# IDIOPATHIC INFLAMMATORY MYOPATHY/MYOSITIS

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## ABSTRACT

**Introduction:** Myopathy inflammation idiopathic (IIM) is a rare autoimmune disorder characterized by muscle weakness, proximal and symmetrical weakness, except distal and asymmetric weakness in inclusion body myositis (IBM). The diagnosis is based on clinical examination, laboratory tests, increased creatine kinase (CK) and autoantibodies, electromyography (EMG), and histopathology. Extramuscular involvement can influence cases like lungs interstitial (ILD), dermatomyositis skin (DM), systemic or joints, and increases the risk of malignancy, especially in DM. Treatment is mainly immunosuppressive, with most cases requiring more than one agent. Line drugs include mycophenolate mofetil, cyclosporine, tacrolimus, rituximab, etanercept, and cyclophosphamide.

**Conclusion:** Myositis, a rare disorder, can be differentiated into four forms: DM, PM, N A M, and IBM. Treatment is largely based on experience, with IBM remaining a challenge due to its complex pathogenesis. Developing new treatments is justified due to growing interest in rare disorders.

**Keywords:** Idiopathic Inflammatory Myopathy, Myositis

## INTRODUCTION

Myopathy inflammation idiopathic is group marked conditions with inflammation muscles ( myositis ) and systems body other. Myopathy inflammation idiopathic (IIM) consists from abnormality autoimmune rare heterogeneous marked occurrence with weakness muscle proximal and symmetrical, except distal and asymmetric weakness in inclusion body myositis (IBM).

The diagnosis is made based on inspection clinical ( distribution of paresis) combined with mark laboratory, increase creatine kinase (CK) and autoantibodies, electromyography (EMG) and histopathology muscle frame. Use of magnetic resonance imaging (MRI) of muscles frame No only help identify adequate muscle for biopsy, but also for show pattern affected muscles externally appearance helpful clinical rule out, for example, dystrophy muscle. Apart from frequently enhancement creatine kinase (CK), electromyogram ensure exists myopathy irritative. Involvement extramuscular influence a number big case disease lungs interstitial (ILD), dermatomyositis skin (DM), manifestations systemic or joints and increases risk malignancy especially in DM. Autoantibodies specific myositis affects IIM phenotype. Jo-1 antibodies frequently linked with ILD and antibodies a new HMG-CoA reductase explained is characteristics myopathy necrotizing autoimmune disease (NAM). Pathology muscle range from exudate inflammation with distribution varies, up to invasion fiber muscle intact, necrosis, phagocytosis, and deep case vacuole IBM- framed and protein deposits.

Therapy immunosuppressive is treatment mainstay for patients with disease related active with DM, PM and NAM. Autoimmune NAM often more resistant to therapy immunosuppressive compared to DM and PM, especially If there is disease malignancy or statin triggers. The majority (23/25) of SANAM cases require more from One agent immunosuppressive with recurrence in 12 cases after subtraction therapy immunosuppressive. However as in DM and PM, immunosuppressants like prednisone combined with methotrexate (MTX) or azathioprine ( AZA) is therapy line first in autoimmune NAM. For resistant cases or severe, added immunoglobulin intravenous (IVIG) possible Can help. Line drugs third including mycophenolate mofetil, cyclosporine, tacrolimus, rituximab, etanercept and cyclophosphamide.

myositis reference article is to provide information and use as learning material regarding the signs and symptoms, diagnosis and management of myositis.

## DEFINITION

*Idiopathic inflammatory myopathies* (IIM) consist from abnormality autoimmune heterogeneous be marked with inflammation muscle ( myositis ). IIMs can classified in three subtypes, polymyositis (PM), dermatomyositis (DM), and *inclusion body myositis* (IBM), however recently these, are also subgroups others, like *necrotising autoimmune myopathy* (NAM) and *antisynthetase syndrome* has been identified. [1]

Apart from frequently enhancement creatine kinase (CK), EMG confirmed exists myopathy irritative. Involvement extramuscular influence a number big case *interstitial lung disease* (ILD), dermatomyositis skin (DM), manifestations systemic or joints and increases risk malignancy especially in DM. Autoantibodies specific myositis affects IIM phenotype. Jo-1 antibodies frequently linked with ILD and antibodies HMG-CoA reductase is NAM characteristics. Pathology muscle range from exudate inflammation with distribution varies, up to invasion fiber muscle intact, necrosis, phagocytosis, and deep case vacuole IBM- framed and protein deposits.

## EPIDEMIOLOGY

IIMs are abnormality rare sporadic happen with incident annual whole around One from 100,000. Except *juvenile* dermatomyositis (JDM), IIM is diseases in adults and other than IBM, diseases This more Lots attack woman compared to man. In a research in the Netherlands that does not including IBM, NAM represented 19%, whereas DM and non- specific myositis accounted for 36% and 39% of all IIMs. [2]

Unlike findings from study else, PM reported seldom happens, just covers 2% of IIM case. However, phenotype clinical PM is most common cause from deep PM pathology Suite case *Mayo Clinic*. The incidence of PM and DM in South Australia is 1.0 to 1.4 per million population, but in Olmstead County it is 9.6 per million resident. PM incidents in South Australia obtained from findings biopsy muscle and review record medical four times more tall versus DM, respectively 4.1 to 6.6 per million versus 1.0 to 1.4 per million. A study recently This show level prevalence in South Australia was 1.97 and 7.2 per 100,000 for DM and PM, respectively. In survey population Taiwanese national between 2003 and 2007, overall incident Annual DM and PM were 7.1 (95% CI 6.6–7.6) and 4.4 (95% CI 4.0–4.8) cases per million resident. The incidence of DM and PM is increasing along increase age and reach peaks at age 50–59 years. [3,4]

## GENERAL CLINICAL MANIFESTATIONS

Patients with IIM have difficulty using proximal muscles, such as getting up from a chair, climbing stairs, or lifting objects. Tasks requiring distal muscles, such as buttoning or holding objects, were affected early in IBM but only in cases of PM, DM, and NAM. Eye muscles are not present in all subtypes, but facial muscles are commonly affected in IBM. In all subtypes, the neck extensor muscles and pharyngeal muscles can be affected, causing difficulty lifting the head ( *head drop* ) or dysphagia. In advanced and rare acute cases, respiratory muscles may be affected. Muscle atrophy is detected in phase early IBM, with selective atrophy of the quadriceps and forearm muscles, but progresses in all subtypes if the weakness is severe and chronic. Myalgia and muscle pain may occur, especially in patients with *antisynthetase syndrome*. [5]

Extramuscular manifestations can occur in all IIM subtypes, although they occur only in IBM; these manifestations include systemic symptoms, such as fever, arthralgia, and Raynaud's phenomenon, as seen in *antisynthetase syndrome*; cardiac arrhythmia or ventricular dysfunction, in rare cases where the affected heart muscle has clinical symptoms; and pulmonary complications, mainly caused by ILD, which are reported to occur in 10 to 40% of patients. The prevalence of ILD reaches 70% among patients with anti-histidyl transfer RNA (tRNA) synthetase (anti-Jo-1) or anti-melanoma differentiation. -associated protein (MDA)–5 antibodies. [6,7]

## CLASSIFICATION AND CLINICAL MANIFESTATIONS

### Dermatomyositis (DM)

The clinical picture of DM is skin, muscle, or both with acute progressive proximal muscle weakness. As with PM and N A M, DM patients have difficulty using their arms when raised above their heads and are unable to get up from a chair, get off the floor, or climb stairs. Grip strength is reduced in chronic DM and PM compared with controls. Weakness is painless except in patients with acute conditions and/or subcutaneous calcifications. DM can cause bulbar muscle weakness which manifests as dysphagia, difficulty chewing, weakness in opening the jaw and sometimes dysarthria. In addition, systemic involvement is common in JDM which generally presents as muscle weakness and pain following episodes of fever and skin rash.

