MMED RESEARCH ASSIGNMENT

A descriptive study of patients with inflammatory myopathies at Tygerberg Academic Hospital and a review of current classifications

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ABSTRACT

Introduction:

Idiopathic inflammatory myopathy (IIM) is a rare chronic disease of skeletal muscle. Determining its exact prevalence is complicated by the lack of uniformity of the definition and hence the classification of this condition. Therapeutic choices vary considerably because of the paucity of randomized controlled trials for this condition.

Aims:

To determine the prevalence of inflammatory myopathy in our drainage area, categorise our cases and to describe their extra-muscular and extra-cutaneous manifestations; to examine the utility of current classifications of IIM in our setting and propose an alternative classification; and to review the details and the effectiveness of the therapies given.

Methods:

A retrospective, cross-sectional, descriptive study was conducted. Information was obtained from the records of patients attending the clinic between January to June 2008. Demographic, clinical and laboratory data were extracted using a standardised data sheet.

Results:

Out of 1495 patients, 31 subjects with IIM were found. Estimated prevalence was 15.5 per million population. There were 28 females (90%) and 3 males (10%). The mean age of the patients was 45.2 years. Six (19.4%) had dermatomyositis (DM), 2 (6.5%) had polymyositis (PM) and 23 (74.2%) had connective tissue disease-associated myopathy (CAM). Muscle power in most patients was 4/5 (72.2%). Interstitial lung disease was the most common extra-muscular-/extra-cutaneous feature (25.8%). Antinuclear antibodies (ANA) were positive in 24 (77.4%) patients. There was a statistically significant difference of creatinine phosphokinase (CPK) levels between DM/PM versus CAM at presentation (p=0.024).

Conclusion:

IIM in our study population is more common compared to previous reports in the literature. CAM is the commonest cause by far, a finding not previously noted. Malignancy-associated inflammatory myopathy is rare. Studies evaluating the muscle biopsy findings in patients with CAM are required. There is a need for a new classification - we propose the umbrella term “auto-immune inflammatory myopathy”. We confirmed that IIM is a chronic debilitating condition requiring long term immunosuppressive therapy.

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are diseases of primary, auto-immune-mediated inflammation of skeletal muscle, characterised by symmetrical, proximal muscle weakness. It is reported to be a rare condition with an estimated incidence ranging between 2.2 to 7.7 per million populations (pmp) per year[1] and a prevalence ranging from 0.5 to 9.3 pmp.[2] It is more commonly found in females, with a female to male ratio of 2-3:1 and a median age of onset ranging from 45 – 55 years. However, when associated with connective tissue disease the female to male ratio is 8-9:1.[3]

There is lack of uniformity in the classification of IIM. One of the most widely used is the following proposed by Dalakas[4] who regards a muscle biopsy as the most definitive method for diagnosis: [5]

1. Polymyositis (PM)
2. Dermatomyositis (DM)
3. Inclusion body myositis (IBM)

Another commonly used classification is the one proposed by Bohan and Peter: [6; 7]

1. Primary idiopathic PM
2. Primary idiopathic DM
3. PM or DM associated with neoplasia
4. Childhood DM (or PM) associated with vasculitis
5. PM or DM with associated collagen-vascular diseases

Our analysis of the literature suggests that the incidence and prevalence of IIM is probably an overestimation.[8; 9] Prior to the more frequent use of muscle biopsies some cases of IBM, muscular dystrophies, drug-induced myositis and metabolic myopathies were probably misdiagnosed as “pure” IIM. Another consequence of the different classifications is the big difference in the perception of the frequency of “pure” PM -

varying from around 25% of IIM to as low as 5-10% using more recent classifications.[8; 10] This is important as the prognosis of pure PM is poorer.[9]
In view of this we contend that neither of the classifications mentioned is entirely satisfactory and we support the call for an alternative classification.[8, 11]

The association of IIM with collagen vascular diseases have been reported to occur in approximately one-third of cases.[1, 12] Our experience suggests that this may be an underestimation.

Due to the paucity of randomized controlled trials there is no clear consensus regarding optimal therapy for IIM. IBM generally responds poorly to treatment. PM also responds less favourably. Corticosteroids in high doses are generally recommended as initial therapy, with or without other immunosuppressive therapy. Approximately 30% of patients with IIM will respond.[13] Additional immunosuppressive therapy are recommended for severe disease or cases resistant to corticosteroids.

