

## Inflammatory Idiopathic Myopathies: Clinical, Laboratory Features and Prognostic Observations in 118 Hispanic-Mestizo Patients

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### Abstract

**Objective:** To determine the clinical and laboratory features, malignancy, outcome and their association in a Hispanic mestizo population with Inflammatory Idiopathic Myopathies (IIM).

**Material and methods:** The medical records of Hispanic mestizo patients with dermatomyositis, polymyositis or overlap syndrome from a single center were reviewed. Several variables were studied with emphasis on malignancy.

**Results:** We report the clinical and laboratorial features of 118 patients with IIM; the female to male ratio was 2.3:1. Elevated CK, proximal weakness, compatible biopsy and elevated LDH were the most frequent findings. Malignancy was found in 9.3%, gynecological tumors were the most common (55%). Mortality was 10.2%, mainly related to infections and respiratory failure.

**Conclusions:** The overall rate of malignancy in this large series of patients with IIM was 9.3%. The majority of our patients reached a good outcome. No risk factors for malignancy were found.

**Keywords:** Inflammatory myopathies; Dermatomyositis; Polymyositis; Overlap syndrome; Malignancy

### Materials and Methods

At a single referral center, a retrospective review of the records from patients with the diagnosis of IIM was made from 1986-2004; we excluded patients with age <15 years (the hospital treats only adult patients), incomplete or unclear diagnosis or data and follow up <1 year. We studied the following: demographic information, type of IIM, weakness at onset, signs of systemic involvement (fever, weight loss or both), Raynaud's phenomena, cutaneous findings (heliotropic rash, Gottron papules, malar erythema, poikiloderma, periungual telangiectasias, V sign, Shawl sign), serum levels of creatine kinase (CK), Complete Blood Count (CBC), Creatinine (Cr), Erythrocyte Sedimentation Rate (ESR), Albumin (Alb), Lactate Dehydrogenase (LDH), Antinuclear Antibodies (ANA); Electromyographic findings (EMG), muscle biopsy features (fiber atrophy, inflammation, nuclear internalization, blood vessel wall infiltration, necrosis), a modified functional disability score [7], mortality and cause of death; association and type of malignancy, follow-up. The diagnosis of definite/probable/possible myositis were according to the Bohan and Peter [5,6] criteria, and the clinical overlap features were defined as described by Troyanov et al., for this reason, inclusion body myositis (IBM) was excluded based on previously accepted criteria [8-10]. Institutional Research Committee approved the study.

### Introduction

Inflammatory idiopathic myopathies (IIM) include [1] dermatomyositis (DM), polymyositis (PM), overlap syndromes (OS) - also referred as overlap myositis [2] - and inclusion body myositis (IBM); the first three have been associated with malignancy since last century [3], with no risk factors yet identified. Scarce reports have included a Hispanic mestizo population [4]. The aim of this large series is to describe the clinical and laboratory features of IIM, the frequency of malignancy and associated risk factors in a Hispanic mestizo population.

The old criteria of Peter and Behan proposed in 1975 have served the community well for years but cannot explain the differences in the subsets of inflammatory myopathies [5,6]. Troyanov et al. developed an interesting clinicoserologic classification where overlap clinical features as well as myositis-associated autoantibodies (MAAs) and myositis specific autoantibodies (MSAs) were positioned at the core of the classification system [2]. One major difficulty, both in terms of diagnosis and classification, is that it excludes the now recognized IBM, most likely incorporating those cases in the PM subgroup. Likewise, IBM was not included in the new clinicoserologic classification of IIM by Troyanov et al., or in the last European Neuromuscular Centre (ENMC) international workshop on adult IIM.

## Results

We report the findings of 118 patients; 74 (63%) with DM, 20 (17%) PM and 24 (20%) OS. There were 83 women (70%) and 35 men; the female to male ratio was 2.3:1. Mean age was 37 years (IQR 24-49

years). The mean follow up was 68.3 months (range 14-97 months). Table 1 describes demographic, clinical and laboratory features accordingly to type of IIM.