The characteristic skin rash precedes or occurs simultaneously with the onset of muscle weakness, thus providing an initial clue to the diagnosis of classic DM. Adermatopathic DM is more difficult to recognize because it is histopathologically proven to be DM without a rash. Amopathic DM presents with only a skin rash and no weakness although muscle histology

shows some inflammation. Although the classic DM rash can be very subtle, the heliotrope rash is distinctive and consists of purplish discoloration of the eyelids that is often associated with periorbital edema. However, generalized or extremity edema is a rare manifestation of DM. Gottron's papules, a pathognomonic purple lichenoid papular scaly rash, appear on the extensor surfaces of the hands, elbows, and sometimes on the toes. When located on the volar aspect, papules are referred to as Inverse Gottron Papules. Macular erythematous rash can affect the face, neck and anterior chest ("V sign"), upper back (" *shawl sign* "), extensor surfaces of the elbows, knuckles, knees or toes (Gottron sign). Occasionally, the nail bed has dilated capillaries with periungal hyperemia. Nailfold capillary density is reduced in JDM and is inversely correlated over time with muscle and skin disease activity. Subcutaneous calcinosis of the elbows and knees with occasional ulceration is common in JDM but rare in DM mature age. " *Mechanic's hand* ", which manifests as thickened and cracked skin on the dorsal and ventral surfaces of the hand, is found in patients with *antisynthetase syndrome* (arthritis, Raynaud's phenomenon, ILD ). Skin symptoms, including prominent pruritus, have a significant impact on quality of life. [8.9]

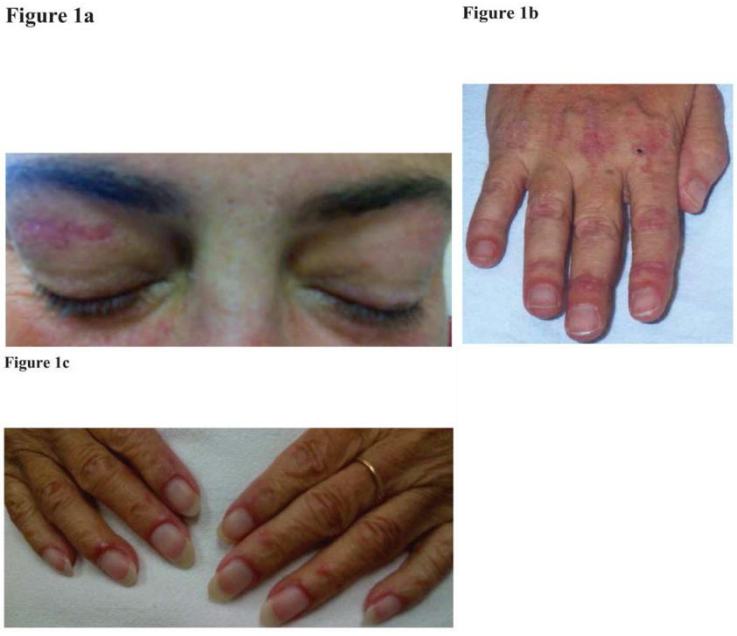


**Figure 1.** Manifestation DM clinical. Figure 1a. Heliotrope rash and periorbital edema and erythema in DM; Figure 1b. Papular rash scaly erythematous colored purple on DM - Gottron's papules, with ulceration skin and hyperemia perinungal.; Figure 1c. Hyperemia periungal in DM

Bohan and Peter described 5 criteria favoring definitive DM including proximal weakness, elevated CK, EMG myopathy, inflammatory pathology and a characteristic rash that differentiates it from PM. Since then, a modification of Bohan and Peter was reported by Targoff and colleagues who introduced a sixth criterion of myositis-specific autoantibodies as performed with validated assays. This allows patients who meet 4 of the 6 criteria to be diagnosed with definitive DM or PM. An international group of experts met in Naarden and published proposed IIM classification criteria to improve the specificity of diagnosis. This system is based on clinical criteria, CK elevation, other laboratory criteria, and more defined muscle biopsy criteria. DM is classified as definitive DM, *probable*, amyopathy, and *probable* DM *sine* dermatitis. Definitive DM requires pathological evidence of perifascicular atrophy whereas probable DM is based on perivascular inflammatory cell infiltration, MAC deposition in small vessels, decreased capillary density, tubuloreticular inclusions in endothelial cells on EM, or MHC-1 expression in perifascicular fibers. This pathological picture without the characteristic skin rash is sufficient for the diagnosis of *probable* DM *sine* dermatitis. Muscle biopsy in DM amyopathy does not show features consistent with definitive or *probable DM*.

**Table 1.** Bohan and Peter's criteria for DM and PM

| |
|---|
| 1. Weakness symmetrical, usually progressive, in the muscles *limb-girdle* with or without dysphagia and weakness muscle Respiratory |
| 2. Biopsy muscle proof exists myositis |
| Necrosis fiber muscle type I and type II; phagocytosis, degeneration, and regeneration myofibers with variation size myofiber ; cell mononuclear endomysial, perimysial, perivascular, or interstitial. |
| 3. Improvement serum enzyme levels related muscle (CK, LDH, transaminase, aldolase) |
| 4. EMG triad of myopathy |
| A. Polyphasic motor unit potential short, small, amplitude low |
| B. Potential fibrillation, even moment Rest |
| C. Discharge strange repetition and frequency tall |
| 5. Characteristics of the rash dermatomyositis |
| Definitive PM : fourth element first, PM probability : 3 of the first 4, PM probability : 2 of the first 4. |
| Definitive DM : rash plus 3 others, possible DM: rash plus 2 others, possible DM: |

| |
|---|
| rash plus 1 more |

**Table 2.** Component Classification IIM criteria ( except IBM) according to ENMC 2004

| |
|---|
| 1. Criteria clinical |
| *Criteria inclusion* |
| a. Onset is usual more from 18 years ( post puberty ), possible onset occurs in childhood in DM and myositis nonspecific |
| b. Subacute onset or dangerous |
| c. Weakness pattern : symmetrical proximal > distal, flexor neck > extensors neck |
| d. Typical DM rash : heliotrope periorbital edema ( purple ); papules colored purple ( Gottron papules ) or macula ( Gottron's sign ), scaly If chronic, in the joints metacarpophalyngeal and interphalyngeal as well as protrusion bone other ; erythema of the chest and neck ( V sign ) and back top ( sign shawl ) |
| *Criteria exclusion* |
| a. Clinical picture of IBM: weakness asymmetrical, flexor wrist hands / fingers The same or more bad from deltoid; extensor knee and/ or ankle dorsiflexors are the same or more bad from flexor hips |
| b. Weakness eyes, dysarthria isolated, weakness extensor neck more bad compared to weakness flexor neck |
| c. Myopathy toxic ( eg exposure drug myotoxic recently this ), endocrinopathies active ( hyper or hypothyroidism, hyperparathyroidism ), amyloidosis, history dystrophy muscle in family, or neuropathy motor proximal |
| 2. Improvement rate Serum creatine kinase |
| 3. Criteria laboratory other |
| a. Electromyography : |
| *Criteria inclusion* |
| 1. Enhancement activity insertion and spontaneous in form potential fibrillation, waves sharp positive, or release complex repetition |
| 2. Analysis morphometrics disclose exists duration short, amplitude small, polyphasic MUAP |
| *Criteria exclusion* |
| 1. Release myotonic showing dystrophy myotonic proximal or channelopathy other |
| 2. Analysis morphometics indicates MUAP duration length and amplitude big |
| 3. The decline pattern MUAP recruitment |

b. MRI: improvement diffuse signal (edema). or No evenly inside network muscles on STIR images
c. Antibody Specific myositis detected in serum

