, hyperglycemia, Cushing syndrome
Antimalarial	1 chloroquine 2 hydroxychloroquine	Short term: corneal opacity, central retinopathy, visual field disturbances. Long term: bleaching of hair, agranulocytosis.
Methotrexate	2	Liver toxicity, kidney toxicity, gastric disturbances

Level 1 = prospective clinical study with >20 cases, lacking adequate controls

Level 2 = small clinical study with < 20 cases with significant design limitations, retrospective

Steroid-sparing agents frequently used are anti-malarial agents and methotrexate (11). Co-administration of corticosteroid-sparing agents and topical steroids are beneficial in accelerating dose reduction of systemic steroids (32).

A proposed algorithm by an American author, Haimovic, is an easy guide to managing patients with cutaneous manifestation of sarcoidosis (31). The latest treatment modalities,

including tumor necrosis factor alpha inhibitors (TNF- α inhibitors), have been shown to be of benefit in recalcitrant sarcoidosis subtypes (46). TNF- α inhibitors target the release of the TNF molecule that plays a role in the formation and sustainability of the non-caseating granuloma (46, 47). The **Figure 1.2** elaborates on the management approach proposed.

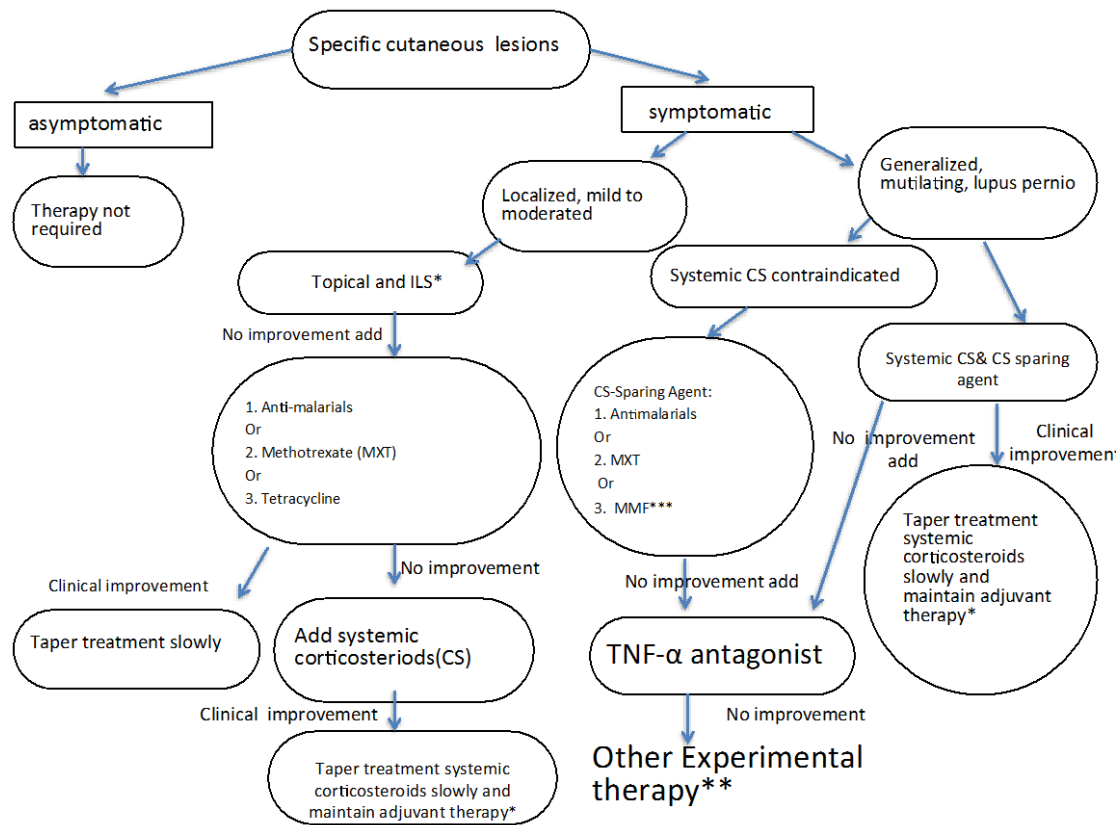


Figure 1.2: A proposed therapeutic ladder for the treatment of skin sarcoidosis (adapted from Haimovic A. *et al.* 2012 (31))

* Intra-lesional steroids

**Experimental therapy including: laser ablation, surgery; ultraviolet therapy

***Mycophenolate mofetil

CS = corticosteroids

1.2.9. Conclusion

Although recent statistics show a more defined approach in the description of the cutaneous spectrum of sarcoidosis, there are still gaps in the South African literature, particularly since

the last South African study was published 18 years ago. Poor access to healthcare, as well as migratory patterns, may have had an influence on epidemiological trends of cutaneous sarcoidosis in this country. The patterns, chronicity and severity associated with systemic involvement may change as access to healthcare in the post-apartheid era has improved.

CHAPTER TWO

METHODOLOGY

2.1. Introduction

The purpose of this chapter is to provide information on how this investigation was carried out. The target population, sampling, research design, data collection methods, data analysis and ethical considerations are discussed in this chapter.

2.2. Study design

This is a descriptive retrospective study.

2.3. Study setting

The Division of Dermatology in the Department of Internal Medicine at the University of the Witwatersrand in Johannesburg, South Africa, offers dermatological care to patients in a number of public hospitals, one of which is Chris Hani Baragwanath Academic Hospital (CHBH). The clinic is staffed by three registrars, one medical officer, a specialist dermatologist, two staff nurses and two enrolled nurses. The health personnel are assisted by visiting nursing students from CHBH Nursing School. An average of 400-800 patients a month attend the Dermatology Clinic, and skin biopsies are performed on all new patients where a definitive clinical diagnosis cannot be made.

2.4. Study population

The study was conducted at a tertiary academic institution, Chris Hani Baragwanath Academic Hospital (CHBH), located in Gauteng. CHBH provides healthcare to a large drainage area in the south of Johannesburg (Figure 3) i.e. Soweto and its neighbouring

townships, Lenasia and Eldorado Park. CHBH is a 3000+ bed hospital serving a catchment population of 1.3million in Soweto, where 40% of the population in Johannesburg resides.



Figure 2.1 Map showing the study area (Source: Google Maps)

2.5. Selection criteria and sample size

This study focused on South African residents who reside in the CHBH drainage area (as described above) who presented to the Dermatology outpatient department with cutaneous manifestations of sarcoidosis. The study specifically reviewed the medical records of those patients that were seen at the Dermatology outpatient clinic at their first visit and those referred from the Pulmonology outpatient clinic with extra-cutaneous involvement and suspicious skin lesions suggestive of sarcoidosis. A total of 100 files of patients of all ages, fulfilling the definitive diagnosis of cutaneous sarcoidosis, with or without systemic involvement, were included. This study spans from 1991 to 2015. Further information was obtained from the history and clinical findings that were provided for the histology specimens submitted to the National Health Laboratory Services (NHLS).

2.6 Data collection (see Appendix A for the data collection sheet)

Patients were included if the records showed features compatible with a diagnosis of sarcoidosis and the exclusion of other granulomatous diseases. The data extracted also

included findings from the history, physical examination and laboratory tests. Some clinical characteristics of patient information collected demonstrate the chronicity and severity of the disease progression, an evaluation of the number of areas involved, including the extent of lung involvement which was assessed by using information from two of the three methods (10) used to determine the extent of lung involvement (Appendix A, page 58) i.e. these methods included: chest radiography (CXR) findings including radiographic staging and high resolution computerized tomography (HRCT) scans (Appendix A, page 58). The grading of dyspnoea, as a third method to evaluate the extent of lung involvement, was not extracted from the records. In addition, the histopathology data extracted comprised reports by designated pathologists who made a clinicopathological conclusion consistent with sarcoidosis. The site of tissue obtained for histological confirmation was recorded, as well as the organ systems involved (i.e. skin, lung, eye, lymph node and other organs).

2.6.1 Measurements

Information regarding patients' demography (gender, age, race), duration of disease, age of onset, occupations, clinical data on the distribution and the extent of disease, treatment modality and the type of cutaneous manifestation of sarcoidosis was extracted from the patient files and transferred into a data collection sheet (attached). In addition, biopsy data, radiological data (chest X-rays (CXR), hand X-rays (HXR), high resolution computerized tomography (HRCT)) and pulmonary function tests were recorded. Particular attention to exclude patients with other granulomatous diseases was ensured.

Methods used in histological specimens to exclude other granulomatous disease aetiologies included the use of special stains (Periodic acid–Schiff (PAS), Grocott, Ziehl-Neelsen and FITE stains) to exclude tuberculosis and deep fungal infections, and the GeneXpert polymerase chain reaction test to exclude tuberculosis. Sputum for acid-fast bacilli (AFB), where appropriate, was negative. Tissue samples were considered compatible with sarcoidosis if they demonstrated non-caseating granulomas without evidence of other granulomatous disease aetiologies. Organ involvement (cutaneous and extra-cutaneous) was determined in each patient, based on the information obtained from the records such as history, physical examination, and laboratory testing. The radiological findings were recorded as normal or abnormal, and the CXR evaluated using the Scadding criteria. The Scadding criteria, is a chest radiographic staging system used in sarcoidosis and is defined as follows: Stage 0:

normal chest X-ray; Stage I: hilar lymphadenopathy alone; Stage II: hilar lymphadenopathy plus interstitial lung disease; Stage III: interstitial lung disease alone; and Stage IV: lung fibrosis. The findings of HRCT scans, where performed, were noted. Spirometry was recorded as obstructive, restrictive or normal. Blood investigations, including complete blood count, liver functions, serum angiotensin converting enzyme (ACE) and calcium were extracted and interpreted according to the reference ranges of the local laboratory (NHLS). Other investigations included electrocardiograms (ECG) and ophthalmological examinations. CD4 counts and HIV viral loads were recorded for HIV seropositive patients.

