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MMED

Prevalence of tuberculosis and associations in patients with pulmonary sarcoidosis

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the Degree of Master of Medicine 2020.

i . Declaration

I, Rosalia Shivute, declare that this MMED research report is my own work which is being submitted to fulfil the Master of Medicine degree (in the submissible format with my protocol and an extended literature review) in the department of Internal Medicine at the University of the Witwatersrand, Johannesburg. This document has not been submitted before for any degree or examination at this or any other University.



……

The..27th....day of .....August.....2020

ii. Dedication

To my father, Dr Nestor Shivute, who continuously challenges and inspires me daily.

To my mother, Loide whose emotional support has been the most comforting.

My brothers; Peter, Andrew, Simon and my sister Dr Tukuhole Shivute, thank you for your endless patience, love and encouragement throughout this journey.

iii. Ethical Considerations

Permission for this retrospective study was obtained from Dr A. Black and Dr A. Graham (respectively former and current Heads of Pulmonology department, Helen Joseph Hospital, Faculty of Health Sciences, University of the Witwatersrand), Dr M Mukansi (Clinical Director, Helen Joseph Hospital) and the Human Research Ethics Committee of the University of Witwatersrand (clearance number – M170627).

iv. Abstract

Background

The incidence of sarcoidosis in South Africa is unknown, however, the incidence in the northern hemisphere is estimated to be between 5- 40 per 100 000 and over three times more common in individuals of African American descent[1-3]. South Africa suffers from dual epidemics of both human immunodeficiency virus (HIV) and tuberculosis (TB), and the incidence of TB is about 450,000 cases annually with 73% co-infected with HIV[4]. Sarcoidosis and TB may present similarly and consequently sarcoidosis is often misdiagnosed as TB[5].

Objectives

To describe the HIV and TB treatment history as well as co-morbidities in this cohort of patients with sarcoidosis.

Methods

A retrospective study of patients diagnosed with pulmonary sarcoidosis at Helen Joseph Hospital, Johannesburg during January 2012 to June 2019.

Results

The study identified 46 patients with sarcoidosis. Thirty-four were female. Median age was 51.5 years. Five patients were HIV infected, and virologically suppressed on antiretroviral treatment. Thirteen patients (28.3%) were treated for TB, ten (77%) were started on TB therapy after their diagnosis of sarcoidosis. The most common comorbidities were gastroesophageal reflux disease (17%) and hypertension (17%) Most patients (87%) were treated with prednisone.

Conclusion

Empiric treatment for TB prior to the diagnosis of sarcoidosis was uncommon. Once on immune therapy for sarcoidosis there was an increase of both empiric and microbiologically driven TB therapy which suggests a need for improved TB prevention strategies for these patients.

v. Acknowledgements

The support and assistance of the following persons in preparation of this research report is gratefully acknowledged:

Dr Andrew Black and Dr Anita Graham – my two supervisors, who guided, encouraged and reviewed this manuscript.

Dr Black, your ongoing motivation, support, and availability throughout this process, as well as your intimate knowledge of the field solidified the foundation from which I could accomplish and complete this project.

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ix. Nomenclature

AIDS – Acquired Immunodeficiency Syndrome

BAL – Bronchoalveolar lavage

CT – Computed Tomography

CI- Confidence Interval

GORD – Gastroesophageal Reflux Disease

HRCT – High Resolution Computed Tomography

HAART – Highly Active Anti-Retroviral Therapy

HIV – Human Immunodeficiency Virus

HJH – Helen Joseph Hospital

IRIS- Immune Reconstitution Inflammatory Syndrome

PET – Positron Emission Tomography

ROPD – Respiratory Out Patient Department

S-ACE – Serum Angiotensin Converting Enzyme

SD- Standard Deviation

TB – Tuberculosis

WHO – World Health Organization

CHAPTER 1:

1.1. Protocol with Extended Literature Review

1.1.1. History

1.1.1.1. Sarcoidosis

In 1869, an English surgeon, Jonathan Hutchinson, originally described sarcoidosis as 'Mortimer's malady' in an attempt to explain the difference in the cutaneous plaques found in tuberculosis (TB) and systemic lupus erythematous (SLE) [6, 7]. A French dermatologist, Ernest Besnier, devised the term 'lupus pernio' in 1889, which described chronic raised purplish indurated skin lesions seen on the nose, ears, cheeks, lips, forehead and fingers, which to this day are still pathognomonic of sarcoidosis[7]. Caesar Peter Boeck, a Norwegian dermatologist, described the diffuse systemic manifestation of the condition. He described the cutaneous lesion as resembling a benign mesenchymal cell tumour (sarcoma) with characteristic granulomas under microscopy and thus coined the condition as 'sarcoid'[7]. Sarcoidosis is defined as an inflammatory disease characterised by clumps of inflammatory cells with non-caseating granulomas infiltrating organs triggering an inflammatory response. A definition was formally proposed in 1991 at the World Congress of Sarcoidosis in Kyoto, Japan where sarcoidosis was defined as a multi-system disease of unknown aetiology characterised by tissue infiltration with non-caseating granulomas[8].

Two distinct syndromes associated with sarcoidosis were initially described: Heerfordt syndrome in 1909, characterised by uveitis, parotid and submaxillary salivary gland enlargement, cutaneous lesions and cranial nerve palsies; and Löfgren syndrome described in 1953, characterized by: fever, bilateral hilar lymphadenopathy, erythema nodosum and polyarthritis[6, 7]. A diagnostic test created by Angsar Kveim and further improved by Louis Siltzbach at Mount Sinai Hospital in 1941 improved the diagnosis of sarcoidosis by administering pieces of sarcoid tissue intradermally. The test was deemed positive if skin papules appeared weeks later, similar to the TB Mantoux dermal test[9].

1.1.1.2. Tuberculosis

TB in humans can be traced back 9,000 years ago to Atlit Yam, a city now under the Mediterranean Sea, off the coast of Israel[10]. The earliest historical writings of TB were in India roughly 3300 years ago, and in China 2300 years ago[10]. Throughout the 1600-1800s in Europe, TB went by many names and caused 25% of all deaths[10]. In the 1700s, TB was called "the white plague" due to the paleness of the patients and later "consumption" as patients wasted away with the disease[10].During the Middle Ages, TB of the cervical lymph nodes was referred to by the Latin word "scrofula-small breeding sow"[4, 10]. Johann Schonlein coined the term "tuberculosis" in 1834 and Dr. Robert Koch discovered that *Mycobacterium tuberculosis*, as the bacterium that causes TB in 1882[10]. *Mycobacterium tuberculosis* through inhalation or direct inoculation causes an inflammatory condition primarily in the lungs and other less common systems such as; skin, lymphatic, skeletal and nervous systems which is commonly characterized by caseating granulomas on microscopy[5].

