Cutaneous sarcoidosis at the Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital. A retrospective record review.

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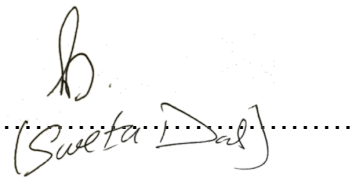
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Medicine in Dermatology.

Johannesburg 2020

DECLARATION

I, Sweta Das, declare that this Research Report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Dermatology at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



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9th day of July 2020.

DEDICATION

I dedicate this project to our creator, God Almighty, for the strength, inspiration and wisdom that He granted me to complete this work.

To my father, Dr. Ashok Kumar Das, who is my backbone and my strength which makes me believe that I am strong and special. To my mother, Sanchita Das, thank you so much for all the support and love. To my sister and nephew, I really appreciate your continuous support emotionally. To Rusheel Bhana, who has given me endless support and love. And to all my friends who supported me through this journey.

ACKNOWLEDGEMENTS

I would not have been able to walk this journey successfully on my own; hence I would like to sincerely express my gratitude to the following individuals who contributed extensively towards the success of this project.

I will forever be indebted to my supervisor, Professor Deepak Modi, for his guidance, support, dedication and hard work.

I would also like to mention my teacher Professor Joy Schulz for her passion and dedication in imparting the knowledge in the field of dermatology. I also thank the Library staff at Wits Medical School, for their assistance in getting relevant academic resources.

Also, the support I got from Philip Tobias Research Team is unimaginable. You are excellent at your job and assistance.

ABSTRACT

Background: Sarcoidosis is a long-standing, granulomatous, inflammatory dermatosis which may affect multiple organ system. The aetiology of the disease is unknown. [1] Cutaneous disease occurs in 20% to 35% of patients. [2] Studies on cutaneous disease in South Africa remains limited. [15]

Objectives: To demonstrate the demographic, clinical and histological characteristics of patients with biopsy proven cutaneous sarcoidosis diagnosed at Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital from 1 July 2007 to 30 June 2018.

Methods: Detailed information of patients with a biopsy confirmed diagnosis of cutaneous sarcoidosis were retrospectively evaluated from histopathology reports and categorized according to gender, race, age group, clinical features and histopathology patterns found in biopsy of the skin lesions.

Results: Cutaneous sarcoidosis was established in seventy-three patients. There was a marked predominance of female (71%) and black (70%) patients. The mean age at diagnosis was forty-five years. Papule, plaques and annular lesions were the most common clinical presentations. Naked sarcoidal granuloma (81%) remains the most common specific finding on histopathology. Dermal collagen sclerosis (10%) was noted as the most common nonspecific feature in this study.

Conclusions: This study highlights the combined role of the dermatologist and the pathologist to recognize and diagnose cutaneous sarcoidosis simultaneously. It increases the awareness of the loopholes in our setting and enhances future possibilities of prompt diagnosis by providing minor essential details to the pathologist. The demographic, clinical features and histopathology findings in this study were mostly consistent with those published in the literature with minimal differences. Annular lesions were a common specific clinical presentation and dermal collagen sclerosis were a common nonspecific histopathology finding in this setting.

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ABBREVIATIONS:

HIV	Human immunodeficiency virus.
USA	United States of America
MRI	Magnetic resonance imaging.
APC	Antigen-presenting cells.
TNF-α	Tumour necrosis factor alpha.
MIP-1	Macrophage inflammatory protein 1.
MCP-1	Monocot chemotactic protein 1.
GM-CSF	Granulocyte macrophage colony-stimulating factor.
CD4	Cluster of Differentiation 4.
ACE	Angiotensin-converting enzyme.
CO2	Carbon dioxide
ARV	Antiretroviral therapy.
OPD	Outpatient department.
H&E	Haematoxylin and eosin stain.
PAS	Periodic acid–Schiff.
ZN	Ziehl-Neelsen stain.
NHLS	National Health Laboratory Services.
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital.
HJH	Helen Joseph Hospital.
ICU	Intensive Care Unit.
CEO	Chief Executive Officer.

CHAPTER 1: EXTENDED LITERATURE REVIEW

1.1Introduction:

Sarcoidosis is a long-standing, granulomatous, inflammatory dermatosis which may affect multiple organ system. The aetiology of the disease is unknown. [1]Over 90% of patients develop pulmonary, eye, and/or skin involvement. Cutaneous disease occurs in 20% to 35% of patients.[2] A recent survey showed cutaneous disease occurring in 33% of patients with sarcoid in France and 30% in Germany.[3,4] Cutaneous sarcoid is either isolated or associated with other organ involvement.[2] The recent study on sarcoid in general by Li C-W et al (Table 1.1)show various organ involvement in six hundred and thirty six patients over six years.[5] The result showed that lung was the most common organ involved followed by skin. This is in keeping with literature.

Table 1.1 Organ involvements with sarcoidosis in China. (Li-C-W et al)[5]

Organ	***N (%)**
Isolated pulmonary involvement	378(59.4)
Pulmonary plus other organ involvement	258(40.6)
Extra pulmonary lymph node	147(23.1)
Skin	86(13.5)
Eyes	8(1.3)
Bones/ joints	8(1.3)
Liver	4(0.6)
Nose	4(0.6)
Parotid/salivary	3(0.5)
Spleen	2(0.3)
Renal	2(0.3)
Cardiac	1(0.2)
Muscle	1(0.2)

*Total number in frequency table is greater than the total number of patients because eight patients had more than one organ involvement. N=frequency. [5]

Sir Jonathan Hutchinson was the first to discover the existence of this disease in his patient. Caesar Boeck eventually coined the name “sarcoid” due to its striking resemblance to sarcoma clinically. [6]

Sarcoidosis affects all age groups, gender and ethnicities. Its incidence and clinical presentation vary widely throughout the world perhaps due to various environmental and genetic factors. [1]

1.2Age and gender prevalence:

Majority of patients are female but male predominance is seen in Northern Europe. [1] The disease onset is bi-modal, peaking in the thirties and fifties. [7, 8]

1.3Ethnicities:

Sarcoidosis most frequently affects African-Americans compared to other races.[1] In darker population ulcerative plaques, hypo-pigmented lesions, plaques, erythrodermic, and ichthyosiform sarcoidosis is seen more often.[9] Lupus pernio is an aggressive and destructive manifestation which is seen mostly in dark skinned patients.[10] The prognosis is poor in black population, who have higher extra-pulmonary manifestations, especially advanced lung disease, chronic uveitis, liver and bone disease.[11]

Erythema nodosum, a nonspecific reactive process has a better prognosis. It is observed mostly in Caucasians or Asians. Subcutaneous nodules are extremely infrequent in black patients. [12]

Black women are most severely affected than any other population, and have a higher mortality rate. The long term prognosis is poor and they exhibit a higher rate of relapse. The diagnosis is often missed until the disease reaches an advanced state of cutaneous or systemic involvement. [11]

1.4 Clinical presentations:

Wide variability of clinical findings makes this disease a great mimicker. [1]A review of various studies around the world on cutaneous sarcoidosis confirms that as described earlier, the clinical presentations vary widely based on its influence by genetic and environmental factors (Table 1.2).

Table 1.2 Spectrum of cutaneous sarcoidosis from studies in the world literature. [2, 13, 14, 15]

Previous studies in literature	**Taiwanese/Chinese. [2]**	**Lebanese. [13]**	**Chinese, Indian and Eurasian. [14]**	**South Africa. [15]**
No. of patients	38	76	25	54
Age range (years)	19-76	19-74	15-72	20-62
Sex (%):				
Male	18.4	21.1	60	16.7
Female	81.6	78.9	40	83.3
*Predominant lesion (Frequency of types of cutaneous lesions):				
Papule	6	22	18	5
Plaques	18	37	8	13
Nodules	12	14	18	16
Scar	2	5	1	1

*Some patients in this table show variable morphology. The Chinese, Indian and Eurasian study describes papules and nodules as one category as most patients had both types of lesions. The frequency of both these lesions is therefore considered the same. Predominant or dominant skin lesions only are tabulated to compare the variability.

Table 1.3 shows the variable morphology of cutaneous sarcoid in relation to the ethnicity and geographic differences. [16]

Table 1.3 Geographic and racial variation worldwide. [16]

Country	Ethnicity	Predominant Lesions	References
Denmark	Caucasian	Plaques, annular lesions.	Veien et al.1987. [17]
India	Indian	Combination of multiple papule, nodules and plaques.	Mahajan et al.2007. [18]
Nigeria	African	Scar.	Olumide et al.1989. [19]
Portugal	Caucasian	Nodular plaques, papule.	Mangas et al.2006. [20]
Singapore	Mixed	Papule, nodule, plaque, Scarring alopecia.	Chong et al.2005. [14]
South Africa	Black African	Nodules, plaques.	Jacyk 1999. [15]
South Korea	Korean	Nodular plaques, papule.	Jung& Roh. 2011. [21]
Taiwan	Taiwanese	Papule, nodule, plaque.	Chao et al.2000. [22]
Tunisia	North African	Papule (micro nodular).	Khaled et al.2008. [23]
USA, West Coast	African American mainly	Erythema Nodosum, papule, plaques.	Sharma 1972. [24]
USA, South Carolina	African American	Papular, hypo-pigmented macule.	Minus&Grimes 1983. [9]

The lesions of cutaneous sarcoidosis are usually divided into specific lesions and non-specific lesions. The specific lesions are all marked by a similar histopathology; however, they can vary greatly in their clinical appearances. The nonspecific lesions are reactive processes seen in patients with sarcoidosis.[25]

1.4.1 Specific lesions:

Cutaneous presentation ranges from specific to nonspecific. Variety of specific lesions is documented in literature. Papule, plaque, nodule, scar and lupus pernio are common specific presentations. Less distinctive variants include Darier-Roussy disease, annular, angiolupoid, psoriasiform, hypo pigmented, and atrophic, ulcerative, erythrodermic and ichthyosiform lesions. These presentations can mimic a number of other diseases

clinically.[8] Table 1.4 shows differential diagnosis of various cutaneous presentations of sarcoidosis.

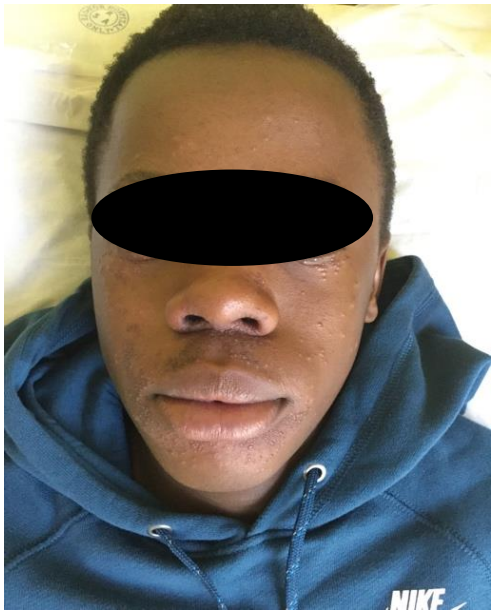
Table 1.4 Differential diagnoses of specific sarcoid lesions. [16, 26-29]

Papular sarcoid	Lichen planus, xanthomas, syringoma, lupus erythematous, adenoma sebaceum, granulomatous rosacea, trichoepithelioma, perifollicular fibroma, foreign body reaction, secondary syphilis.
Scalp sarcoid	Seborrheic dermatitis, alopecia areata, cicatricial alopecia due to discoid lupus erythematosus, lichen planopilaris, pseudopelade of Brocq, alopecia due to metastatic disease and other causes of alopecia.
Plaque sarcoid/ Annular sarcoid	Psoriasis, lupus vulgaris, necrobiosis lipoidica, leishmaniasis, discoid lupus erythematosus, leprosy, nummular dermatitis, cutaneous T-cell lymphoma, erythema gyratum, granuloma annulare, Kaposi sarcoma, secondary or tertiary syphilis.
Verrucous sarcoid	Squamous cell carcinoma, deep fungal infection, cutaneous Crohn's disease, foreign body granulomatous reactions, tuberculosis, leishmaniasis.
Angiolupoid sarcoid	Plaque sarcoidosis, basal cell carcinoma, rosacea.
Lupus pernio	Chilblain pernio, Jessner's lymphocytic infiltration, pseudo lymphoma, lupus vulgaris, chilblain lupus.
Nodular sarcoid	Foreign body reactions, granuloma annulare, rheumatoid nodules, lymphocytoma cutis, lipoma, cyst, pseudo lymphoma, cutaneous metastasis, dermatofibrosarcoma, reticulohistiocytosis, atypical mycobacterial infections.
Darier-Roussy sarcoid	Subcutaneous granuloma annulare, erythema nodosum, foreign body granulomas, lupus panniculitis, lymphomas, lipomas and other panniculitides.
Sarcoidal scar	Hypertrophic scars or keloids, lupus erythematosus, squamous cell carcinoma.
Atrophic sarcoid	Localized scleroderma, mycosis fungoides.
Ulcerative sarcoidosis	Necrobiosis lipoidica, lipodermatosclerosis, squamous cell carcinoma, basal cell carcinoma.
Hypo-pigmented sarcoid	Mycosis fungoides, leprosy, pityriasis alba, pityriasis lichenoides chronica, tinea versicolor, vitiligo, post inflammatoryhypo pigmentation, idiopathic guttate hypo melanosis.
Mucosal	Oral: Orofacial granulomatosis, Crohn's disease, bacterial or fungal infection, Melkersson-Rosenthal syndrome, foreign body granuloma, granulomatous cheilitis, malignancy. Genital: Tuberculosis, Crohn's disease, foreign body granuloma, anogenital

	granulomatosis, malignancy.