Chronicity of cutaneous sarcoidosis was determined by examining the clinical outcomes of the lesions. The follow-up was determined with a guide from Marcoval *et al.* (22) of active lesions over a period of more than 24 months.

2.8 Data entry

Information was collected by the investigator making use of a data collection sheet recording the following: year of diagnosis, age at diagnosis, gender, race, occupation. It was then captured into a Microsoft Excel spreadsheet for data cleaning and coding purposes.

2.9 Data analysis

The data were coded and entered into Microsoft Excel (MS Excel) and later transferred into the Statistical Package for IBM Social Science (SPSS) version 21, 2016; for the purpose of analysis. Descriptive analyses (means, percentages, frequency, tables and graphs) were carried out to summarise demographic characteristics of patients and categorical variables such as race, gender, histology, HIV status, organ involvement and cutaneous lesions. Bivariate analysis was performed to examine the relationship between independent variables (age, gender, and race) and dependent variables (clinical presentations and organ involvement). P-values less than 0.05 were deemed significant. Results are presented with tables and charts.

2.10 Ethical approval and other considerations

Approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. Protocol number: M 150237 (Appendix B). Data for this research will only be for the purpose of this study. To ensure confidentiality and anonymity of the participants, code numbers were used during data processing and reporting. Consent was obtained from the Chief Executive Officer and Heads of the Departments of all clinics at Chris Hani Baragwanath Academic Hospital.

2.11 Conclusion

This chapter provides information on how this study was carried out, whereby the methods include the target population, sampling, research design, data collection methods, and data analysis. The following chapter reports the results that were obtained during the conduction of the thesis.

CHAPTER THREE

RESULTS

3.1 Introduction

This chapter presents the findings of this study. The findings are presented according to the study objectives with the use of tables and charts.

3.2 Demographic characteristics

Data were available for 100 patients with cutaneous sarcoidosis during the study period 1991-2015. Eighty-three participants were women and 17 were men. As shown in **Figure 3.1**, the age range of patients was 20 - 79 years. In males, the age group 40-49 years was the most affected, whilst female patients in the age group 50-69 years was most affected.

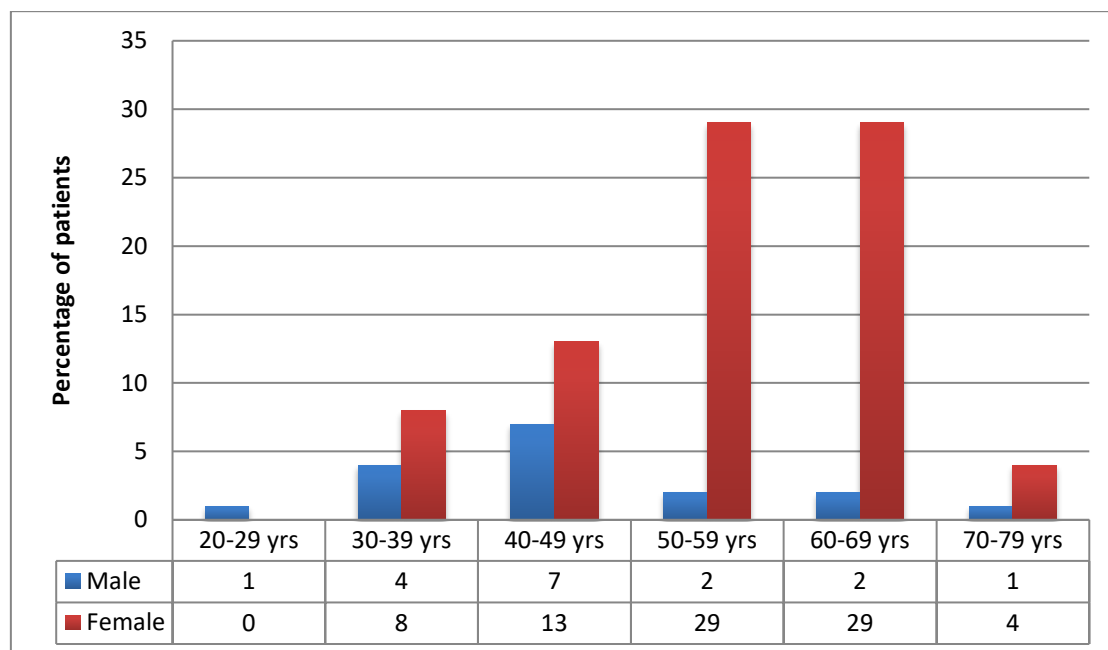


Figure 3.1: Percentage of patients with cutaneous sarcoidosis by age and sex

3.3 Distribution of patients with sarcoidosis by occupation

Unfortunately, the majority of patients (n=75) did not have any occupational status recorded, making any statistical conclusions regarding occupational associations impossible.

Most of the female patients with sarcoidosis were above the age of 45 years. Ninety-six patients were Black Africans and four were Asians, in keeping with the demographics of the geographic region served by the hospital. Therefore this study reflects data of Black patients mainly.

3.4 Demographic characteristics of patients and clinical cutaneous manifestations

The most common specific skin lesions were papules and plaques (see **Table 3.1**). Of the enrolled patients, 68 had papules, 28 plaques, 17 subcutaneous nodules, and 11 lupus pernio. Only one patient presented with psoriasiform cutaneous lesions. Although there are marked differences in the proportion of male to female patients, there appears to be no significant differences in the manifestations by gender. Papules (68.8%) and plaques (27.1%) were the most common specific cutaneous lesions in Black African patients. Of the four Asians, only one presented with papules, two with plaques and the other presented with scar sarcoidosis.

Table 3.1: Types of cutaneous lesions by gender and race

Types of cutaneous lesions	Total n=100 (%)	Gender		Race	
		Male n=17 (%)	Female n=83 (%)	Black African n=96 (%)	Asian n=4 (%)
Papules	68 (68.0)	8 (47.1)	60 (72.3)	67 (69.8)	1 (25.0)
Plaques	28 (28.0)	5 (29.4)	23 (27.7)	26 (27.1)	2 (50.0)
Scar	4 (4.0)	1 (5.9)	3 (3.6)	3 (3.1)	1 (25.0)
Lupus Pernio	11 (11.0)	1 (5.9)	10 (12.0)	11 (11.5)	---
Psoriasiform	1 (1.0)	---	1 (5.9)	1 (1.0)	---
Subcutaneous Nodules	17 (17.0)	6 (35.3)	11 (13.3)	17 (17.7)	---
Hypopigmented Macules	3 (3.0)	---	3 (3.6)	3 (3.1)	---
Ulcerative	4 (4.0)	---	4 (4.8)	3 (3.1)	1 (25.0)
Erythrodermic	1 (1.0)	---	1 (1.2)	1 (1.0)	---
Ichthyosiform	---	---	---	---	---
Sarcoid (Alopecia) and Nails	3 (3.0)	--	3 (3.6)	3 (3.1)	---
Prurigo	5 (5.0)	1 (5.9)	4 (4.8)	4 (4.2)	1 (25.0)
Dactylitis	12 (12.0)	1 (5.9)	11 (13.3)	12 (12.5)	---

The study also examined the association between cutaneous manifestation and age. As shown in **Figure 3.2**, about 70% of the age group 45 years and above presented with papules, compared to 59.1% of the age group less than 45 years. There was no statistically significant difference between the cutaneous lesions and the age of patients, except for subcutaneous

nodules. Patients aged less than 45 years were more likely to present with subcutaneous nodules compared to older patients (relative risk 2.7; CI 95% [1.3, 5.4]; p=0.012).