Azathioprine has a steroid-sparing effect in addition to its beneficial effect on the underlying IIM .[14] Although there are no reported randomised controlled trials for the use of methotrexate [15, 16] there are numerous case controlled trials supporting its use. In a case controlled trial the combination of methotrexate and azathioprine has been shown to be of benefit in treatment-resistant cases.[17]
Because of the high number of treatment resistant cases second-line immunosuppressant drugs including cyclosporine have to be employed.[18] Interestingly plasma exchange has not been demonstrated to be of any benefit[19] but intravenous immunoglobulin (IVIg) has been shown to be beneficial.[18] In the case of IVIg its wider use is not advocated because of the limited duration of action and cost factors.

HIV is now a well-known cause of inflammatory myopathy [20; 21; 22; 23; 24], occurring in up to 26 % of patients in one study[25]. Data regarding the prevalence of IIM in HIV patients in South Africa are lacking.

We therefore embarked on a descriptive study of patients with IIM at the adult Rheumatology Clinic at Tygerberg Academic Hospital (TAH). Our objectives were to determine the prevalence of inflammatory myopathy at TAH, to describe the extra-muscular and extra-cutaneous manifestations of our patients, and their response to therapy. We also examined the utility of current classifications of IIM in our setting and propose an alternative classification. Furthermore we also reviewed the details and the effectiveness of the therapies given.

METHODS

A retrospective, cross-sectional, descriptive study was conducted. Information was obtained from the records of patients attending the clinic between January to June 2008. Demographic, clinical and laboratory data were extracted using a standardised data sheet.

Consent to examine patients' records was obtained from the Ethics Committee at Stellenbosch University (SU). The study was conducted in accordance with MRC and ICH guidelines. In accordance with the Helsinki Declaration of 2008, patients' data was anonymized and their records treated with confidentiality. Identifying details such as name and hospital number was not recorded on the data capture sheet, or linked directly to the data set.

The SU Centre for Statistical Consultation assisted with appropriate analysis of the data. Descriptive statistics, Wilcoxon rank sum tests were performed using STATA®.

RESULTS

The records of patients attending the clinic from January 2008 to the end of June 2008 were reviewed. Out of a total of 1495 patients, 31 subjects with IIM were found, a prevalence in our clinic population of 2.1%. Based on a Western Cape population of 5 million at the time of the study (source: Stats SA), our clinic serves approximately 2 million people, yielding a prevalence of 15.5 pmp. See Discussion.

There were 28 females (90%) and 3 males (10%). The mean age of the patients was 45.2 years (range 22 – 61). Figure 1 illustrates the age distribution.

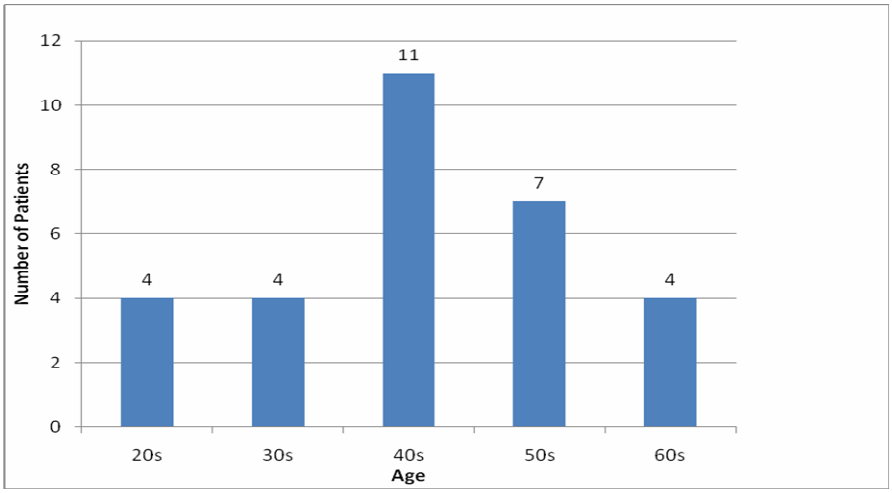
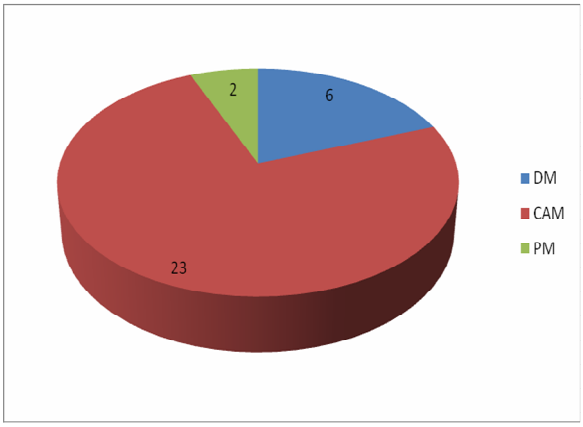