1.1.2. Epidemiology

1.1.2.1. Sarcoidosis

Epidemiological studies of sarcoidosis in South Africa are unclear, unlike the United States where the prevalence rates are 11 cases per 100,000 population in whites and 34 cases per 100,000 population in African Americans[11]. The highest prevalence rates in the world, with >50 cases per 100,000, are in Scandinavian countries and in some clustered African-American populations in the United States[12]. African-Americans present with more severe form of sarcoidosis than Caucasians, who usually present with a mild or asymptomatic form of the disease[8].

Sarcoidosis typically affects adults in the second and third decades of life. However, in Scandinavian countries studies have shown a bimodal peak with the disease also occurring in the fourth to sixth decades with an overall mortality rate of 1–5%[13]. Disease onset is approximately ten years earlier in blacks than in whites[14, 15]. The peak age of incidence for women shifted from 40 to 59 years in the 1950s to 50 to 69 years in 2010. For men, the peak age at incidence shifted

from 30 to 49 years in 1950s to 40 to 59 years in 2010[14]. Sarcoidosis is an inflammatory condition that has does not have clear aetiology. However, some scientists postulate that sarcoidosis and TB are one disease on a spectrum of granulomatous diseases including leprosy and schistosomiasis[16]. Agrawel et al. postulates that all granulomatous disease like sarcoidosis are caused by an infective agent which has yet to be identified and which causes a multisystem granulomatous inflammation[16]. Nonetheless, the most widely accepted hypothesis suggests there may be multiple risk factors that trigger this inflammatory process. Some risk factors include genetic predisposition, virus, bacterial infection and toxin exposure to name a few[17].

1.1.2.2. Tuberculosis

As long ago as the seventeenth century TB was first identified in South Africa and thought to have been brought by the migrant European population[6.7]. With the advent of African urbanization and migrant labour, the disease spread to epidemic proportions in both urban and rural areas[4, 18].

1.1.3. Diagnosis and laboratory testing

1.1.3.1. Sarcoidosis

A specific diagnostic test for sarcoidosis is currently not available[19-22]. The diagnosis of sarcoidosis requires three specific criteria: appropriate clinical and radiographic findings, histopathological features of non-caseating granulomas on biopsy and the exclusion of other diseases processes that may manifest in a similar manner[19-22].

Laboratory investigations includes a full blood count, where a normocytic anaemia is commonly seen and is usually a result of anaemia of chronic disease, hypersplenism, bone marrow involvement, or autoimmune haemolytic anaemia[23, 24]. A differential count may illustrate a leukopenia (five to ten percent of patients), eosinophilia (three percent of patients), and thrombocytopenia[25-27].

The erythrocyte sedimentation rate (ESR) and C-reactive protein are commonly elevated in patients with sarcoidosis[28]. The serum angiotensin converting enzyme (s-ACE) level is usually raised in 75 percent of patients with untreated sarcoidosis; however, s-ACE has a poor sensitivity and

specificity[29-31]. Hypergammaglobulinemia and a moderately elevated serum alkaline phosphatase concentration are commonly seen with diffuse hepatic granulomatous infiltration in patients with sarcoidosis[28]. Hypercalcemia and hypercalciuria are more commonly observed in granulomatous conditions including sarcoidosis[32].

The Kveim test utilizes a suspension of heat-sterilized splenic cells from patients with sarcoidosis referred to as the Kveim-Siltzbach reagent, to evoke a sarcoid granulomatous response by injecting the Kveim-Siltzbach reagent intradermally and observing a reaction after four to six weeks[9, 32]. The Kveim test is now obsolete and used for research due to the limited availability of the reagent and risk of transmitting disease[9, 32].

1.1.3.2. Tuberculosis

Pulmonary TB should be suspected in patients with a relevant epidemiological and clinical history in conjunction with suggestive radiological imaging. Patients commonly presents with constitutional symptoms of a fever, night sweats and loss of weight in addition to, respiratory symptoms of a cough, pleuritic chest pain, dyspnea and generalised lymphadenopathy, which is also commonly seen in patients with sarcoidosis.

Common abnormalities caused by TB on blood analysis include: anaemia of chronic disease, thrombocytosis to pancytopaenia if there is bone marrow infiltration. A high ESR and serum calcium may also be observed. A low serum albumin, and elevated serum alkaline phosphatase and gamma glutamyl transferase(infiltrative pattern of liver function test) may be seen.

The gold standard for diagnosing TB is the isolation of *Mycobacterium tuberculosis* from fluids (commonly sputum, pus, pleural, blood, bone marrow, peritoneal, cerebrospinal) or tissue (commonly lung, lymph nodes or bone) on culture. Additional diagnostic tests include acid fast stain demonstrating bacilli (AFB) on smear, nucleic acid amplification test such as the GeneXpert MTB/RIF® and line probe assay tests, Mantoux tuberculin skin test and interferon gamma release assay.

1.1.4. Imaging

1.1.4.1. Sarcoidosis

Pulmonary imaging plays an essential diagnostic role in both TB and sarcoidosis, commonly employing plain chest radiograph and high resolution computed tomography (HRCT)[33]. Chest radiograph commonly shows hilar adenopathy and pulmonary infiltrates, which is a classic finding for both diseases. The lung parenchymal findings can range from a normal film to diffuse reticular or ground glass opacities, nodular consolidation, cystic infiltrates to diffuse fibrotic changes[27, 33].

Pulmonary sarcoidosis is staged radiologically using the Scadding staging system[28] from stage 0 to stage 4:

Stage 0: no lung parenchymal or lymph node involvement

Stage I: the presence of bilateral hilar adenopathy, often associated with an enlarged right paratracheal node

Stage II: bilateral hilar adenopathy and reticular infiltrate

Stage III : reticular opacities with shrinking hilar adenopathy

Stage IV: reticular opacities with evidence of volume loss and fibrosis.

Pleural involvement is unusual in pulmonary sarcoidosis and seen in less than five percent of patients, but can be a result of lymphocytic exudative effusion, chylothorax, haemothorax, and pneumothorax[34-37]. HRCT is superior and is the gold standard of imaging patients with pulmonary sarcoidosis. Other imaging modalities include fluorodeoxyglucose positron emission tomography (18FDG-PET) which is used to ascertain abnormal metabolically active areas in organs of the body[38].

1.1.4.2. Tuberculosis

A chest radiograph is commonly used in the initial diagnostic evaluation in a patient with suspected TB[33]. In primary pulmonary TB, the chest radiograph can be normal. Active pulmonary tuberculosis often cannot be distinguished from inactive disease on the basis of chest radiography alone as one may see old cavities or bronchiectatic fibrotic lung in both[39]. It is therefore pertinent

to interpret these findings in the context of the relevant history and clinical presentation. Pulmonary TB on chest imaging classically presents with focal infiltration of the upper lobes with hilar or mediastinal adenopathy, reticulonodular lesions, cavities and pleural effusions[39].