	DM	PM	OS
	74 (100%)	20 (100%)	24 (100%)
Age (mean ± SD; Range 15-70), years	35.01 ± 15.43	41.45 ± 12.1	41.88 ± 15.54
Female	50 (68)	15 (75)	18 (75%)
Male	24 (32)	5 (25)	6 (25%)
Follow-up (mean ± SD), months	61.64 ± 56.1	76.4 ± 63.67	82.42 ± 73.93
Diagnostic Criteria			
Proximal weakness	73 (99%)	20 (100%)	24 (100%)
High CK UI/L (>263)	61/73 (84%)	19/20 (95%)	18/23 (78%)
Myopathic changes on EMG	49/50 (98%)	16/16 (100%)	13/15 (87%)
Muscle biopsy	3/52 (6%)	3/16 (19%)	0
Normal	2/52 (4%)	0	1/20 (5%)
Atrophy	4/52 (8%)	1/16 (6%)	3/20 (15%)
Inespecific regeneration	43/52 (83%)	12/16 (75%)	16/20 (80%)
Compatible			
Cutaneous findings	74 (100%)	0	12 (50%)
Bohan and Peter	57 (77%)	11 (55%)	14 (58%)
Definite	16 (22%)	6 (30%)	8 (33%)
Probable	1 (1%)	3 (15%)	2 (8%)
Possible			
Other clinical features:			
Systemic symptoms	36 (49%)	15 (75%)	13 (54%)
Weight loss only >5%	23 (31%)	11 (55%)	7 (29%)
Fever only	4 (5%)	0	1 (4%)
Both	9 (12%)	4 (20%)	5 (21%)
Raynaud's phenomenon	14 (19%)	1 (5%)	8 (33%)
Other laboratory data:			
High LDH (>164 UI/L)	62/70 (89%)	19/19 (100%)	20/24 (83%)
Low Hemoglobin (<14 g/dL)	26 (35%)	6 (30%)	12 (50%)
Low Albumin (< 3.5 g/dL)	31/70 (44%)	5/18 (28%)	14/24 (58%)
Elevated ESR	26/69 (38%)	4/18 (22%)	12/21 (57%)
Positive ANA	33/62 (53%)	4/17 (24%)	17/21 (81%)

CK= Creatine Kinase; EMG= Electromyography; LDH= Lactate Deshydrogenase; ESR= Erythrocyte Sedimentation Rate; ANA= Antinuclear Antibodies.

**Table 1:** Demographic, clinical and laboratory findings in 118 patients with Dermatomyositis (DM), Polymyositis (PM) or overlap syndrome (OS).

According to Bohan and Peter's criteria, 69.5% had definite diagnosis, 25.5% probable and 5% possible. Proximal weakness was present at the time of diagnosis in 99%. As systemic manifestations of

the disease, 35% had weight loss only>5%, 4.2% fever only and 15.3% both.

Characteristic dermatologic findings were found in 73% of the patients, 100% in those with DM, 0% PM and 50% of OS. Raynaud's phenomenon was present in 19.5% of the patients. Of the 24 patients with OS, according clinical overlap features described by Troyanov et al., 6 (25%) had mixed connective tissue disease, 6 (25%) rheumatoid arthritis, 4 (17%) scleroderma, 4 (17%) Sjögren's disease and 4 (17%) lupus.

Laboratory features included an elevated CK in 84.4%, high LHD in 90%, seric hemoglobin levels and albumin were low in 37% and 45% respectively, creatinine elevation was seen in only 0.8%, and high ESR was detected in 39%. ANA were positive in 54% of the studied population.

The electromyography showed a myopathic pattern (increased insertional and spontaneous activity in the form of potentials positive sharp waves, and complex repetitive discharges, and low-amplitude, short-duration polyphasic motor unit action potentials) in 96%.

Muscle biopsy showed a compatible diagnosis (Dermatomyositis: perifascicular atrophy, or at least two of reduced capillary density, perivascular and/or perimysial inflammatory cell infiltrate; Polymyositis: endomysial inflammatory T-cells surrounding and invading non-necrotic muscle fibers, exclusion of necrotizing myopathies and dystrophies) with IIM in 81%, regeneration 9%, normal 7%, atrophy 3%.