Papular sarcoidosis:

Papule is the most common amongst all specific presentations. They often simulate wide number of diseases. [30] They are discrete, commonly noticed on the face, eyelid and naso-labial folds. They resolve with no scarring. The color of the lesions can vary from red, brownish-red, and brown to violet. This form represents an acute disease state (Figures 1.1, 1.2). [26]



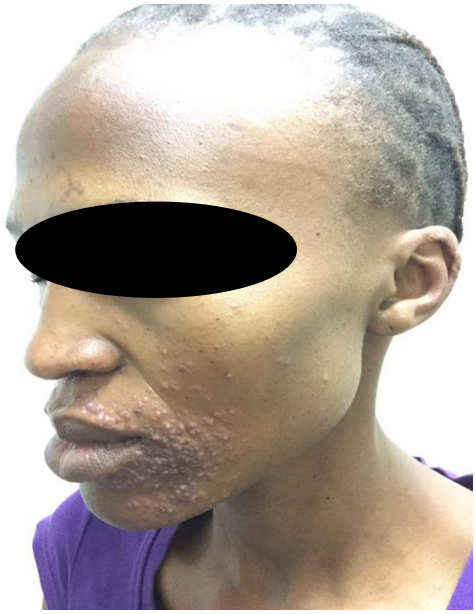


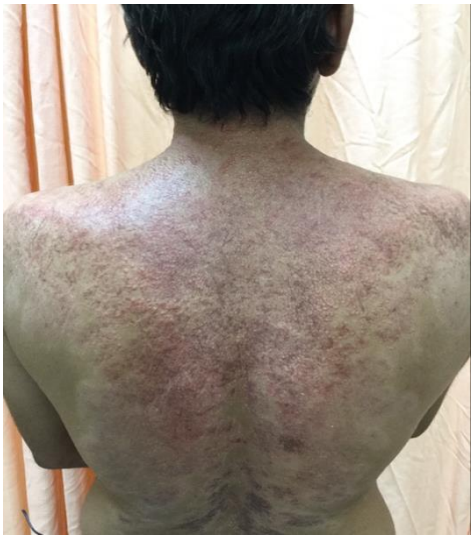
Figure 1.1 **Figure 1.2**

Papular sarcoidosis

Acute systemic signs, like the sudden onset of lymph-adenopathy, acute arthritis, uveitis, and enlargement of the parotid gland have been tied to these maculo-papular eruptions. Even without treatment, they usually disappear within years without leaving any significant scarring. Systemic involvement is rarely seen. When involved they are usually less severe as compared to other clinical presentations. [16]

Plaque sarcoidosis:

Plaque sarcoidosis present as round, oval or annular, discrete plaques which maybe flesh-colored, erythematous, or red-brown. The extensor surface of the extremities, buttocks, face, and back are most often the sites of involvement (Figures 1.3, 1.4). [26]



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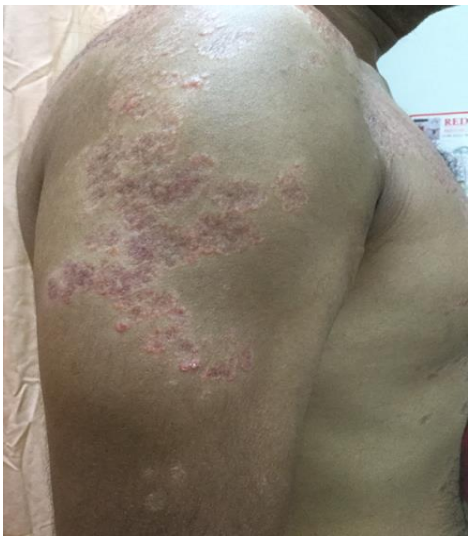


Figure 1.4

Plaque sarcoidosis

The plaques are significantly indurated and unlike papular variant, heal with permanent scarring or pigmentation. Plaque sarcoidosis is often associated with chronic systemic diseases, such as pulmonary disease, uveitis, and lymph-adenopathy. [26]

Many other skin conditions share similar clinical feature with plaque sarcoidosis, and they should be considered in the differential diagnosis. Presence of large telangiectatic vessels or thick silvery scales can imitate psoriasis. Central atrophy with scaling plaques especially on the face imitates discoid lupus. [31] The other examples of disorders, resembling plaque sarcoidosis are listed in Table 1.4. Less common types are verrucous sarcoidosis, angiolupoid sarcoidosis and psoriasiform sarcoidosis.

Verrucous sarcoidosis:

Verrucous sarcoidosis can easily be missed clinically, unless a biopsy is appropriately performed. It is a very rare variant. [32] Histology findings show significant verrucous epidermal hyperplasia with dermal involvement by typical non-caseating sarcoid granulomas. According to Shaffer and Beerman, the verrucous epidermal changes are observed as a skin reaction due to extreme and persistent rubbing and scratching. [33] These patients almost always have a long-standing systemic involvement.

Angiolupoid sarcoidosis (Brocq-Pautrier angio-lupoid):

Angiolupoid sarcoidosis is very uncommon. They are one or a few erythematous to violaceous hemispheric papulo-nodular lesions with telangiectasia. They are seen on either side of the nasal bridge in close proximity to the inner canthus. Divided opinions make this entity, mysterious and confusing. Some suggests that they are just a subtype of plaque sarcoidosis with prominent large telangiectasia while some even consider it as a subtype of lupus pernio. A significant feature, telangiectasia is due to the use of high-potency topical steroid regularly. [26, 29]

Psoriasiform sarcoidosis:

Psoriasiform sarcoidosis is another rare cutaneous manifestation of the disease. Only 0.9% of the patients with sarcoidosis have been reported to develop this form. Majority of them are dark-skinned patients. [34] The plaques can be confused as psoriasis; however, these resolve with significant scarring, hypo-pigmentation, or atrophy. Psoriasis may develop also in patients with sarcoidosis; yet, the simultaneous and parallel occurrence is seldom reported in the literature. The increased expression of TNF-α in both entities can be a viable explanation for the psoriasiform patterns seen as a secondary change in sarcoidal lesions. [34] Another hypothesis explains that

Sarcoidosis may develop as a Koebner phenomenon on a pre-existing psoriasis lesion rather than a cutaneous sarcoidosis clinically resembling psoriasis. [11, 34]

Lupus pernio:

Papule, nodules and plaques characterize lupus pernio. The nose, ears and cheeks are cold sensitive areas which are primarily seen affected (Figures 1.5 and 1.6).

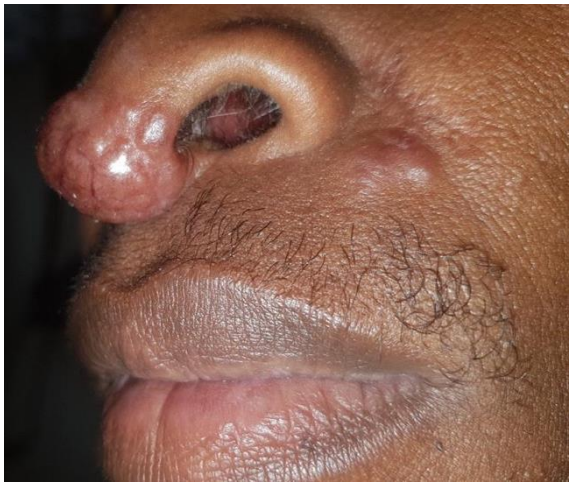


Figure 1.5

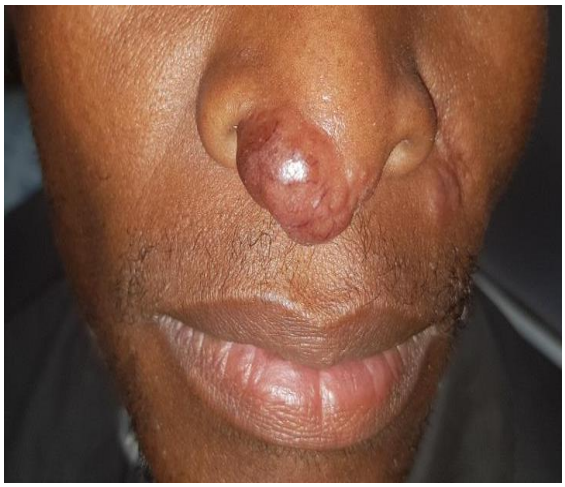


Figure 1.6

Lupus pernio

African-American race and female patients are risk factors associated with these lesions. When they are unattended and left without treatment, they slowly and progressively infiltrate into the skin and indurate. They are aggressive and dangerously destructive. As the disease evolves, they erode the underlying cartilage and bone, resulting in massive destruction and disfigurement. [29] Lupus pernio is a chronic disease lasting longer than two years and has alarming risk of chronic progressive organ disease. [26] Even a tiny discrete papule in this area might be associated with granulomatous infiltration of the nasal mucosa and upper respiratory tract. This eventually complicates forming enormous masses, ulceration, or even life-threatening airway obstruction. [31] Lupus pernio sometimes appear on the dorsal hands, fingers, and toes. When they do, they have related secondary complications like bone cyst

formation, dystrophic nail changes, and destructive bony lesions. [26] They can be easily misdiagnosed as chilblain pernio. Lupus pernio is a very stubborn variant. They are recalcitrant to treatment and rarely respond. [26]

Plaques may appear in unusual places like on the arms, thighs and buttocks. A sausage-shaped expansion and broadening of the phalanges have been reported in a handful of cases. [8, 26, 28] Lupus vulgaris can mimic lupus pernio especially when it affects the nose. [8, 26, 29] Similarly, papule, nodule and plaque sarcoid lesions in this distribution can imitate lupus pernio. However, the former variants are quick treatment responsive. Lupus pernio is highly recalcitrant. [8]

Mutilating sarcoidosis:

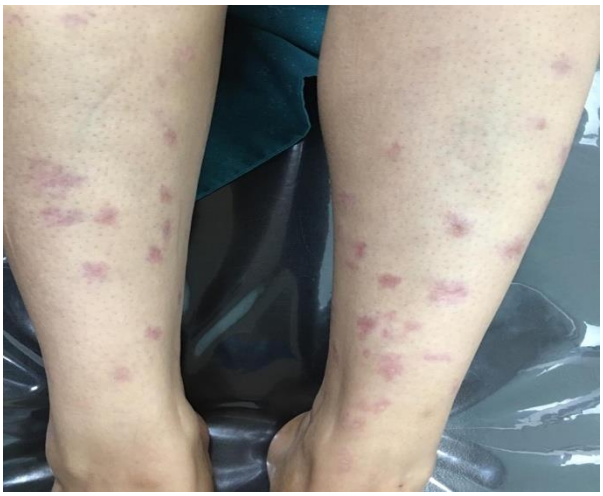
Mutilating sarcoidosis is a severe form of lupus pernio. They are large centro-facial tumors which extend into the oral cavity and the upper respiratory tract. Clinically, they mimic Wegener's granulomatosis as well as malignant pleomorphic lymphoma. [29]

Nodules:

Nodular lesions develop sarcoidal granulomas in the dermis or even subcutaneous tissues. They are associated with long-standing systemic involvement. These lesions can raise diagnostic challenges. Conditions mentioned in Table 1.4 may simulate their clinical appearances. [8, 26, 29]

Subcutaneous sarcoidosis:

The terms "Darier-Roussy sarcoidosis" is used to describe nodular sarcoidosis which primarily targets the subcutaneous tissue. They can be solitary or multiple, asymptomatic to tender, erythematous, flesh-colored, violaceous, to hyper-pigmented nodules. These lesions are often distributed along the forearms in a linear pattern. (Figures 1.7, 1.8) [26, 29, 30, 31] .