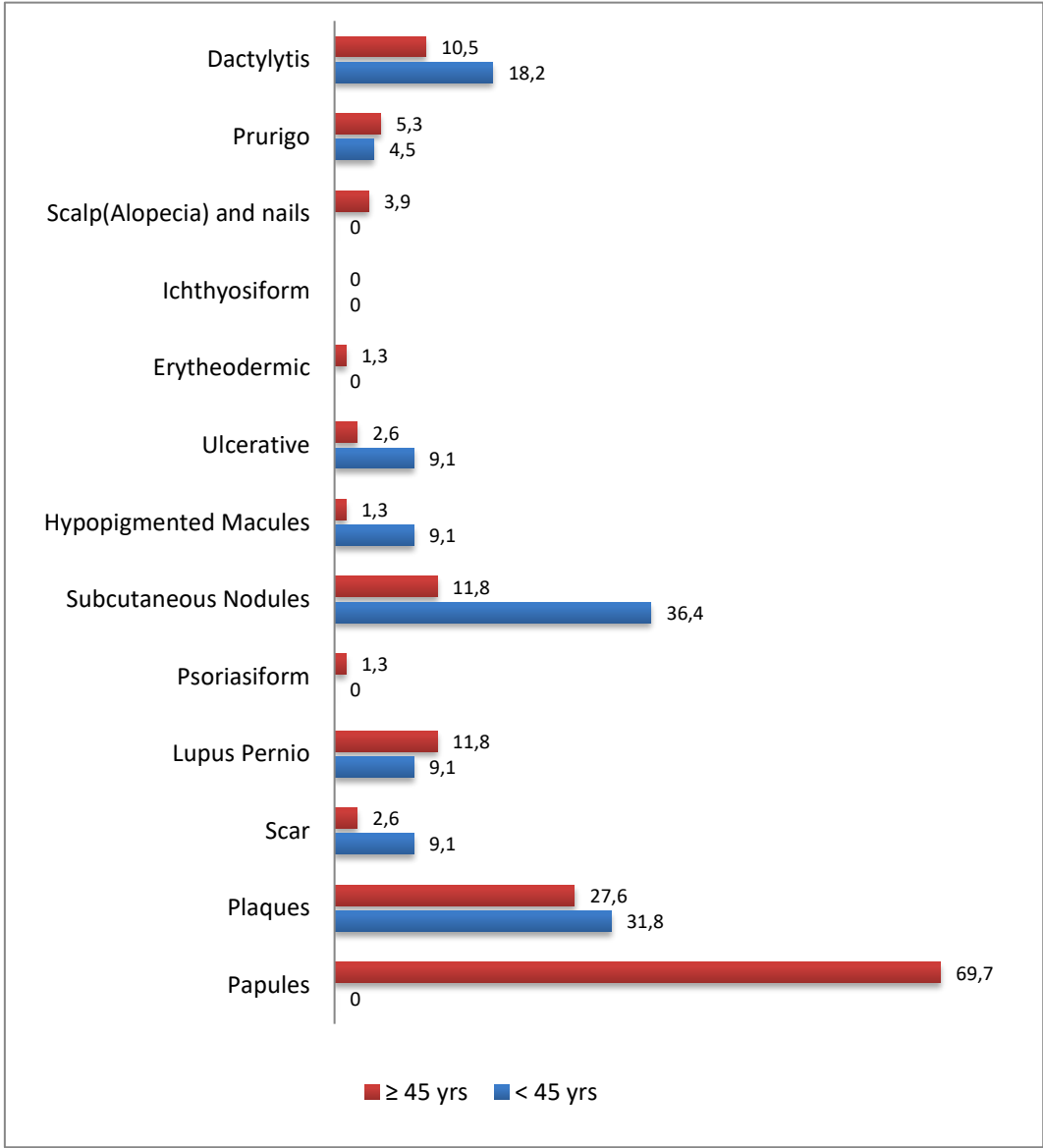


Figure 3.2: Types of cutaneous lesions by age (years)

yr = years

3.5 Extra-cutaneous organ involvement

This study also examined the patterns, severity and chronicity of cutaneous manifestations in sarcoidosis patients and the findings are presented in this section. Patterns of presentation are interpreted in relation to extra-cutaneous involvement, the extent of involvement, the number of organs involved, and the outcomes post therapy or in response to therapy. As shown in

Figure 3.3, the most frequent extra-cutaneous organ involvement is lung involvement in 53 cases, eyes 14 cases, bone/joint 10 cases, lymph nodes and the liver 8 cases each, spleen 6 cases, nervous system and the heart 3 cases each, mucosa 2 cases. Kidney and bone marrow were observed in one case each in each organ.

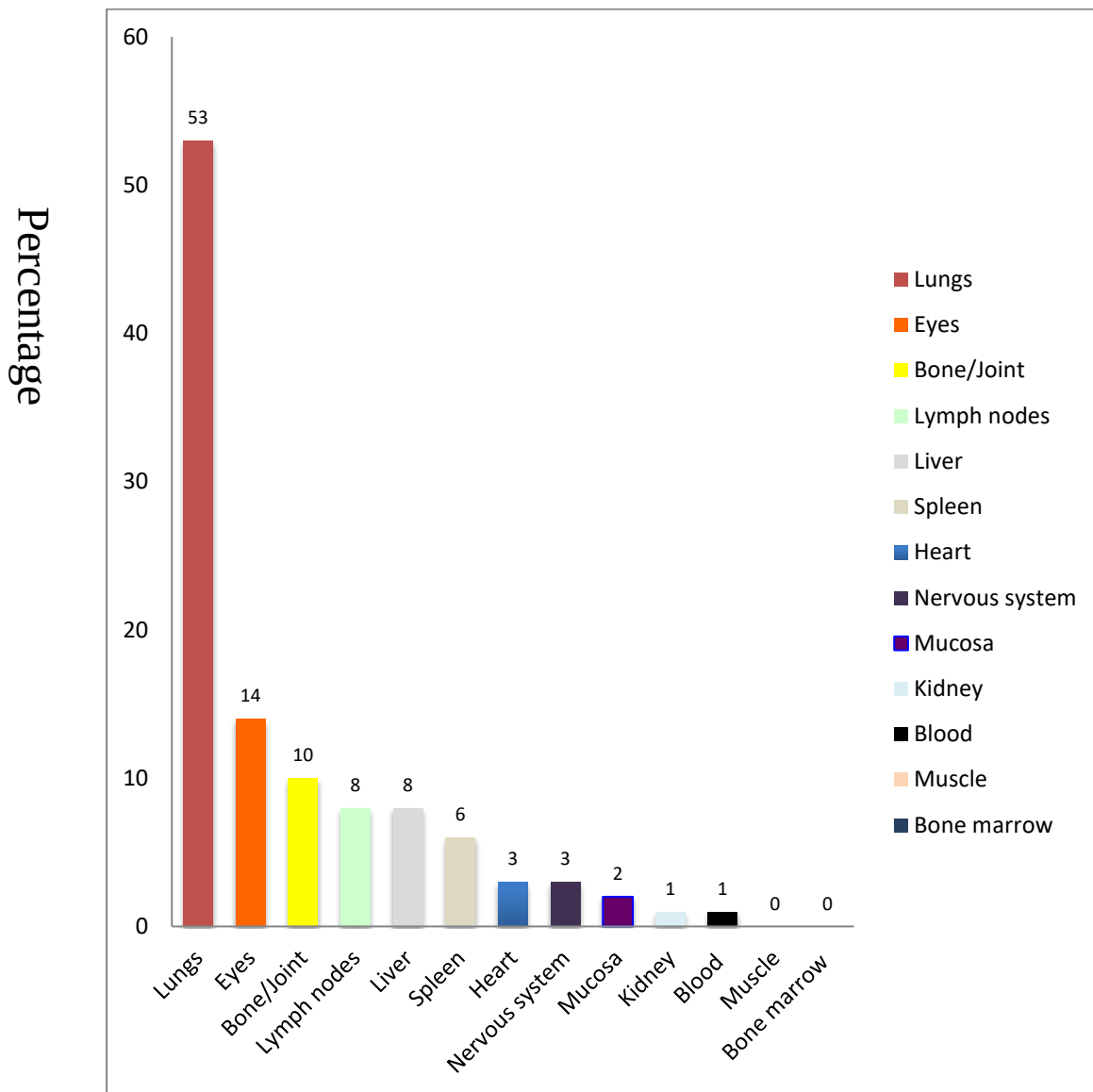


Figure 3.3: Extra-cutaneous organ involvement

3.5.1 Number of organs involved

As indicated in **Figure 3.4**, 36% of the cutaneous sarcoidosis patients had only skin involvement. Similarly, 36% of the cutaneous sarcoidosis patients had two organs involved.

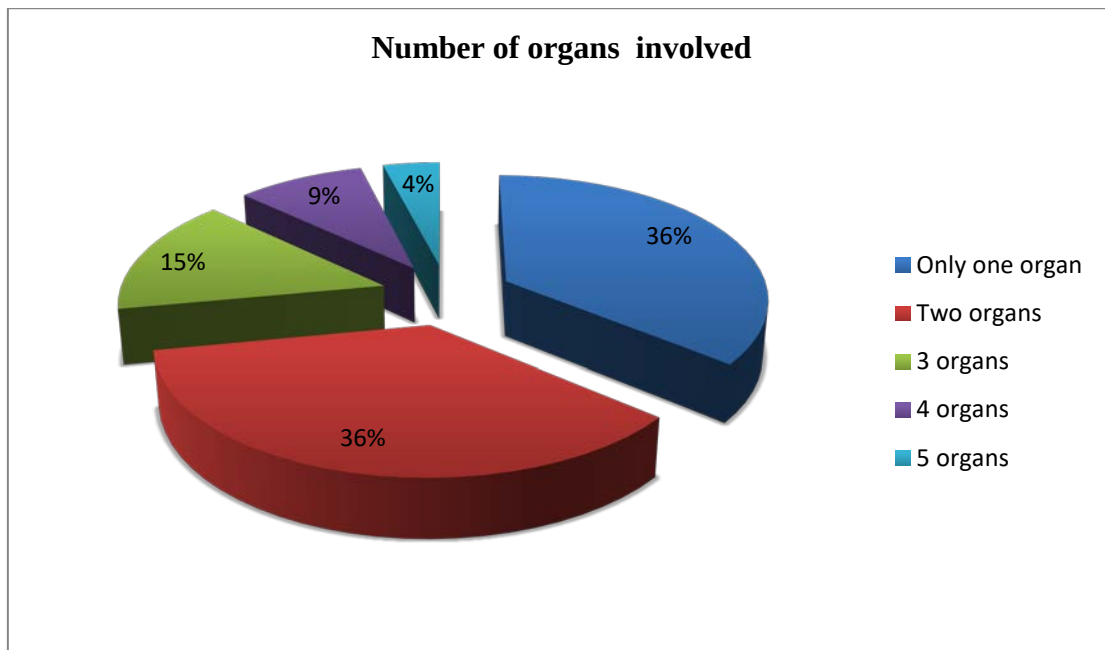


Figure 3.4: Number of organs involved

Of the patients with two organs involved, the skin and lungs were the most common organs involved (29 of 36). **Table 3.3** below elaborates on the number of organs involved.