Malignancy was diagnosed in 11 (9.3%) patients (Table 2). Location included uterine cervix in 4, unknown primary in 2, salivatory gland in 1, endometrial 1, ovary 1, urinary tract 1, cecal appendix 1. According to histopathological findings, 5 were epidermoid carcinomas and 6 adenocarcinomas. All were suspected during an initial clinical evaluation. No differences between the groups were found.

	DM N=74	PM n=20	OS n=24	Total n=118
Malignancy	6 (8%)	3 (15%)	2 (8.3%)	11 (9.3%)
Before the diagnosis of IIM	1	-	-	1
After the diagnosis of IIM	5	3	2	10
Location of malignancy	1	1	2	4
Cervix	1	-	-	1
Endometrium	1	-	-	1
Ovary	-	1	-	1
Urinary Tract	1	-	-	1
Cecal appendix	2	-	-	2
Unknown primary	-	1	-	1
Salivatory gland	-	-	-	-
Histological variant	4	1	1	6
Adenocarcinoma	2	2	1	5
Epidermoid	-	-	-	-

**Table 2:** Malignancy characteristics in 118 patients with Dermatomyositis (DM), Polymyositis (PM) or Overlap Syndrome (OS).

Treatment and outcome are shown in Table 3, corticosteroids were used in 97.5% of the patients, a dose >40 mg/day was needed in 73%; concomitant use of cytotoxic drugs were prescribed in 82%, methotrexate was the most commonly used (41%), followed by azathioprine in 32%, both in 21% and cyclophosphamide 6%. Chloroquine was used in 26%, most frequently to treat DM (87%).

	DM n=74 (%)	PM n=20 (%)	OS n=24 (%)
Prednisone	71 (96)	20 (100)	24 (100)
<40 mg/day	17 (23)	3 (15)	9 (37)
>40 mg/day	54 (73)	17 (85)	15 (63)
Cytotoxic drugs	63 (85)	16 (80)	18 (75)
MTX <15mg/week	18 (24)	7 (35)	4 (17)
MTX >15mg/week	7 (10)	2 (10)	2 (8)
AZA <50 mg/day	0	0	2 (8)

AZA >50 mg/day	22 (30)	2 (10)	5 (21)
Both	12 (16)	4 (20)	4 (17)
Cyclophosphamide	4 (5)	1 (5)	1 (4)
Chloroquine	37	20	0
Functional status at first visit	3 (4)	1 (5)	0
I	32 (43)	7 (35)	9 (37)
II	30 (41)	11 (55)	11 (46)
III	9 (12)	1 (5)	4 (17)
IV	0	0	0
V	-	-	-
Functional status at last visit	55 (74)	13 (65)	16 (67)
I	8 (11)	5 (25)	3 (12)
II	2 (3)	1 (5)	0
III	-	-	-
IV	2 (3)	0	1 (4)

V	7 (9)	1(5)	4 (17)
Response to therapy	63 (85)	18 (90)	19 (79)
Death	7 (9)	1 (5)	4 (17)
Cause of death	3/7 (43)	1/1 (100)	2/5 (40)
Infections	1/7 (14)	0	0
Respiratory failure	2/7 (29)	0	1/5 (20)
Malignancy	1/7 (14)	0	1/5 (20)
Unknown	0	0	1/5 (20)
Cardiovascular			

**Table 3:** Treatment and outcome in 118 patients with Dermatomyositis (DM), Polymyositis (PM) and Overlap Syndrome (OS),

The functional status (FS) at admission was I, II, III, IV and V in 3, 41, 44, 12 and 0% in that order, the FS during the last reported visit was I, II, III, IV and V in 71, 14, 2.5, 2.5 and 10.2% equally.

The mortality in our series was 10.2%. The most common cause were lower respiratory tract (LRT) infections (50%), malignancy (25%), and other determined causes included respiratory failure due to weakness or aspiration and cardiovascular disorders.

## Discussion

In order to make a more reliable diagnosis of IIM, as suggested by many [11-17] we included only patients who had a complete diagnostic work-up; this included a re-review of the muscle specimens that were available (88/118) [18].

All our patients with DM had featured cutaneous findings described elsewhere [19-22] and none had amyopathic dermatomyositis as anticipated [23].