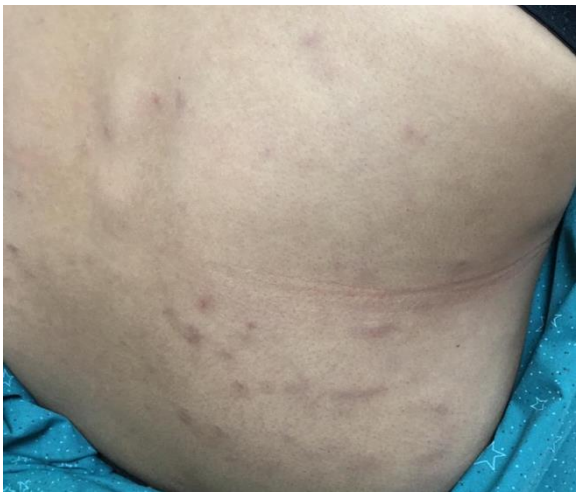


Figure 1.7 **Figure 1.8**

Subcutaneous sarcoidosis

The skin layers above the nodules remain unchanged. They can undergo spontaneous remission. They are considered as the first sign indicating systemic presentation of the disease. The diagnosis should be reached only after excluding other more common diseases which can present with subcutaneous nodules. Subcutaneous granuloma annulare, foreign body granulomas, lupus panniculitis, lymphomas, benign tumor lesions like lipomas, cysts, and panniculitis present with same feature. A skin punch biopsy confirming a naked sarcoidal granuloma in subcutaneous or deep dermal layer can efficiently exclude the other entities. [26, 29, 30, 31]

Erythema nodosum must always be considered as a possibility in sarcoidosis patients with nodular lesions on the legs. They affect the legs while subcutaneous sarcoid favors the forearms. It is only mildly tender as opposed to erythema nodosum which is extremely tender. A biopsy should be performed to help distinguish these diagnoses. [26, 29, 30, 31]

Infiltrative scars:

Scar sarcoidosis may appear on a tattoo, incision or even a lesion of discoid lupus erythematosus. [31] The erythematous or violaceous scar may indicate reactivation of the underlying sarcoidal process. [26, 29]

Atrophic sarcoidosis:

The atrophic type is characterized by hypo-pigmented, shiny areas, cigarette paper–like central atrophy, and even a morphea form plaque. [26] Secondary changes like erythema and poikiloderma may imitate localized scleroderma or mycosis fungoides. In diabetic patients especially in African American population, necrobiosis lipoidica diabeticorum is also considered as a differential diagnosis with this presentation. [29]

Ulcerative sarcoidosis:

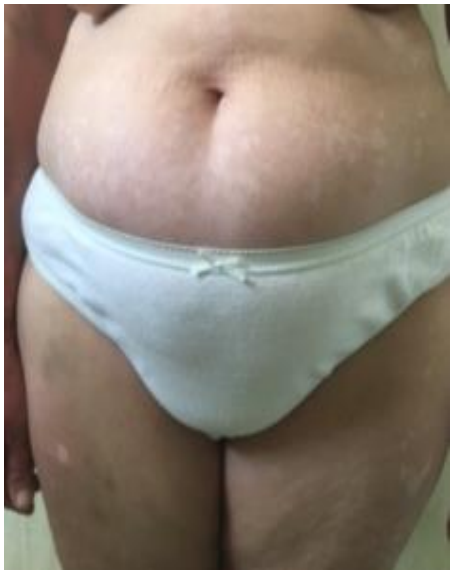
Ulcerations may occur independently or as a complication and secondary change to a different variant. Atrophic and papulo-nodular lesions mostly ulcerate with worsening condition. Again, these findings can be confused with other conditions (Table 1.4) and requires exclusion. [26, 29]

Ichthyosiform sarcoidosis:

This occurs infrequently on the legs. Secondary scaling and xerosis can be misleading and maybe misdiagnosed as a form of ichthyosis. The scales are, however, unique. They exhibit central adherence, giving a “pasted on” appearance. If the condition is neglected or untreated they can progressively become worse and present as ichthyosiform erythroderma. [35] Icthyosiform mycosis fungoides, a rare variant of the lymphoma also has similar features. Clinicians require high degree of suspicion especially in elderly patients. A histopathology evaluation again distinguishes both conditions easily and therefore is highly encouraged. [28, 35]

Hypo-pigmented sarcoidosis:

Hypo-pigmented sarcoidosis is mostly noticeable in Fitzpatrick skin type II to VI. The lesion appears as a well demarcated, round to oval plaque (Figures 1.9, 1.10, 1.11). Histology examination helps distinguish it from mimickers. [26]



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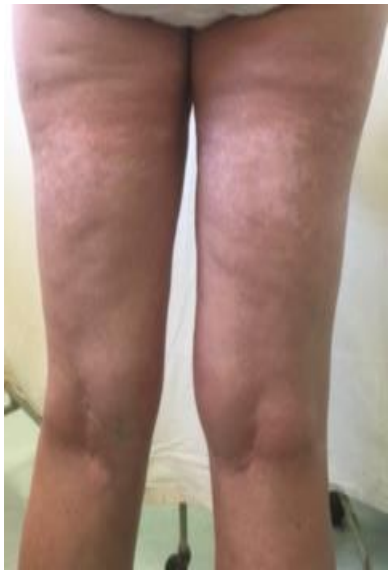

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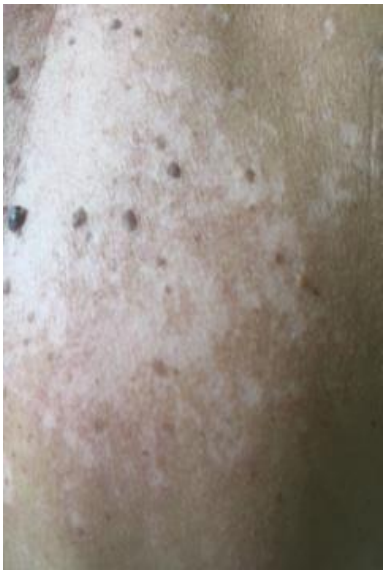

Figure1.11

Hypo-pigmented sarcoidosis

Erythrodermic sarcoidosis:

Erythrodermic sarcoidosis presents with moderately infiltrated, erythematous to yellow-brown localized plaques. These plaques eventually become confluent and desquamate. Classic exfoliative erythroderma is diffuse whereas ichthyosiform erythroderma is more localized, scaly with larger scales. [28, 36] These are subtle differences which are difficult to identify and requires high suspicion and clinical expertise. Studies suggest that Sézary syndrome has epithelioid granulomas that imitate sarcoidosis on histopathology. This condition should be ruled out before deciding on the diagnosis of erythrodermic sarcoidosis. [37]

Scalp sarcoidosis:

This is an uncommon presentation. African-American women are more prone to be affected. [16] Scalp lesions may either be localized atrophic, annular, or indurated plaques or as flesh-colored or erythematous nodules. Early lesions presenting as erythematous scaly plaques can be confused as a seborrheic dermatitis and macular alopecia lesions can mimic alopecia areata. [16, 28] Local destruction and severe, extensive scarring of the hair follicles may lead to permanent scarring alopecia with progression of scalp disease. This condition is indistinguishable from pseudo-pelade of Brocq. [29] Other causes of scarring alopecia, particularly discoid lupus erythematosus, lichen planopilaris, necrobiosis lipoidica, morphea, or alopecia neoplastica should be considered as a differential diagnosis and excluded. [16] With atrophic or annular scarring alopecia, scalp involvement is a sign of an underlying systemic disease and portends a poor prognosis, unresponsive to therapy. [16]

Mucosal sarcoidosis:

Mucosal involvement with papule, nodule, edema, ulcers, gingivitis, gingival hyperplasia or localized swelling is rare. Nodules and localized swelling are most frequent findings in these patients.[29] They also have visceral lesions indefinitely.[39] The diagnosis can be complicated when confused with diseases like orofacial granulomatosis, Crohn's disease, infections, Melkersson-Rosenthal syndrome, foreign body granulomas, and granulomatous cheilitis, as they are all granulomatous oral disorders.[16] Orofacial granulomatosis is a persistent or recurrent orofacial soft tissue swelling and ulceration with no signs of visceral disease. Lymph edema and non-caseating granulomas are the pathologic features of this disease mimicking sarcoid. [16, 40]

Genitourinary tract involvement is rare. Infiltrated plaques on the vulva and perianal area resemble tuberculosis, Crohn's disease, and foreign body granulomas. They can occur in any part of the genitourinary tract and resemble tumor or abscess formation. [40] Ano-genital granulomatosis is a rare chronic inflammatory disorder of unknown etiology that is identical with sarcoidosis clinically and on histology. [40]

Rare variants:

There are many new and rare presentations reported recently.Perforating, erythema multiforme-like, leonine facies, pustular folliculitis, pityriasis rosea-like annular (figures 1.12, 1.13), photo distributed, lymph edematous, polymorphous, and palmo-plantar erythema are few such examples. [11, 16, 28] It is currently unclear if they can be considered variants of sarcoidosis or they are just incidental findings is open to conjecture.[8,10,16] A polymorphous variant exhibiting multiple specific and nonspecific lesions may exist in the same patient mostly when there is multi-system disease involvement.[26,28]

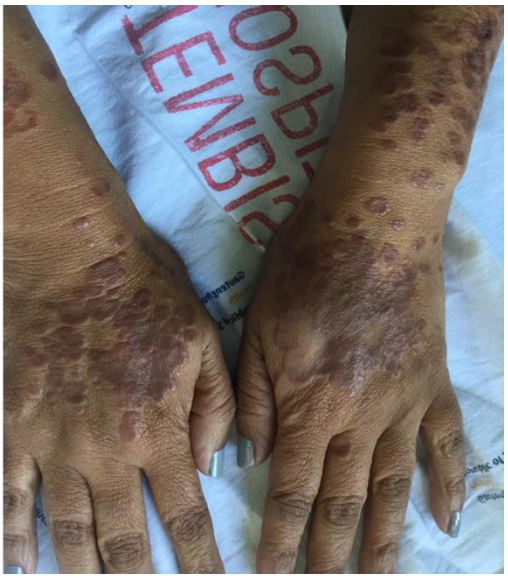

Figure 1.12

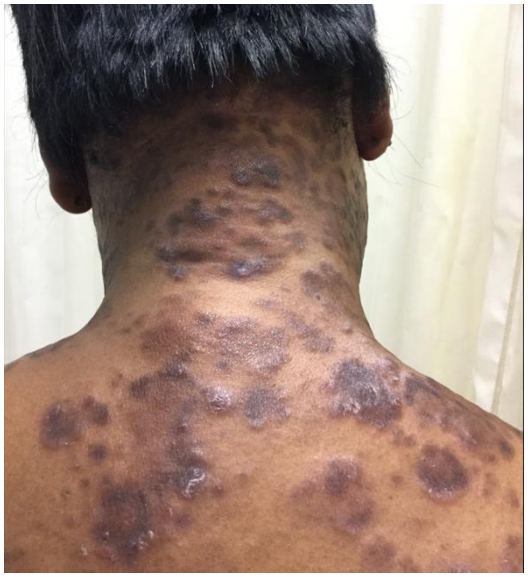

Figure 1.13

Annular sarcoidosis

1.4.2 Nonspecific lesions of sarcoidosis:

Erythema nodosum, erythema multiforme, prurigo, scarring and non-scarring alopecia calcinosis cutis, nail changes and polymorphous eruptions are some of the established nonspecific lesions. [27] Erythema nodosum being the most widely reported finding. Others are rare and not often reported and documented by the clinicians.