Chest computed tomography (CT) is more sensitive than chest radiograph in identifying early or subtle parenchymal and nodal changes[35]. The resolution provided by CT is usually not required for the diagnosis of pulmonary TB and is reserved when an alternative diagnosis is suspected or to monitor treatment response[39].

1.1.5. Biopsy

In patients with suspected TB and sarcoidosis, tissue biopsy aids definitive diagnosis when other tests prove to be undiagnostic[36]. Biopsy specimens allow for both microbiological and histopathologic examination. Biopsy can be taken from any site where TB or sarcoidosis is suspected; common sites include lymph nodes, lung, liver, skin and bone[40].

The main exceptions for the need of a biopsy are in asymptomatic patients with the presence of bilateral hilar adenopathy (Stage I); and in those who present with classical features of Löfgren or Heerfordt syndrome[40]. Patients with erythema nodosum skin lesions usually are not biopsied as the histology will demonstrate panniculitis and not granulomas[40]. Flexible bronchoscopy with bronchoalveolar lavage (BAL), forceps biopsy, and endobronchial ultrasound bronchoscopy (EBUS) with transbronchial fine needle aspiration of lung parenchymal and lymph node tissue are established minimally invasive biopsy methods in the diagnosis of sarcoidosis and pulmonary TB[41].

1.1.6. Histology

The characteristic microscopic morphological feature of sarcoidosis is that of a non-caseating granuloma, which differs from that of a caseating granuloma of TB. In the lung, granulomas are frequently found in the alveolar septa, bronchial walls, and along the pulmonary arteries and veins[11, 42].

The granulomas are areas of focal chronic inflammation formed by the accumulation of monocytes, lymphocytes, Langerhans giant cells, macrophages, epithelial cells and fibroblasts[11].

The centers of tuberculous granulomas often, but not exclusively, have characteristic caseating necrosis, which in an appropriate clinical, epidemiologic and microbiologic setting supports a diagnosis of active TB[11].

1.1.7. Treatment

1.1.7.1. Sarcoidosis

Immunosuppressive and immunomodulatory therapies are used to treat sarcoidosis. Spontaneous resolution of clinical and radiological features is common, however, progressive pulmonary disease occurs in approximately twenty-five percent patients and disabling organ failure can occur in up to ten percent of patients[1, 43, 44].

Therapy in patients with pulmonary sarcoidosis is indicated in the setting of: persistent pulmonary symptoms, deteriorating lung functions and progressively worsening radiological changes such as; worsening of interstitial infiltrates, development of cavities along with the progression of fibrosis complicated by the development of signs of pulmonary hypertension[1, 43, 44]. Immunosuppressive therapy is the mainstay of treatment in patients with sarcoidosis[44]. Mild extrapulmonary involvement of non-critical organs such as the skin and joints are often treated with antimalarials, non-steroidal anti-inflammatory drugs (NSAIDS) or low dose oral or topical corticosteroids, which is tapered off over six months[1].

In severe disease or extra-pulmonary involvement of critical organs such as the liver, heart, eyes kidneys and central nervous system, the use of high dose corticosteroid in addition to steroid sparing agents are employed[43, 44]. Steroid sparing agents such as: azathioprine, methotrexate, chloroquine, mycophenolate mofetil, leflunomide and infliximab have improved the morbidity and mortality in patients with severe sarcoidosis[43, 44]. Organ transplant has been used in a select group of severe end stage sarcoidosis patients with limited success[43, 44].

1.1.7.2. Tuberculosis

The goal of TB treatment is the eradication of *Mycobacterium tuberculosis* infection, preventing the transmission and the relapse of disease in addition to, preventing the development of drug resistance.[45-47] First-line drugs include isoniazid, rifampicin, pyrazinamide, and ethambutol. The intensive phase consists of all four drugs, whilst the continuation phase consists of two drugs namely, isoniazid and rifampicin[47]. Second line drugs are used to treat drug-resistant tuberculosis and there are several combinations available depending on sensitivity, cost, side effect profile and national guidelines. Most regimes use high dose isoniazid, pyrazinamide, ethionamide, a fluoroquinolone-levofloxacin/moxifloxacin, and bedaquiline or an injectable agent instead: such as amikacin, kanamycin, streptomycin or capreomycin[45-47].

Patients with pulmonary sarcoidosis are often misdiagnosed as having TB as both conditions may present similarly and subsequently mistreated; however, the gold standard for differentiating the two pathologies is positive microbiological culture for TB. This delay in diagnosis can worsen their pulmonary function and hasten their disease progression with great morbidity. Alternatively, patients with TB who are misdiagnosed as sarcoidosis can deteriorate on immune modulatory therapy. However, a rarity, there are case reports of patients being treated with immunomodulatory therapies who contracted TB on top of their sarcoidosis[48, 49].

1.2. Study aims and objectives

1.2.1. Aim

- To describe the proportion of TB in patients prior or after their diagnosis of pulmonary sarcoidosis.

- To describe the proportion of HIV and other co-morbidities/associations in patients with pulmonary sarcoidosis.

1.2.2. Objectives

1. To describe the proportion of patients treated for TB and/or HIV before and after their diagnosis of pulmonary sarcoidosis was made
2. What proportion of patients with pulmonary sarcoidosis were infected with HIV and on antiretroviral medications before and after their diagnosis with pulmonary sarcoidosis
3. Describe the different co-morbidities/associations in patients with pulmonary sarcoidosis

a. Methodology

i. Study design

This study is a retrospective descriptive study.

ii. Study setting

The study was conducted at Helen Joseph Hospital, a secondary hospital in Auckland Park, Johannesburg from the Respiratory Outpatient Department (ROPD).

iii. Study period

The study was be conducted between the 15 July 2019 to 15 August 2019 .We aimed to collect data from the ROPD files kept from January 2012 – June 2019, a period of 7 and a half years.

iv. Study population

Adult patients over the age of 18, with a diagnosis of sarcoidosis on histology, attending the HJH ROPD during the study period were included in the study.

b. Patient cohort

Sixty patients were known to have sarcoidosis at the ROPD. Of these patients, 46 had histologically proven sarcoidosis and met the inclusion criteria for the study.