Figure 1. Age distribution of patients with IIM. Total patients = 31.

Of the 31 patients, 6 were diagnosed as having DM. Two of the patients had "pure" PM. The remaining 23 (74.2%) patients had another connective tissue disease (fig 2). Of these patients with connective tissue disease-associated myositis (CAM), 8 patients (34.8%) had systemic lupus erythematosus (SLE), 5 (21.7%) had scleroderma, 9 (39.1%) had mixed connective disease/overlap syndrome and 1 (4.3%) had UCTD. One subject was found to be HIV positive with a CD4+ T-lymphocyte count at diagnosis of 257cells/mm^3 and creatinine phosphokinase (CPK) level of 737 U/L. However, this patient was diagnosed with an overlap syndrome (scleroderma and myositis), rather than an HIV-associated myopathy.

Figure 2. Proportion of patients with dermatomyositis (DM), polymyositis (PM) and connective tissue disease-associated myositis (CAM). Total patients = 31.



Of the patients with DM/PM, seven were female and 1 was male, with ratio of 7:1. Their mean age was 40.75 years (range 22 – 56). Muscle power at presentation was documented in 18 patients. We found 3/5 power in 1 (5.6%), 4-/5 power in 1 (5.6%), 4/5 power in 13 (72.2%), and 4+/5 power in 3 (16.7%) subjects.

The extra-muscular- and extra-cutaneous manifestations of the patients are summarized below.

	Total, n=12 (38.7)	**CAM, n=8 (25.8)**	**DM, n=2 (6.5)**	**PM, n=2 (6.5)**
ILD	8 (25.8)	5 (62.5)	1 (50)	2 (100)
Raynaud's phenomenon	4 (12.9)	3 (37.5)	1 (50)	0 (0)
PIPJ arthritis	1 (3.2)	1 (12.5)	0 (0)	0 (0)
Sicca symptoms	1 (3.2)	1 (12.5)	0 (0)	0 (0)

Table 1. Comparison of clinical manifestations in patients with connective tissue disease-associated myositis (CAM) versus those with dermatomyositis (DM) and polymyositis (PM). Total patients = 31.

Because of lack of diagnostic certainty relating to the cutaneous manifestations of DM in our study we divided the patients with DM into 3 groups:

Category I (diagnostic for DM): heliotrope rash, Gottron's papules/plaques and mechanics hands; category II (highly probable DM): V – sign and shawl sign and category III (probable DM): ragged cuticles, periungual erythema, erythroderma and hyperpigmentation. The cutaneous patterns and ANA serology is summarized in table 2. All category I subjects had positive ANAs ranging from 1:80 – 1:320.

Table2. Profile of cutaneous patterns and ANA serology in 6 patients with dermatomyositis.

	Cutaneous category			
	n=6	ANA positive	ANA negative	ANA not done
Category I	3	3		
Category II	1		1	
Category III	2	1		1

The antinuclear antibodies (ANA) were positive in 24 (77.4%) patients – 4 of the 6 patients with DM had a positive ANA (66.7%), one of the 2 patients with PM (50%) and 19 of the 23 patients (82.6%) with CAM were positive.

Table3. Comparison of serological markers in patients with connective tissue disease-associated myositis (CAM) versus those with dermatomyositis (DM) and polymyositis (PM). Total patients = 31.

Serological tests	Total, n=31 (100%)	CAM, n=23	DM, n=6	PM, n=2
ANA	24 (77.4)	19 (82.6)	4 (66.7)	1 (50)
RF	6 (19.4)	4 (17.4)	2 (33.3)	0 (0)
Anti-U1-RNP	11 (35.4)	11 (47.8)	0 (0)	0 (0)
Anti-Jo-1	1 (3.2)	0 (0)	0 (0)	1 (50)
Anti-Ro/La	3 (9.7)	3 (13)	0 (0)	0 (0)

Note that other than Anti-Jo-1 antibodies we did not measure other myositis specific antibodies which may have some, albeit limited role in prognostication of patients with IIM.[26; 27]

Two patients were found to have neoplastic disease, with follicular adenoma in 1 patient with DM and breast carcinoma in another patient with IIM associated with SLE. Therefore none of the patients fell into the sub-group of "pure" carcinoma-associated IIM.