4. Criteria inclusion and exclusion biopsy muscle
   a. Infiltration cell inflammation endomysial cells (T cells) surround and attack fiber non- necrotic muscle
   b. Surrounding endomysial CD8 + T cells, however No in a way Certain attack fiber non- necrotic muscle, or ubiquitous expression of MHC-1
   c. Atrophy perifascicular
   d. MAC deposition in vessels blood small, or reduced density capillary, or inclusion tubuloreticular in cell endothelium on EM, or MHC-1 expression in perifascicular fibers
   e. Infiltration cell inflammation perivascular and perimysial
   f. Infiltration scattered endomysial CD8 + T cells No surround or invade fiber muscle with clear
   g. Lots of fiber muscle necrotic as description dominant abnormal histology. cells inflammation seldom or only A little perivascular ; infiltration perimysial No seen. MAC deposition in vessels blood small or capillary the pipe stem on the EM can visible, however inclusion tubuloreticular in cell endothelium seldom or No seen.
   h. Vacuoles framed, fiber red rags, lint cytochrome oxidase- negative indicating IBM
   i. deposition in fiber sarcolemma nonnecrotic and indicated dystrophy muscle other with immunopathology

**Table 3.** Criteria Classification for IIMs according to ENMC 2004

| **Polymyositis** |
|---|
| *Definite polymyositis* |
| 1. All criteria clinical except rash |
| 2. Increased serum CK |
| 3. Criteria biopsy muscle includes a; and except c; d; h; i |
| *Probable polymyositis* |
| 1. All criteria clinical except rash |
| 2. Increased serum CK |
| 3. Criteria laboratory others (1 of 3) |
| 4. Criteria biopsy muscle includes b; and except c; d; g; h; i |
| **Dermatomyositis** |
| *Definite dermatomyositis* |

1. All criteria clinical
2. Criteria biopsy muscle includes c

*Possible dermatomyositis*

1. All criteria clinical
2. Criteria biopsy muscle includes d or e, or increased serum CK, or criteria laboratory others (1 of 3)

*Amyopathic dermatomyositis*

1. Typical DM rash : heliotrope, periorbital edema, papules / Gottron's sign, V sign, *shawl sign, Holster sign*
2. Biopsy skin show decline density capillaries, deposition of MAC in vessels blood small throughout dermal-epidermal junction, and decoration various kerotinocytes for MAC
3. There isn't any weakness objective
4. Serum CK is normal
5. Normal EMG
6. Biopsy muscle, if done, no show appropriate image with DM for sure or probable

*Possible dermatomyositis sine dermatitis*

1. All criteria clinical except rash
2. Increased serum CK
3. Criteria laboratory others (1 of 3)
4. Criteria biopsy muscle includes c or d

**specific myositis**

1. All criteria clinical except rash
2. Increased serum CK
3. Criteria laboratory others (1 of 3)
4. Criteria biopsy muscle includes e or f ; and exclude others

***Immune-mediated necrotizing myopathy***

1. All criteria clinical except rash
2. Increased serum CK
3. Criteria laboratory others (1 of 3)
4. Criteria biopsy muscle includes g; and exclude others

**Table 4.** Component 2017 EULAR/ACR classification for adult and youth IIMs

| Variable | Score |
|---|---|

| | Without biopsy auto | With biopsy muscle |
|---|---|---|
| Age emergence symptom First assumed relate with disease ≥18 and <40 years | 1.3 | 1.5 |
| Age emergence symptom First assumed relate with disease ≥40 years | 2.1 | 2.2 |
| Weakness muscle | | |
| Weakness symmetrical objectively, usually progressive, in the extremities on proximal | 0.7 | 0.7 |
| Weakness symmetrical objectively, usually progressive, in the extremities lower proximal | 0.8 | 0.5 |
| Flexor neck relatively more weak compared to extensor neck | 1.9 | 1.6 |
| In the legs, muscles proximal relatively more weak compared to distal muscles | 0.9 | 1.2 |
| Manifestation skin | | |
| Heliotrope rash | 3.1 | 3.2 |
| Gottron papules | 2.1 | 2.7 |
| Gottron Sign | 3.3 | 3.7 |
| Manifestation clinical other | | |
| Dysphagia or dysmotility esophagus | 0.7 | 0.6 |
| Measurement laboratory | | |
| There are anti-Jol autoantibodies | 3.9 | 3.8 |
| Enhancement serum levels of CK or LDH or ASAT/AST/SGOT or ALAT/ALT/SGPT | 1.3 | 1.4 |
| Biopsy muscle | | |

| | |
|---|---|
| Infiltration endomysial cell surrounding mononuclear, but No attack, myofibres | 1.7 |
| Infiltration perimysial and/ or perivascular cells mononuclear | 1.2 |
| Atrophy perifascicular | 1.9 |
| Vacuoles framed | 3.1 |

**Polymyositis (PM)**

PM was defined as diagnosed in patients who did not have a rash or muscle or nerve disease. PM attacks adults over the age of 20 years and occurs more often in women than men. Because there is no pathognomonic skin rash, diagnosis is often more delayed in PM than in DM. Patients experience progressive weakness of the neck flexor muscles and symmetrical proximal extremity muscles subacutely or insidiously over weeks to months. Distal muscles are relatively spared. Although myalgia and muscle pain are common, this does not cause complaints but weakness or dysphagia occurs in one third of patients. In patients with acute quadriparetic presentation, weakness is present Jaw opening is noted in 71% of PM/DM cases whereas this is rare (4%) in Guillain-Barré syndrome. Tendon reflexes are normal except in very weak muscles where the reflex is reduced. [5]