Inclusion criteria:

1. Adults over the age of 18 years with clinical and histological evidence of sarcoidosis.

Exclusion criteria:

1. Adults over 18 years with no clinical and/or histological evidence suggestive of sarcoidosis.

c. Measurements

Data collection was captured using a case report form/data sheet (Appendix A). The source data included patient medical records, radiological records, and laboratory results documents. The following information has been collected from the respiratory outpatient department files:

1. Demographics: age, race and gender
2. HIV status, CD4 cell count, viral load and if they were on antiretroviral treatment
3. Co-morbidities/ medications including history of cancers/ transplantations/immunosuppressive medications
4. Confirmed TB – culture positive on sputum: pleural fluid, blood culture, fine needle aspiration, compatible histology demonstrating AFB, or molecular confirmation with GeneXpert MTB/RIF®
5. Empiric TB – based on clinical, radiological and biochemical features with no culture or molecular confirmed TB
6. Confirmed sarcoidosis – clinical, radiological and histology features consistent with sarcoidosis
7. Frequency of immunosuppressive treatment for sarcoidosis utilized at the ROPD

d. Limitations and bias of the study

- Incomplete information – missing or incomplete patients's files

- Given the limited numbers, sub-group analysis was restricted.

e. Retrospective data processing and data analysis

The patients's names have been kept anonymous and entered as study numbers on a case report form/data collection sheet. Data was compared within the patient population. Continuous variables were presented as means with standard deviation (for normally distributed data) and medians with interquartile range (for non-normally distributed data), and categorical data as frequencies and percentages. Categorical data was analysed using the Fishers exact test. Statistical significance has been calculated at a 95% confidence interval. Results were taken as statistically significant if p-values were less than 0.05.

f. Retrospective ethical considerations

All information has been collected anonymously in the data collection sheet using study numbers. Access to data was limited to the principal researcher and supervisors in order to ensure confidentiality. Permission and authorisation to conduct the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand and the Hospital Management.

Authorisation was obtained from Chief Executive Officer of Helen Joseph Hospital, as well as the heads of the both the departments of Internal Medicine and Pulmonology at Helen Joseph Hospital.

g. Time Schedule

	JUN 2017	JUL 2019	SEPT 2019	DEC 2019	JUN 2020
Research proposal and ethics approval:	[redacted]				
Data collection:		[redacted]	[redacted]		
Data analysis and interpretation			[redacted]	[redacted]	
Write up				[redacted]	
Submission					[redacted]

h. Funding

No costs are anticipated other than that necessary for stationery, photocopying, printing, and binding which will be covered personally.

CHAPTER 2 – Submissible Article

2.1. Article

Sarcoidosis at Helen Joseph Hospital: a retrospective, descriptive study of the frequency of TB and associated comorbidities

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Short title: Pulmonary sarcoidosis at Helen Joseph Hospital: a retrospective, descriptive study of the frequency of TB and associated conditions

Conflict of Interest: Nil

Keywords: Sarcoidosis, TB, HIV, South Africa

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2.2. Abstract

Background

The incidence of sarcoidosis in South Africa is unknown, however, the incidence in the northern hemisphere is estimated to be between 5- 40 per 100 000, and over three times more common in individuals of African American descent[1-3]. South Africa suffers from dual epidemics of both human immunodeficiency virus (HIV) and tuberculosis (TB); the incidence of TB is about 450,000 cases annually with 73% co-infected with HIV[4]. Sarcoidosis and TB may present similarly and consequently sarcoidosis is often misdiagnosed as TB[5].

Objectives

To describe the HIV and TB treatment history as well as co-morbidities in our patients with sarcoidosis.

Methods

A retrospective study of patients diagnosed with pulmonary sarcoidosis at Helen Joseph Hospital, Johannesburg during January 2012 to June 2019.

Results

The study identified 46 patients with sarcoidosis. Thirty-four were female. Median age was 51.5 years. Five patients were HIV infected, and virologically suppressed on antiretroviral treatment. Thirteen patients (28.3%) were treated for TB, ten (77%) were started on TB therapy after their diagnosis of sarcoidosis. The most common comorbidities were gastroesophageal reflux disease (17%) and hypertension (17%). Most patients (87%) were treated with prednisone.

Conclusion

Empiric treatment for TB prior to the diagnosis of sarcoidosis was uncommon. Once on immune therapy for sarcoidosis there was an increase of both empiric and microbiologically driven TB therapy which suggests a need for improved TB prevention strategies for these patients.

2.2.1. Introduction

Sarcoidosis is a multi-system disease of unknown aetiology characterised by tissue infiltration with non-caseating granulomas defined at the World Congress in Kyoto in 1991[8]. The granulomas may occur in any organ; however, the most frequently affected sites include: lungs, lymph nodes, skin, eyes, and liver. Lungs are commonly affected in approximately 90 percent of patients, and is responsible for the vast majority of morbidities and mortalities[50].

A specific diagnostic test for sarcoidosis is currently not available[19-22]. The diagnosis of sarcoidosis requires three specific criteria: appropriate clinical and radiographic findings, histopathological features of non-caseating granulomas on biopsy, and the exclusion of other diseases processes that may manifest in a similar manner[19-22]. The most common presenting respiratory symptoms include dyspnoea, cough and pleuritic pain[3, 51]. These are frequently accompanied by constitutional symptoms: fatigue, malaise, fever, and weight loss which are also commonly seen in other respiratory illness, notably tuberculosis[7, 52].

The incidence of sarcoidosis in South Africa is unclear, however, the incidence in the northern hemisphere is estimated to be between 5-40 per 100 000 [1, 2]. Sarcoidosis commonly varies in incidence between geographic regions and can aggregate in specific families and racial groups.

HIV infection can alter both cellular and adaptive immune response[53, 54]. In sarcoidosis an intact CD4 T cell response is a prerequisite for granuloma formation, which is lacking in advanced HIV positive/AIDS patients(53, 55). Therefore, the coexistence of both sarcoidosis and HIV infection is infrequently reported [53]. With the dawn of HAART, the occurrence of sarcoidosis after the initiation of HAART as part of an immune reconstitution inflammatory syndrome (IRIS), is more commonly observed as numbers of CD4 T cells increase[56].

TB clinically and radiologically presents very similarly to sarcoidosis. South Africa has one of the highest burdens of TB and HIV in the world[57]. In light of this, many patients usually arrive on empiric TB chemotherapy with a non-resolving lung infiltrate and worsening clinical symptoms where the diagnosis of sarcoidosis is only then entertained.

The aim is to describe the overlapping controversies between TB and sarcoidosis, the diagnostic inaccuracy and delay in the diagnosis of sarcoidosis, and the immunosuppressive therapies which may predispose patients with sarcoidosis to TB.

2.2.2. Aims

- To describe the prevalence of TB in patients prior to, or after, their diagnosis of pulmonary sarcoidosis.

- To describe the prevalence of HIV and other co-morbidities/associations in patients with pulmonary sarcoidosis.

2.2.3. Justification for the study

There is a paucity of literature that describes patients with pulmonary sarcoidosis in the endemic milieu of HIV and TB in South Africa.

2.2.4. Materials and Methods

Study population

Data was collected in a retrospective manner from the respiratory outpatient department (ROPD) at Helen Joseph Hospital, a secondary hospital in Johannesburg, South Africa that caters to a predominantly lower economic class mixed race and black population. The data was collected from patients' files between January 2012 to June 2019 at the ROPD. We reviewed 60 files of patients with sarcoidosis of which 46 met the inclusion criteria: adults with clinical, radiological, and histological features suggestive of pulmonary sarcoidosis. All patients were over the age of 18 years and either referred to the clinic by other specialist clinics, private pulmonologists or were recently discharged from the wards and referred for follow up. The patients referred to our clinic included both those with pre-existing pulmonary sarcoidosis and suspected pulmonary sarcoidosis.