Erythema nodosum:

Erythema nodosum can occur due to various underlying factors such as infections, drugs and medications, and inflammatory conditions like sarcoidosis itself. It is a hypersensitivity reaction to such stimuli. Typically, they are extremely tender and present as a subcutaneous erythematous nodule, usually on the shin. Histopathology examination of erythema nodosum shows panniculitis with septal inflammation. [16, 30, 31]

Nail sarcoidosis:

Nail dystrophy is the most common nail finding. Other nonspecific findings are Nail thickening, longitudinal ridging, discoloration, splinter hemorrhages, onychorrhexis, onycholysis, pterygium, subungual hyperkeratosis, lamellar splitting, clubbing, nail pitting, cracking, and brittleness. These features are noted in wide variety of diseases. They are non-diagnostic. However, they do indicate active disease. [28] Lupus pernio, a more persistent and recalcitrant variant may complicate with bulbous swelling of the fingertips, “drumstick dactylitis,” and ultimately distortion of the nails. [28] Suspected nail sarcoidosis patients must always undergo radiologic study to reveal possible bony cysts and pulmonary involvement. [28, 29]

1.5 Syndromes and cutaneous sarcoidosis:

1.5.1 Lofgren's syndrome:

Lofgren's syndrome is an acute clinical condition. It was first described by Sven Lofgren (1910-1978) as a collection of acute onset erythema nodosum, bilateral hilar lymph-adenopathy, fever, and migratory poly-arthritis, without any granulomatous skin involvement. It has a sudden onset, appearing with systemic clinical signs like fever, malaise, and poly-arthralgia. This syndrome differs from sarcoidosis in terms of treatment, prognosis, and recurrence. They also have a favorable prognosis. The differential diagnosis is wide, including atypical mycobacterial and fungal infections, drug-induced serum sickness, lymphoma, reactive arthritis, and vasculitis. [41]

1.5.2 Heerfordt's syndrome:

Heerfordt's syndrome is characterized by the facial nerve palsy, parotid gland enlargement, anterior uveitis, and low grade fever [42]. Recently, this syndrome is considered as a subtype of sarcoidosis. A complete form of Heerfordt's syndrome constitutes only 0.3% of all cases of sarcoidosis.[7] According to the guidelines proposed by the Japan Society of Sarcoidosis and other Granulomatous Disorders in 2006 [11] Heerfordt's syndrome is classified into complete and incomplete type. Patients with complete type, all four main symptoms are presented. In incomplete type, only two out of the three symptoms of facial nerve palsy, parotid gland enlargement, and anterior uveitis are noted. There are no standard treatment guidelines available for Heerfordt's syndrome. This is due to the rarity of this syndrome and very few studies which are at their infancy stage. Currently, it is treated similar to neuro-sarcoidosis as facial nerve palsy is frequently observed. 5–15% of sarcoidosis patients have neurological complications. The facial nerve being one of the most frequently affected cranial nerves. Corticosteroids are the first-choice treatment. The response rate to corticosteroids are high, however, the tapering of the corticosteroid dose can trigger immediate relapse of disease. In such circumstances, immunosuppressive agents, including azathioprine,

Methotrexate, cyclosporine A, and cyclophosphamide, can be considered in combination with the corticosteroids. It is crucial that we diagnose and treat Heerfordt's syndrome appropriately in cooperation with specialists in respiratory medicine and ophthalmologists. It is usually a self-limiting disease that resolves within 12 to 36 months. Sometimes they have a prolonged course. Prognosis of the disease is variable with 1-5% mortality rate. They vary according to the duration, severity and the organs affected. [42]

1.5.3 Mikulicz Syndrome:

Mikulicz Syndrome is a rare, chronic disease characterized by abnormal enlargement of the lacrimal and parotid glands. It is a benign self-limiting condition. Classic symptoms are xerostomia, parotid swelling and dry eyes. The glandular enlargement can be both bilateral and unilateral in distribution. They can be in concurrence, or in isolation. There are considerable amount of debates about the entity. Multiple aetiology factors have been established for Mikulicz syndrome that includes Sjogren's syndrome, sarcoidosis, lymphoma, and tuberculosis. Females are affected more than male patients and they are typically in their middle years. The treatment and prognosis are dependent on the underlying cause. MRI scan and sialography can assist to visualize the glandular enlargement and abnormal ductal architecture respectively. It is important to rule out Sjögren's syndrome as they also exhibit similar clinical features. They are usually corticosteroid responsive and are the treatment of choice in acute phase. Surgical excision can be considered for large parotid glands. Prognosis is variable and indefinite due to lack of studies. [7, 28, 29]

1.6 Sarcoidosis and systemic disease:

As discussed earlier, sarcoidosis is a multi-system disease. Table 1.5 below shows various manifestations of systemic involvement.

Table 1.5 Extra cutaneous manifestations of sarcoidosis. [16,30,31]

Organ involvement	**Findings**
Pulmonary	Bilateral hilar lymphadenopathy Mediastinal lymphadenopathy Parenchymal infiltrate Pneumothorax Respiratory failure Pulmonary hypertension Pulmonary fibrosis
Ocular	Uveitis Keratoconjunctivitis sicca Adnexal granulomas Retinal vasculitis Retinal peri phlebitis Vitreous opacities Multiple chorioretinal peripheral lesions Nodular or segmental peri phlebitis Optic disc nodules or granulomas Solitary choroidal nodule Optic neuropathy
Upper respiratory tract disease	Laryngeal sarcoid: Supra-glottis, sub-glottis Nasal and sinus sarcoid: Rhino-sinusitis, nasal obstruction, epistaxis and nasal polyposis, mucosal

	hypertrophy
Exocrine glands	Painless swelling of the salivary and parotid glands Xerostomia Keratoconjunctivitis sicca
Cardiovascular	Heart block and arrhythmias Ventricular tachycardia Heart failure Valvular dysfunction Simulated infarction Pericardial disease Pulmonary hypertension Cor pulmonale Sudden death
Lymphadenopathy	Hilar or paratracheal mediastinal adenopathy Peripheral lymphadenopathy Intra-abdominal lymphadenopathy
Liver	Liver function test abnormalities Hepatomegaly
Spleen	Splenomegaly Splenic nodule Hypersplenism
Musculoskeletal system	Acute poly-arthritis Chronic arthritis with periosteal bone resorption Diffuse granulomatous myositis
Neurologic system	Cranial neuropathy Cognitive manifestations Peripheral neuropathy

	Myopathy Meningeal disease
Renal	Nephrocalcinosis Nephrolithiasis Hypercalciuria Chronic renal failure End-stage renal disease Interstitial nephritis Glomerulonephritis Nephropathy Hypertension
Endocrine	Anterior pituitary infiltrate Thyroid infiltrate
Genitourinary tract	Endometrium, ovary, and uterine fibroids. Testicular infiltrate

1.7 Sarcoidosis and associated diseases:

Sarcoidosis, especially systemic sarcoidosis, is associated with hypertension, thyroid disorders, diabetes mellitus and malignancies. [2]There are very few studies on association between cutaneous sarcoidosis and comorbidities. Table1.6 represents two such studies showing associated co-morbidities in literature. [2]

Table 1.6Comparison of co morbidities of patients diagnosed with sarcoidosis. [2]

Extracutaneous involvement Comorbidities	**Taiwanese/Chinese Liu et al. (2017) N(%).[2]**	**Lebanese Ishak et al. (2015)[13]**
Type 2 diabetes mellitus	10 (26.3)	5 (6.6)
Hypertension	5 (13.2)	9 (11.8)
Dyslipidaemia	6 (15.8)	5 (6.6)
Cerebrovascular accident	3 (7.9)	
Benign thyroid disorders	3 (7.9)	NA
Hepatitis C virus infection	3 (7.9)	NA
Hearing loss	4 (10.5)	NA
Eye diseases	3 (7.9)	NA
Malignancy	5 (13.2)	NA

N: Frequency.

1.8 Pathogenesis:

The aetiology of the disease remains unknown. According to the hypothesis various antigens like infectious agents, organic and inorganic agents of environmental origin triggers an exaggerated immune response in genetically susceptible hosts. Antigen-presenting cells (APC) produce a high level of tumour necrosis factor alpha (TNF-α), interleukin 12, 15 and 18, macrophage inflammatory protein 1 (MIP-1), monocyte chemotactic protein 1 (MCP-1), and granulocyte macrophage colony-stimulating factor (GM-CSF). The main feature of sarcoidosis is the presence of CD4+ T cells which interacts with APCs to form granulomas.[1; Figure 1.14]

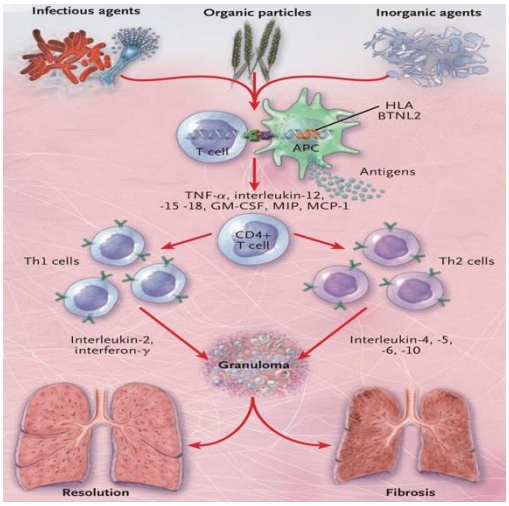

Figure 1.14 Hypothesised immune-pathogenesis of sarcoidosis. [1]

1.9 Diagnosis:

Due to the varied presentations as well as multi system involvement, diagnosis of the disease becomes complex. It cannot be diagnosed by a simple single test. Many diseases can mimic sarcoidosis both clinically as well as on histology evaluation. Hence it becomes extremely difficult for a clinician as well as for the pathologist to diagnose it confidently.[32] The exact diagnosis can be achieved by collaboration of clinical findings, biopsy confirmed non-caseating granuloma, laboratory test supporting the diagnosis as well as radiology investigation to establish the extent of systemic involvement and exclusion of other possible diseases that can mimic this entity. Skin biopsy is suitable for cutaneous disease but in presence of chest symptoms lymph node or lung biopsy is indicated. [8, 32]

1.9.1 Diascopy:

This simple bedside tool can assist with the diagnosis; however, it is not a confirmatory test. The examination shows “apple jelly” colour of the lesion and pressure induces blanching. Apple jelly appearance is a clue and it is also seen in other granulomatous

conditions such as tuberculosis, granulomatous rosacea, lupus miliaris disseminatus faciei, leprosy and granulomatous periorificial dermatitis. [8, 16]

1.9.2 Dermatoscopy:

This simple bedside examination again can only be used to support the diagnosis and is not confirmatory. Examination shows yellow-orange globules with structure less whitish areas. Linear vessels can sometimes be noted in the white areas. This is again seen in various other granulomatous diseases thereby making it a supportive tool. [8, 30]

1.9.3 Histopathology:

The biopsy specimen ideally should be deep as the pathology is in the dermis and sometimes even involves the subcutaneous layer. Histology examination shows characteristic non-caseating granulomas. They are also called naked or sarcoidal granuloma. [20, 21, 43]

These granulomas have an infiltrating pattern. Macular lesions sometimes may not show granulomas which makes the diagnosis difficult. In such scenarios the clinician should consider multiple biopsies of suspicious lesions. A typical sarcoidal granuloma show multinucleated giant cells and epithelioid cells within the granuloma. Characteristic cytoplasmic inclusions, such as asteroid bodies, Schaumann bodies, birefringent crystalline calcium oxalate and other calcium salt particles are major features of a sarcoidal granuloma. [20, 21, 43]

Sometimes, small focus of central fibrinoid necrosis can be noticed. But it is not a characteristic feature of a sarcoidal granuloma. When seen in large amount, an alternate diagnosis should be considered. Many nonspecific histology findings have been noted in various studies. These are atypical and not diagnostic. Pathologists should be aware of such findings. These include presence of necrosis, foreign material, periadnexal and interstitial distribution of granulomas, coexistence of lichenoid and granulomatous infiltrate, granulomatous vasculitis, and epidermal changes. [43]

A descriptive study by Ball NJ et al in Canada on twenty-eight biopsy specimens of patients confirmed with sarcoidosis is seen in Table 1.7. It shows various non-specific histological findings in addition to the usual naked granulomas typical of sarcoidosis. [43]

Table 1.7 Histological findings in a study of twenty-eight sarcoidosis patients. [43]

