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Clinical spectrum and outcomes of idiopathic inflammatory myopathies at Chris Hani Baragwanath Academic Hospital

Birch, Candice Tatum

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CLINICAL SPECTRUM AND OUTCOMES OF IDIOPATHIC INFLAMMATORY MYOPATHIES AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

Dr Candice Tatum Birch

A research report submitted to the University of the Witwatersrand, in fulfilment for the requirements of the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg 2022

DECLARATION

I, Candice Tatum Birch, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



……

……19th……day of ……September……2022

List of abbreviations

IIM	Idiopathic Inflammatory Myopathy
DM	Dermatomyositis
PM	Polymyositis
sIBM	Sporadic Inclusion Body Myositis
HIV	Human Immunodeficiency Virus
HTLV-1	Human T-cell Lymphotropic Virus
CADM	Clinically Amyopathic Dermatomyositis
EMG	Electromyography
EULAR	European League Against Rheumatism
ACR	American College of Rheumatology
MSA	Myositis Specific Antibody
AST	Aspartate transaminase
ALT	Alanine transaminase
LDH	Lactate dehydrogenase
ILD	Interstitial lung disease
CK	Creatine kinase
MMF	Mycophenolate Mofetil

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CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.0 Introduction

Myopathies are skeletal muscle disorders which involve a structural change or a functional impairment to muscle, which in turn causes persistent muscle weakness. They may be congenital or acquired in origin. Acquired myopathies may be idiopathic inflammatory or caused by infections, endocrinopathies or drugs.

The idiopathic inflammatory myopathies (IIMs) constitute the largest group of acquired myopathies. These conditions are characterised by muscle inflammation (myositis) and widespread inflammation of other organ systems (Oldroyd, Lilleker and Chinoy, 2017). They cause significant morbidity and mortality (Essouma et al., 2022).

Traditionally, the IIMs were classified into 3 main groups namely polymyositis (PM), dermatomyositis (DM) and sporadic inclusion body myositis (sIBM). The disorders typically present as symmetrical proximal muscle weakness related to muscle inflammation and necrosis (Meyer et al., 2015). More recently however, distinct subtypes of IIM's have been recognized. Dermatomyositis and polymyositis remain distinct clinical entities, whereas juvenile DM, amyopathic DM, anti-synthetase syndrome and immune-mediated necrotizing myopathy have now also been described (Oldroyd, Lilleker and Chinoy, 2017).

Amyopathic dermatomyositis (historically termed "dermatomyositis sine myositis") occurs with the cutaneous manifestations of DM without muscle weakness. The association with malignancy and the risk for interstitial lung disease (ILD) remain the same (Oldroyd, Lilleker and Chinoy, 2017).

For DM and PM, the age at onset ranges from 45 to 60 years (Oldroyd, Lilleker and Chinoy, 2017). In a systematic review published in *Rheumatology* the age at disease onset was 44.2 years and the age at disease diagnosis was 55.1 years. The median time to diagnosis was 3 to 6 months (Meyer et al., 2015). PM and DM are more common in women than men (ratio 2:1) (Oldroyd, Lilleker and Chinoy, 2017). The reported incidence and prevalence of IIMs are inconsistent and variable due to the rarity of these diseases (Meyer et al., 2015) however, there is an estimated global prevalence of 14/100,000 (Oldroyd, Lilleker and Chinoy, 2017).

The aetiology of the IIMs is currently unknown. Several studies have suggested that there may be environmental triggers such as infections, toxins or ultraviolet radiation. These triggers may lead to abnormal immune system activation in patients who are genetically susceptible (Meyer et al., 2015). The retroviruses namely, HIV and HTLV-1, show the best evidence for an infectious aetiology, where myositis may occur at disease onset or during the course of disease (Oldroyd, Lilleker and Chinoy, 2017). There are also reports on geographic clustering and seasonal disease onset which may also indicate an environmental association. A European study in nine countries showed that there is an increasing prevalence of DM with decreasing geographical latitude, indicating that photosensitivity may act as a trigger for disease, however, no association was found with PM and the seasons (Meyer et al., 2015).

1.1 Clinical Features and Diagnosis

The diagnosis of IIM should be suspected based on clinical findings and confirmed by laboratory findings, electromyography (EMG) and histology. The most commonly used diagnostic criteria for IIM were developed by Bohan and Peter and are as follows (Bohan and Peter, 1975):

1. Symmetrical proximal muscle weakness
2. Elevated serum levels of skeletal muscle enzymes
3. Myopathic changes on electromyogram
4. Characteristic muscle biopsy features
5. Typical rash of dermatomyositis

Patients with a definitive diagnosis of PM must fulfil criteria 1 to 4. Those with a definitive diagnosis of DM must fulfil criterion number 5 plus 3 other criteria. The use of these criteria for diagnosis assume that other causes of myopathy have been excluded.

The criteria have a sensitivity of 98% and a specificity of 55% and are still widely used but have limitations. They do not take into account new discoveries about auto-antibodies and they do not include the more recently described subtypes of IIMs. The newer EULAR/ACR criteria have sensitivity of 93% and a specificity of 88% and can distinguish the major subgroups of IIM (Bottai et al., 2017).

In this study we are using the Bohan and Peter criteria because they are currently more practical than the American College of Rheumatology and the European League against Rheumatism (ACR/EULAR) criteria, and they are the criteria currently used at the Chris Hani Baragwanath Rheumatology clinic.