Fourteen patients were excluded from the study. Reasons included: no histology recorded, under 18 years of age, unclear diagnosis and incomplete data. Seven patients had been given immunomodulatory therapy with resolution of the disease before presenting to the ROPD and thus could not be biopsied and two patients refused biopsy to be done. Two of the patients excluded from the study were treated with empiric TB treatment before referral to ROPD.

Data Capturing

Data collection from cases was captured on a case report form (Appendix 1.1 Data Collection sheet). The data collection sheet included patients' demographics, date of sarcoidosis diagnosis, date of HIV diagnosis and whether receiving HAART, date of TB diagnosis, medical, histological, radiological and laboratory records.

Statistical analysis

Comparison of continuous variables were presented as means with standard deviation for normally distributed data and medians with interquartile range for non-normally distributed data and categorical data as percentages. Categorical data was analysed using the Fisher's exact test.. Statistical significance has been calculated at the 95% confidence level.

2.2.5. Results

In this study 46 patients with histologically confirmed sarcoidosis were identified between the period January 2012 and June 2019. The majority were female (n=30; 65.2%) compared to male (n=16; 34.8%). Racial distribution was black 69.6%, white 15.0%, Indian 11.1%, and mixed race/coloured 4.3% (Table 1). The median age of presentation was 51.5 years, with men presenting more than ten years before women (Table 1). In the cohort, eight women and five men in total were diagnosed with TB; eleven of the cases were black (85%) and two were white (15%) (Table 1).

Thirteen patients were on TB chemotherapy (Table 4) three before and ten after the diagnosis of sarcoidosis was made (p value > 0.05) (Table 4). Five patients (10%), (95%CI: 5%- 28%) of the thirteen patients had a documented positive TB culture (Table 4). TB was documented in two of the fourteen patients excluded in the study, which was both empiric and before the diagnosis of sarcoidosis was entertained.

The most frequent comorbid conditions at the time of diagnosis was both gastroesophageal reflux disease (GORD) in eight patients (17%) and hypertension in eight patients (17%); osteoporosis in six patients and type 2 diabetes mellitus in five patients (Figure 2). Five smokers were identified in this cohort, all of whom were HIV negative and not treated for TB (Table 1).

In this cohort only 27 patients (59%) had recorded serum angiotensin converting enzyme (s-ACE) levels at the time of diagnosis. A s-ACE level above 50 units per litre was observed in 24 patients at the time of diagnosis, with all black patients having a level of greater than 100 units per litre.

Eight patients (11%) were smokers and 20% of the cohort were non-smokers; 69% of the cohort did not have a documented smoking history. (Table 1).

The most frequent system involved was the pulmonary system with lung parenchyma changes in 34 patients, followed by hilar adenopathy in seventeen patients (Table 2). This was followed by ocular involvement in nine patients, seven patients with anterior uveitis and two patients with keratitis (Table 2). Skin involvement was noted in nine patients with six exhibiting erythema nodosum, two with lupus pernio and one plaque sarcoidosis (Table 2).

Majority (79.4%) of the cohort had a Scadding pulmonary staging of either 3 or 4 (Figure 1). Seven of the thirteen patients with TB had a Scadding score of stage 3 or 4; of these TB was confirmed microbiologically in two cases.

The most common site for biopsy was the lung; of the pulmonary biopsies, twenty-two were transbronchial and seven were open lung biopsies (Table 3).

Five patients who tested HIV positive were women and four of those women were black (Table 1). All of the five women were diagnosed with sarcoidosis after their diagnosis of HIV. The median difference between HIV and sarcoidosis diagnosis was 4 years. Four of the five women had CD4 counts of more than 400 and three of the five women were treated for TB (Table 1). All five patients with HIV were virally suppressed on first-line regimen antiretroviral therapy (tenofovir, lamivudine, efavirenz) and one patient being on second- line regime (zidovudine, lamivudine and lopinavir/ritonavir) (Table 5). Eight patients did not have a documented HIV status, while 33 patients were documented as HIV negative (Table 1).

In this cohort, 44 patients (96%) were on immunomodulatory therapy for their sarcoidosis. Most of these patients n= 40 (87%) were on glucocorticosteroids (Table 6).

2.2.6. Discussion

Manifestations

All suspected or confirmed patients with sarcoidosis who had either respiratory symptoms, change in lung function or abnormal chest imaging were referred to ROPD. Staging was done using chest x-ray with pulmonary disease on all these patients. Most of the cohort had stage four pulmonary disease (34.8%), followed by stage one disease (23.9%) and then stage three disease (21.7%) (Figure 1).

The most common organ system involved was the pulmonary system with parenchymal changes seen on 34 patients and hilar lymphadenopathy identified on seventeen patients (Table 2). There is a bias to this as patients were being followed up at the respiratory outpatient clinic**.** The second most common system involved was the skin – nine patients, all of whom were black. Six exhibited erythema nodosum, two lupus pernio and one plaque sarcoidosis (Table 2) Nine patients had ocular sarcoidosis – seven cases with anterior uveitis and two cases with keratitis. Less common systems involved included the nervous system – five patients: three cranial nerve mononeuropathies, two peripheral neuropathies with one case of a brain granuloma (Table 2). Two patients had cardiac system involvement in the form of atrioventricular heart blocks (Table 2).

Most biopsies were taken from the lung; twenty-two were transbronchial and seven were open lung biopsies. Other biopsies included skin – nine, and peripheral lymph node – three (Table 3). This was guided by clinical presentation, imaging, availability of resources and utilizing methods that were the least invasive.

TB/HIV

One of the main objectives of the study was how many patients with sarcoidosis were treated for tuberculosis. Thirteen patients of the cohort (95% CI:0.17-0.43) were put on TB treatment (Table 1). In our study, the majority of patients who received tuberculosis chemotherapy were black(eleven patients) and female (eight patients), this correlates to the female and black

predominance of the study population. Seven patients with sarcoidosis were placed on empiric TB treatment after sarcoidosis was diagnosed. All of these patients were on glucocorticosteroids and none of these patients were on isoniazid prophylaxis at the time of TB diagnosis. The possibility that these patients had a sarcoid flare producing symptoms similar to TB, cannot be excluded. Limited information was available to justify initiation of empiric TB treatment or the patients' response to empiric TB treatment; however it was documented that five patients improved clinically in response to the TB treatment. Only five of the thirteen cases, 38% (95% CI:18%-65%), had microbiologically confirmed TB either on culture or GeneXpert MTB/RIF®, two on sputum, one on blood, one on urine and one pyothorax (Table 4). Two of the five patients with microbiologically confirmed TB were put on TB treatment before the diagnosis of sarcoidosis 40% (95%CI:20%-94%) and three patients with microbiologically confirmed TB developed TB after their diagnosis of sarcoidosis and initiation of glucocorticosteroid therapy 60% (95%CI:10%-61%).