Naked sarcoidal granulomas	89% (25/28 biopsy specimen)
Non sarcoidal granulomas	11%
Other non-specific findings:	
Tuberculoid granulomas	4/28 biopsy specimen
Interstitial granulomas	5/28 biopsy specimen
Birefringent foreign material	50%
Focal necrosis	43%
Elastophagocytosis	39%
Linear perineural granulomas	25%
Increased dermal mucin	18%
Lichenoid inflammation	14%

Non-caseating granulomas are sensitive however not specific for sarcoidosis. It can be seen in other diseases like tuberculoid leprosy, cutaneous Crohn's disease, beryllium granulomas, foreign material, immunodeficiency disorders, lympho-proliferative disorders and drug eruptions. [29, 32] Just like the clinical picture, histopathology of sarcoidosis can mimic other conditions. Differential diagnosis of sarcoidosis based on histopathology would be tuberculosis, atypical myco-bacteria, fungal infection, and foreign body reactions like beryllium, zirconium, tattoo, rheumatoid nodules, leishmaniasis, and Melkersson-Rosenthal syndrome. [8, 16, 29]

1.9.4 Laboratory findings:

A baseline workup should always be considered when a patient presents with cutaneous sarcoidosis to rule out underlying systemic involvement. The findings that can be seen in laboratory tests are anaemia, leucopoenia, or lymphopenia, hyper-calcemia, abnormal liver, and kidney function test. Elevated serum alkaline phosphatase level indicates diffuse hepatic involvement. [28, 30, 31, 44, 45] The hyper-calcemia is seen as a result of abnormal production of calcitriol by granulomas, and activated macrophages. The erythrocyte sedimentation rate and C- reactive protein can be elevated in active state of disease. Pulmonary disease shows hilar and paratracheal adenopathy predominantly in the upper lobe bilaterally on chest radiography. Serum Angiotensin-converting enzyme (ACE) levels are increased in 60% of the patients. Hence it is considered as a potential diagnostic test for sarcoidosis. Elevated ACE level is produced by epithelioid cells in granulomas. ACE level cannot be used for diagnostic testing to ascertain disease activity as it has a poor sensitivity (false negative outcome) and insufficient specificity (almost a 10% rate of false positive results). A gallium-67 scan is a tool used to monitor lymphadenopathy, parotid and lacrimal gland involvement. Tuberculin skin test is always encouraged as it helps to distinguish it from tuberculosis. [28, 30, 31, 44, 45]

Any organ can be involved at any stage of the disease. Previously unaffected organs can eventually develop the disease. As the disease progresses affected organs can heal or get impaired. There are no established guidelines currently available to monitor disease activity limited to the skin for the development of systemic sarcoidosis. If new extra-cutaneous symptoms manifest, additional physical examination, or laboratory tests should be performed to establish disease activity. Following that the patient should be referred to an appropriate specialist for further investigation and management. [28, 30, 31, 44, 45] Table 1.8 includes the laboratory tests used for preliminary screening and more advanced tests for special organ involvement.

Table 1.8Preliminary and advanced investigations for systemic sarcoidosis. [44, 45]

	Preliminary screening	**Advanced tests**
Baseline laboratory tests	Complete blood count. Biochemical tests(creatinine, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, calcium level). Urine analysis. Serum angiotensin-converting enzyme level.	24-hour urinary secretion of calcium.
Lung	Chest radiography Pulmonary function test. Tuberculin skin test.	High-resolution computed tomography. Bronchoalveolar lavage. Fluorine18fluorodeoxyglucose-positron emission tomography. Gallium-67, thallium-201, and technetium single photon emission computed tomography.
Cardiac	Echocardiography.	24-hour Holter monitoring. Positron emission tomography. Gadolinium-enhanced cardiac magnetic resonance imaging scans.
Ophthalmologic	Fundoscopic and slit-lamp examination. Visual acuity. Tonometry.	Fundus fluorescein angiography. Optic coherence tomography.
Other	Tuberculin skin test or interferon gamma release assay. Antinuclear antibodies.	Adenosine deaminase. Serum amyloid A. Soluble interleukin-2 receptor. For specific involvement: Laryngoscopy. Bone radiography.

		Abdominal computerized tomography. Positron emission tomography. Magnetic resonance imaging.

1.10 Management:

Corticosteroids are the treatment of choice as first-line therapy. Skin directed therapies, topical or intra-lesional steroid, are used for localized cutaneous sarcoidosis. [24, 28] Other treatments for local disease include topical tacrolimus, topical retinoid as well as photodynamic therapy, ultraviolet A therapy, laser therapy (pulsed dye and CO2 lasers), and surgical excision of treatment resistant lesions. Patients exhibiting progressive disease, refractory to local treatment, severely scarring sarcoid, or cutaneous and systemic involvement, may require systemic corticosteroids at higher doses. [24, 28, 30]

Second-line therapies are anti-malarial therapy and cytotoxic agents, such as methotrexate, azathioprine, leflunomide, and Mycophenolate Mofetil. [30, 38]
Third-line therapies are newer biologic agents. Infliximab is the most studied drug in this class. Alternative therapies are thalidomide, isotretinoin, allopurinol, cyclosporine, and laser therapy. Recently, repository corticotrophin injections and rituximab have also been studied and noted as effective treatment. [30, 38]

Surgical removal of inactive sarcoid scars can stimulate reactivation. Methotrexate, which reportedly has a response rate of 60 to 80%, can be used in severe recalcitrant disease. Other oral disease-modifying anti-rheumatic drugs include azathioprine, leflunomide, and mycophenolate mofetil, thalidomide and tetracyclines have limited studies and are controversial. [24, 28, 30, 38]

Anti -TNF agents i.e. biologics have emerged as an effective treatment for cutaneous sarcoidosis in the last decade. They are now often used when other treatments fail. Reports demonstrate infliximab and adalimumab to be effective for severe cutaneous lesions like lupus pernio and ulcerative sarcoidosis and are indicated when systemic

corticosteroids have failed. A clinical trial of etanercept for pulmonary sarcoidosis showed lack of benefits, increased side-effects and less effectiveness for the disease. Therefore, as an anti-TNF agent for cutaneous sarcoidosis, etanercept is best avoided. [38]

1.11 Natural History:

A spontaneous remission is usually seen in about two thirds of the patients. About 10% to 30% of patients progress to a chronic course.[1] In early disease, the prognosis for remission is favourable, with spontaneous remission observed in 50% to 90% within the first two years of diagnosis.[1] Lofgren's syndrome has an excellent prognosis, with spontaneous remission in up to 80% of patients, usually in months.[41] Black patients are more likely to have a symptomatic, severe, and chronic disease than white patients.[9] Lung is the most common organ involved. Patients with cutaneous disease may also have chest involvement. A radiological staging of pulmonary sarcoid have been devised. This is extremely useful to plan management and predict the prognosis of these patients. Staging by chest radiography is inversely correlated with the possibility of spontaneous resolution (Table 1.9). [46]

Table 1.9 Radiologic staging of sarcoidosis. [46]

Staging	Chest radiography results	Rates of spontaneous resolution	Suggested follow-up
0	Normal	-	-
1	Bilateral hilar lymphadenopathy	55% to 90%	At first every six months, then annually when disease is stable.
2	Bilateral hilar lymphadenopathy with pulmonary infiltrate	40% to 70%	Every three to six months indefinitely.
3	Pulmonary infiltrate without bilateral hilar lymphadenopathy	10% to 20%	Every three to six months indefinitely.

4	Pulmonary fibrosis	0% to 5%	Every three to six months indefinitely.

1.12 Prognosis:

The prognosis of patients with cutaneous sarcoidosis is directly proportionate to the extent of systemic involvement. Patients with only skin disease have a better prognosis as compared to patients with systemic involvement with or without cutaneous lesions. The severity of the skin lesions and the extent of systemic involvement are not related. Information on the prognosis and the extent of systemic involvement can be established by further evaluation of various organ systems. [11] Lupus pernio is more chronic and has a refractory course. [26, 29, 31]

Lofgren syndrome and the presence of mediastinal lymph-adenopathy presenting as erythema nodosum, a nonspecific sarcoidal lesion, has an acute course but a good prognosis. [41]Older age, along with respiratory and splenic involvement, are associated with poor outcomes. Maculopapular and subcutaneous variants associated with radiologic stage 1, have a good prognosis. Plaque-type and lupus pernio variants are usually associated with improved radiologic stages but higher recurrence of systemic disease thereby showing a poorer prognosis. [5, 38, 46]

1.13 Cutaneous sarcoidosis and African studies:

There have been only a handful of publications on cutaneous sarcoidosis in Africa. [47] Papule is the most predominant lesion seen in the Ivory Coast.[47] In Nigeria, scar sarcoid due to tribal markings were the most common presentation followed by facial maculo-papular lesions.[19,48]The study conducted in Tunisia interestingly showed a higher predominance of childhood cases and the most common presentation found to be micro-nodular lesions.[23] The study by Jacyk WK on a group of black South African patients in Pretoria published in 1999 showed that cutaneous sarcoidosis mostly presented as nodules, plaques followed by lupus pernio and hypo-pigmented lesions.[15] Sarcoidosis in this particular study is characterized by lesions that are

morphologically extremely variable and atypical. And on histopathology they often demonstrate fibrinoid necrosis which is atypical and not characteristic. [15]

1.14 Cutaneous sarcoidosis and HIV:

This association is extremely rare. Introduction of antiretroviral therapy (ARV) also causes substantial increase in CD4-T lymphocyte level. This leads to “immune restoration disease”. This is also known as Immune Reconstitution Inflammatory Syndrome (IRIS). Initiation of antiretroviral therapy can result in the development of sarcoidosis as an IRIS response. Infected individuals after ARV initiation undergo a “paradoxical reaction”. It is almost like a clinical flare. It is described as a gradual worsening of pre-existing disease or appearance of a new disease. HIV infected population have a very low CD4-T lymphocyte count. The relative lack of these lymphocytes inhibits the development of sarcoidosis. Use of systemic steroid for sarcoid in HIV remains controversial. It is reserved mostly for symptomatic and severe cases. [49]

1.15 Aim and Objectives:

1.15.1 Aim:

The aim of this study is to determine the spectrum of cutaneous sarcoidosis both clinically and histological in a selected South African population at the Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital.

1.15.2 Objectives:

- To describe the demography and clinical presentation of patients with cutaneous sarcoidosis.
- To describe the histological variability of cutaneous sarcoidosis seen in our patients.

CHAPTER 2: METHODOLOGY

2.1 Study design:

This was a retrospective, descriptive study of patients seen at Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital who had a skin punch biopsy done and were proven to have cutaneous sarcoidosis on histology from 1 July 2007 to 30 June 2018.

The skin biopsy is used to obtain information required for the study. The dermatologist provides critical details in histology forms. This includes demographic data (age, gender and race) and a clinical description of the skin lesions. Clinical details such as the morphology, suspected diagnosis, differential diagnosis and a brief clinical history are important. This information is transcribed onto the histopathology report and is followed by a description of the histological findings and a final diagnosis by the pathologist. These details were captured as per the Data Sheet. In case of missing or limited information, files from Dermatology OPD were retrieved and information was collected by using hospital numbers.

When a patient is suspected to have skin sarcoidosis a 3mm punch biopsy is taken and sent for histopathology analysis. The pathology specimen is sent in formalin and the volume should be 10-20 times the volume of the specimen. In the laboratory the specimen is fixed in formalin and remains in this fixation medium for at least six hours. The aim of fixation is to preserve the skin specimen indefinitely in a 'life like' state. Tissue processing then follows with the purpose to remove the extractable water from the skin and to provide a supporting matrix (paraffin) so that the tissue can be cut with minimal distortion. After fixating the specimen, an automatic processor is used to process it. The specimen then passes through ethanol for dehydration, followed by xylene for lipid extraction and clearing of alcohol. Then finally the tissue is melted with hot paraffin so that the specimen can be easily cut. They are usually sectioned using a microtome into sections 3-5 microns. Routine staining with H&E is done. With this staining method, nuclei stain blue (basophilic) and collagen, muscles nerves stain red

(eosinophilic). Special stains such as PAS, Grocott, ZN stain and others are further used to eliminate other diseases provided as differential diagnosis. The stained slide is then processed again though water, alcohol and xylene. A resin is applied to glue a cover slip and the slide is ready to be examined by the pathologist.