1. Symmetrical proximal muscle weakness

Typical muscle weakness is symmetrical, painless and involves proximal muscles, those being the large muscle groups of the upper arms, thighs, neck and trunk. The weakness may develop over weeks to months. The majority of PM patients will present with muscle weakness but in DM cutaneous manifestations may precede muscle weakness or occur simultaneously.

2. Elevated serum levels of skeletal muscle enzymes

The creatine kinase enzyme (CK) is the most sensitive of the skeletal muscle enzymes and the level usually parallels disease activity. The CK level can be increased up to fiftyfold in active disease (Malik et al., 2016). Levels may be used to monitor disease activity however CK may be normal in some cases. Other enzymes may also be elevated and those include aldolase, aspartate transaminase (AST), alanine transaminase (ALT) and lactate dehydrogenase (LDH).
Autoantibodies form an important part of the diagnosis of IIMs. Serum antibodies are found in more than 80% of patients with PM or DM (Ghirardello et al., 2014). There are 2 major groups of antibodies found in IIMs. The myositis-specific antibodies (MSAs) are found predominantly in those patients with DM and PM. The MSAs have a specificity of over 90%. The traditional antibodies are the aminoacyl-tRNA synthetases (anti-ARS), the anti-Mi-2 and the anti-SRP (Ghirardello et al., 2014). Anti-Jo-1 is the most common of the anti-ARS antibodies and is useful because 60 - 70% of these patients will have ILD (Ghirardello et al., 2014). The myositis-associated antibodies (MAAs) are found in up to 50% of myositis patients, but they are not disease specific and can be found in other connective tissue disorders. Major MAAs include anti-Ro/SSA, anti-PM/Scl, and anti-Ku and anti-U1RNP antibodies (Ghirardello et al., 2014).

3. Myopathic changes on electromyogram

Typical EMG findings show myopathic potentials which are characterized by short duration low-amplitude polyphasic units on voluntary activation and increased

spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves (Malik et al., 2016). The findings are not diagnostic of an inflammatory myopathy specifically but exclude neurogenic disorders.

4. Characteristic muscle biopsy features

The distinctive feature on muscle biopsy is inflammation but each subtype of DM and PM have characteristic features. In PM there are CD8+ T-cell infiltrates within muscle fascicles surrounding individual muscle fibres causing phagocytosis and necrosis. In contrast, the infiltrate in DM is CD4+ dominant and the inflammation is mainly peri-vascular or in the septae between muscle fascicles rather than within them. There is typically a frank vasculitis demonstrated in DM which is not present in PM. The cellular infiltrate comprises B lymphocytes and plasmacytoid dendritic cells. There is perifascicular atrophy at the periphery of the fascicles (which is diagnostic of DM even in the absence of inflammation)(Longo et al., 2012).

5 Typical rash of dermatomyositis

The pathognomonic rashes of DM are Gottron's lesions and the heliotropic rash. The heliotropic rash presents as upper eyelid swelling with an associated violaceous discolouration. Gottron's papules are red, scaly papules on the extensor surfaces of the metacarpophalangeal joints, proximal or distal interphalangeal joints. Gottron's sign describes papules which may occur elsewhere such as on the elbows and knees. Other typical rashes are shawl sign - with erythema on the upper back, shoulders and neck, V sign, which is similar but on the front of the chest, and holster sign over the lateral hip. All of these rashes may be exacerbated by UV light. There may also be periungual erythema or swelling of the blood vessels in the nail folds (Manie, 2015).

A severe subtype of IIM called the anti-synthetase syndrome is defined by the presence of an anti-synthetase antibody and one or more of the following clinical features namely: myositis, ILD, Raynaud's phenomenon, mechanic's hands, arthritis or fever. Mechanic's hands manifest with scaling and cracking along the lateral and palmar aspects of the fingers (Oldroyd, Lilleker and Chinoy, 2017).

IIMs may also present clinically with certain extra-muscular manifestations to a varying degree, which may contribute to morbidity and mortality:

- Constitutional – fever, malaise, weight loss, Raynaud's phenomenon.

- Joints - arthralgia, synovitis, deforming arthropathy may occur in association with anti-Jo 1 antibodies, and joint contractures in DM.
- Pulmonary - related to weakness of the thoracic muscles and diaphragm, ILD, drug-induced pneumonitis, infection or aspiration pneumonia. The EuroMyositis registry found ILD to be present in 30% of patients mostly in association with the anti-synthetase syndrome (Lilleker, Vencovsky and Wang, 2018) and is a major source of morbidity.
- Skin – subcutaneous calcifications (calcinosis) occurring in DM.
- Cardiac – atrioventricular conduction defects, tachyarrhythmias, dilated cardiomyopathy and congestive cardiac failure. A systematic review of cardiac involvement in IIM showed an incidence of 9% to 72%. Heart failure was the most common presentation, however most cardiac involvement is subclinical (Lu et al., 2018).
- Gastrointestinal – dysphagia secondary to oropharyngeal and oesophageal muscle involvement.

It is well documented that there is an increased incidence of malignancy in patients with IIMs. The risk is 2 to 7 times higher than that of the general population (Oldroyd, Lilleker and Chinoy, 2017). Previous studies have consistently shown malignancies to be more common in patients with DM than PM, although overall frequency of malignancies is highly variable in different populations. An Israeli study (Maoz et al., 1998) showed frequencies as high as 45% and 27% in DM and PM patients, respectively. Breast and ovarian cancers are common in women, whereas prostate and lung cancers are common in men. Other malignancies include lymphoma, colon, pancreatic, and bladder cancer (Malik et al., 2016).
Part of the work-up of a patient with IIM should involve cancer screening. That should include a comprehensive history and examination. Investigations such as PSA should be done in men, mammogram and ovarian ultrasound should be considered in women, and colonoscopy should be done in men and women over the age of 50 years. There are no guidelines for screening, but if initial screening is negative, repeat screening should be considered after 3 to 6 months and 6 monthly thereafter (Malik et al., 2016).