The HIV status of 38 patients of the cohort was known; 33 patients were HIV negative and five patients were HIV positive; of which all five were on HAART and virologically suppressed. All of the five HIV positive were women and four were black. The median CD4 cell count in HIV positive patients with sarcoidosis was 670 cells/μL (IQR: 410-845). The diagnosis of sarcoidosis was made in all five cases after their diagnosis of HIV, so these patients may have developed an IRIS as their cellular immunity improved on HAART, as robust cellular immune system with adequate CD4 T cells is a prerequisite for granuloma formation in the development of sarcoidosis. However, the median difference in years between the HIV diagnosis with initiation of HAART and sarcoidosis was four years, making a sarcoidosis IRIS less likely.

Three cases were diagnosed with both HIV and TB, two cases had microbiologically confirmed TB which was contracted before they were diagnosed with both HIV and sarcoidosis. The third case was treated empirically for TB after their diagnosis for both HIIV and sarcoidosis.

No clear comparable studies exist in this subset population in Africa, however, the notion that a patient with an intact immune system needs to elicit an immune response for sarcoidosis seems to hold true. No patients with untreated HIV infection and immune compromise were diagnosed with sarcoidosis during this time, despite the high burden of HIV in the HJH patient population, this supports the notion that sarcoidosis seems to be rare in immune compromised states such as HIV/AIDS[55].

Treatment

In this cohort; 44 patients (96%) were on immunomodulatory therapy for their sarcoidosis. Most of these patients; 40 (87%) were on glucocorticosteroids with or without a steroid sparing agent (Table 6). The most frequent steroid sparing agent employed was methotrexate (17.45%). This is on par with international guidelines for the treatment of pulmonary sarcoidosis[43, 44]. Ten patients developed TB after initiation of glucocorticosteroids. None of these patients received isoniazid prophylaxis.

Comparative Studies

This study reports on comparative and descriptive data of 46 patients, with both clinical features and histologically confirmed sarcoidosis, seen at Helen Joseph Hospital, Johannesburg over the period of January 2012 to June 2019. The aim was to describe the proportion of TB and HIV in patients attending the respiratory outpatient department. Previous descriptive studies have been undertaken in South Africa; however, the paucity of literature poses a challenge.

This study correlated epidemiologically well with another recent South African study done in Johannesburg by Morar et al.[5] who described a cohort of 102 patients at Charlotte Maxele Johannesburg Hospital over a five-year period: 2002 to 2006. His cohort consisted of 59 patients who were Black, 28 Indians, 8 Whites and 7 Coloureds[5]. Females were the majority at 68%, which correlated to the female and black predominance in our study. The median age of the group was 44.6 years which was younger than that of our cohort at 55 years[5]. Seventeen percent had been treated for TB, prior to being diagnosed with sarcoidosis, and two patients developed TB whilst being treated for sarcoidosis on immunosuppressive therapy[5]. This differs from our findings where only 7% were treated for TB prior to diagnosing sarcoidosis and 22% were considered to have developed TB after their diagnosis of sarcoidosis. Both cohorts had a similar percentage of patients on glucocorticosteroid treatment: 84% in Morar's study and 87% in our study (Table 6).

Another study done in Johannesburg by Smith et al.[58] retrospectively collected comparative data from 82 patients from Johannesburg General and Hillbrow hospitals from January 1965 to October 1987 which demonstrated that the majority of the cohort was black (62%) and female (64%). This study also demonstrated that the three most common sites of involvement were the pulmonary

system, lymphadenopathy and skin, which was similar to this study. They noted that 18% of their cohort was on TB therapy as compared to 13% in our study[58].

Benatar et al. described 110 patients over a 7 year period (1969-1975) with sarcoidosis in the Cape Peninsula, South Africa[59]. He reported that the majority of his cohort were mixed race, 71 patients (65%) and 25 patients (23%) were black, with the remaining 14 patients (12%) being white. This does reflect the different demographics groups in the Cape as opposed to Johannesburg. Benatar et al. showed both 50% male to female distribution, the majority of patients in his cohort on TB chemotherapy were on empiric treatment and coloured.

Most patients in our study, 87%, were treated with prednisone as a first line immunomodulatory treatment which was similar to with both Benatar et al., Smith et al. and international reviews[43, 58-60]. Combination therapies with steroids and either methotrexate, azathioprine and chloroquine were seen in 25% of this cohort.

Limitations

Sarcoidosis is an uncommon disease worldwide and in Africa which was reflected in the low number of patients with sarcoidosis seen at Helen Joseph Hospital (HJH) over the five-year period. Helen Joseph Hospital serves a predominantly mixed race and black population from low to medium social economic backgrounds in Johannesburg, South Africa which creates a selection bias in the data collected. Furthermore, the small cohort group made analysis and generalisation difficult. In addition, the collection of retrospective data was limited by the quality of records available, which at times was incomplete and difficult to interpret.

Despite these limitations, our findings add valuable epidemiological knowledge to the paucity of data that exists for pulmonary sarcoidosis, in the setting of HIV and TB in sub-Saharan Africa.

2.2.7. Conclusion

Among the patients with sarcoidosis, a diagnosis of TB was not uncommon, both prior to (7%) and after the diagnosis of sarcoidosis (22%). A large proportion of our patients were started on empiric TB treatment, which possibly overestimated the true proportion of TB cases in this group. The majority of the cases were started on TB treatment after their diagnosis of sarcoidosis, which was

an unexpected finding. This may be due to sarcoidosis itself predisposing to TB or as a result of chronic immune suppression from treatment. These patients would benefit from TB prophylaxis, faster immunosuppressive weaning and frequent TB surveillance, as well as separate clinics to prevent exposure to other respiratory cases which may well be infected with TB.

Despite the impression of sarcoidosis being commonly misdiagnosed initially as tuberculosis, this study did not support this commonly held notion. Only one patient in our cohort was treated for TB empirically prior to their sarcoidosis diagnosis. Future studies could explore this commonly held notion further in a bigger cohort. Of concern is the number of patients started on TB therapy after their diagnosis of sarcoid and the need to recognise the risk of TB developing in patients on immune suppression.

Notwithstanding the limitations in this study, our findings add valuable epidemiological knowledge to the paucity of data that exists for pulmonary sarcoidosis, in the setting of HIV and TB in sub-Saharan Africa.

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Nil

Disclosure statement

The authors have no conflict of interest to declare.