Definitive diagnosis is based on histopathology diagnosis of cutaneous sarcoidosis with identification of the naked sarcoidal granulomas on skin tissue. In some cases typical naked granuloma cannot be observed. Tuberculoid, interstitial and palisading granulomas, as well as, other nonspecific findings are sometimes present. The diagnosis is then made with clinical correlation, repeated biopsy and collaboration of laboratory results like serum ACE level, calcium level. All this information was obtained from the Department of Anatomical Pathology at Charlotte Maxeke Johannesburg Academic Hospital using the National Health Laboratory Services (NHLS). The Track-care system was used and results accessed using the Snomed coding using key words e.g. naked granuloma, sarcoidal granuloma, granulomatous dermatitis, etc. Total number of biopsies done was obtained from the Central Data Warehouse.

In certain cases where valuable information is not recorded in the histopathology form of patients confirmed with the disease, the hospital number was used to search for the results in the Track-care system as well as from patient out patient records.

2.2 Data variables:

Demographic data- age, race, gender

Clinical findings - primary lesion and secondary changes.

Histology findings - sarcoidal granuloma, non-sarcoidal granuloma (type), distribution of granuloma, additional non-specific features.

2.3 Study population:

Patients in whom the Dermatology Department at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Helen Joseph Hospital (HJH) performed skin biopsies. The relevant time period is 1 July 2007 to 30 June 2018.

2.4 Inclusion criteria:

Patients, in whom the diagnosis of cutaneous sarcoidosis was confirmed, based on relevant histology results.

2.5 Exclusion criteria:

- Inconclusive biopsy reports and patients who have not been biopsied within the time period.
- Patients with cutaneous sarcoidosis misdiagnosed as diseases other than sarcoidosis.
- Patients with any condition other than cutaneous sarcoidosis.
- Patients with incomplete histology requests were data couldn't be retrieved from hospital file or NHLS database using Track-care system.

2.6 Site of study:

Charlotte Maxeke Johannesburg Academic Hospital , a one thousand and eighty eight bed public sector hospital and Helen Joseph Hospital, also a tertiary hospital that has admission wards, nine medical wards, four surgical wards, two orthopaedic wards, one psychiatric unit, an ICU unit and a high-care unit. Both the hospitals are affiliated to the university and based in Johannesburg, South Africa, serving primarily the population of Gauteng Province, in addition to the neighbouring provinces.

2.7 Data processing and analysis:

Information was obtained from National Health Laboratory System (NHLS) track-care records using SNOWMED extract application at CMJAH. Data on the histology report was extracted. Demographic details of the patient such as age, sex, race, clinical features and histological findings were recorded following the Data sheet.

In case of limited or missing information, files from Dermatology OPD were retrieved and information was collected. After all details were extracted, data cleaning processes such as checking for duplicate and missing values were done. All dataset was stored in a Microsoft Excel program.

The data was then analyzed using statistical software program Stata version 15.0 (StataCorp LD College Station, Tx).

All categorical variables were presented as frequencies and percentages and continuous variables as mean, range and median. Findings were also being presented in frequency tables, bar graphs and pie charts.

Age: The age was grouped as 0-10, 10-20, 20-30, etc. The number of patients in each group was captured as frequency and percentage in a table format and depicted in a bar graph. The mean age and range in this study were noted.

Ethnicities: The patients with confirmed disease were grouped as white, afro-descendants, Indians and Mixed. The frequency and percentage in each group were tabulated. This was further depicted in a pie chart.

Gender: The frequency, percentage and ratio of male versus female population with the diagnosis were established. A pie chart depicting the result was added.

Clinical presentations: The morphology of all patients was extracted from the report. They were grouped as per the data sheet. Some patients with dual morphology were

grouped separately. They were represented as frequency and percentage in a table and depicted in a bar graph.

Histology findings: The findings were grouped as per the data sheet. Other features from the biopsy report were also collected and recorded as this could add valuable information to the study and help enhance the awareness of pathologists and dermatologists to diagnose the disease more efficiently in future. These findings were tabulated as frequency and percentage. A bar graph was further used to represent the findings.

2.8 Ethics Clearance:

Permission was obtained from the CEO of both the hospitals, the Head of Department of Anatomical Pathology as well as the Head of Department of Dermatology. The study proposal was approved by the Human Research Ethics Committee of the University of Witwatersrand. To protect patient confidentiality, the data was sent in an anonymous format with unique identifying numbers. Further all information provided was stored in password protected devices. Photography consent form was also signed by patients when photos were used in the report to demonstrate various clinical presentations.

CHAPTER 3: RESULTS

A total of seventy-five patients were identified with cutaneous sarcoidosis diagnosed on histopathology done at Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital from 1 July 2007 to 30 June 2018.Of the seventy-five patients initially collected with a confirmed diagnosis of cutaneous sarcoidosis, two patients for whom there was no clinical information were excluded. This information could not be extracted from hospital number either. Therefore, seventy three patients were studied.

Demographics:

Age:

The mean age of diagnosis was forty-five years and the median age was forty-four years from the sample of seventy-three patients. The youngest patient was eleven years old and the oldest was ninety-seven years. The median age for female population was forty-eight years and for male was forty years. The mean age for female patient was forty-six years and male patient was forty-two years. The maximum cases were between 31-40 years closely followed by 41-50 and 51-60 years. Table3.1 is a representation of age in frequency and percentage.

Table 3.1 Age represented as frequency and percentage.

Age	Percentage	Frequency
10-20	1%	1
21-30	12%	9
31-40	29%	21
41-50	25%	18
51-60	19%	14
61-70	10%	7
71-80	3%	2
81-90	0	0
91-100	1%	1

Gender:

There was a female predominance noted in this study. The male to female ratio was approximately 1:2.47, with twenty-one males (29%) and fifty-two females (71%). This is represented in Table 3.2.

Table 3.2 Gender represented as frequency and percentage.

Gender	Frequency	Percentage
Male	21	29%
Female	52	71%

Ethnicities:

The study population includes ethnicities like White, Black, Mixed race and Indian patients. The majority of patients were Black followed by White then Mixed and lastly Indian. Out of seventy-three patients, fifty-one (70%) of them were Black, nine (12%) were White, seven (10%) were Mixed and six (8%) were Indian. Table 3.3 depicts the findings discussed.

Table 3.3 Race represented as frequency and percentage.

Race	Percentage	Frequency
Black	70%	51
Mixed	10%	7
White	12%	9
Indian	8%	6

Clinical presentation:

The clinical characteristics of the seventy-three patients are summarized in Table 3.4. The clinical morphology of lesions was recorded from the histopathology form. The results show that sixty-four (87.7%) patients had one type of lesion documented while nine (12.3%) patients had mixed lesions. Specific cutaneous lesions observed were plaques in twelve patients (16.44%), followed by annular plaques in eleven (15.07%), papule in ten (13.70%), plaques and papule as mixed findings in seven (9.59%), hypo-pigmented lesions in seven (9.59%), subcutaneous nodules in six (8.22%), lupus pernio in five (6.85%), nodules in five (6.85%) and scar in three (4.11%) patients. Ulcerative lesions and Lofgren's syndrome, which presents as erythema nodosum in an acute phase, were seen in only two (2.74%) patients respectively. A combined presentation of plaques and hypo pigmented lesions was seen only in one (1.37%) patient. Another mixed presentation of papule with subcutaneous nodules was also seen in only one (1.37%) patient. Verrucous plaques are rare presentations of sarcoidosis and were only seen in one (1.37%) out of all seventy-three patients. Nine patients had skin lesions confined to the face (12.3%). Thirty-one patients (42.5%) had cutaneous involvement except the face. Thirty-three patients (45.2%) presented with lesions on the face and other sites. Predominantly the lesions were reddish brown followed by hypo-pigmented in appearance. Subcutaneous nodules showed minimal surface changes with slight hyper pigmentation. Verrucous surface changes were seen only in one patient as mentioned earlier. Table 3.4 is a summarized clinical morphology in this study population.

Table 3.4 Clinical presentations represented as frequency and percentage.

Clinical presentations	Frequency	Percentage
Papules	10	13,70%
Plaque	12	16,44%

Papule, Plaque	7	9,59%
Hypo pigmented macules	7	9,59%
Plaque, Hypo pigmented macule	1	1,37%
Nodule	5	6,85%
Papule ,subcutaneous nodule	1	1,37%
Subcutaneous nodule	6	8,22%
Annular plaque	11	15,07%
Scar	3	4,11%
Ulcer	2	2,74%
Verrucous plaque	1	1,37%
Lupus pernio	5	6,85%
Lofgren's Syndrome	2	2,74%

Histopathology Findings:

Histopathology findings of all seventy three patients were noted. (Table 3.5) Fifty-nine (81%) showed characteristic naked sarcoidal granuloma. Only fourteen (19%) patients showed non-sarcoidal granuloma. Figure 3.1 is a pie chart showing the percentage of sarcoidal versus non-sarcoidal granulomas.

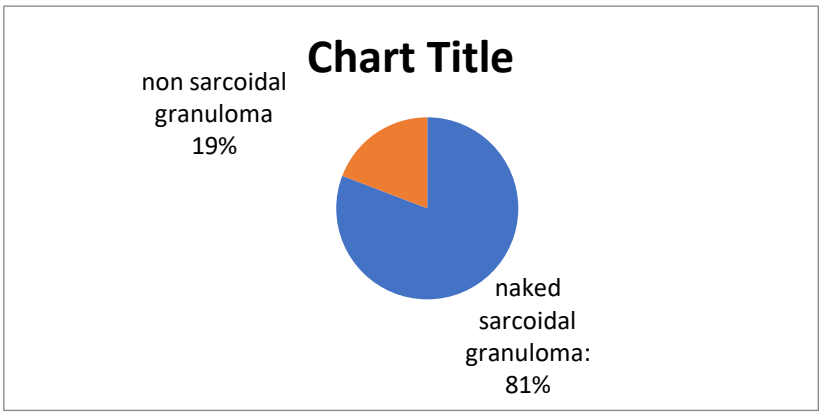

Figure 3.1Sarcoidal versus non sarcoidal granuloma.

Out of the fourteen patients with non-sarcoidal granuloma, four (29%) featured tuberculoid type granuloma, six (43%) had palisading granuloma; three (21%) patients had interstitial type granuloma and only one (7%) patient showed foreign body type granuloma. Eight (11%) of these patients showed a typical perivascular distribution of granulomas, three (4%) patients had a periadnexal pattern of the granulomas and two (3%) only showed perineural distribution pattern. (Figure 3.2)

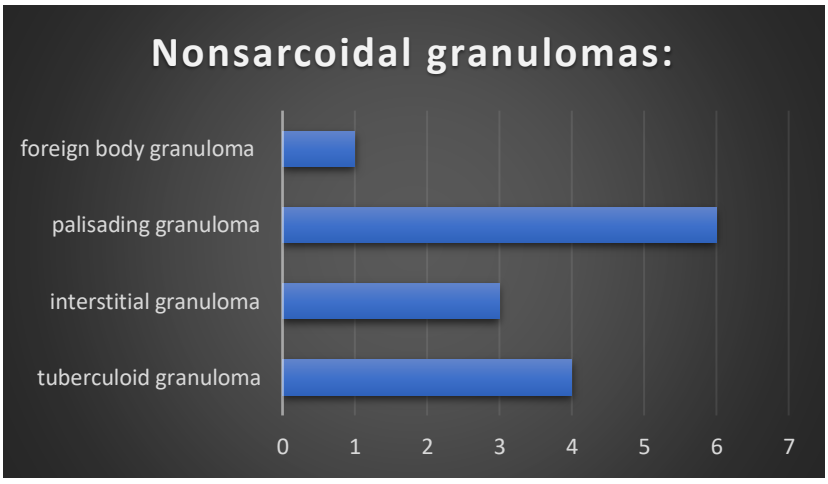

FIGURE 3.2 Graphic representations of various non sarcoidal granulomas.

Table 3.5Histology findings represented as frequency and percentage.