1.2 Management

1.2.1 Pharmacologic Management

The aim of therapy is to improve muscle weakness and prevent the development of extra-muscular manifestations. The current pharmacological management for IIMs is based on information obtained from observational studies. There have been no randomised controlled trials performed in this area and there are no standard therapeutic guidelines (Moghadam-Kia, Aggarwal, Oddis, 2016). Pharmacological management involves induction and then maintenance of remission. Glucocorticoids form the basis of treatment for induction of remission. Patients are started on prednisone 1mg/kg/day and continued for 4-6 weeks, after which the dose should be tapered (Malik et al., 2016). Pulsed intravenous methylprednisolone should be given to patients with severe disease manifestations, such as profound muscle weakness, dysphagia or ILD, followed by high dose prednisone and an immunosuppressive drug (Moghadam-Kia, Aggarwal, Oddis, 2016; Findlay, Goyal, Mazaffar, 2015). The total duration of steroid therapy should be 9-12 months, however 50% of patients will not completely respond to steroids alone (Moghadam-Kia, Aggarwal, Oddis, 2016). Most patients will require an immunosuppressive drug in instances of refractory disease, multiple flares, or to reduce the dose and duration of prednisone.

The immunosuppressive drugs used most commonly for IIM treatment are methotrexate, azathioprine, mycophenolate mofetil (MMF) and cyclophosphamide. Methotrexate and azathioprine form part of conventional first line therapy. A Cochrane review found no evidence of either drug being superior to the other (Clark and Isenberg, 2018). A combination of methotrexate and azathioprine was also found to be beneficial in those patients who previously had inadequate responses to either drug alone. MMF may be efficacious in treating refractory cutaneous DM. Some studies have reported improvement in patients with ILD with the use of MMF (Moghadam-Kia, Aggarwal, Oddis, 2016).

Cyclophosphamide is usually reserved for patients with severe ILD or patients who are refractory to other second line therapies. There is a lack of data for its use in DM or PM without ILD. Cyclophosphamide may be considered in patients who have severe or rapidly progressive ILD (Moghadam-Kia, Aggarwal, Oddis, 2016).

Intravenous immunoglobulin (IVIg) is an immunomodulatory agent which may be used simultaneously with other immunosuppressive agents. It may be reserved for

patients with refractory disease or ILD that is resistant to immunosuppressive therapy (Moghadam-Kia, Aggarwal, Oddis, 2016).

Rituximab is a monoclonal antibody against the B cell CD20 surface marker. In the biggest randomized double blinded controlled trial in IIM - The Rituximab in myositis trial (Oddis et al., 2013), 83% of patients (78% PM, 82% DM) met the definition of improvement according to International Myositis Assessment and Clinical Studies Group (IMACS) criteria during the course of the trial. Rituximab also showed a significant steroid-sparing effect (Moghadam-Kia, Aggarwal, Oddis, 2016).

1.2.2 Non-Pharmacologic Management

Those patients with skin disease should avoid UV light and use sunscreen. Hydroxychloroquine may also be used for skin manifestations but has no benefit for muscle disease (Malik et al., 2016). Other non-pharmacological treatment includes exercise regimens personalised to a patient's ability using a physiotherapist, management of any aspiration risk, prophylaxis against infections and osteoporosis, and social and psychological support.

1.3 Response to Treatment and Prognosis

In 2016, EULAR/ACR developed treatment response criteria for PM and DM (Rider et al., 2017). A scoring system was developed under the following headings with a value from 0 to 100:

1. Physician global activity
2. Patient global activity
3. Manual muscle testing
4. Health Assessment Questionnaire (HAQ)
5. Enzymes
6. Extra-muscular activity

In adults, a total improvement score of 20 or higher would suggest minimal improvement, 40 or higher would suggest moderate improvement, and 60 or higher would suggest major improvement.

These criteria have been validated for use specifically in clinical trials, but can also be used to determine treatment response in individual patients (Rider et al., 2017).

The prognosis of PM and DM is worse if patients present with severe disease at diagnosis, if treatment is delayed, or in cases where severe dysphagia or respiratory disease exist. The 5-year survival rate for patients with IIM who receive treatment is approximately 95% and the 10-year survival rate is approximately 84% (Taborda, Azevedo and Isenberg, 2014). The cause of death is usually related to respiratory failure, cardiovascular disease, infection or malignancies. Older patients and patients with malignancy have a worse prognosis. DM has a better prognosis than PM (Oldroyd, Lilleker and Chinoy, 2017).

1.4 IIM in Africa

Generally, there is a lack of data available on black South African and African patients with IIM. There were three articles published on PM and DM in South African journals in the 1960's (Findlay, 1969; Gelfand and Taube, 1966; Horsfall, 1965). This was also before the advent of serological tests for auto-antibodies. One of the articles states that DM was common in the African population. The findings in Caucasian patients were presentation at 2 age peaks those being juvenile and adult (age 40 to 60 years), however in the African population this was not found. The study also noted a clustering of cases of DM presenting to hospital potentially related to an infectious aetiology. They proposed that the increased frequency in the African population may be related to a higher frequency of TB. The only other recent sub-Saharan African study of 104 patients with IIM, including those with overlap syndromes, was undertaken in Durban, South Africa (Chinniah and Mody, 2020). There were only two other African studies found, a case series from Nigeria involving 14 patients, and a retrospective study of 21 patients in Senegal. The study in Nigeria found the mean age to be 35 years. Muscle and liver enzymes were raised in all patients. ANA was positive in 8 patients (Adelowo, Edomwonyi and Olaosebikan, 2013). The Senegalese study found that the mean age of patients was 52 and the male to female ratio was 0.6. Initial manifestations were dermatological, lung and muscle weakness in that order. Malignancy was found in 3 of the 21 cases of DM (Diallo et al., 2010).