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2.4. Tables and Figures

Table 1: *Demographic characteristics of patients diagnosed with pulmonary sarcoidosis at Helen Joseph Hospital Respiratory Outpatient Department from Jan 2012- June 2019.*

	TB	NO TB	HIV POSITIVE	HIV NEGATIVE
GENDER				
Females	8	22	5	18
Males	5	11	0	15
AVERAGE AGE (Years)				
Female	52.4	55.0	56.8	51.3
Male	34.2	38.9	0	40.1
RACE				
Black	11	21	4	24
Coloured	0	2	1	1
Indian	0	5	0	4
White	2	5	0	4
SMOKING				
Non Smoker	4	4	1	7
Smoker	0	5	0	5
HIV PARAMETERS				
AVERAGE CD4				
<50	0	0	0	-
50-200	0	0	0	-
200-400	1	0	1	-
>400	2	2	4	-
SCADDING SCORE				
0	0	2	0	2
1	2	9	1	8
2	2	3	0	4
3	3	8	0	7
4	4	12	4	10

Figure 1 *- Scadding staging on imaging among patients diagnosed with pulmonary sarcoidosis at Helen Joseph Hospital Respiratory Outpatient Department from Jan 2012- June 2019*

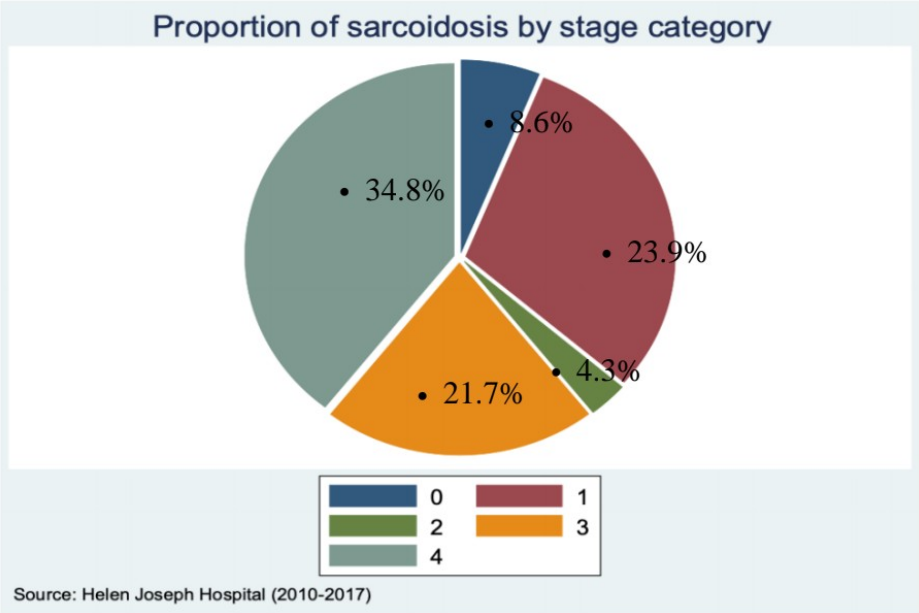


Figure 2 *- Comorbid Conditions among patients diagnosed with pulmonary sarcoidosis at Helen Joseph Hospital Respiratory Outpatient Department from Jan 2012- June 2019*

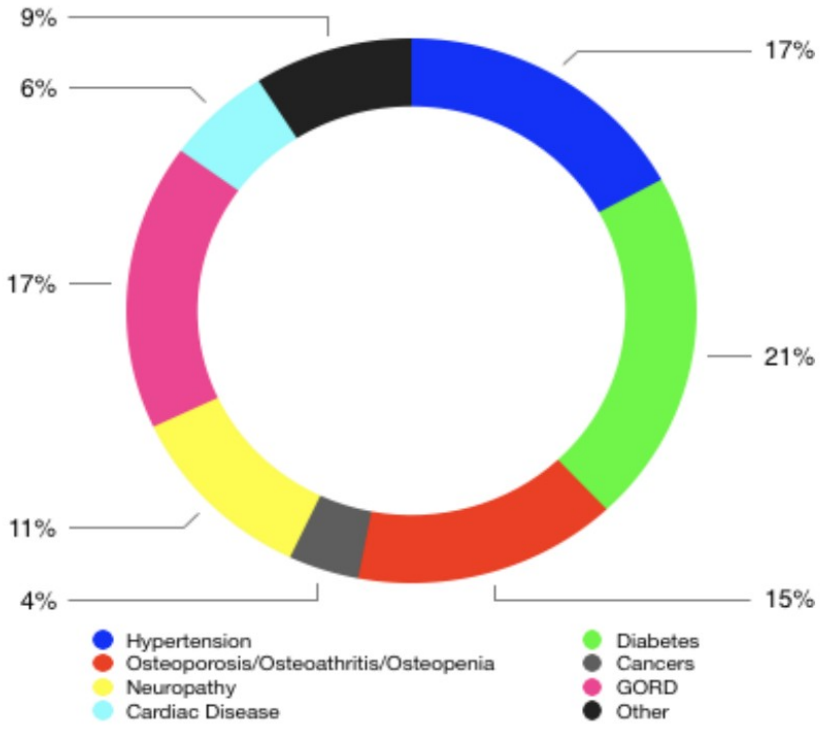


Table 2: *System involvement among patients diagnosed with pulmonary sarcoidosis at Helen Joseph Hospital Respiratory Outpatient Department from Jan 2012- June 2019*

System	Frequency
Lung parenchyma:	**34**
Hilar adenopathy:	**17**
Ocular:	**9**
Skin: Lupus Pernio/Erythema nodosum/Other:	**9**
Nervous system:	**5**
Cardiovascular:	**2**
Lymphadenopathy:	**1**
Nephrolithiasis:	**1**
Parotidomegaly:	**1**
Arthropathy:	**1**

Table 3: *Types of biopsy taken in making the diagnosis of sarcoidosis in patients diagnosed with pulmonary sarcoidosis at Helen Joseph Hospital Respiratory Outpatient Department from Jan 2012- June 2019*

Type of biopsy	Frequency
Transbronchial biopsy	22
Skin biopsy	9
Open lung biopsy	7
Peripheral lymph-node biopsy	3
Other (Parotid/Gastric/EBUS)	3
Mediastinoscopy	2
Total	46

Table 4: *Proportion of patients on TB treatment before and after being diagnosed with Pulmonary Sarcoidosis*

Diagnosis of TB	**Was sarcoidosis diagnosed before or after TB diagnosis?**		**Total*/ 95%CI)**
	After (n, 95%CI)	Before (n, 95%CI)	
Empiric	7 (0.39-0.90)	1 (0.06-0.80)	8 (0.35-0.82)
Microbiological	3 (0.10-0.61))	2 (0.20-0.94))	5 (0.18-0.65)
Total*	10 (0.49-0.93)	3 (0.08-0.51)	13

*P-value (Fischer exact test)>0.05, not significant due to cohort size.