Histology findings:	Frequency	Percentage
GRANULOMA		
naked sarcoidal granuloma:	59	81%
non sarcoidal granuloma	14	19%
NON SARCOIDAL GRANULOMA		
tuberculoid granuloma	4	29%
interstitial granuloma	3	21%
palisading granuloma	6	43%
foreign body granuloma	1	7%
NON SPECIFIC FINDINGS		
focal necrosis	2	3%
increased mucin	3	4%
perivascular distribution	8	11%
peri adnexal infiltrate	3	4%
sclerosis	7	10%
foreign body	1	1%
lichenoid infiltrate	2	3%
perineural infiltrate	2	3%

Besides the specific types of granulomas biopsies also featured several other non-specific findings. The most common non-specific findings seen in this study was sclerosis of the dermal collagen seen in seven (10%) patients. Increased mucin deposits in the dermis were seen in three (4%) patients. Focal areas of necrosis was eminent in two (3%) patients and lichenoid infiltrate was an additional feature in two (3%) of the patients. Only one (1%) patient had foreign body deposit in the dermis. This was the same patient who showed foreign body type granuloma.

CHAPTER 4: DISCUSSION

In this study, we observed certain demographic, clinical and histological characteristics of cutaneous sarcoidosis in Johannesburg, South Africa. The findings were compared to the studies recorded in literature.

Age:

Studies have shown that the disease show a bimodal age group of onset, peaking in thirties and fifties.[7,8] In our population the maximum number of cases reported were between 31-40 years closely followed by 41-50 and 51-60 years of age(Figure 4.1). The mean age of both male and female patients was in forties. The findings noted were similar to that recorded in literature. Our clinicians and pathologists should be more suspicious and alert when it comes to middle aged and elderly patients as they are more likely to have the disease. This would lead to a more proactive diagnosis thereby managing the patients with cutaneous sarcoidosis successfully.

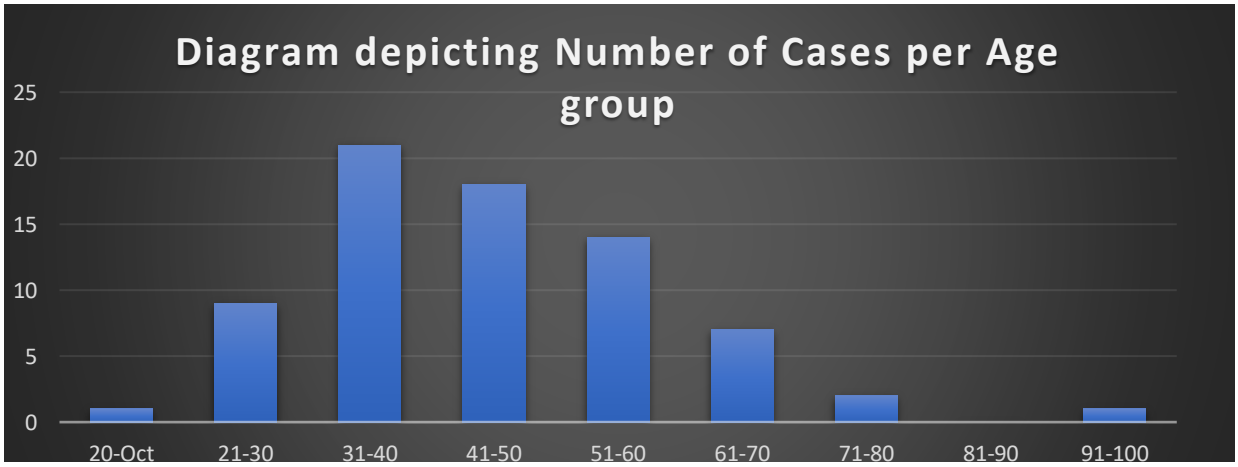

Figure 4.1Bar graph illustrating age distribution

Gender:

The disease is usually more common in female population, but male predominance is seen in Northern Europe. Our data showed a marked female predominance similar to the findings reported in previous case studies (Figure 4.2).[1] The male to female ratio was approximately 1:2.47.Our clinicians and pathologists should be more suspicious and alert when it comes to female patients as they are more likely to have the disease. This would lead to more proactive diagnosis thereby managing the patients with cutaneous sarcoidosis successfully.

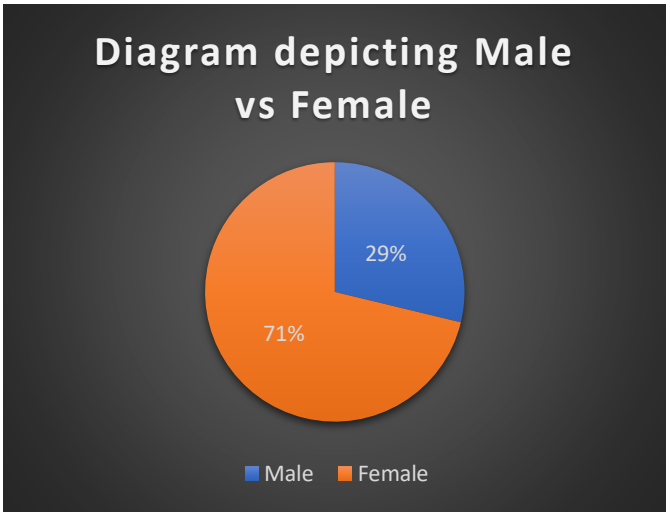

Figure 4.2 Pie chart depicting gender.

Ethnicities:

Literature shows that sarcoidosis most frequently affects Black population compared to other races. [1] In this study we were fortunate enough to include various races. Table 3.3 shows the races presented as frequency and percentage. Unlike the previous South African study by Jacyk et.al, 1999, this was not focused solely on black South African patients.[15] Our study included White, Black, Mixed and Indian patients. This is

particularly a valuable input from this study as the previous study did not reflect the ethnic variation in cutaneous sarcoid in our hospital setting .The majority of patients were Black followed by White then Mixed and Indian. Fifty-one (70%) of them were Black patients (Figure 4.3). These results are in-fact representative of the population of the hospitals studied. Our clinicians and pathologists should be more suspicious and alert when it comes to Black patients as they are more likely to have the disease. This would lead to more proactive diagnosis of the disease thereby managing the patients with cutaneous sarcoidosis successfully.

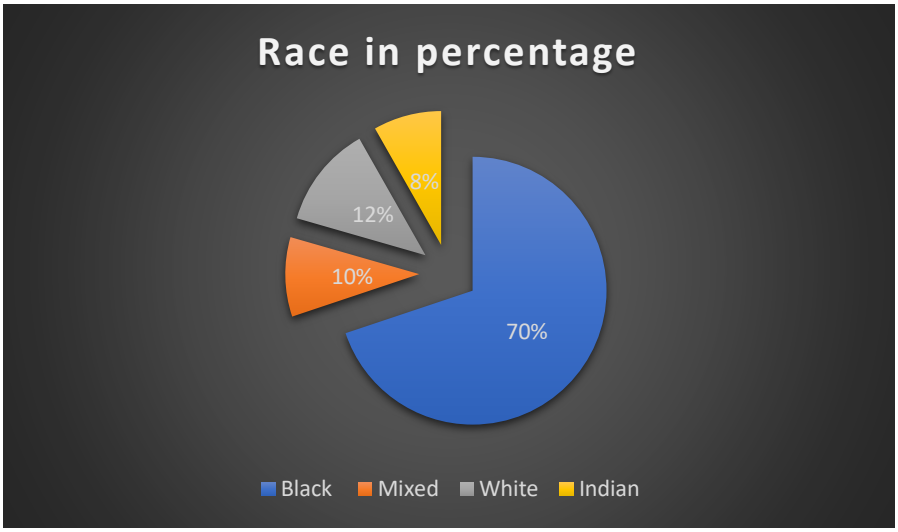

Figure 4.3 Pie chart demonstrating racial variation.

The demographic trends were consistent with the literature. It highlights significant association of cutaneous sarcoidosis with older age, female gender and black race in our study. It reminds clinicians and pathologists to be alert to the possibility of finding cutaneous sarcoidosis in elderly, female and black population.

Clinical presentations:

Plaques were the most frequent clinical presentation in our study, consistent with the study by Ishak et al. [13] Papule, nodules, and plaques were the most common cutaneous manifestations in most studies. [2, 13, 14, 15] In our study plaques, annular

lesions and papules were common findings (Figure 4.4). Unlike other studies, annular lesions were seen more than nodules. This is in contrast with the previous South African study by Jacyk et al, 1999, which showed that nodules were most common followed by plaques and papule. [15] Due to the limitation of a retrospective study, the exact duration for plaques appearing in our patient is difficult to identify. The cutaneous presentations revealed no significant difference between those with and without systemic sarcoidosis.

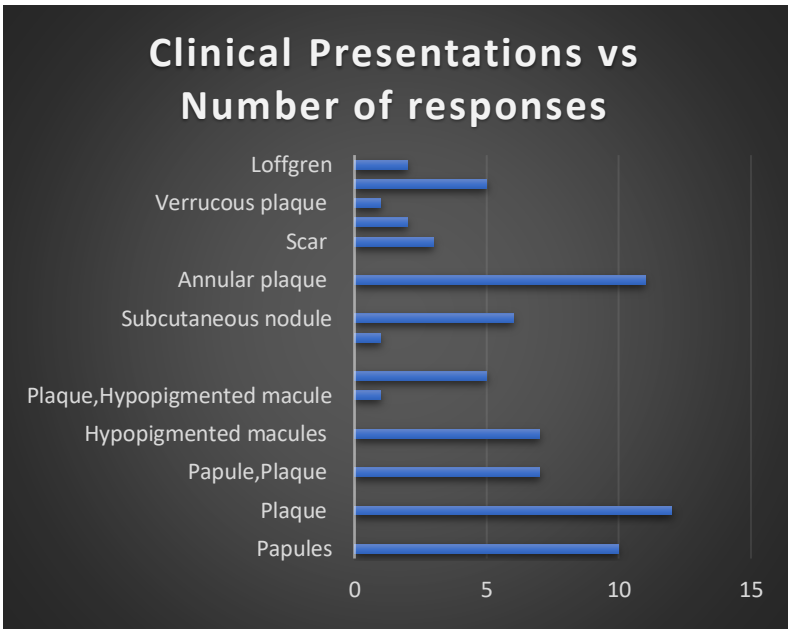

Figure 4.4 Graphic representations of clinical findings.

Clinical trends were partly consistent with the literature. Plaques and papules were most significant presentations. This is in keeping with the literature. Annular lesions were, however, also more in number. While nodules were much less in number unlike other studies worldwide as well as in South Africa. Clinicians and pathologists in our hospital setting should therefore be aware of annular lesions as a possible presentation of sarcoidosis.

Histopathology:

Naked sarcoidal granuloma remains the main histology feature of sarcoidosis. Majority of patients (81%) had this type of presentation. Only few patients showed non-sarcoidal granulomas. This was in keeping with the findings in literature.

Patients with non-sarcoidal granulomas were further collaborated and confirmed with serum ACE level and adjunct diagnostic tool. They were also confirmed by exclusion of other conditions like tuberculosis, granuloma annulare and foreign body reactions. The distribution of the granuloma was uncharacteristic. However some patients had a typical perivascular or periadnexal or perineural distribution.

Besides the specific types of granulomas, biopsies also featured several other non-specific findings. The most common non-specific findings seen in this study was sclerosis of the dermal collagen. Increased mucin deposits in the dermis, focal areas of fibrinoid necrosis and lichenoid infiltrate, foreign body deposit in the dermis were other nonspecific findings. The foreign body deposit was seen in the same patient who showed foreign body type granuloma.

The nonspecific features have also been previously established in literature. Focal areas of fibrinoid necrosis was the most significant nonspecific feature noted in the previous South African study by Jacyk et al, 1999.[15] In this study dermal sclerosis was the most significant bystander finding. It could be due to scarring in lesional skin. This could mean that the patients seek medical attention much later than the onset of the cutaneous sarcoidosis. Another feature noted in some cases was increased mucin deposits. Granuloma annulare is a cutaneous disease which should be excluded in such cases. Mucin deposits can simply be a secondary process to the disease.

The histopathology trends in this particular study are in keeping with the literature. Sarcoidal granuloma remains the most significant feature on biopsy. However clinicians and pathologists should be aware of other presentations like non sarcoidal type granuloma. The diagnosis can easily be missed in patients and misdiagnosed as

another condition completely delaying the prompt medical care required. Dermal collagen sclerosis was found to be a prominent nonspecific feature in this study. This finding can be simply due to delay in seeking medical attention.