A retrospective study done in New Zealand found a female to male predominance with a ratio of 4:1. Malignancy occurred in 20% of patients overall, with DM exceeding PM. Muscle weakness was the most common presenting complaint. CK

was elevated in 94% of the patients. All patients were treated with high dose prednisone but the majority (70%) required additional immunosuppressive treatment. Methotrexate and azathioprine were most commonly used (Lynn et al., 2005).

A similar study done in England found a male to female ration of 2.5:1. The mean of age diagnosis was 38.5 years. The median follow up was 11.5 years and 14.4% of patients demised. Pulmonary involvement was observed in 18.9% of patients. Male gender, ILD, chronic progressive course and use of Rituximab had a statistically significant association with death. This study's 5-year survival rate was 100% (Taborda, Azevedo and Isenberg, 2014).

1.5 Justification for the study

The rationale for doing this study was owed to the lack of data available in Sub-Saharan Africa. The need for our study is therefore to collate more data specifically from African populations.

1.6 Objectives

The primary objectives of the study are as follows:

- To describe the spectrum of disease of patients in terms of
    - population demographics
    - clinical features, including extra-muscular manifestations
    - laboratory results

The secondary objectives are as follows:

- To determine if there is any association between seasonal variation and disease onset
- To measure response to treatment with regards to laboratory data and clinical assessment from baseline up until the last clinic visit
- To compare differences between dermatomyositis and polymyositis in terms of age, gender, seasonal variation, extra-articular manifestations and auto-antibodies

1.7 Methods

1.7.1 Study Population

The study population included patients attending a tertiary connective tissue disease clinic in Soweto South Africa who were 18 years and older at initial presentation for definite or probable IIM as defined by the Bohan and Peter classification criteria (Bohan and Peter, 1975) for inflammatory myopathies.

1.7.2 Study Design

A retrospective record review of patients with IIM was performed. Clinical data were extracted from case records of patients attending the clinic between 1 January 1990 and 31 December 2019. Demographic, clinical, laboratory and treatment data were extracted from the clinical notes. Patients who had any overlapping connective tissue disease, as well as patients who had no follow up visits after their baseline visit, were excluded from this study.

1.7.3 Data Analysis

Statistical analysis of the data will include descriptive and inferential statistics. The Chi-squared test, or where necessary the two-tailed Fisher's exact test, will be applied for nominal variables. In the case of continuous variables, the Student's T-test will be applied. In the case of non-normally distributed data, the Mann Whitney U test will be applied. A p value <0.05 will be considered significant.

1.8 Limitations of the study

Limitations of the study include the retrospective nature of the work, particularly with respect to missing data, inconsistencies in documenting clinical features, screening for malignancies, and a substantial proportion of patients lost to follow-up.

1.9 Ethics permission

The Head of the Department of Internal Medicine and the Medical Superintendent of the Chris Hani Baragwanath Academic Hospital granted permission to conduct the present study and research.

The Human Research Ethics Committee of the University of the Witwatersrand (Certificate no: M190565) granted ethical approval for this study.

1.10 Funding

Minimal costs were incurred doing this research.

1.11 Time frame

	Aug 2019	Sept 2019	Oct 2019	Nov 2019	Dec 2019	Jan 2020	Feb 2020	Aug 2020	Sept 2020
Literature review									
Preparing Protocols									
Protocol Assessment									
Ethics Application									
Data Collection									
Data Analysis									
Writing Up Reports									

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CHAPTER 2: SUBMISSIBLE ARTICLE

CLINICAL SPECTRUM AND OUTCOMES OF IDIOPATHIC INFLAMMATORY MYOPATHIES AT CHRIS HANI BARAGWANATH HOSPITAL

Candice Birch[1], Mohammed Tikly[2], Nimmisha Govind[2]

[1]Department of Internal Medicine, University of the Witwatersrand, [2]Division of Rheumatology, Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand.

Corresponding author: Dr Candice Birch

Abstract

Background: Idiopathic inflammatory myopathies (IIM) are rare diseases for which there is a paucity of data in Africa. We undertook a retrospective records review of clinical and laboratory features of patients with IIM attending a tertiary service in Gauteng, South Africa.

Patients and methods: Case records of patients seen between January 1990 and December 2019 and fulfilling the Bohan and Peter criteria for IIM were reviewed for demographics, clinical features, special investigations and drug therapy.

Results: Of 94 patients included in the study, 65 (69,1%) had dermatomyositis (DM) and 29 (30,9%) had polymyositis (PM). Overall, the mean (SD) age at presentation and disease duration were 41,5 (13,6) and 5,9 (6,2) years, respectively. 88 (93,6%) were Black Africans. The most common cutaneous features in DM patients were Gottron's lesions (72,3%) and abnormal cuticular overgrowth (67,7%). Dysphagia was the most common extra-muscular feature (31,9%), more so in PM than DM (p=0,02). Creatine kinase, total leucocyte count and CRP were similarly higher in PM than DM patients (p=0,006, 0,002, 0,01, respectively). Anti-nuclear and anti-Jo-1 antibodies were positive in 62,2% and 20,4% of patients tested, respectively, the latter significantly more in PM than DM patients (OR=5.1, p=0,03) and more likely to be positive with ILD (p=0,001). Corticosteroids were prescribed in all patients, 89,4% had additional immunosuppressive drugs and 6,4% required intensive/high care. Malignancies occurred in three patients, all of whom had DM. There were seven known deaths.