Table 5: Proportion of patients diagnosed with pulmonary sarcoidosis at Helen Joseph Hospital Respiratory Outpatient Department from Jan 2012- June 2019 on HAART

HIV status known	**Proportion of patients with sarcoidosis were on HAART**		**Total***
	No (95% CI)	Yes (95%CI)	
No	33 (88-100)	0 (0-12)	33
Yes	0 (0-49)	5 (51-100)	5
Total	33(72-95)	5 (5-28)	38

Table 6: *Treatment modalities in patients diagnosed with pulmonary sarcoidosis at Helen Joseph Hospital Respiratory Outpatient Department from Jan 2012- June 2019*

Treatment n-46	Frequency	Percentage
None	2	4.35%
Unknown	2	4.35%
Chloroquine	2	4.35%
Prednisone	26	56.52%
Prednisone/Chloroquine	3	6.51%
Prednisone/Methotrexate	8	17.39%
Prednisone/Chloroquine/Methotrexate	2	4.35%
Prednisone Chloroquine/Methotrexate/Azathioprine	1	2.18%

CHAPTER 3 – Appendices

3.1. Data Collection Sheet

Study Number: _____ Date: _____

Gender: ☐ Male ☐ Female **Age: ____**

Date of birth (DD/MM/YYYY): _____

HIV STATUS

Known HIV positive _____Date of Dx

☐ HIV Negative

☐ HIV Unknown

Nadir CD4_____ Latest CD4: _____

No CD4 available

Latest Viral load: _____ No viral load available

If HIV positive

Currently on ART: ☐ Yes ☐ No
If on ART, initiation date (MM/YYYY): _____

Defaulted ☐

Date of default (MM/YYYY): _____

Co-morbidities

☐ Diabetes Mellitus	☐ Hypertension	☐ Heart Disease
☐ Asthma	☐ VTE/PE	☐ COPD
☐ Malignancy	☐ Liver Disease	☐ Kidney Disease
☐ Thyroid Disease	☐ Ophthalmological	☐ Other_____

Smoking history

Have you ever smoked ☐ no ☐ yes

How many pack years: _____

Tuberculosis Date of Diagnosis_____

Tuberculosis Diagnosis based on

☐ CLINICALLY FEATURES ☐ CXR/CT CHEST

☐ GENXPERT ☐ TB CULTURE (Sputum/blood/etc.)

☐ CYTOLOGY/HISTOLOGY

Sarcoidosis Date of Diagnosis_____

Sarcoidosis Diagnosis based on

☐ CLINICALLY FEATURES ☐ CXR/CT CHEST

☐ CYTOLOGY/HISTOLOGY ☐ DERMATOLOGICAL BIOPSY

3.2. Ethics Clearance Form

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Drs RR Shivute and A Graham

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170627

NAME: (Principal Investigator)	Drs RR Shivute and A Graham
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Prevalence of Tuberculosis and associated risk factors in patients with Pulmonary Sarcoidosis
DATE CONSIDERED:	30/06/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr A Black
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	10/07/2019

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

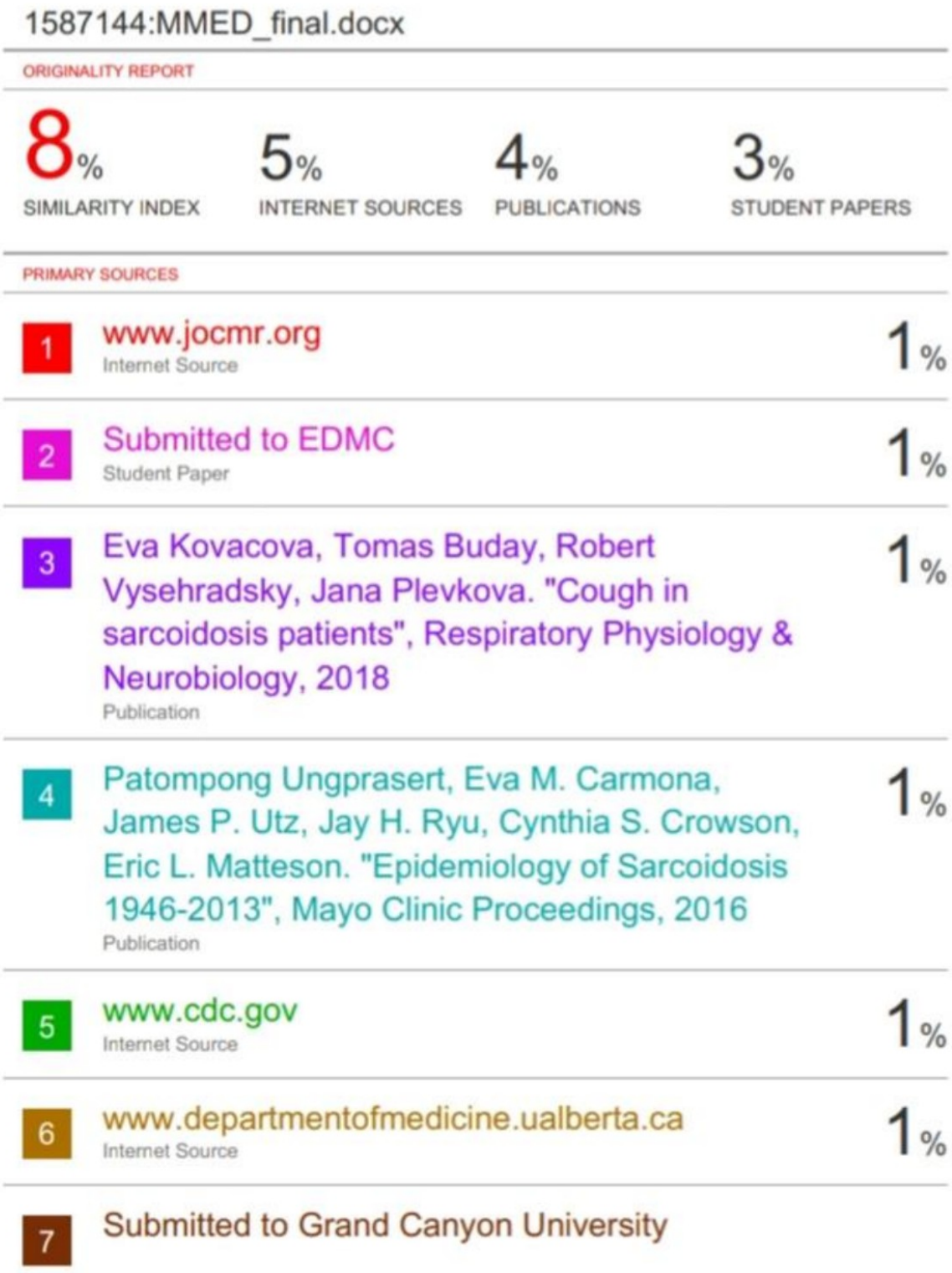
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
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 submit details to the Committee. I **agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore reports and re-certification will be due early in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature — Date: 10/07/2019

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

3.3. Turnitin Report



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