CPK was raised (normal range in our laboratory 26 – 140 U/L) in 25 (78%) patients. The median CPK at presentation for subjects with DM/PM was 2109U/L (inter-quartile range 871.5 – 7207U/L) compared to subjects with CAM of 519 U/L (inter-quartile range 162 – 1093U/L), 4 times greater (fig 3). By the Wilcoxon rank-sum test p=0.024.

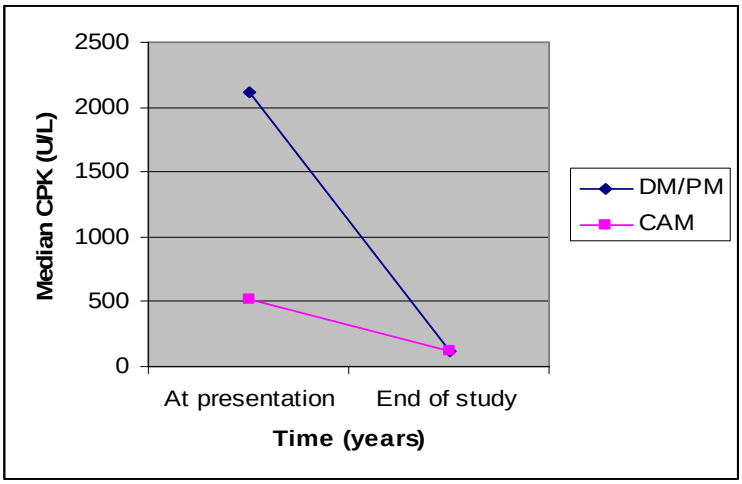


Figure 3. Creatinine phosphokinase (CPK) levels on presentation and on treatment in patients with dermatomyositis (DM)/polymyositis (PM) and connective tissue disease-associated myositis (CAM).

One third of subjects had an electromyogram (EMG). Seven were compatible with myopathy, which revealed polyphasic, small amplitude, short duration motor unit action potentials (MUAP), and early recruitment. One was normal, and 2 were inconclusive. Five of the subjects with DM as well as the 2 subjects with CAM had a compatible EMG.

Three muscle biopsies were done on patients included in our study. However, these muscle biopsy results could not be located. One patient with DM had a skin biopsy taken from the upper arm. It revealed mild perivascular dermatitis with lymphocytes and increased stromal mucin. No interphase dermatitis was found. The findings were reported as being in keeping with either DM or SLE.

All subjects were on treatment, which included various combinations of azathioprine, methotrexate, prednisone, cyclosporine and cyclophosphamide. Table 4 summarizes the therapy. Of the 6 patients with DM, 4 were on prednisone plus an immunosuppressive agent while 2 were receiving prednisone plus 2 immunosuppressive agents. Those with PM were on prednisone plus an immunosuppressive agent. The average doses of medication were as follows, prednisone 27.5mg daily (range 5mg – 50mg daily), methotrexate 20mg per week (range 15mg – 25mg per week) and azathioprine 175mg daily (range 100mg – 250mg daily). Only one subject received cyclosporine (150mg daily) and another received cyclophosphamide (50mg alternating with 100mg daily).

Drug Therapy	Total, n=31(100%)	CAM, n=23	DM, n=6	PM, n=2
Methotrexate	14 (45.2)	9 (39.1)	5 (71.4)	0 (0)
Prednisone	27 (87.1)	19 (82.6)	6 (100)	2 (100)
Azathioprine	16 (51.6)	13 (56.5)	2 (33.3)	1 (50)
Cyclosporine	1 (3.2)	0 (0)	1 (16.7)	0 (0)
Cyclophosphamide	1 (3.2)	0 (0)	0 (0)	1 (50)

Table4. Comparison of treatment regimens in patients with connective tissue disease-associated myositis (CAM) versus those with dermatomyositis (DM) and polymyositis (PM). Total patients = 31.