Table 3.3: Patients with three organs involved

Organs involved	Number of patients
Skin, lymph nodes, and bone and joints	2
Skin, lungs and eyes	7
Skin, lungs and lymph nodes	1
Skin, lungs, and heart	1
Skin, lungs, bone and joints	3
Skin, lungs, and spleen	1

3.5.2 Patients with four and five organs involved

Only nine patients had four organs involved. Four percent of the cutaneous sarcoidosis patients had five organs involved.

3.5.3 Association of demographical characteristics and number of organ involvement

The relationship between demographic characteristics and the number of organs involved was examined and the results are presented in **Table 3.4**. There was no significance difference in number of organs involvement and patients' age or sex.

Table 3.4: Number of organs involved by age, gender and race

Organ involvement	Sex		Race			Age	
	Male n=17 (%)	Female n=83 (%)	Black n=96 (%)	African	Asian n=4 (%)	Age <45	≥45
Only one organ	2 (11.8)	34 (41.0)	36 (37.5)		0 (0.0)	8 (36.4)	26 (34.2)
Two organs	10 (58.8)	26 (31.3)	33 (34.3)		3 (75.0)	7 (31.8)	29 (38.2)
Three Organs	2 (11.8)	13 (15.7)	15 (15.6)		0 (0.0)	4 (18.2)	11 (14.5)
Four organs	3 (17.6)	6 (7.2)	9 (9.4)		0 (0.0)	2 (9.1)	7 (9.2)
Five organs	0 (0.0)	4 (4.8)	3 (3.1)		1 (25.0)	1 (4.5)	3 (3.9)

3.5.6 Extra-cutaneous organ involvement by specific type lesion

The study also examined the association between organ involvement and patterns of cutaneous manifestation. The results are presented in **Table 3.5**. Of the 53 patients with lung involvement, the most common cutaneous pattern was papules (n=39). The second most common pattern was plaques (n=20). Regardless of organ involvement, papules remained the most common pattern of clinical presentation as shown in **Table 3.5**

Table 3.5: Extra-cutaneous organ involvement by specific type lesion

	Lung	LN	Eyes	Nervous	BM	BV	Heart	Bone/joint	Muscle	Liver	Spleen	Mucosa	Kidney
	n=53	n=8	n=14	n=3	n=0	n=1	n=3	n=10	n=0	n=8	n=6	n=2	N=1
Papules n=68	39	4	10	2	0	1	2	5	0	6	5	2	1
Plaques n=28	20	1	3	1	0	0	0	3	0	2	1	0	0
Lupus n=11	6	0	0	1	0	0	1	0	0	0	0	1	0
Scar n=4	3	0	0	0	0	0	0	0	0	1	1	0	0
Subcutaneous n=16	7	4	3	0	0	0	1	2	0	2	1	0	0

LN- lymph node; BM- bone marrow; BV- blood vessel

3.6 Clinical patterns of cutaneous sarcoidosis and the chest X-ray findings

Pulmonary involvement was assessed using the method of radiographic staging (Scadding criteria) and pulmonary function tests. The majority of cases were classified as Stage 0 or 1 according to the Scadding criteria. Only four patients were in radiographic Stage 4. The patterns of clinical presentation were not associated with the degree of lung involvement. **Table 3.6** below elaborates.

Table 3.6: Pattern of clinical presentation by chest X-ray finding

Cutaneous presentation	Staging by CXR (Scadding criteria)				
STAGE:	0	1	2	3	4
Papules n=58	15	23	9	8	3
Plaques n=26	4	12	4	4	2
Scar n=3	1	2	0	0	0
Lupus Pernio n=8	1	5	1	1	0
Psoriasiform n=1	0	0	1	0	0
Subcutaneous Nodules n=17	8	4	3	2	0
Hypopigmented Macules n=3	0	2	0	1	0
Ulcerative n=4	0	4	0	0	0
Erythematous n=1	1	0	0	0	0
Scalp (alopecia) and nails n=2	0	1	1	0	0
Prurigo n=4	3	1	0	0	0
Dactylitis n=10	4	2	2	0	2

The pulmonary function test results showed that 45 patients had normal lung function. Of the 41 patients with an abnormal lung function, 19 patients had restrictive lung function, 19 patients had obstructive lung function, and only 3 patients had mixed pattern lung function. There were no records of pulmonary function tests for 14 patients.

3.7 Chronicity of cutaneous sarcoidosis

Active lesions with progression (worsening) and active lesions with no change (static) while on therapy that were found on record were classified as not resolved. Lesions that were recorded as absent and then reappear post-therapy were recorded as waxing and waning. Of all the patients, there was complete resolution in 28 patients over 24 months, waxing and waning in 33 patients, static involvement in 12 patients, and worsening lesions in 2 patients. Clinical outcomes could not be determined in 25 patients due to inadequate records.

The study also examined the clinical outcomes by patterns of presentation (**Table 3.7**). Of the patients that presented with papules (n=69), there was complete resolution in only 17. A significant proportion of patients that presented with papules had either static involvement (10 patients), waxing and waning (24 patients), or worsening (2 patients).

Of the 28 patients presenting with plaques, waxing and waning lesions were the most common pattern. However, for the four patients that presented with scar sarcoidosis, there was complete resolution in two. Patients that presented with lupus pernio presented with waxing and waning or with static lesions. Complete resolution was common only in patients who presented with subcutaneous nodules.

Table 3.7: Clinical outcomes of sarcoidosis patients according to patterns of presentation

Patterns of presentation	Clinical Outcomes				
	Wax & wane	Static	Worsening	Resolved	Undetermined
Papules n=69	24	10	2	17	16
Plaques n=28	11	2	0	5	10
Scar n=4	1	0	0	2	1
Lupus pernio n=11	5	2	0	2	2
Psoriasiform n=1	0	1	0	0	0
Subcutaneous nodules n=17	4	1	0	8	4
Hypopigmented macules n=3	2	0	0	0	1
Ulcerative n=4	1	0	0	1	2
Erythrodermic n=1	0	0	0	1	0
Scalp (alopecia) and nails n=2	3	0	0	0	0
Prurigo n=5	3	1	0	1	0
Dactylitis n=12	7	2	0	3	0

The clinical outcomes of cutaneous sarcoidosis patients were examined in relation to the number of organs involved. There was complete resolution in 7 of the 36 patients with only skin involvement. The rest were either waxing and waning or no change (static) in nature.

Of the 36 patients with skin and one more organ involvement, there was complete resolution in 10 patients. However, there was no record to determine clinical outcomes in 14 patients with skin and one more organ involvement. **Table 3.8** demonstrates the clinical outcomes of sarcoidosis patients based on the number of organs involved

Table 3.8: Clinical outcomes of sarcoidosis patients based on the number of organs involved

No. of systems involved	Outcomes				
	Waxing & waning	Static	Worsening	Resolved	Undetermined
Skin only n=36	15	7	0	7	7
Skin +1 n=36	9	3	1	10	14
Skin + 2 n=15	4	2	1	5	3
Skin +3 n=9	2	0	0	4	1
Skin +4 n=4	2	0	0	2	0

Some patients presented with multiple morphologies. The clinical outcomes of sarcoidosis patients based on the number of morphologies were examined and the results are presented in **Table 3.9**.

Table 3.9: Clinical outcomes of sarcoidosis patients based on number of morphologies on presentation

No.of morphologies	Outcomes				
	Waxing &waning	Static	Worsening	Resolved	Undetermined
One lesion (n=57)	15	6	2	18	16
Two lesions (n=31)	11	5	0	8	7
Three lesions (n=10)	5	1	0	2	2
Four lesions (n=1)	1	0	0	0	0
Five lesions (n=1)	1	0	0	0	0

3.8 Treatment

Topical and oral corticosteroids were administered to 35 patients, whilst 24 patients were given a combination of topical corticosteroids, oral corticosteroids and an anti-malarial drug. A combination of topical and oral corticosteroids, anti-malarials, and methotrexate was administered to 10 patients. Ten patients were given topical corticosteroids only. **Table 3.10** summarizes the drugs most commonly prescribed.