Management:

In our setting patients with limited cutaneous presentations are mostly managed with topical steroids. They remain the treatment of choice as first-line therapy. Occasionally, intra-lesional steroids are used for recalcitrant localized lesions as an adjunct to topical treatment. Other treatments for local disease including topical tacrolimus, topical retinoid, photodynamic therapy, ultraviolet A therapy, laser therapy are usually not considered due to lack of availability in our hospital setting and as the disease can successfully be controlled by the former therapy. We also monitor the long term side effects of the corticosteroid use.

Patients exhibiting progressive disease, refractory to local treatment, severely scarring sarcoid, or cutaneous and systemic involvement, are treated with systemic corticosteroids at higher doses and second-line therapies such as chloroquine, methotrexate, azathioprine, and Mycophenolate Mofetil. The systemic steroids are slowly weaned off over a period of six months to one year while continuing the second line therapy. Patients with systemic involvement are also monitored by respective specialists in collaboration with us.

Individual management study of each and every patient is beyond the scope of this retrospective study. The aim and objective of this particular study focuses on the demography, clinical presentations and histopathology findings in our hospital setting.

CHAPTER 5: LIMITATIONS

This was a retrospective design and there was data that was missing or not documented correctly. In our study we relied on the information from the laboratory report which meant it is only a summarized version of the information obtained from patient. Information like race was not always documented in some cases. It is a valuable piece of information and should be added in future by the Dermatologists along with the other information's. It was retrieved using hospital numbers.

Serum ACE level, an important marker of active sarcoidosis was not mentioned in the reports. This information would be valuable if it is provided by the clinician along with other details like age, race, gender and clinical presentations.

Co-morbidity and other organ involvement are important information which could be valuable in this study. Laboratory reports as well as clinic files of most patients lacked information regarding these variables. Thus it could not be included in this study.

The clinical picture was a subjective assessment by other doctors, the accuracy of which depends upon the experience of the dermatologist and there was no standardised reporting format. Due to the retrospective design duration of lesions were not established.

The histopathology findings were also not consistent in the manner in which they were reported and in some cases stains were not done to rule out other infectious diseases which were considered as a differential. Characteristic cytoplasmic inclusions, such as asteroid bodies, Schaumann bodies, and birefringent crystalline calcium oxalate and other calcium salt particles are major features of a sarcoidal granuloma. These were not mentioned by the pathologist is the reports.

CHAPTER 6: CONCLUSION

The demographic, clinical and histopathology findings in the present study were mostly similar to those published in the literature.

The present study demonstrates a striking predominance of middle aged to elderly, female and Black population. This research contributes to the knowledge already available on the demography in literature and also confirms the understanding in our setting. Clinical presentations of plaque and papule were most common. Additionally, annular lesions were significant in this study population. This is a unique contribution from this study as clinicians will be more aware now to consider sarcoidosis as a differential when presented with an annular plaque in our hospital setting. Sarcoidal granuloma remains diagnostic on histopathology. However, presence of other non-sarcoidal granulomas doesn't necessarily exclude the disease until proven otherwise. Dermal collagen sclerosis is the most frequent nonspecific feature of the study population in this setting. This is likely due to a delay in seeking medical attention.

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CHAPTER 8: APPENDICES

8.1 ETHICAL CLEARANCE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Sweta Das

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190322

NAME: (Principal Investigator)	Dr Sweta Das
DEPARTMENT:	Dermatology Helen Joseph Hospital Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Cutaneous sarcoidosis at the Charlotte Maxeke Johanesburg Academic Hospital and Helen Joseph. A retrospective record review
DATE CONSIDERED:	29/03/2019
DECISION:	Approved
CONDITIONS:	Approval in Charlotte Maxeke Johannesburg Academic Hospital is subjuect to providing permission letter
SUPERVISOR:	Prof D Modi
APPROVED BY:	Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/04/2019

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

DECLARATION OF INVESTIGATORS

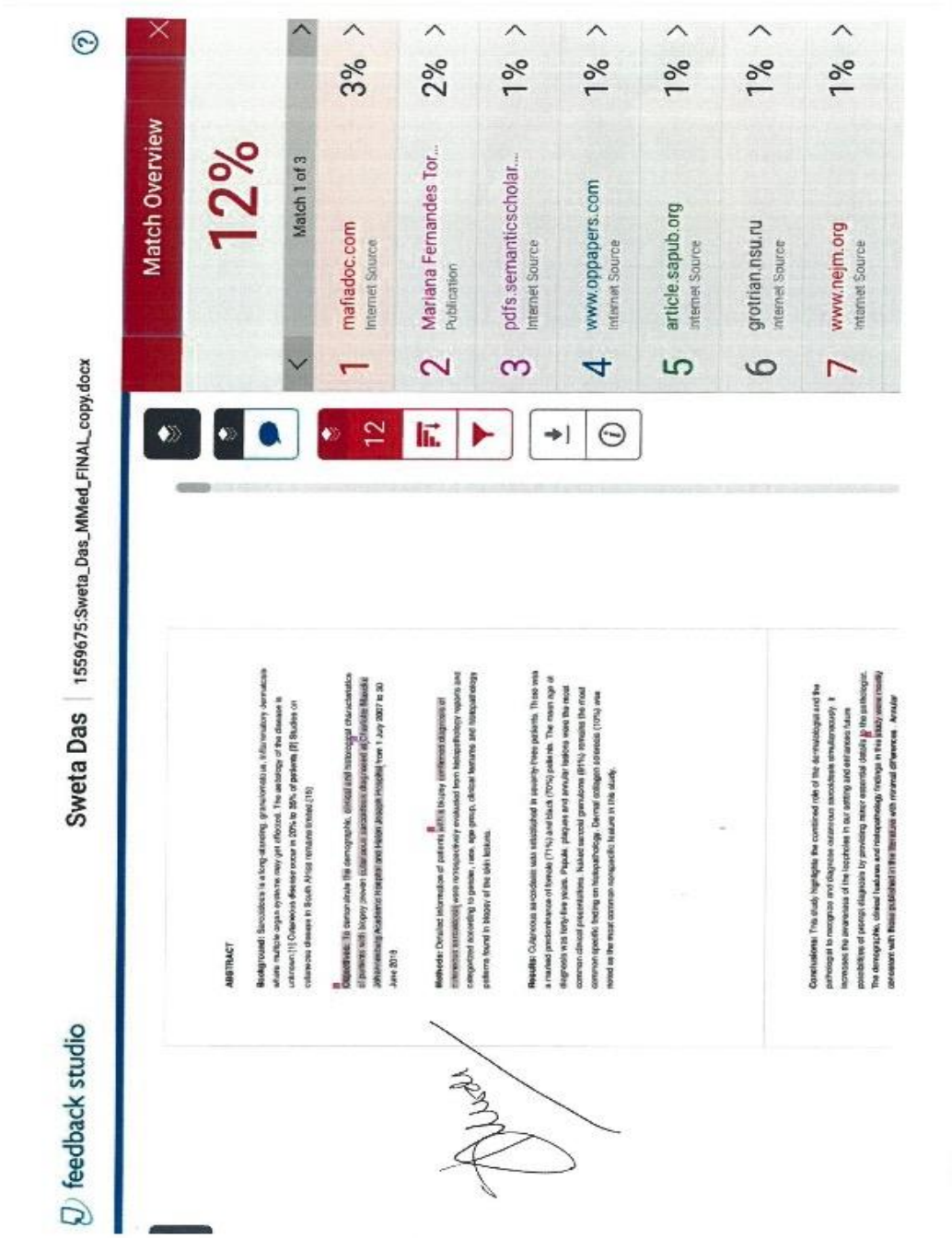
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

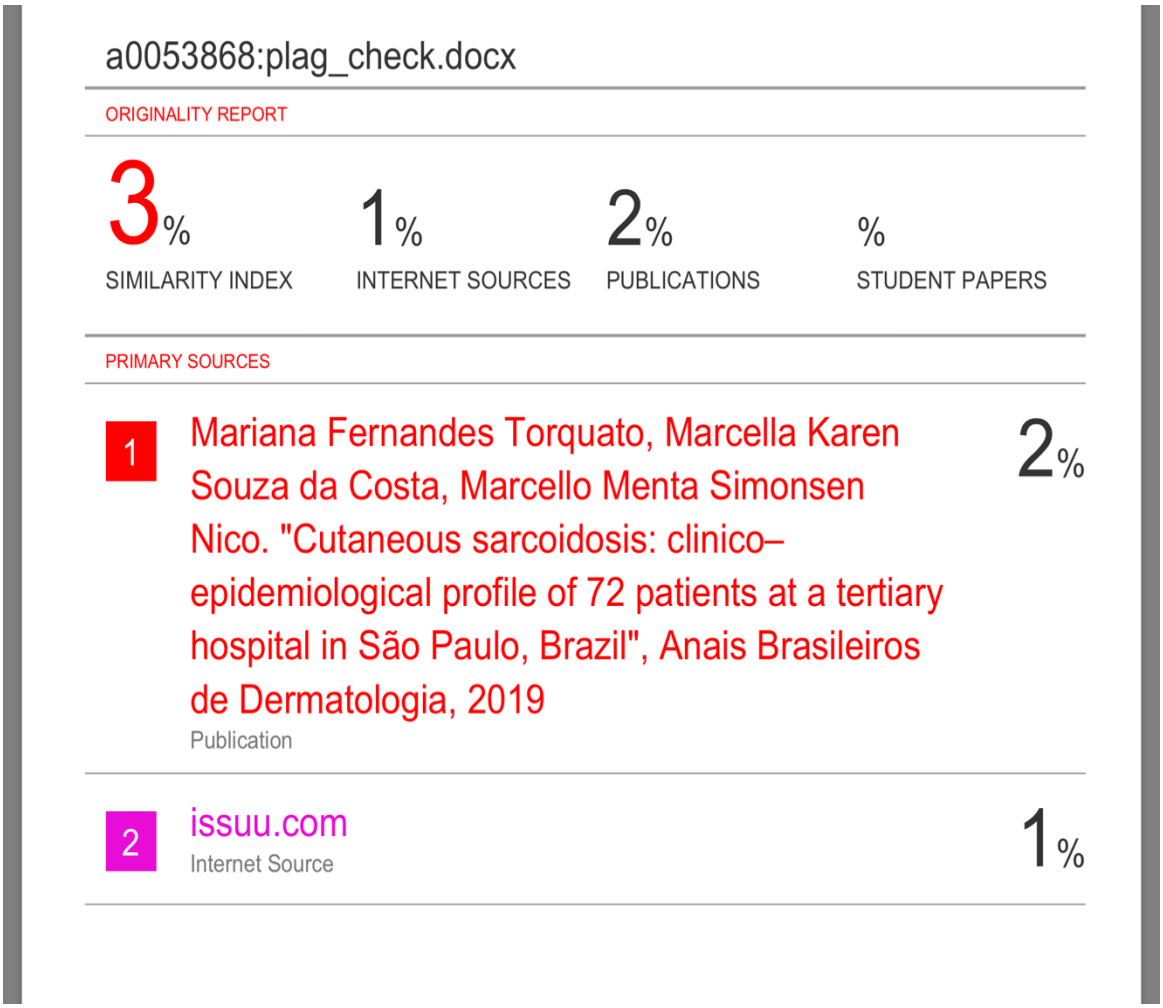
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

8.2PLAGIARISM TURNITIN REPORT



PLAGIARISM TURNITIN REPORT



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ORIGINALITY REPORT

3%	1%	2%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Mariana Fernandes Torquato, Marcella Karen Souza da Costa, Marcello Menta Simonsen Nico. "Cutaneous sarcoidosis: clinico–epidemiological profile of 72 patients at a tertiary hospital in São Paulo, Brazil", Anais Brasileiros de Dermatologia, 2019 Publication	2%
2	issuu.com Internet Source	1%

8.3DATA COLLECTION SHEET

Study number:	
Gender:	☐ Male
	☐ Female
Age	
Race	☐ Black
	☐ White
	☐ Indian
	☐ Colored
Clinical findings:	☐ Nodules
	☐ Plaques
	☐ Lupus Pernio
	☐ Scar
	☐ Hypopigmented
	☐ Annular
	☐ Subcutaneous
	☐ Ulcer
	☐ Other
Histopathology Findings:	☐ Naked sarcoidal granulomas
	☐ Tuberculoid granulomas
	☐ Interstitial granulomas
	☐ Foreign material
	☐ Focal necrosis
	☐ Elastophagocytosis
	☐ Linear perineural granulomas
	☐ Increased dermal mucin
	☐ Lichenoid inflammation
	☐ Other