The overall frequency of malignancy in patients with IIM varies, according to geographical area and racial trait studied, from 6-45% [1,8,24-29]. In our series 6 of 74 patients (8%) with DM, 3 of 20 (15%) with PM and 2 of 24 (8%) with OS had malignancy. If we excluded cervix uteri as an associated malignancy, the frequency would be 7, 10 and 0% correspondingly; these results are comparable to the aforementioned reports. Cancer types varies among different series, in ours uterine/cervical cancer was the most common, even if we discarded the association of this neoplasm with the disease[26,28] an incidence of 5% should draw our attention to this co-morbidity. Other sites of neoplasm, in our studied population, included mainly genitourinary tract (endometrium, ovary, ureter), 2 were found in the GI tract (salivatory gland, cecal appendix) and no site was evidenced in 2. One patient had the diagnosis of malignancy (cecal appendix) before the IIM was evident, and for the rest, a latency of 1 to 39 months was required; the temporal association of malignancy with IIM has been considered of outmost importance in order to consider the IIM as paraneoplastic disorders [28,29]. Some rheumatic diseases [29-31], as well as the IIM have reported a high incidence of malignancy; clinical and laboratorial actions should be taken, to make a prompt diagnosis and adequate treatment. To achieve the diagnosis of malignancy, clinical examination and routine tests sufficed in 11/12, CT scan was the preferred method for sustaining the diagnosis of malignancy besides the obligatory pathological confirmation. Routine examination

and in some cases a CT scan might be enough to search for malignancy in patients with IIM [32].

The mortality in this series (10%) is comparable to what others have found [29, 33-36], and infectious disease was the main cause in ours.

Conventional treatment of the patients [37-39] was mainly based on corticosteroids, chloroquine and/or steroid sparing agents.

Functional status was assessed by a modified Functional Disability Score [7], we added a Grade V for death, this scale was used because it is easy to document and there has not been any universally accepted system or criteria [40]. Response to therapy, defined as an improvement in functional status and good outcome, defined as a FS grade I or II, was reached in 85% as seen in other centers [36,41,42].

We searched among the studied variables for risk factors that predicted malignancy, none were found, as seen in table 4. For mortality, the use of cytotoxic drugs was the only variable that reached statistical significance, patients who did not used these medications died more frequently (7/21) than those who did (5/97), the significance of this is yet to be elucidated. Finally, a referral basis must be taken into account.

	Malignancy n (%)		Death n (%)	
	Yes	No	Yes	No
DM	6 (8.1)	68 (91.9)	7 (9.5%)	67(90.5%)
PM	3 (15)	17 (85)	1(5)	19 (95)
OS	2 (8.3)	22 (91.7)	4 (16.7)	20 (83.3)
Female	9 (10.8)	74 (89.2)	7 (8.4)	76 (91.6)
Male	2 (5.7)	33 (94.3)	5 (14.3)	30 (85.7%)
High CPK	11 (11.2)	87 (88.8)	9 (9.2)	89 (90.8)
Cutaneous signs	7 (8.1)	79 (91.9)	9 (10.5)	77 (89.5)
Raynaud phenomenon	0	23 (100)	3 (13)	20 (87)
Low Hb	4 (9.1)	40 (90.9)	3 (6.8)	41 (93.2)
High Cr	0	1 (100)	0	1 (100%)
Low Alb	4 (8)	46 (92)	7 (14)	43 (86)
High LDH	11 (10.9)	90 (89.1)	10 (9.9)	91 (90.1)
High ESR	3 (7.1)	39 (92.9)	4 (9.5)	38 (90.5)
Corticosteroid use	11 (9.4)	104 (90.4)	10 (8.7)	105 (91.3)
Cytotoxic drugs use	6 (6.2)	91 (93.8)	5 (5.2)	92 (94.8)
Chloroquine use	2 (6.9)	29 (93.5)	1 (3.2)	30 (96.8)

Table 4: Analyzed risk factors for malignancy and mortality.

## Conclusion

In a mestizo-hispanic population with IIM treated at our center, the frequency of malignancy was 9.3%. The majority of our patients reached a good outcome. A mortality of 10% was observed, with LRT infections being the most common cause. No risk factors for malignancy were found.

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