Table 3.10: Treatment combinations administered to patients

Treatment	No. of patients	Percent
Topical corticosteroids only	10	10.0
Topical and oral corticosteroids	35	35.0
Topical corticosteroids and anti-malarial	2	2.0
Topical and oral corticosteroids and anti-malarial	24	24.0
Topical and oral corticosteroids, anti-malarial and methotrexate	10	10.0
Topical and oral corticosteroids, and methotrexate	6	6.0
Oral corticosteroids only	3	3.0
Topical and oral corticosteroids, anti-malarial and Azathioprine	3	3.0
Topical and oral corticosteroids, methotrexate, and Azathioprine	2	2.0
Topical corticosteroids and methotrexate	1	1.0
Topical corticosteroids, antimalarial, and Azathioprine	1	1.0
Topical and oral corticosteroids and Potassium permanganate	2	2.0
Oral corticosteroids and methotrexate	1	1.0

3.9. Histology findings

Designated pathologists confirmed sarcoidosis in all 100 patients. The summary of the site of biopsy is summarized in **Table 3.11**.

Table 3.11: Site of biopsy

Site of biopsies taken	Frequency	Percentage
Skin	79	79.0
Skin & extra-cutaneous site	14	14.0
Extra-cutaneous site only	7	7.0

As shown in **Table 3.12**, naked granulomas surrounded by a few epithelioid cells were the most common presentation (70% of cases). The next common presentation was naked granulomas with epithelioid cells and giant cells (41% of cases). The least common histological presentations were granulomas extending to the subcutis (4%) and granulomas with giant cells and asteroid bodies (1%).

Table 3.12: Frequency distribution of granulomatous reaction patterns

Granulomatous reaction pattern	Frequency	Percent
Naked granulomas surrounded by epithelioid cells and few lymphocytes	70	70.0
Granulomas with fibrinoid necrosis	14	14.0
Granulomas extending to the subcutis	4	4.0
Naked granulomas comprising epithelioid cells and giant cells	41	41.0
Granulomas with giant cells and asteroid bodies	1	1.0

The patterns of presentation versus the histological findings are presented in **Table 3.13**. The histological feature of papules showing naked granulomas surrounded by epithelioid cells with a few lymphocytes was the most common presentation, found in 50 of the cases. Plaques were the second most common clinical pattern, which was found with naked granulomas surrounded by epithelioid cells with a few lymphocytes (n=20). Fibrinoid necrosis was seen in 12% of the cases with papules and the least (4%) in cases with plaque

Table 3.13: Pattern of presentation versus histological results of patients

Pattern of presentation	Histology patterns				
	Naked granulomas surrounded by epithelioid cells and few lymphocytes	Granulomas with fibrinoid necrosis	Granulomas extending to the subcutis	Naked granulomas comprising epithelioid cells and giant cells	Granulomas with giant cells and asteroid bodies
Papules n=69	50	12	1	28	0
Plaques n=28	20	4	1	15	0
Subcutaneous nodules n=17	10	3	4	6	1
Lupus pernio n=11	7	4	1	5	0
Dactylitis n=12	9	1	0	4	1
Psoriasiform n=1	0	0	0	1	0
Hypopigmented Macules n=3	2	0	0	3	0
Ulcerative n=4	3	0	1	1	0
Erythrodermic n=1	1	1	0	0	0
Scar n=4	2	0	1	1	0
Scalp (alopecia) and nails n=3	3	1	0	0	0
Prurigo n=5	4	0	0	2	0

3.10 Sarcoidosis in people living with HIV

Of the 100 patients included in this study, 12 were living with HIV infection. All were female and Black African. Their age ranged from 21 to 39 years. Seven were diagnosed

between 2010 and 2014, whereas only three of them were diagnosed between 2003 and 2005. At diagnosis, their CD4 counts were low (mean 248 cells/mm³), but increased as their sarcoid disease evolved. All on HAART, and those with initial high viral loads responding to antiretroviral treatment displayed concomitant progression of their sarcoidosis. Four had only skin involvement, six had both skin and lung involvement, one had skin, lung and eye involvement and another had disease involving the skin, lungs, bone and joints. Five presented with papules and plaques; three had papules only. One presented with erythroderma, and another presented with lupus pernio, papules, and subcutaneous nodules. Their calcium levels were normal, both before and after therapy. Three had chest X-ray changes and three had only skin involvement. The remaining patient, who was initially recorded with skin only involvement, had Stage two chest radiographic changes. The chest x-ray reports of the six who had skin and lung involvement, indicated that two had Stage three radiographic changes, and four had Stage one radiographic changes.

3.11 Summary

It is important to describe a sample population in terms of its demographics and clinical profile, in order to know the population better and to be able to establish areas of concern and areas for further research. In this study we have managed to identify the demographics of the population group most affected by cutaneous sarcoidosis (Black females older than 45 years of age). Patterns of presentation of cutaneous sarcoidosis have been described and the pattern of progress in patients who have both HIV and cutaneous sarcoidosis has been noted and remarked on. The next chapter entertains a discussion on the study findings, explores the limitations and makes recommendations.

CHAPTER FOUR

SUMMARY OF FINDINGS, DISCUSSION, CONCLUSION

4.1 Introduction

This chapter presents a discussion of the study findings, conclusions and recommendations. The discussion is based on the study objectives and attempts are made to explain the key findings of the study. Where necessary, the findings of this study are compared to previous studies on cutaneous sarcoidosis.

4.2 Summary of findings

The key findings of this study are summarised as follows:

- Cutaneous sarcoidosis disease was more common in females than males.
- Cutaneous sarcoidosis disease was more common in older females above the age of 45 years.
- The patterns of cutaneous sarcoidosis were predominantly papules and plaques.
- The lung was the most commonly affected extra-cutaneous organ.
- The Scadding staging of the lungs in patients with cutaneous sarcoidosis was mainly zero and one.
- There was complete resolution of cutaneous sarcoidosis in only 28 cases over 24 months.
- Of the patients that presented with papules (n=69), there was complete resolution only in 17 of them. The clinical course of a significant proportion of patients that presented with papules was static (10 patients), waxing and waning (24 patients) or worsening (2 patients).
- Of the 28 patients that presented with plaques, waxing and waning was the most common outcome. However, of the four patients that presented with scar sarcoidosis, there was complete resolution in two. Waxing and waning and static were the common outcomes of patients that presented with lupus pernio. Complete resolution was common only in patients who presented with subcutaneous nodules.

4.3 Discussion of results

This study evaluated the spectrum of cutaneous manifestations of sarcoidosis among patients attending the Chris Hani Baragwanath Academic Hospital Dermatology outpatient clinic from 1991 – 2015. Studies on cutaneous sarcoidosis in the South African setting are limited. Besides the Mosam and Morar study in 2004, which focused only on recalcitrant patterns, the only reported work on the spectrum of cutaneous sarcoidosis in South Africa was conducted in 1999 by Jacyk *et al.* (17, 39). The current study provides a detailed description of the various patterns, severity and chronicity of cutaneous sarcoidosis over two decades. This study also examines the co-morbidity of HIV/AIDS and cutaneous sarcoidosis.

Results presented below are a summary of the main findings in an attempt to answer the research questions, with a focus on both the specific and global findings, and what, in particular, was uncovered that is new to the body of existing knowledge on cutaneous sarcoidosis in South African patients. Some findings had to be interpreted with caution, since the sample examined and analysed was a randomly selected cohort of patients seen between 1991 and 2015, and does not reflect the total number of patients who presented with the disease during this period.

4.3.1 Where are we today?

It appears that cutaneous sarcoidosis was first recognized in the nineteenth century; due to a lack of a standardised investigative tools at that time; it is not possible to confirm this, as investigators relied on the clinical and unique histological appearance of this disease entity (1). It is only in the mid-twentieth century that radiological findings were used when patients presented with cutaneous lesions, and lung disease was suspected (6, 62). In the twenty-first century (ACCESS Research group, 1999) (6), high resolution computerised tomography became easily available and exposed the X-ray's limitations (6). With an increased incidence of tuberculosis in Africa (63), it became apparent that this granulomatous disease had some histological resemblance to sarcoidosis. This made it difficult to differentiate between the two pathologies. But with the advance in diagnostic tools, it became possible to exclude other granulomatous conditions (42, 64, 65).

In this study of cutaneous sarcoidosis, all patients were confirmed by biopsy. Some also had radiological features of intrathoracic sarcoidosis. All had compatible clinical presentations and exclusion of other granulomatous diseases.

4.3.2 Correlations between demographic characteristics and patterns of cutaneous sarcoidosis

In answer to the research question of whether there were correlations between demographic characteristics and cutaneous patterns of sarcoidosis, the researcher was able to confirm the following:

- Cutaneous sarcoidosis was more common in females than in males.
- Cutaneous sarcoidosis was more common in older women (above the age of 45 years) than in younger women.

In this study, the peak incidence of cutaneous sarcoidosis was in the age group of 50 to 69 years and is relatively compatible with recent epidemiology studies (14, 21). Although there is no consensus or evidence for the factors causing the increase in age, which has been shown in international studies, the hypothesis made here suggests that changes in the practice and use of diagnostic imaging technology could account for the higher incidence in older women. Another proposed reason for the high incidence in older women is that they may seek professional help for physical disorders more willingly and frequently than younger women do. This speculation prompts a need for a study.