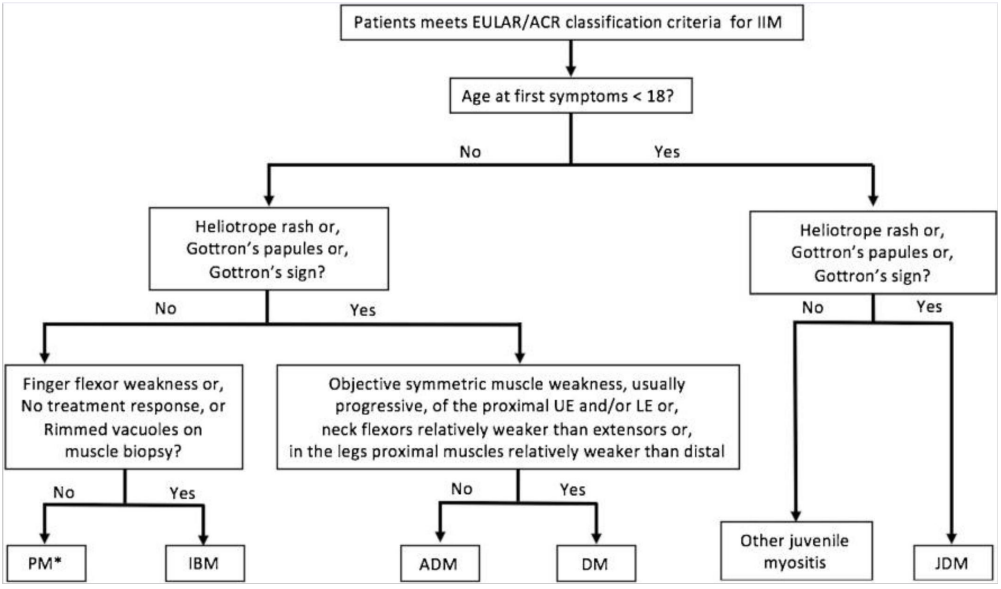


**Figure 2.** Eular IMM Classification

***Overlap myositis* (OM)**

*Overlap myositis* (OM) is known as Individual forms of myositis are heterogeneous and encompassing the largest myositis subgroup. Patient with OM coming with weakness I or subacute in the arms and legs, similar with type myositis mentioned above. Usually there is enhancement enzyme muscle including CK. OM can diagnosed simultaneously with abnormality other collagens such as Sjögren's syndrome, sclerosis systemic, or *systemic lupus erythematosus* (SLE). The most common condition in OM is *antisynthetase syndrome* (ASS), which can considered as different subforms of myositis. ASS consists from gathering symptom typical clinical including myositis, Raynaud's phenomenon, inflammation joints, hands mechanics, ILD and the presence of anti-transfer RNA synthetase auto- antibodies. [10]

***Inclusion body myositis* (IBM)**

IBM is inflammation muscle especially idiopathic attack man skin white who is over 50 years old. Onset of onset more slow and can attack muscle proximal nor distal muscles. Weakness muscle usually bilateral, but often No symmetrical. Limbs more often attacked compared to arms, especially muscles anterior thigh with atrophy muscle prominent. Muscle axial Possible affected, which causes camptocormia ( bone behind bow to front ) or head fell. Dysphagia happens to more than 50% of patients. [11,12]

**Table 5.** IBM classification according to ENMC 2011

| classification | Findings clinical | Findings biopsy |
|---|---|---|
| IBM based clinicopathologist | Duration weakness >12 months<br>Creatinine kinase <15x ULN<br>Onset age < 45 years<br>Weakness of finger flexion > weakness shoulder abduction<br>And/ or<br>Weakness extension knee > hip flexor weakness | All matter following :<br>Infiltrate inflammation endomysial<br>Vacuoles walled<br>Protein accumulation or 15-18nm filament |
| IBM based clinical | Duration weakness >12 months<br>Creatinine kinase <15x ULN<br>Onset age < 45 years<br>Weakness of finger flexion > weakness shoulder abduction<br>And<br>Weakness extension knee > hip flexor weakness | One or more, however No all, from :<br>infiltrate inflammation endomysial<br>Upregulation of MHC class I<br>Vacuoles walled<br>Protein accumulation or 15-18nm filament |

| | | |
|---|---|---|
| Probable IMM | Duration weakness >12 months<br>Creatinine kinase <15x ULN<br>Onset age < 45 years<br>Weakness of finger flexion > weakness shoulder abduction<br>Or<br>Weakness extension knee > hip flexor weakness | One or more, however No all, from :<br>infiltrate inflammation endomysial<br>Upregulation of MHC class I<br>Vacuoles walled<br>Protein accumulation or 15-18nm filament |

***Necrotizing autoimmune myopathy*** **(NAM)**

NAM is subtype occurs more often compared to polymyositis, countable up to 19% of all over myopathy inflammation. This matter can happens to everyone age but especially seen in adults ; disease This started in a way acute, reaching peak during a number of day or week, or in a way subacute, developing continues and causes malaise and levels very high creatine kinase. NAM happened Alone or after viral infections, related with cancer, in patients with abnormality connective tissue like scleroderma, or in patients taking statins, whose myopathy Keep going worsened after statin discontinuation ( if myopathy improved in time 4 to 6 weeks afterwards. statin discontinuation, p This Possible caused by effects toxic medicine and not Because myopathy immune ). Most patient with NAM has antibody to *signal recognition particle* (SRP) or against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). [13]

## PATHOGENESIS

### Immunopathology

Cause IIM doesn't is known with sure, however pathogenesis autoimmune involved in IIM journey. In DM, C5b-9 *membranolytic attacks complex* complement activated more beginning ( before damage fiber muscle seen clear ) and stored in cells endothelium, causing necrosis, decline density capillary endomysial, ischemia, and damage muscle. - destruction fiber resemble microinfarction ; remaining capillaries has a widened lumen For compensate ischemia. Residual perifascicular atrophy is described hypoperfusion endofascicular, most prominent at the periphery fascicles. Activation *Membranolytic attack complex* trigger release cytokines proinflammatory, increasing regulations molecule adhesion to cells endothelium, and facilitates migration lymphocytes activated, incl B cells, CD4+ T cells, and cells Dendritic *plasmacytoid*, to room perimysial and endomysial. Immunity default also plays role which is based on improvement type I interferon- induced protein expression in the perifascicular region,

the area where the molecule inflammatory, degenerative, or regenerative others are also expressed in a way excessive; Still must determined is effect immunity default caused by induced gene 1 signaling sour retinoic as response to signal local from damaged fibers, which causes autoamplification perifascicular inflammation with activates interferon-ß and MHC class I. In JDM, maternal chimeric cells Possible contribute to disease pathogenesis. [14,15]