Conclusion: The present study provides further insights into the spectrum of clinical features of IIM, especially cutaneous features of DM, anti-Jo-1 antibodies and associated ILD, in a cohort of predominantly black African patients.

Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogenous group of rare autoimmune diseases that affect predominately skeletal muscle and skin, but also other organ systems such as joints, lungs, heart and gastrointestinal tract. The estimated global prevalence of IIM is 14/100,000 (Oldroyd, Lilleker and Chinoy, 2017) and they are known to occur in all populations. These diseases can cause significant morbidity and mortality (Essouma et al., 2022).

Polymyositis (PM) and dermatomyositis (DM) are the two main types of IIM, the main clinical difference being that patients with DM have a spectrum of cutaneous features such as Gottron's lesions, nailfold cuticular overgrowth, skin rashes and calcinosis cutis. Myositis-specific antibodies (MSA) occur in up to 50% of patients, mostly the aminoacyl-tRNA synthetases, of which anti-Jo-1 antibodies are most common. Other MSAs are anti-Mi-2, anti-SRP and anti-MDA5 antibodies (Ghirardello et al., 2014). Corticosteroids are first line treatment for IIM, with immunosuppressive agents like methotrexate and azathioprine indicated for inadequate responders or as steroid-sparing therapy. Response to these drugs is generally very good but a small proportion of patients with IIM have long-term disability and succumb to the disease.

There is a dearth of published data on IIM in Africa, particularly in South Africa. A recent systemic literature review of adult IIM in 39 African studies between 1958-2019, showed an estimated prevalence of 11,49/100,000 population. Most patients were female, had DM, and age at onset ranged between 20 to 57 years. Early mortality varied between 7,8-45% and deaths were mainly due to infections, cancers and cardiorespiratory complications (Essouma, Noubiap, Singwe-Ngandeu and Hachulla, 2022).

The present study was undertaken to investigate the spectrum and frequency of clinical, laboratory, electromyographic (EMG) and histological abnormalities, therapy and outcomes in adult patients with either DM or PM, excluding those with overlap syndromes, in patients attending a tertiary service in southern Gauteng, South Africa. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M190565).

Patients and Methods

A retrospective records review of patients with IIM attending a tertiary Connective Tissue Clinic in southern Gauteng, South Africa, between January 1990 and December 2019 was performed. Only patients who fulfilled the 1975 Peter and Bohan criteria for IIM (Bohan and Peter, 1975), ≥18 years at diagnosis and had at least 3 months of follow-up data, were included. Data on patients with clinically amyopathic DM (CADM) according to the Sontheimer criteria (Ghazi, Sontheimer and Werth, 2013), were documented separately. Patients with overlap connective tissue diseases were excluded from the analysis.

Data extracted from clinical records included demographics, clinical features, EMG, laboratory, histological findings and immunosuppressive drug therapy. Clinical findings of cutaneous features and other extra-muscular organ involvement, malignancies and comorbidities were recorded. Baseline full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine kinase (CK), aldolase, aspartate transaminase (AST) and alanine transaminase (ALT), and HIV, antinuclear antibody (ANA) and anti-Jo-1 antibody status during the course of the disease, were also captured. Drug therapy data included use of corticosteroids, methotrexate, azathioprine, mycophenolate mofetil (MMF), cyclophosphamide, rituximab and intravenous immunoglobulins (IVIg).

Statistical analysis

Data were collected on an Excel datasheet. The Chi-square test or two-tailed Fisher's exact test was applied to compare nominal variables between groups, and Student's T-test or Mann Whitney U test was applied for continuous normal and non-normal distributed data, respectively. All analyses were done using TIBCO Statistica v.13.3.0 (TIBCO Software Inc, Palo Alto, CA, USA; 2017). A p value <0.05 was considered significant.

Results

Of the 138 records reviewed, 94 fulfilled the study criteria. Additionally, 8 met CADM criteria. Most patients were black females (81,9%), with a mean age and follow-up duration of 41,5 and 5,9 years, respectively (Table 1). Median (IQR) creatine kinase (CK) for the overall cohort was 3437 (921-7495). Baseline muscle enzymes (CK and/or aldolase) were raised in 96,8% of patients. Subgroup analysis showed

significantly higher CK and aldolase in the PM group than the DM group (p=0,006 and p=0,04, respectively). In those patients in whom EMG and muscle histology were performed, 87,5% and 89,6% respectively were compatible with an inflammatory myopathy.