The predominance of Black females in this study is similar to the findings in literature globally (8, 10). Of note is the fact that the women were over 45 years of age. Apart from the role of improved diagnostic tools, the increased tendency for older women to develop skin lesions maybe related to the lack of exposure to endogenous female hormones in older women. Hence being pre-menopausal may confer a reduced risk of sarcoidosis (66, 67). The lack of evidence for this conclusion, however, makes this speculation.

A supportive hypothesis which may contribute to the high female to male ratio includes the possibility that females have a greater tendency than males to observe their body or skin for these type of lesions (14, 27).

4.3.3 Patterns, severity and chronicity of cutaneous manifestations of sarcoidosis in patients

In an attempt to answer the research question regarding patterns, severity and chronicity of cutaneous sarcoidosis, the researcher was able to confirm that

- the patterns of manifestation were predominantly papules and plaques;
- skin and lungs were the most commonly affected organ systems;
- the Scadding staging of lung disease was mainly zero and one.

Recognition of specific lesions is important as they provide clues for diagnosis. Skin lesions are easily accessible to use as tissue specimens to evaluate for definitive histological diagnosis; moreover, a punch biopsy is a simple technique to learn and provides a high diagnostic yield.

Skin lesions often appear at the onset of the disease, but may appear at any stage (31, 32). In this study, apart from the skin, the most frequent extra-cutaneous organ involvement was the lungs (53 cases), followed by eyes (14 cases) and bones/joints (10 cases); the least affected was bone marrow and kidneys. In a recent study by Marcoval *et al.*, it was concluded that specific cutaneous lesions did not have a predictive factor for the disease severity and prognosis (22, 27). However, there is an exception with erythema nodosum, a non-specific pattern of presentation of cutaneous sarcoidosis. It is associated with a good outcome. Lupus pernio, a more specific pattern of presentation, is associated with severity and chronicity of cutaneous sarcoidosis (17, 27, 32). In this study, none of our patients presented with erythema nodosum. However, the subcutaneous pattern of presentation had a p-value = 0.012. It is reported in the literature that due to a limited number of case reports, the characteristics of subcutaneous sarcoidosis in relation to systemic disease have not been elucidated (32). The significant finding in this study on the subcutaneous patterns of presentation is similar to the findings of the current literature. A recent study in America reported on twenty-one cases and found that this form of cutaneous sarcoidosis has no correlation with severe systemic involvement and has a relatively good outcome. The strength of the American study was the significant follow-up period of 32 years (68). Literature from the east of Africa (Ethiopia) and the west of Africa (Nigeria) reports that the pattern of presentation mostly demonstrated subcutaneous nodules and scar sarcoidosis respectively (35, 36); these were associated with better prognostic outcomes (32).

Regardless of the number of organs involved, papules were the most common pattern of clinical presentation demonstrated in this study. This concurs with findings globally. Some authors report that this type of specific cutaneous lesion does not determine the severity and chronicity of this disease entity (22, 32). This seems to be confirmed in this study, because in a number of patients the clinical presentation was of one type of lesion co-existing with another, i.e., poly-morphology (papules with plaques, papules with lupus pernio). It is up to the individual clinician's discretion to determine which lesion forms the most predominant pattern. In a study conducted by Mañá and colleagues, a correlation was found between specifically papular lesions with an acute form of sarcoidosis, which included involvement of other organs (hilar lymphadenopathy, peripheral lymphadenopathy, parotid enlargement, EN, and acute uveitis); this form usually resolved within two years (3, 32).

Regarding chronicity of the presenting patterns, the following is found:

In answer to the research question regarding chronicity, a significant proportion of patients with papules (24.6%) and subcutaneous lesions (100%) are frequently associated with complete resolution of the lesions. Apart from having a patient profile with papules that may resolve completely, on the contrary papules can be (36 cases) persistent. Similarly patients who presented with lupus pernio had chronic persistent lesions.

Our population sample is predominantly Black Africans who presented most frequently with papules and plaques. Whether these features of presentation may be attributed to early diagnosis or management factors or whether the minimal presence or absence of other aetiologies causing granulomatous changes may have been misdiagnosed, cutaneous sarcoidosis remains to be further investigated.

4.3.4 Histopathological findings of biopsy specimens of cutaneous lesions of sarcoidosis

Regarding the histopathological findings of biopsy specimens, and taking into consideration the frequent clinical presentation of papules, the histological patterns which were seen most frequently, were classic naked granulomas, in 70% of the cases. Only 12% had findings of fibrinoid necrosis, similar to the histological findings described in Black South Africans in the

literature almost two decades ago by Jacyk, and earlier by Benatar (17, 19). Perhaps improved access to care and earlier diagnosis and treatment interventions now play a role in influencing the pattern of presentation, since the natural course of the disease may be changed or halted with better access and earlier diagnosis. The notion of advanced and mutilating patterns associated with Black Africans and African Americans race could have been influenced by late presentations at first visits to outpatient clinics, which in turn could have been influenced by racially prejudiced health care policies at the time. These factors prevailed right through the eighteenth, nineteenth and early twentieth century. The current findings regarding manifestation of the disease entity at first visit may well be strongly influenced by better access and earlier presentation.

4.3.5 Association between HIV infection and cutaneous or systemic sarcoidosis

The last research question posed at the outset of this study was the question of a possible correlation between manifestations of cutaneous or systemic sarcoidosis and the presence of HIV infection. In this study, people living with both HIV and sarcoidosis interestingly demonstrated an inversely proportional association of the disease entity with the CD4 count. Disease progression is noted with CD4 increments that occur after initiation of therapy. Similarly, those with high viral loads experienced progression of sarcoidosis as their viral loads declined with HAART. Although half of the patients (six cases) had more than one organ involvement (skin and lung involvement), there was no correlation between the Scadding stage and lung function, as 2 patients had normal lung function tests with Stage 3 chest X-rays.

The clinical patterns of sarcoidosis in the HIV-positive patients did not differ from the non-HIV infected individuals reported globally, including in the histological findings (69). Some reports in the literature do, however, describe a challenge in the management of cutaneous and systemic sarcoidosis where an IRIS is present (53, 56).

There is a need for further studies on the coexistence of HIV/AIDS and sarcoidosis. Clarity of the immunological relationship needs to be investigated further and more patient reports described. There is opportunity to expand such information into a case series.

4.4 Limitations

Limitations are presented here in list form for clarity:

- Many clinical records were incomplete.
- Some patients were excluded because their files were missing. This limited the sample size. The small sample size hindered the ability to make significant statistical associations.
- The data was dependent on how well clinical and laboratory information was recorded.
- The study was conducted for outpatients only. It would have been interesting to see the differences in presentation between inpatients and outpatients, to give a broader picture.
- Patient records from this study included patients from Dermatology and Respiratory outpatient clinics only – this does create a bias for patients with lung involvement as an extra-cutaneous manifestation.
- This study, which was conducted with records from 1991- 2015 that had not been collected consecutively, limited the author from obtaining data regarding incidence and changes in trends.

4.5 Conclusion

The study aimed at describing the cutaneous patterns of sarcoidosis in the population that presented at the outpatient Dermatology clinic at Chris Hani Baragwanath Academic Hospital. This was a retrospective review and the first, to my knowledge, to describe this population at CHBH. Further research and collaboration with other countries in southern Africa is recommended for a more significant and statistically relevant contribution to the spectrum and management of this rare disease entity.

REFERENCES

1. Boeck C. Multiple benign sarkoid of the skin. *Arch Dermatol.* 1982;118 (10):710-20.
2. Lazarus A. Sarcoidosis: epidemiology, etiology, pathogenesis, and genetics. *Disease-a-Month.* 2009;55 (11):649-60.
3. Mañá J, Marcoval J, Graells J, Salazar A, Peyrí J, Pujol R. Cutaneous involvement in sarcoidosis: relationship to systemic disease. *Arch Dermatol.* 1997;133 (7):882-8.
4. Mañá J, Marcoval J. Skin manifestations of sarcoidosis. *La Presse Médicale.* 2012;41 (6):e355-e74.
5. Allwood B, Ainslie G. Sarcoidosis: CME2013,vol. 31 (9) 326-330.
6. "Statement on sarcoidosis". Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med.* 1999;160:736-55.
7. Newman LS, Rose CS, Maier LA. Sarcoidosis. 1997; 336 (17):1224-34.
8. English JC, III, Patel PJ, Greer KE. Sarcoidosis. *J Am Acad Dermatol.* 2001; 44 (5):725-46.
9. Rybicki BA, Major M, Popovich J, Maliank MJ. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol.* 1997;145 (3):234-41.
10. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager Jr H, Bresnitz EA, et al., Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med.* 2001; 164 (10):1885-9.
11. Heath CR, David J, Taylor SC. Sarcoidosis: are there differences in your skin of color patients? *J Am Acad Dermatol.* 2012; s66 (1):121. e1-. e14.
12. Collin B, Rajaratnam R, Lim R, Lewis H. A retrospective analysis of 34 patients with cutaneous sarcoidosis assessed in a dermatology department. *Clin Exp Dermatol.* 2010;35 (2):131-4.
13. Rybicki BA, Iannuzzi MC, editors. *Epidemiology of sarcoidosis: recent advances and future prospects. Seminars in respiratory and critical care medicine*; 2007: Copyright© 2007 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.