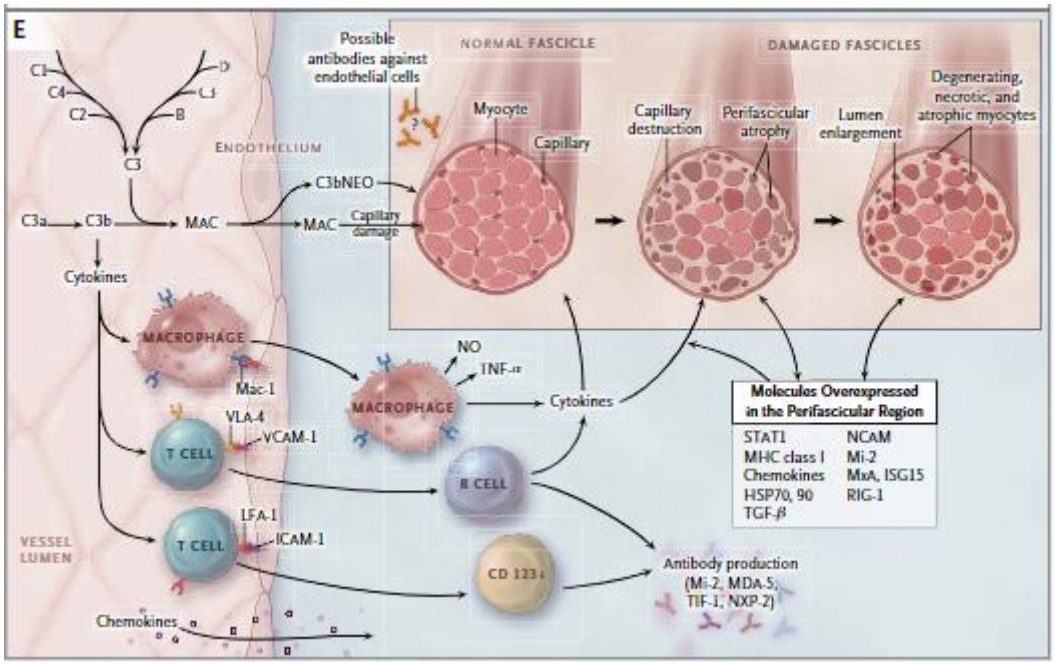


**Figure 3.** Schematic diagram immunopathogenesis of DM

In PM and IBM, CD8+ cytotoxic T cells surround and invade fiber muscle healthy nonnecrotic and expresses MHC class I deviate. MHC class I expression, which does not found in the sarcolemma fiber Normal muscles, probably caused by cytokines secreted by activated T cells. The class I CD8-MHC complex is characteristics of PM and IBM, and their detection help in confirm the histological diagnosis. CD8+ T cells contain directed perforin granules to surface fiber muscle, which causes myonecrosis moment released. Analysis molecule receptor T cells expressed by infiltrating CD8+ T cells show expansion clonal chain receptor T cells and conserved circuits in the binding region antigen, which indicates response antigen- driven T cells. This matter furthermore supported by expressions molecule costimulation and enhancement regulations molecule adhesion, chemokines, and cytokines4547. Th17 cells and regulatory T cells 48 participate in the immune process. Enhancement regulations and advantages MHC class I load can also be cause error folds glycoproteins, which suppress reticulum endoplasm myofibers. Activation B cells also occur, most prominently in IBM

( although No clear is muscle can maintain formation germinal centers ), where anti-CN1A autoantibodies were also detected.

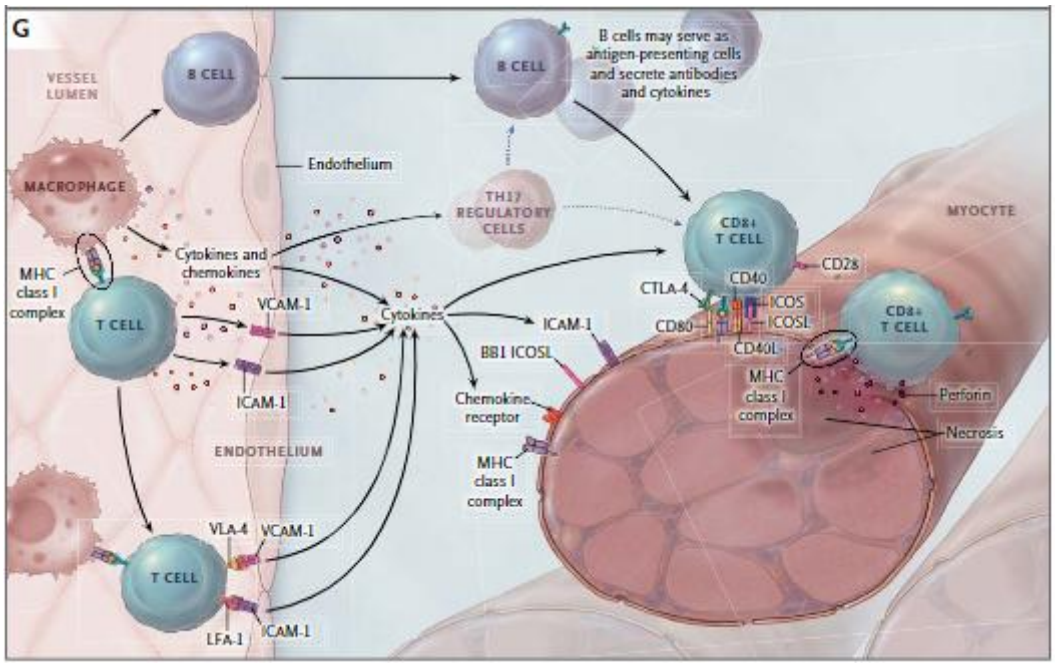


**Figure 4.** Mechanism damage mediated muscles T cells in PM and IBM

Triggering factors disease inflammation muscle Still Not yet is known. Risk factors genetic control response immune to agent environment that has not defined has proposed. Interaction genetic supported by relationships between HLA-DRB1*03 and anti-Jo-1, between HLA-DRB1*11:01 and anti-HMGCR- positive NAM, and between HLA-DRB1*03:01 and HLA-DRB1*01:01 and IBM. Viruses maybe responsible answer For bother tolerance immunity body, however effort For amplify viruses - including coxsackie virus, influenza virus, *paramyxovirus, cytomegalovirus,* and Epstein-Barr virus of muscle has fail. Best evidence For The viral link involves retroviruses, as PM or IBM develops in infected people *human immunodeficiency virus* (HIV) or lymphotropic virus human T cells. However, retroviral antigens only detected in macrophages endomysial and not in fiber muscle. Autoinvasive T cells moved in a way clonal, and some of them Specific against retrovirals. HIV -related PM and HIV -related IBM must differentiated from myopathy mitochondria toxicities caused by antiretroviral drugs, which improved when drug stopped. [14,15]

**Component IBM Degenerative**

IBM is complex disorders because, besides component autoimmune, there is component important degenerative, which is marked with exists precipitate amyloid congophilic inside a number of fiber. Similar to what is seen in Alzheimer's disease, deposits This react immune to precursor proteins amyloid, amyloid -ß42, apolipoprotein E, a-synuclein, presenilin, ubiquitin, and phosphorylated tau, indicating exists protein aggregation. Deposition of TDP43, a translocated DNA- binding protein in a way deviate from nuclei to cytoplasm, and p62, a transport protein that transports polyubiquitinated proteins, was detected in fiber muscle with using immunostaining, has recommended as diagnostic marker. [16,17]

In vitro evidence suggests that amyloid - ß42 and its oligomers involved in track toxicity intracellular, however Still Not yet clear How these protein aggregates, which are also seen in myopathy vacuolar others, induce myopathy inflammatory and degenerative as well as trigger the disease., inflammation, or protein aggregation. Laser microdissection of the invaded fibers T cells compared with Fiber does n't invaded or divacuole has show difference regulations signal inflammation, for example interferon- receptor signals. Strong evidence show that aging, abnormal proteostasis ( network that controls proteins), disorders autophagy, stress cells caused by MHC class I or oxide nitrates, long-lasting inflammation, and cytokines proinflammatory such as interferon-y and interleukin-1ß can in a way cumulative trigger or increase degeneration, which leads to accumulation more carry on molecule trigger stress and misfolded proteins. [16,17]