The response to therapy was assessed by comparing the serum CPK at presentation with serum CPK at the end of June 2008. Due to incomplete documentation, activities of daily living (ADL) and improvements in muscle power could not be reliably evaluated. By the end of the study, the median CPK for subjects with DM/PM was 119U/L (inter-quartile range 93.5 – 498U/L), and 119U/L (inter-quartile range 73 – 274U/L) in subjects with CAM (p=0.56) (fig 3). Therefore despite the clinically significant differences in CPK levels at presentation between the 2 groups there was no significant difference between the 2 groups at the end of the study.

DISCUSSION

This study revealed that IIM is approximately twice as common in our study population compared to the figures quoted in the literature. According to Statistics S.A. the estimated mid-year census for the Western Cape in 2008 was 5 million. Approximately 50% of this total is under the care of our sister academic hospital in Cape Town, Groote Schuur Hospital. Of the remaining 2.5 million approximately 20% is seen in the private health sector (rheumatologists, neurologists and physicians) and secondary hospitals in the Cape Town East Metropole. Thus, the estimated population served by the adult rheumatology clinic at TAH is 2 million. Based on this the prevalence of IIM at this clinic is approximately 15 per million population. Several patients (at least 3) missed their follow-up appointments during the period of this study and were therefore not picked up. Thus the exact prevalence is even greater than that reported in our results.

Historically, as alluded to in the introduction, inflammatory myopathies are defined as primary, auto-immune-mediated inflammation of skeletal muscle, characterised by symmetrical, proximal muscle weakness. Clearly, based on an assessment of the literature and previous experience, as well as the findings of this study, the current classifications are unsatisfactory. An appropriate classification may be that of an immune – mediated inflammation of skeletal muscle with chronic inflammatory cell

infiltrates, caused by an underlying auto-immune disease such as DM, PM, other CTDs (which occur either in isolation or as part of an overlap syndrome or MCTD), or alternatively, as part of undifferentiated CTD (UCTD). Some cases, however, may be associated with underlying malignancy, HIV, and other rarer miscellaneous causes including drugs, granulomatous myositis, eosinophilic myositis and macrophagic myositis. For purposes of this discussion, we were at variance with that of *Dalakas'* classification, and excluded IBM as a true IM. There is little evidence to support IBM as a true cause of IIM and IBM is thought to be a rare, largely non-inflammatory cause of myopathy.

Approximately 20% of patients were diagnosed with DM, 2 with PM while approximately three quarters were diagnosed with CAM. This emphasizes the rarity of "pure" PM and supports the contention that its frequency was overestimated in earlier reports in the literature.

IIM was more common in females than in males, with a ratio of 9:1. The average age of onset was 45.2 years, which was similar to that found in other studies.[3]

Of the patients with DM three patients had category I cutaneous manifestations (clearly diagnostic features). There was one patient with category II – (strongly characteristic skin lesions). Of the remaining 2 patients in category III: one had no ANA documented but a skin biopsy was in keeping with DM. The other had a positive ANA with category III cutaneous lesions.

Of the 31 patients, 23 had CAM – this is much more common than previously reported in the literature [1;12]. Thus in our study population this group comprises approximately three-quarters – the overwhelming majority of patients with IIM. The most common CAM was in patients with MCTD (9/23), followed by SLE (8/23) and scleroderma (5/23). One of 23 had UCTD.

Seventy-two percent of patients at presentation had muscle power of 4/5. However, this is based on an assessment of only 18 patients where muscle power was adequately documented. Thirty-eight percent of patients with IIM had extra-muscular and extra-

cutaneous manifestations. The most common was interstitial lung disease (ILD) found in 8 patients. These comprised 1/6 with DM, 2/2 with PM and 5/22 with CAM. This is in keeping with figures reported in the literature.[28]

Raynaud's phenomenon was only found in only 13% of patients, but this is probably not a true reflection and due to incomplete documentation. However, most of the patients with Raynaud's phenomenon were found in those with CAM. This finding compares well with other studies where it was most frequently associated with MCTD/overlap syndrome.[29]

Arthritis is said to occur in approximately 25% of patients with DM/PM[30]; however, this study did not support this. Arthritis in our study was rare occurring in only one patient who had UCTD. The reasons for this limited occurrence of arthritis are unclear.