14. Ungprasert P, Carmona EM, Utz JP, Ryu JH, Crowson CS, Matteson EL. Epidemiology of Sarcoidosis 1946-2013. *Mayo Clin Proc.* 1991 (2):183-8.
15. Morrison J. Sarcoidosis in the Bantu. *Br J Dermatol.* 1974;90 (6):649-55.
16. Edmondstone W, Wilson A. Sarcoidosis in Causians, Blacks and Asians in London. *Br J Dis Chest.* 1985;79:27-36.
17. Jacyk WK. Cutaneous sarcoidosis in black South Africans. *Int J Dermatol.* 1999;38 (11):841-5.
18. James DG, Neville E, Siltzbach LE, Turiaf J, Battesti JP, Sharma OP, et al. A Worldwidereview of sarcoidosis. *Ann N Y Acad Sci.* 1976; 278 (1):321-34.
19. Benatar S. Sarcoidosis in South Africa: a comparative study in Whites, Blacks and Coloureds. *S Afr Med J.* 1977; 52 (15):602-6.
20. Rybicki BA, Kirkey KL, Major M, Maliarik MJ, Popovich J, Chase GA, et al. Familial risk ratio of sarcoidosis in African-American sibs and parents. *Am J Epidemiol.* 2001; 153 (2):188-93.
21. Yanardag H, Tetikkurt C, Bilir M, Demirci S, Iscimen A. Diagnosis of cutaneous sarcoidosis; clinical and the prognostic significance of skin lesions. *Multidiscip Respir Med.* 2013; 8 (1):26.
22. Marcoval J, Mañá J, Rubio M. Specific cutaneous lesions in patients with systemic sarcoidosis: relationship to severity and chronicity of disease. *Clin Exp Dermatol.* 2011; 36 (7):739-44.
23. Jacyk W. Sarcoidosis in the West African. a report of eight Nigerian patients with cutaneous lesions. *Trop Geogr Med.* 1984; 36 (3):231-6.
24. Ando M, Miyazaki E, Hatano Y, Nishio S, Torigoe C, Yamasue M, et al. Subcutaneous sarcoidosis : a clinical analysis of nine patients. *Clin Rheumatol.* 2016; 35 (9):2277-81.
25. Olive KE, Kataria YP. Cutaneous manifestations of sarcoidosis relationships to other organ system involvement, abnormal laboratory measurements, and disease course. *Arch Intern Med.* 1985; 145 (10):1811-4.
26. Wu M, Lee JY. Cutaneous sarcoidosis in southern Taiwan: clinicopathologic study of a series with high proportions of lesions confined to the face and angiolupoid variant. *J Eur Acad Dermatol Venereol.* 2013; 27 (4):499-505.
27. Yanardağ H, Pamuk ÖN, Karayel T. Cutaneous involvement in sarcoidosis: analysis of the features in 170 patients. *Respiratory medicine.* 2003; 97 (8):978-82.

28. Hillerdal G, Nöu E, Osterman K, Schmekel B. Sarcoidosis: Epidemiology and Prognosis: A 15-Year European Study 1. *Am Rev Respir Dis*. 1984; 130 (1):29-32.
29. Parkes SA, Baker S, Bourdillon R, Murray C, Rakshit M, Sarkies J, et al. Incidence of sarcoidosis in the Isle of Man. *Thorax*. 1985; 40 (4):284-7.
30. Veien NK, Stahl D, Brodthagen H. Cutaneous sarcoidosis in Caucasians. *J Am Acad Dermatol*. 1987; 16 (3):534-40.
31. Haimovic A, Sanchez M, Judson MA, Prystowsky S. Sarcoidosis: a comprehensive review and update for the dermatologist: part I. Cutaneous disease. *J Am Acad Dermatol*. 2012; 66 (5):699. e1-. e18.
32. Sanchez M, Haimovic A, Prystowsky S. Sarcoidosis. *Dermatol Clin*. 2015; 33 (3):389-416
33. Spiteri M, Matthey F, Gordon T, Carstairs L, James D.G. Lupus pernio: a clinico-radiological study of thirtyfive cases. *Br J Dermatol*. 1985; 112 (3):315-22.
34. Baughman RP, Lower EE. Evidence-based therapy for cutaneous sarcoidosis. *Clin Dermatol*. 2007; 25 (3):334-40.
35. Olumide Y, Bandele E, Elesha S. Cutaneous sarcoidosis in Nigeria. *J Am Acad Dermatol*. 1989; 21 (6):1222-4.
36. Tsega E, Getahun B, Teklehaimanot R. Sarcoidosis in Ethiopia. *Tubercle*. 1978; 59 (4):261-8.
37. Moche M, Glassman S, Modi D, Grayson W. Cutaneous annular sarcoidosis developing on a background of exogenous ochronosis: A report of two cases and review of the literature. *Clin Exp Dermatol*. 2010; 35 (4):399-402.
38. Motswaledi M, Khammissa R, Jadwat Y, Lemmer J, Feller L. Oral sarcoidosis: A case report and review of the literature. *Aust Dent J*. 2014; 59 (3):389-94.
39. Mosam A, Morar N. Recalcitrant cutaneous sarcoidosis: an evidence-based sequential approach. *J Dermatolog Treat*. 2004; 15 (6):353-9.
40. Hartshorne S. Dermatological disorders in Johannesburg, South Africa. *Clin Exp Dermatol*. 2003; 28 (6):661-5.
41. Smith C, Feldman C, Reyneke J, Promnitz D, Kallenbach J, Zwi S. Sarcoidosis in Johannesburg--a comparative study of black and white patients. *S Afr Med J*. 1991; 80 (9):423-7.
42. Cardoso J, Cravo M, Reis J, Tellechea O. Cutaneous sarcoidosis: a histopathological study. *J Eur Acad Dermatol Venereol*. 2009; 23 (6):678-82.

43. Mangas C, Fernández-Figueras MT, Fité E, Fernández-Chico N, Sàbat M, Ferrándiz C. Clinical spectrum and histological analysis of 32 cases of specific cutaneous sarcoidosis. *J Cutan Pathol*. 2006; 33 (12):772-7.
44. Weedon D. - The granulomatous reaction pattern. *Weedon's Skin Pathology* (Third edition). Edinburgh: Churchill Livingstone; 2010. p. 169-94.e17.
45. Calonje E, Brenn T, Lazar A, McKee PH. *McKee's pathology of the skin*: Elsevier/Saunders; 2012.
46. Wijnen PA, Cremers JP, Nelemans PJ, Erckens RJ, Hoitsma E, Jansen TL, et al. Association of the TNF- α G-308A polymorphism with TNF-inhibitor response in sarcoidosis. *Eur Respir J*. 2014;43 (6):1730-9.
47. Gerke AK, Hunninghake G. The immunology of sarcoidosis. *Clinics in chest medicine*. 2008; 29 (3):379-90.
48. Serio RN. Infliximab treatment of sarcoidosis. *Ann Pharmacother*. 2003; 37 (4):577-81.
49. Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, et al., The WASOG Sarcoidosis Organ Assessment Instrument: an update of a previous clinical tool. **Sarcoidosis**. *Vasc Diffuse Lung Dis*. 2014; 31 (1):19-27.
50. Harrington D, Major M, Rybicki B, Popovich J, Maliarik M, Iannuzzi M. Familial sarcoidosis: analysis of 91 families. *Sarcoidosis*. 1994;11:240-.
51. Blanche P, Passeron A, Gombert B, Ginsburg C, Salmon D, Sicard D. Sarcoidosis and HIV infection: influence of highly active antiretroviral therapy. *Br J Dermatol*. 1999;140 (6):1185.
52. Roustan G, Yebra M, Rodriguez-Braojos O, Banos I, Jaurena J, Simon A. Cutaneous and pulmonary sarcoidosis in a patient with HIV after highly active antiretroviral therapy. *Int J Dermatol*. 2007; 46 (1):68-71.
53. Mirmirani P, Maurer TA, Herndier B, McGrath M, Weinstein MD, Berger TG. Sarcoidosis in a patient with AIDS: a manifestation of immune restoration syndrome. *J Am Acad Dermatol*. 1999;41 (2):285-6.
54. Morris DG, Jasmer RM, Huang L, Gotway MB, Nishimura S, King TE. Sarcoidosis following HIV infection: evidence for CD4+ lymphocyte dependence. *CHEST Journal*. 2003;124 (3):929-35.
55. Gowda KS, Mayers I, Shafran SD. Concomitant sarcoidosis and HIV infection. *CMAJ*. 1990;142 (2):136.