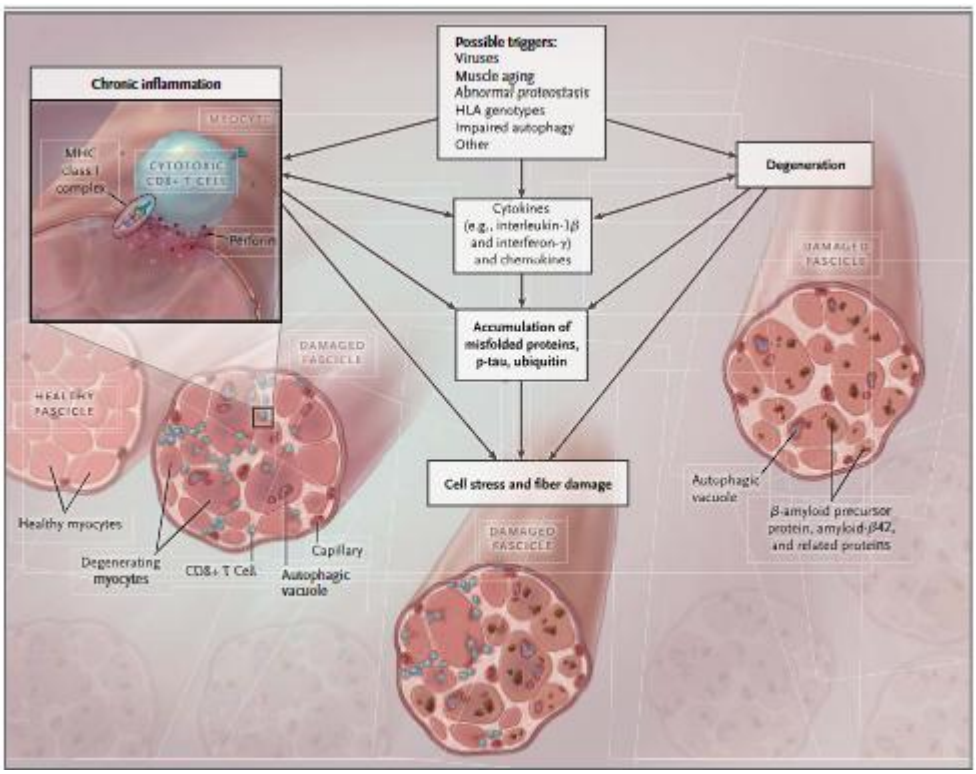

**Figure 5.** Mechanism Pathogenesis in IBM

## DIAGNOSIS

### Inspection Support

Typical skin changes, with or without muscle weakness, indicate DM ; proximal myopathic weakness presenting subacutely suggests PM or NAM ; and proximal weakness and Slowly progressive distal with selective atrophy suggests IBM.

Among the muscle-derived enzymes in serum, the most sensitive indicator of IIM is creatine kinase (CK), which is elevated in patients with active disease. The highest levels, up to more than 50 times the upper limit of normal, were seen in patients with NAM, and the lowest (less than 10 times the upper limit of normal) were seen in patients with IBM. SGOT, SGPT and aldolase levels will also increase, as will the erythrocyte sedimentation rate (ESR) and *C-reactive protein* (CRP). In the urine you will also find increased levels of myoglobulin and creatine.

Electromyography (EMG) may demonstrate myopathic motor unit potentials (short duration, low amplitude polyphasic units on voluntary activation) and increased spontaneous activity with fibrillation, complex repetitive discharges, and positive sharp waves. These findings are useful in determining whether the myopathy is active or chronic and in ruling out neurogenic disorders, but cannot be used to differentiate inflammatory myopathy from toxic myopathy or dystrophy. MRI can be used to identify edema, inflammation of the muscle or fascia, fatty infiltration, fibrosis, or atrophy. It is useful to assess the degree and selectivity of muscle involvement, especially in cases of inclusion body myositis; to identify disease activity; and to guide selection of muscles with the greatest degree of inflammation for biopsy. [18]

### Inspection Histopathology

In DM, inflammation is perivascular and most prominently located in the interfascicular septa or fascicle edges. Muscle fibers experience necrosis and phagocytosis, often in the muscle fasciculus or fascicle periphery due to microinfarction which causes hypoperfusion and perifascicular atrophy. Perifascicular atrophy, characterized by a layer of atrophic fibers at the periphery of the fascicles, often with perivascular and interfascicular infiltrates, is diagnostic of dermatomyositis (or superimposed myositis, when skin changes are absent or transient). [19,20]

In PM and IBM, inflammation is perivascular and usually concentrated in a few foci within the endomysium; consists mostly of CD8+ T cells that attack nonnecrotic muscle fibers that appear healthy and express major histocompatibility complex (MHC) class I antigens (normal muscle fibers do not express these antigens). Findings of MHC and CD8+ T cell expression (called the MHC-CD8 complex) are useful to confirm the diagnosis and rule out disorders resulting from nonimmune inflammation, as seen in some muscular dystrophies. [20,22]

In OM, picture histology covers perifascicular necrosis and perifascicular ligation of MHC class I and class II antibodies as well binding complement on the sarcolemma in the same area of the muscle frame.

In NAM, there are many necrotic fibers that are attacked or surrounded by macrophages. Lymphocytic infiltrates are rare, and MHC class I upregulation is often prominent outside the necrotic fibers. NAM is most often mediated by specific antibodies against SRP or HMGCR, often by complement deposition in capillaries. [20,22]

IBM has all the inflammatory features of polymyositis, including CD8-MHC complexes, but in addition it also has chronic myopathic changes with increased connective tissue and fiber size variability, autophagic vacuoles whose inner walls are lined with a bluish material. with hematoxylin and eosin or modified Gomori's trichrome, " *ragged-red* " or cytochrome oxidase-negative fibers representing abnormal mitochondria, and congophilic amyloid deposits next to the vacuoles, which are best visualized with crystal violet or fluorescent optics. Electron microscopy shows tubulofilaments 12 to 16 nm in diameter next to the vacuole. In up to 30% of patients with the typical IBM clinical phenotype, vacuoles or amyloid deposits are not found in muscle biopsy samples and only inflammation is seen, leading to an incorrect diagnosis of PM. The patient was diagnosed with "clinical IBM " based on clinicopathological correlation. Data-based criteria confirm that weakness of the finger flexors or quadriceps, inflammation around nonnecrotic fibers with MHC class I expression, and cytochrome oxidase-negative fibers, even without vacuoles, are specific for the diagnosis of clinical inclusion body myositis. [21]

**Inspection Autoantibodies**

The most common and longest known autoantibody associated with the classic form of DM is the Mi-2 antibody, which is found in 20% of DM patients. MDA5 antibodies were first described in 2009 and are present in ~10-30% of DM patients, especially in cases with vasculitic skin lesions and ILD severe with increased mortality. The common antibody in DM with a frequency of about one third of cases is anti-TIF-1a/B/y antibody. TIF-1 antibodies are

associated with malignancy in 75% of adult patients; in children, they show one of the most common antibodies and are associated with JDM, but not with tumors in this age group. Another antibody with a strong tumor association is the NXP2 antibody with reported tumor rates of up to 37.5%. NXP2 is also the second most common auto-antibody in children with a frequency of up to 22% and can have high rates of calcinosis. A recently identified antibody associated with ~8% of DM cases is SAE. Patient with antibody it often shows an *amyopathic*