Table 1 Demographic and clinical characteristics of 94 patients with idiopathic inflammatory myopathy

Variable	**Total**	**DM**	**PM**	**P value**
	n=94	**n=65**	**n=29**	
Females, n (%)	82 (87,2)	59 (90,8)	23 (79,3)	0,2
Black African, n (%)	88 (93,6)	59 (90,8)	29 (100)	0,2
Age at diagnosis, mean (SD), in years	41,5 (13,6)	41,2 (14,3)	42,2 (11,9)	0,6
Disease duration from diagnosis, mean (SD), in years	5,9 (6,2)	5,2 (5,6)	4,9 (7,1)	0,3
Bohan and Peter criteria				
Proximal myopathy, n (%)	94 (100)	65 (100)	29 (100)	1,0
Raised muscle enzymes n (%)	91 (96,8)	62 (95,4)	29 (100)	0,6
creatine kinase U/l, median (IQR)*	3437 (921-7495)	2354 (654-5050)	7180 (1868-10000)	0,006
aldolase U/l, median (IQR)* (n=61)	26 (14-56)	20 (12-49)	39 (26-65)	0,04
Typical electromyographic changes, n (%)	63/72 (87,5)	42/50 (84,0)	21/22 (95,4)	0,3
Abnormal muscle histology, n (%)	60/67 (89,6)	40/43 (93,0)	20/24 (83,3)	0,2
Dermatologic features				
Calcinosis cutis, n (%)		7 (10,8)	-	
Cuticular disease/ragged cuticles, n (%)		44 (67,7)	-	
Gottron's lesions**, n (%)		47 (72,3)	-	
Heliotrope rash, n (%)		40 (61,5)	-	
Shawl Sign, V sign, Holster sign, n (%)		26 (40,0)	-	
Mechanic's hands, n (%)		6 (9,2)	-	

*At presentation, **Gottron’s papules and Gottron’s sign. DM = dermatomyositis, PM = polymyositis, SD = standard deviation, IQR = interquartile range

As shown in Table 2, dysphagia was the most common extra-muscular manifestation occurring in about a third of patients, significantly more in the PM group than the DM group (p=0,03). Patients who reported dysphagia had higher baseline AST levels (median (IQR)=262 (69-494) vs 101 (58,5-246) compared to patients without dysphagia, p=0,04) and a trend towards being more likely to be treated with IV pulse corticosteroids (9/30 vs 8/63 without dysphagia, OR (95%CI=2,9 {1,0-8,6}, p=0.05). Raynaud's phenomenon, inflammatory arthritis and interstitial lung disease (ILD) were observed in approximately a quarter of patients. Malignancies of breast cancer (n=1), lymphoma (n=1) and lung cancer (n=1) occurred exclusively in the DM group. None of CADM patients had any documented malignancies. Ten (10.8%) of the patients tested positive for HIV.

Anaemia, leucocytosis and thrombocytosis at presentation were noted in 27%, 25% and 13,5% of patients, respectively. Baseline median white cell count (p=0,002), CRP (p=0,01) and ALT (p=0,04) were higher in the PM group than the DM group. Most patients had raised AST (85,5%) and ALT (71,1%) levels >40U/l.

The ANA test was positive in 62,2% of patients, more in the DM group than the PM group (p=0.02). Anti-Jo-1 antibody positivity was lower in the DM group (p=0,03). Moreover, none of the patients who tested anti-Jo-1 antibody positive had a heliotrope rash (0/21 vs 11/33 without heliotrope, OR (95% CI=0.09 {0,01-0,73}, p=0,003). In contrast, patients with ILD were more likely to test positive for anti-Jo-1 antibodies (8/18 vs 2/35 without ILD, OR (95%CI=13.2 {2,4-72,5}, p=0,001)). Patients with ILD had a lower AST (median (IQR)=77,5 (52-125) vs 178 (67-385,5) in patients without ILD, p=0,03) and a lower CK at baseline (median (IQR)=1105 (463-4539) vs 3648 (1178-8088) in patients without ILD, p=0,05).

Table 2 Other clinical and laboratory features and outcomes in 94 patients with idiopathic inflammatory myopathy

Variable	**Total**	**DM**	**PM**	**P value**
	n=94	**n=65**	**n=29**	
Raynaud's phenomenon, n (%)	24 (25,5)	20 (30,8)	4 (13,8)	0,1
Arthritis, n (%)	24 (25,5)	18 (27,7)	6 (20,7)	0,6
Dysphagia, n (%)	30 (31,9)	16 (24,6)	14 (48,3)	0,03 OR (95% CI=2,9 (1,1- 7,2)
Interstitial lung disease, n (%)	23 (24,5)	15 (23,1)	8 (27,6)	0,8
Malignancies, n (%)	3 (3,2)	3 (4,6)	0 (0)	0,6
Laboratory findings				
ANA, n (%)	56/90 (62,2)	44/62 (68,8)	12/28 (42,9)	0,02 OR (95% CI= 3,0 (1,2-7,3)
Anti-Jo-1, n (%)	11/54 (20,4)	4/36 (11,1)	7/18 (38,9)	0,03 OR (95% CI=5,1 (1,2-20,8)
Anaemia**, n (%) *	24/89 (27,0)	18/64 (28,1)	6/20 (30,0)	0,8
Total WCC $X10^9$, median (IQR)*	7,5 (5,5-10,0)	7,0 (5,0-9,0)	9,2 (7,3-12,0)	0,002
Platelet count $X10^9$, median (IQR)*	319 (252-397)	303 (248-393)	359 (296-404)	0,1
CRP (mg/L), median (IQR)*	9,5 (4,6-42,5)	8,0 (4,0-24,0)	37,2 (7,0-80,1)	0,01
ESR (mm/hr), median (IQR)*	27 (15-51)	25 (15-42)	29 (17-62)	0,3
ALT (U/L), median (IQR)*	92 (37-222)	83 (32-173)	157 (61-288)	0,04
AST (U/L), median (IQR)*	114 (59-322)	105 (58-283)	259 (98-404)	0,06

*At presentation, DM = dermatomyositis, PM = polymyositis, OR = odd's ratio, CI = confidence interval, ANA = antinuclear antibody, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, WCC = white cell count, AST = aspartate transaminase, ALT = alanine aminotransferase, ICU = intensive care unit, HCA = high care area. **Anaemia in females Hb < 12g/dl, anaemia in males Hb < 13g/dl.