56. Osei-Sekyere B, Karstaedt A. Immune reconstitution inflammatory syndrome involving the skin. *Clin Exp Dermatol*. 2010; 35 (5):477-81.
57. Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. *Clin Exp Dermatol*. 2006; 24 (4):549-70.
58. Trevenzoli M, Cattelan A, Marino F, Marchioro U, Cadrobbi P. Sarcoidosis and HIV infection: a case report and a review of the literature. *Postgrad Med J*. 2003; 79 (935):535-8.
59. Volden G. Successful treatment of chronic skin diseases with clobetasol propionate and a hydrocolloid occlusive dressing. *Acta Derm Venereol*. 1991; 72 (1):69-71.
60. Ffrooz A, Tehranchia-Nia Z, Ahmed A. Benefits and risks of intralesional corticosteroid injection in the treatment of dermatological diseases. *Clin Exp Dermatol*. 1995; 20 (5):363-70.
61. Badgwell C, Rosen T. Cutaneous sarcoidosis therapy updated. *J Am Acad Dermatol*. 2007;56 (1):69-83.
62. Wurm K, Reindell H, Heilmeyer L. *Der Lungenboeck im Röntgenbild*: Thieme; 1958; 118 (4):229-43
63. Chaisson RE, Martinson NA. Tuberculosis in Africa—combating an HIV-driven crisis. *N Engl J Med*. 2008; 358 (11):1089-92.
64. Ball NJ, Kho GT, Martinka M. The histologic spectrum of cutaneous sarcoidosis: a study of twenty-eight cases. *J Cutan Pathol*. 2004; 31 (2):160-8.
65. Ishak R, Kurban M, Kibbi AG, Abbas O. Cutaneous sarcoidosis: clinicopathologic study of 76 patients from Lebanon. *Int J Dermatol*. 2015; 54 (1):33-41.
66. Cozier YC, Berman JS, Palmer JR, Boggs DA, Wise LA, Rosenberg L. Reproductive and Hormonal Factors in Relation to Incidence of Sarcoidosis in US Black Women: The Black Women's Health Study. *Am J Epidemiol*. 2012; 176 (7):635-41.
67. Chida K, Shirai M, Sato M, Sato J, Nakamura H. Successful treatment of hepatic sarcoidosis with hormone replacement in a postmenopausal woman. *Respirology*. 1999; 4 (3):259-61.
68. Ahmed I, Harshad SR. Subcutaneous sarcoidosis: is it a specific subset of cutaneous sarcoidosis frequently associated with systemic disease? *J Am Acad Dermatol*. 2006; 54 (1):55-60.
69. Lowery W.S, Whitlock WL, Dietrich RA, Fine JM. Sarcoidosis complicated by HIV infection: three case reports and a review of the literature. *Am Rev Respir Dis*.

1990;142 (4):887-9.70. UNAIDS, Jointed United Nations Programme on HIV/AIDS 2016). UNAIDS Report on the global AIDS epidemic 2016. www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf

71. Haimovic A, Sanchez M, Judson MA, Prystowsky S. Sarcoidosis: a comprehensive review and update for the dermatologist: part II. Extracutaneous disease. *J Am Acad Dermatol.* 2012; 66, (5): 719.e1–719.e10.
72. Chesnutt AN. Enigmas in sarcoidosis. *West J Med.* 1995;162 (6):519.

APPENDIX A (Data collection sheet)

DATA COLLECTION SHEET PATIENT CODE: -----

Age:.....

Sex:

.....

Race:.....

Occupation:.....

Histological confirmation of sarcoidosis.....Year of diagnosis:.....

Type of organ specimen: skin ☐ non-skin ☐ specify type of viscera:.....

For the following, if yes, give details of histological findings:.....

Granulomatous reaction pattern	Yes	No	Mixed
Naked granulomas surrounded by epithelioid cells and a few lymphocytes			
Granulomas with fibrinoid necrosis			
Granulomas extending to the subcutis			
Naked granulomas comprising epithelioid cells; giant cells			
Granuloma with giant cells and asteroid bodies			
Other			

Co-morbidity:

HIV status	Reactive	Non-reactive	Unknown
------------	----------	--------------	---------

HAART therapy yes: ☐ no: ☐

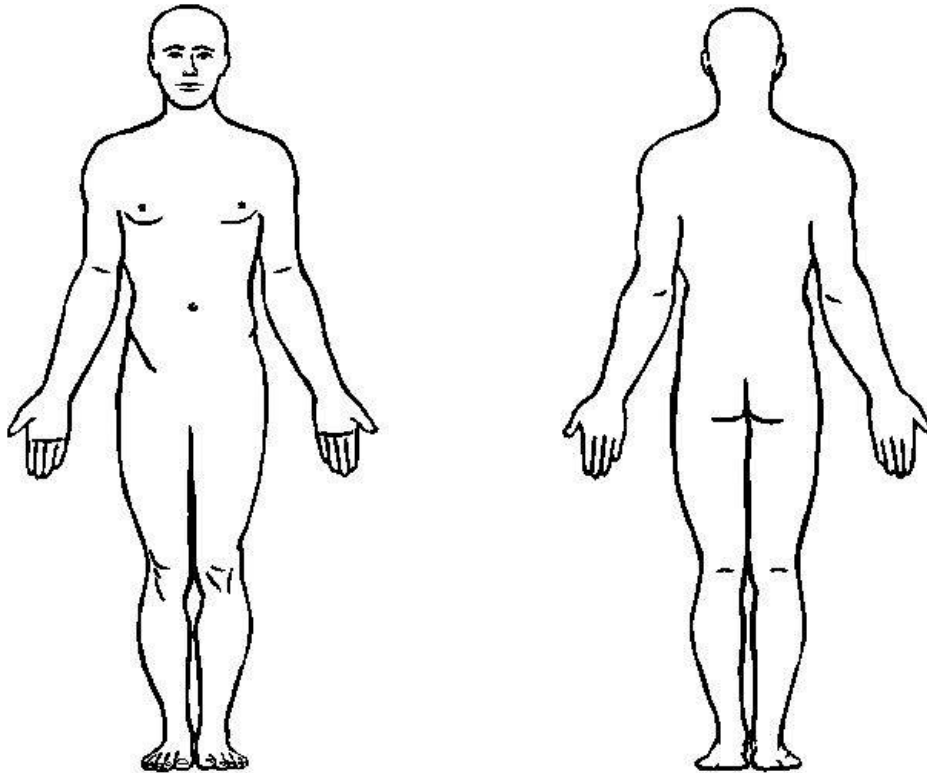
CD4: Before HAART ☐ Current ☐

Viral load: Before HAART ☐ Current: ☐

Organ Involved:	Cutaneous involvement:	Extra-cutaneous involvement:
Yes		
No		

Interval between diagnosis of sarcoidosis and eruption of skin lesions:.....

(Body map for back and front)



Documented cutaneous lesion:

Specific skin lesions		Non-specific skin lesions
Distinct lesions	Non-distinct lesions	<u>Erythema nodosum</u>
Papules	Subcutaneous nodule	Calcification
Plaques	Hypopigmented macules	Prurigo
Lupus pernio	Ulcerative sarcoidosis	Dactylitis
Scar sarcoidosis	Psoriasiform lesions	
	Alopecia and nail sarcoidosis	
	Ichthyosiform presentation	
	Erythrodemic presentation	

Tattoo reactions: ☐ other:.....

No. of morphology per lesion:

Lesion	No.

Associated Pain: ☐ Pruritus: ☐

Investigations conducted: Time commenced: before treatment ☐ after treatment ☐

Tested normal results abnormal result: - raised: low:

Full blood count: ☐ ☐

Urea, electrolytes and ☐ ☐

Creatinine ☐ ☐

Liver function test: ☐ ☐
.....

Serum calcium: ☐ ☐

Serum ACE: ☐ ☐
.....

Chest radiography:.....☐☐

.....grade: zero
.....grade: one
.....grade: two
.....grade: three
.....grade: four

Investigations conducted: Tested normal results abnormal result:- raised: low:

Hand radiography: ☐☐ osteolytic changes

Pulmonary function tests: ☐☐
.....

Electrocardiography: ☐☐
.....

Ophthalmology examination: ☐☐
.....

Tuberculin Test: ☐☐
.....

Other: specify:..... ☐☐
.....

Treatment options:

Name	Dose	Duration	Discontinued/reason

Treatment response: excellent ☐ good ☐ fair ☐ poor ☐

APPENDIX B (Ethics Certificate)



R14/49 Dr Babalwa Phindiswa Zinziswa Mbuqe-Limba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150237

NAME: Dr Babalwa Phindiswa Zinziswa Mbuqe-Limba
(Principal Investigator)

DEPARTMENT: Dermatology
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: The Spectrum of Dermatological Disorders in Patients with Sarcoidosis Presenting to the Dermatology Outpatient Clinic at Chris Hani Baragwanath Academic Hospital

DATE CONSIDERED: 27/02/2015

DECISION: Approved unconditionally

CONDITIONS:
SUPERVISOR: Prof Michelle Wong

APPROVED BY: 
Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 02/03/2015
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

APPENDIX B (Ethics Certificate continued)

Chris Hani Baragwanath Academic Hospital

Division of Pulmonology, Department of Medicine

P O Bertschers, 2033, South Africa • Telephone: +27 11 933 8940 • Fax: +27 11 938 1454



26 March 2015

Protocol Review Committee
School of Clinical Medicine
Faculty of Health Sciences

Dear Colleagues

CORRECTIONS TO MMed PROTOCOL

I am a co-supervisor of Dr Babalwa Phindiswa Zinziswa Mbuqe-Limba's MMed research project, "The Spectrum Of Dermatological Disorders Found In Patients With Sarcoidosis Presenting To The Dermatology Outpatient Clinic At The Chris Hani Baragwanath Academic Hospital".

I am satisfied that she has amended her protocol for this study according to the recommendations of the Protocol Review Committee as discussed at the meeting held on 10 March 2015.

Yours sincerely

A handwritten signature in blue ink, appearing to read "M. Wong".

Prof M. Wong

Head: Division of Pulmonology, Chris Hani Baragwanath Academic Hospital