| | Auto-antibodi | Frekuensi | Manifestasi Klinis |
|---|---|---|---|
| ASS | Anti-tRNA: Jo-1, PL-7, PL- 12, HA (YRS/Tyr), OJ, KS. ZO, EJ | anti-tRNA: 30% pada miositis | Angka ILD dan mortalitas lebih tinggi pada PL-7/PL-12 dibandingkan Jo-1 |
| OM | Anti-SS-A/Ro52/Ro60 SS-B/La | Jo-1: 15-20% pada miositis PL-7 dan PL-12: masing-masing 3-4% Lainnya <2%. | Terkait dengan sindrom Sjögren., SLE dan sklerosis sistemik. Ro52 lebih sering terjadi pada miositis dibandingkan Ro60; keduanya terjadi pada CTD. Ro52 dan Jo-1-double positif: tingkat keganasan yang tinggi, prognosis yang lebih buruk. |
| | U-snRNP | SS-A: hingga 19% pada miositis, 25% pada OM, SS-B: 7% pada miositis, 12% pada OM Ro52 sering bersamaan dengan anti-synthetase, misalnya. 56-72% dari Jo-1. | Terkait dengan CTD, SLE dan sklerosis sistemik. Seringkali prognosis bagus |
| | PM/Scl | hingga 10% pada miositis | Terkait dengan sklerosis sistemik. Seringkali perjalanan penyakitnya parah dan respons pengobatannya tidak memadai. |
| | Ku | -8-10% pada miositis | Terkait dengan sklerosis sistemik, SLE dan CTD. Tingginya tingkat ILD, yang tidak merespon dengan baik terhadap glukokortikosteroid |
| DM | Mi-2 | hingga 20-30% pada OM | Klinis DM |
| | MDA5 | 5-10% pada DM | Seringkali DM amiopati, sering ILD. |
| | TIF-1a/B/ | 15-30% pada DM | Keganasan umum terjadi (75%) . Paling umum pada JDM-tanpa tumor. |
| | NXP-2 | -20% pada DM | Keganasan sering terjadi (37,5%). Antibodi kedua yang paling umum pada JDM- tanpa keganasan, tetapi sering kali kalsinosis. |
| | SAE | 10-15% pada DM | Seringkali amiopati dan dengan ILD. |
| NAM | SRP | 2-8% pada DM | Seringkali dengan atrofi otot, ILD dan disfagia. Seringkali regimen terapi imunosupresif dasar tidak cukup. |
| | HMGCR | 5% pada miositis | Frekuensi keganasan yang tinggi. |
| IBM | CN1A | 5-8% pada miositis | Sjögren atau SLE positif sebesar 20-30%, bahkan tanpa gejala otot. Di IBM: perjalanan penyakit lebih parah, disfagia, dan angka kematian lebih tinggi |

course and presents with dysphagia and mild to moderate ILD. [23]

**Figure 6.** *Overview* of autoantibodies in IIM and manifestations clinical

Two auto- antibodies has proven relate with NAM. Anti-SRP antibodies are present in approximately 10 to 20% of patients with NAM, though level detection varies widely ( from 0% to 54%). Anti-SRP can linked with cardiomyopathy and travel serious illness with atrophy muscles, ILD and dysphagia. Autoantibodies both identified up to 60% of certain NAM groups is anti-HMGCR. At varying levels, 30-60 % of patient This Once previous exposure to statins. Connection with malignancy has proven more high in patients with anti-HMGCR and without auto- antibodies compared to with patient with anti-SRP. [24]

The most common from eight antibody *anti-synthetase* is Jo-1 antibodies, which are observed in ~30% of patients myositis according to meta-analysis latest. Anti-PL-7 and anti-PL-12 were found in 3-4% of cases and all anti- synthetase antibodies other not enough common (<2%): anti-EJ, anti-ZO, anti-OJ, anti -KS, anti-HA(YRS/Tyr). Apart from antibodies *anti-synthetase,* five antibodies other relate with OM as well abnormality other connective tissue. They can cause syndrome clinically identical with ASS or a number of image, for example. ILD and myositis plus individual symptoms of abnormality respective connective tissue. The most common antibodies is anti-PM/ Scl ( targeting two subunits 75 kDa and 100 kDa complex exosomes nuclear ), which is common linked with sclerosis systemic and occurs in 12% of cases myositis. Anti-U-snRNP antibodies are observed in 3-8% of patients myositis and related with *mixed connective tissue disease* (CTD). Temporary patient with anti-U-snRNP often has a good prognosis, anti-PM/ Scl show journey more disease severe and responsive treatment that is not adequate. Anti-Ku antibodies are associated with sclerosis systemic, SLE and *mixed* CTD and not differentiate other. In myositis, occurrence This seldom happen with frequency 1-3%, but in overlapping syndromes overlap with myositis, occurrence This occurs in 19% of cases. Antibody This have high levels of ILD, which is not respond Good to glucocorticosteroids, meanwhile symptom muscle usually respond. Anti-SS-A/Ro52/R060 and anti-SS-B/La usually found in Sjögren's syndrome, SLE, and sclerosis systemic. Antibody This occurs in patients with myositis with frequency of 19% and 7%, respectively, and on their OM occurs in 25% and 12% of cases. SS-A has. proven present in 6% of JDM patients. More anti-Ro52 subdomains often occurs in patients with myositis compared to Ro60, where both of them You're welcome found on CTD. Anti-Ro52 often appear simultaneously with anti- synthetase antibodies, for example. in 56-72% of patients positive for anti-Jo-1. Patient with results positive double This own risk more violence high and a worse prognosis. [25,26]

The only one associated antibodies with IBM it was CNIA (5NTIA/5NTCIA, originally called "Mup44"). Observation latest show that in part big group, frequency around 30% and rare reaches 60% or more ; What's important, besides other forms of myositis including DM, a lot other conditions such as Sjögren's syndrome and SLE were also positive by ~20-30%, even without exists symptom muscle whatever. Latest data in the IBM group pointed out that the presence of CN1A is associated with journey more disease severe and dysphagia and number higher mortality. [27]

## GOVERNANCE

### Non Pharmacological

In phase acute, sufferer recommended For Rest bed rest. Passive movement must done during the acute period For prevent contracture. Contracture often Happened to JDM. After phase I resolved, sufferer must do exercise active, fine exercise isometric nor isotonic. The role of a physiotherapist is very important, no only For help do test strength muscle, but also deep make training program planning For strengthening muscle. Exercises this is very important For prevent atrophy muscles and contractures. [18]

Apart from improving strength muscle and improve taking oxygen in a way maximum, training exercise resistance in myositis patients results decline gene expression, which reflects decline proinflammatory and profibrotic gene networks, as well decreased tissue fibrosis. In severe cases, therapy started with exercise range motion passive during month First until month third and CK starts respond pharmacotherapy before carry out an exercise program Strict strengthening of very weak muscles. In patients with weakness light until medium, the program starts with strengthening after initiation of steroids. Because of pain arthralgia and possible consequences arthritis reduce with flexion joints, mobilization early important For prevent contracture flexion at the joint big and small, especially on JDM. Supplementation creatine monohydate may also play a role Because increase performance functional without effect significant side. [28]

### Pharmacology

#### *Corticosteroids*

Corticosteroids is drug line First to PM/DM with dose 60 mg/ day up to 2 mg/ kgBB prednisone. Repair clinic will seen on Sunday first treatment or gradually in time 3-6 months. Evaluation strength muscles and CPK levels should done every 3 weeks very. At week 6, the decision steroid dose should be determined. If circumstances patient gets better, then dose Initial steroids were maintained until strength Muscle and CPK levels return to normal. Dose the Still must maintained up to 4-8 weeks then, new lowered in a way slowly, namely 10 mg/ day every month. After dose prednisone up to 10 mg/ day for 1 month, dose lowered Again to 5 mg / day and maintained up to 1 year. If during decline steroid dose arises recurrence, then the steroid dose is increased Again to dose previously.