All patients were treated with oral prednisone and 18,1% required intravenous methylprednisolone (Table 3). Most, 84 of 94 (89,4%), were treated with at least one or more immunosuppressive drug. Methotrexate was the most commonly prescribed immunosuppressant (72,3%), followed by azathioprine (42,6%), mycophenolate mofetil (MMF) (24,4%) and cyclophosphamide (16%). Patients with ILD were more likely to have been treated with MMF (10/23 vs 13/70 patients with no ILD, OR

(95%CI=3,4 {1,2-9,4}, p=0.02) and cyclophosphamide (13/23 vs 2/70 patients with no ILD, OR (95%CI=44,2 {8,7-225,6}, p<0.0001). Rituximab and intravenous immunoglobulin therapy were prescribed in 17% and 6,4% of patients, respectively. Chloroquine was prescribed mostly in DM patients for cutaneous disease (53,8%) and in a minority (10,3%) of PM patients for arthritis.

Overall, 67 (71,3%) patients required hospital admission, with six (6,4%) admitted to ICU or high care for respiratory support. Seven (7,4%) deaths were recorded, five patients with DM and two with PM, and 39 (41,2%) patients were lost to follow-up overall. Known causes of death were one each of metastatic lung cancer, infection, and cor pulmonale with congestive cardiac failure. The causes of death in the remaining four patients were not known.

Table 3 Immunosuppressive therapy and outcomes in 94 patients with idiopathic inflammatory myopathy

Variable	**Total**	**DM**	**PM**	**P value**
	n=94	**n=65**	**n=29**	
Prednisone	94 (100)	65 (100)	29 (100)	1.0
IV prednisone	17 (18,1)	13 (20,0)	4 (13,8)	0,6
Any steroid-sparing agent	84/94 (89,4)	58/65 (89,2)	26/29 (89,7)	1,0
MTX	28 (29,8)	19 (29,2)	9 (31,0)	1,0
CYC	15 (16,0)	10 (15,4)	5 (17,2)	1,0
MMF	2 (2,1)	1 (1,5)	1 (3,4)	0,5
AZA	8 (8,5)	8 (12,3)	0 (0)	0,2
RTX	16 (17,0)	8 (12,3)	8 (27,6)	0,08
IVIG	6 (6,4)	4 (6,2)	2 (6,9)	1,0
Chloroquine	38 (40,4)	35 (53,8)	3 (10,3)	0,0001
Outcome				
Hospital admissions	67 (71,3)	44 (67,7)	23 (79,3)	0,3
ICU/HCA admissions	6 (6,4)	3 (4,6)	3 (10,3)	0,3
Demised	7 (7,5)	5 (7,7)	2 (6,9)	1,0
Lost to follow up	39 (41,2)	24 (36,9)	15 (51,7)	0,3

DM = dermatomyositis, PM = polymyositis, IV = intravenous, MTX = methotrexate, CYC = cyclophosphamide, MMF = mycophenolate mofetil, AZA = azathioprine, RTX = rituximab, IVIG = intravenous immunoglobulin, ICU = intensive care unit, HCA = high care area

The eight patients with CADM had a similar spectrum and frequency of cutaneous features of Gottron's lesions (72,3% vs 87,5%), nailfold cuticular overgrowth (67,7% vs 62,5%), heliotrope rash (72,3% vs 62,5%), shawl/V sign/holster sign (40,1 vs 37,5%) and calcinosis cutis (11,8% vs 12,5%).

Discussion

In this retrospective study of mainly indigent blacks with IIM attending a tertiary rheumatology centre, most patients had DM in whom Gottron's lesions, the pathognomonic cutaneous feature of the disease (Didona et al., 2020), and

abnormal nailfold cuticular overgrowth were the commonest features. Patients with PM had more active and severe disease at presentation as evidenced by a higher frequency of dysphagia and higher muscle enzymes, white cell counts and CRP compared to the DM patients.

Overall, our clinical findings, admission rates and drug therapies are largely like those reported previously (Chinniah and Mody, 2020; Essouma, et al., 2022; Meyer et al., 2015; Ungprasert et al., 2013). Consistent with studies in other populations most patients were female. Peak age of presentation in the fifth decade is similar to studies from other developing countries where most patients present in the third to fifth decades (Essouma et al., 2022; Ungprasert et al., 2013), in contrast to patients from North America (Furst et al., 2012) and Europe who generally present later in the sixth decade (Lilleker et al., 2018).

The predominance of DM patients largely reflects the referral system at our institution where PM patients are mostly referred to Neurology. However, previous studies have suggested UV light exposure in tropical and subtropical regions may explain the higher prevalence of DM in Asia and Africa (Meyer et al., 2014). On the other hand, PM had more severe disease. Dysphagia, which has been shown previously to be associated with weakness of neck and respiratory muscles (Carolina Costi et al., 2019), was common in PM patients. Like in the above study, our patients with dysphagia were more likely to have pulse IV corticosteroid therapy. Moreover, the CK, aldolase, AST and ALT were higher in the PM patients, in keeping with the findings in a US study (Volochayev et al., 2012). In the only other recent sub-Saharan African study of 104 patients with IIM, including those with overlap syndromes, Chinniah et al. found no difference in baseline CK levels between patients with DM and PM and found dysphagia to be more common patients with DM (Chinniah and Mody, 2020). Almost three quarters of patients in the present study had one or more hospital admission, like that reported in an Egyptian cohort (Shenavandeh, Jabbary Lak and Mohammadi, 2019).