One patient with SLE had an associated malignancy while another with DM had a follicular adenoma. This may simply be a chance finding as follicular adenoma is a benign tumour, and not associated with DM.[31; 32]

One patient with an overlap syndrome/MCTD was found to be HIV positive. There were no patients with HIV-associated myopathy. The fact that we serve patients in an area with a high HIV prevalence emphasises the rare nature of this condition.

The median CPK concentration in patients with DM/PM was 4 times greater than in patients with CAM at time of presentation which was statistically significant ($p=0.024$). This finding is consistent with that in the literature.

Finally, the response to therapy could only be assessed using follow-up CPK concentrations and need for steroids and immunosuppressive therapy as muscle power and ADL were not adequately documented. The relative decrease in CPK concentrations in patients with DM/PM when compared to those with CAM was greater. This was likely as a result of the higher concentrations of CPK at presentation in patients with DM/PM.

Regarding steroid dose titration (over the study period only), in those with CAM prednisone was initiated in three, dose was increased in 4, reduced in 5 (this includes one patient in which dose was initially decreased then increased) and remained

unchanged in four. However, in patients with DM prednisone dose was decreased in 1, remained unchanged in 2 and was increased in none in this group. No comment could be made regarding dose titration in 3 patients with DM, both patients with PM and 1 with CAM as there was only one follow-up appointment during the study period. Regarding other immunosuppressive drugs, in the group with DM methotrexate was increased in one, azathioprine was decreased in another and cyclosporine was increased in one. In those with CAM, methotrexate was initially decreased then increased in one and azathioprine was initiated in one and increased in another.

From this it may be concluded that in the CAM group IIM is as disabling if not more debilitating than in patients in the DM/PM group. Thus our experience does not support the perception that in the CAM group, despite the lower average CPK compared to patients with PM/DM the muscle weakness is less severe.

The finding of no need for increasing the steroid dose in patients with DM may be surprising since approximately 30% of patients may be non-responsive to steroids.[13] However, in our study all patients with DM were on combinations of immunosuppressive therapy and that this could explain the lower steroid doses.

CONCLUSION AND RECOMMENDATIONS

This study revealed that the prevalence of IIM in our study population is more common than previously reported in the literature.

There is a need for a review of the current definition of IIM and we propose the following definition: Immune-mediated inflammation of skeletal muscle with chronic inflammatory cell infiltrates, caused by an underlying auto-immune disease such as DM, PM or other connective tissue diseases such as SLE, scleroderma, or part of MCTD/overlap syndrome or UCTD. The following is a simplified way of tabulating our proposed classification.

Proposed Reclassification of Immune Inflammatory Myositis (IIM)
A. Auto-immune inflammatory myopathy associated (AIIM) with:
1. DM
2. PM
3. SLE **4.** Scleroderma
5. MCTD/overlap syndrome
6. UCTD
B. Malignancy-associated inflammatory myopathy
C. HIV-associated inflammatory myopathy
D. Miscellaneous eg. drugs, macrophagic myositis, eosinophilic myositis

This classification strongly emphasises the need to be have a high index of suspicion for features of connective tissue disease be they clinical or serological.

In patients with CAM there are 3 possible histological findings; that of PM, DM and hitherto unknown histological findings as this sub-group is rarely if ever subjected to muscle biopsies. Hence the only way of distinguishing this is by means of a muscle biopsy. This is important as treatment responders may be differentiated from non-responders and thus also contributes to determining prognosis. An evaluation of the literature does not reveal reliable information regarding the histology of the inflammatory myopathy associated with CAM. Thus a follow-up study evaluating the

histology in these patients will greatly contribute to our understanding of IIM in this subgroup – the biggest category in our study population.

In our study population, malignancy-associated inflammatory myopathy as a stand alone entity was present in none of the cases, demonstrating its rarity. In addition we found no cases of HIV associated IIM. This is surprising in view of the large numbers of patients afflicted with this condition in our drainage area.

This study revealed the limited role of EMG in the management of patients with IIM. Our assessment is that it should be reserved for the subgroup of patients with muscle weakness and a normal or modest rise in CPK.

Prognostically this study confirmed that IIM is a chronic debilitating condition requiring long term maintenance therapy with corticosteroids and immune suppressing agents.

Finally it is out contention that our proposed classification would assist in the guiding a more rational approach to the IIM, particularly in the light of the majority of the patients being in the CAM group and requiring as intensive therapy as the PM/DM group.

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