The overall ANA positivity in just under two-thirds of all patients, but more common in DM than PM patients, is not too dissimilar from previous reports where a positive ANA has been found in 24–60% of DM and 16–40% of PM (Malik et al., 2016). The Jo-1 antibody test, the only myositis specific antibody test recorded in the study, was present in one-fifth of patients in whom the test was done, more so in patients with PM than DM and in patients with ILD, as reported previously in several studies

(Ghirardello et al., 2014). The relevance of anti-Jo-1 autoantibodies in patients with definite polymyositis and ILD is being increasingly recognised as common and potentially serious complication of IIM. In the present study, almost a quarter of the patients were documented to have ILD, similar to the 30% reported IIM in the EuroMyositis registry and occurred most frequently in association with the anti-synthetase syndrome (Lilleker et al., 2018).

Malignancies were documented in only three patients (3,2%) in the present study and exclusively in patients with DM similar to the 4,8% in the Chinniah study. Previous studies have consistently shown malignancies to be more common in patients with DM than PM, although overall frequency of malignancies is highly variable in different populations and as high as 45% and 27% of DM and PM patients, respectively in an Israeli study (Maoz et al., 1998). These ethno-geographical differences are thought to be due a combination of factors including referral bias, differences in screening for malignancies, and genetic and environmental factors (Malik et al., 2016).

The drugs used to treat the IIM in the present study are comparable to the current international standard of care with methotrexate and azathioprine being the most commonly prescribed corticosteroid sparing agents (Lilleker et al., 2018; Moghadam-Kia, Aggarwal, Oddis, 2015). Chloroquine has only been evaluated in observational studies for the management of skin in DM and was reported to be effective in 40–75% of patients (Barsotti and Lundberg, 2018).

Limitations of the study include the retrospective nature of the work, particularly with respect to missing data, inconsistencies in documenting clinical features and screening for malignancies, and a substantial proportion of patients lost to follow-up. Moreover, there have been major advances in diagnosis of extra-articular features during the study period, especially with respect to detecting ILD. Newer myositis specific antibodies are not yet readily available. There has also been a change in drug therapy in recent years, particularly the greater availability of rituximab and MMF.

Notwithstanding the limitations, the present study provides further insights into the spectrum of clinical features and differences between patients with DM and PM of predominantly black African extraction. Prospective studies are necessary to better

understand the impact of IIM on health-related quality of life and life expectancy in relation to clinical subsets and myositis-specific antibodies.

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Chapter 3: Conclusion with recommendations

The rationale for doing this study was owed to the paucity of data available in Sub-Saharan Africa and more specifically black African patients in South Africa.

The present study provides further insights into the spectrum of clinical features of IIM, especially cutaneous features of DM. The study also delineates the clinical and biochemical differences between patients with DM and PM and provides further recognition of the relationship between anti-Jo-1 antibodies and associated ILD.

Due to the retrospective nature of the study and the expectation that data collection is a limiting factor, prospective studies are necessary to improve consistency in reporting of clinical features, to better optimize drug therapy regimens, to understand the impact of IIM on health-related quality of life, to establish life-expectancy in relation to clinical subsets and myositis-specific antibodies and to improve screening for malignancies.

Appendix A

Data Collection Sheet

Number _____ Diagnosis: DM ☐ PM ☐

Amyopathic ☐ Malignancy ☐

Disease duration _____

Date of symptom onset_____

Date of diagnosis_____

Age at onset ___

Age at diagnosis ___ Duration of follow up _____

Female ☐ Male ☐

Ethnicity: Black ☐ White ☐ Indian ☐ Mixed ancestry ☐

Does the patient meet Bohan and Peter criteria: Yes ☐ No ☐

Proximal muscle weakness ☐

Raised muscle enzymes ☐

EMG ☐

Histology ☐

Skin ☐

Skin signs: Gottron's lesions ☐

Shawl, V or holster sign ☐

Heliotrope rash ☐

Nail fold changes ☐

Calcinosis ☐

Raynaud's ☐

Extra-muscular manifestations: Arthritis ☐ Cardiac ☐ (specify)

ILD ☐ arrhythmia ☐

Dysphagia ☐ cardiac failure ☐

dilated cardiomyopathy ☐

Laboratory:

	At presentation	At 3 months
Full blood count		
WBC		
Hb		
Platelet		
Inflammatory markers		
ESR		
CRP		
Muscle enzymes		
AST		
ALT		
CK		
Aldolase		
Auto-antibodies		
Anti-Jo1		
ANA		
Other		
HIV		

Biopsy findings:

Typical features Yes ☐ No ☐

EMG findings:

Typical features Yes ☐ No ☐

Admission to hospital Yes ☐ No ☐

Admitted to High care or ICU ☐

Treatments given:

- oral prednisone ☐
- pulse solumedrol ☐
- IVIg ☐
- Cyclosporin ☐
- MTX ☐
- AZA ☐
- MMF ☐
- Cyclophosphamide ☐
- Rituximab ☐

Outcome: Continued follow up ☐ Lost to follow up ☐

Transferred out ☐ Demise ☐

Appendix B

Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Candice Birch

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190565

NAME: (Principal Investigator)	Dr Candice Birch
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital Rheumatology
PROJECT TITLE:	Clinical spectrum and outcomes of idiopathic inflammatory myopathies at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	31/05/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Nimmisha Govind and Prof Mohammed Tikly
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/06/2019

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 **May** and will therefore be due in the month of **May** 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