If in the 6th week after steroids are given No show improvements are expected, then can added azathioprine with dose 2-3 mg/ kgBW, started with dose 50 mg, 1 time/ day. If after 3 weeks No

There is improvement, dosage azathioprine raised to 100 mg/ day and can raised Again until achieved dose maximum 150 mg/ day. During giving azathioprine must Be careful to possibility effect side emphasis marrow bones and disorders function heart.

***Methotrexate***

Methotrexate, co with azathioprine, is considered as agent immunotherapy choice First For treat involvement muscle at IIM. Methotrexate has also been succeed used in treatment manifestation skin DM patients. Methotrexate can given to adults nor children, with dose initially 7.5 mg/ week and can raised up to 15 mg/ week when after 4-6 weeks No obtained expected improvements.

Effect side the most common methotrexate is infection, hepatotoxicity ( increased enzyme liver and cirrhosis ), and changes amount cell blood as well as transaminases and amounts cell blood complete must tested routinely in treated patients with methotrexate. Methotrexate must used in a way be careful of people with disturbance function kidneys and in patients who were also treated with drug nonsteroidal anti-inflammatory. Toxicity lungs in treated patients with methotrexate show effect serious side and not can predicted.

***Azathioprine***

Azathioprine (AZA) is a purine analogue and acts as antimetabolite, blocking purines and metabolism as well as RNA and DNA synthesis. Although therapy combination No more Good than corticosteroids just after 12 weeks, after 3 year extension, combination corticosteroids with AZA it is possible subtraction dose daily prednisone and associated with results more functional Good. AZA usually given started orally with 50 mg/ day and then improved in a way gradually of 25-50 mg every 1-2 weeks up to 2 mg/kg/ day. Amount cell blood complete, enzyme heart, and function kidney must checked routinely in patients receiving AZA.

Effect general side including vomiting, toxicity liver, and suppression marrow bone. Effect next to the last one this is very common happens to people with deficiency genetic enzyme genotyping thiopurine S - methyltransferase before AZA recipe.

***Calcineurin inhibitor***

Cyclophosphamide and cyclosporine -A are rare given to PM/DM though Possible can give good effect. Cyclosporine -A provides good results in myositis with positive anti-Jo-1 and polymyositis refractory. Dose cyclosporine -A for myositis is 2.5-5 mg/ kgBW / day. During

giving cyclosporine -A, pressure blood and function kidney must monitored in a way strict. When pressure blood and levels creatine increased 20% since beginning giving, then dose cyclosporine -A should be tapered. [18]

***Intravenous immunoglobulin (IVIG)***

IVIG, product collected gammaglobulin from a number of thousand blood donors, have mechanism Work complex immunomodulator. Estimated involve modulation production autoantibodies pathogenic and inhibitory binding, emphasis pro- inflammatory cytokines, blockade Fc receptors, factors stimulant colony macrophages and increased chemotactic protein-1 monocytes, changes function T cells, decrease circulation CD54 lymphocytes and cell inhibition. transmigration to muscle. Trials controlled in a way random with *cross-over* optional show that IVIG 2 gm/kg was given every month for 3 months is very effective in 9/12 resistant DM to treatment. Even though it's a trial controlled prospective Still less, IVIG is also felt effective on DM, PM and NAM. Guidelines *The American Academy of Neurology* 2012 recommended that IVIG be effective and considered For treat DM cases that don't responsive. There isn't any Enough proof For support or deny use of IVIG on PM or IBM. In cohorts beginning retrospective recently Currently, 78 cases of JDM were treated with steroids, 30 of them treated with additional IVIG. The IVIG group maintains activity similar disease or more low compared to control. Dose initially is 2 g/kg, given shared for two to five days, and then infusion be repeated every two to four week, with a total dose monthly 0.4 g/kg to 2 g/kg. [29]

Treatment involvement skin on DM with antimalarial drugs such as hydroxychloroquine in combination with corticosteroids with or without immunosuppressor effective in 40-75% of patients and has been entered in consensus latest For treatment rash in juvenile DM. Antimalarial medication apparently No effective on engagement muscle. The most common antimalarial drug prescribed in practice eating regularly is hydroxychloroquine up to 400 mg/ day.

Treatment This usually can tolerated with Good but effect aside, though light, relatively general happen like eruption skin, gastrointestinal toxicity ( nausea, vomiting, diarrhea ), dizziness, and pain head. Antimalarial retinopathy is effect the most serious side ; therefore that, there is recommendation from *American Academy of Ophthalmology* that patient must screened since beginning with examination of the fundus oculi and during care, evaluation periodically with automatic visual field and/ or tomography coherence optics must done every 5 years.

***Therapy biology other***

If the disease No give response to glucocorticoids and immunoglobulins intravenously, patient must evaluated repeat, and if there is uncertainty diagnostics, biopsy muscle repeat must considered. If the diagnosis is confirmed Come back, agent biology that has Approved For treatment disease immunity other can considered as choice treatment experimental. A number of choice including rituximab ( anti-CD20 antibody ), which with dose 2 g ( divided into two infusions with hose 2 weeks ) effective on some patient with DM, PM, or NAM. In research controlled placebo involving 200 patients, in weeks 8th no There is difference between group placebo. groups and rituximab groups, and based on design research, results No significant ; however, on Sunday to 44, when all patient has receiving rituximab, 83% complied definition repair. Patient with anti-Jo-1, anti-Mi-2, or anti-SRP antibodies apparently more Possible give response. Inhibitor factor tumor necrosis (infliximab, adalimumab, and etanercept) does not effective and possible worsen or trigger disease. Other biologic drugs that can considered as treatment experimental including alemtuzumab, which was reported effective in PM; anti-complement C3 (eculizumab), which is effective in mediated disease complementary and effective For treatment of DM and NAM; anti-interleukin-6 (tocilizumab) and anti-interleukin-1 receptor (anakinra), which are effective in cases of that nature anecdote ; anti-interleukin-17; and anti-interleukin-1ß (gevokizumab). By overall, impact period long from IIM has improved in a way substantial, with level continuity live 10 years more from 90%. [31.32]

**IBM Management**

Because of the effect mediated cytotoxicity T cells and increase associated protein aggregates amyloid by cytokines proinflammatory in patients with IBM, agent immunosuppressive 5% has try as treatment For subtype disease this, however everything failed, maybe Because disease This started Far before patient look for help medical, when cascade degenerative Already carry on. Glucocorticoids, methotrexate, cyclosporine, azathioprine, and mycophenolate No effective, and although a number of patient initially experience repair subjective light when treated with one agent this, no There is benefit period length achieved. Immunoglobulin intravenous proven No effective in trials controlled but Possible help a number of patient For temporary, esp those who suffer dysphagia. Alemtuzumab can give stabilization period short, however required studies controlled. Treatment with Anakinra not yet either succeed. Targeted trials inhibitory TGF-β molecules muscle or factor growth muscle currently taking place.

Bimagrumab, an inhibitory antibody signal receptor TGF-β superfamily, indicated in study scale small For increase muscle volume after 8 weeks.

Currently, therapy symptomatic is choice best. For threatening dysphagia a soul that doesn't respond to immunoglobulin intravenous, dilation cricopharynx or myotomy can considered. Like all IIMs, practice resilience that is not exhausting as well as therapy occupation and rehabilitation useful For increase ambulate, prevent fall, avoid atrophy consequences of disuse, and prevention joint contracture. [32]

Although hope life patient with normal IBM, some big patient with end stage disease need tool help like stick, tool help road, or chair wheel.

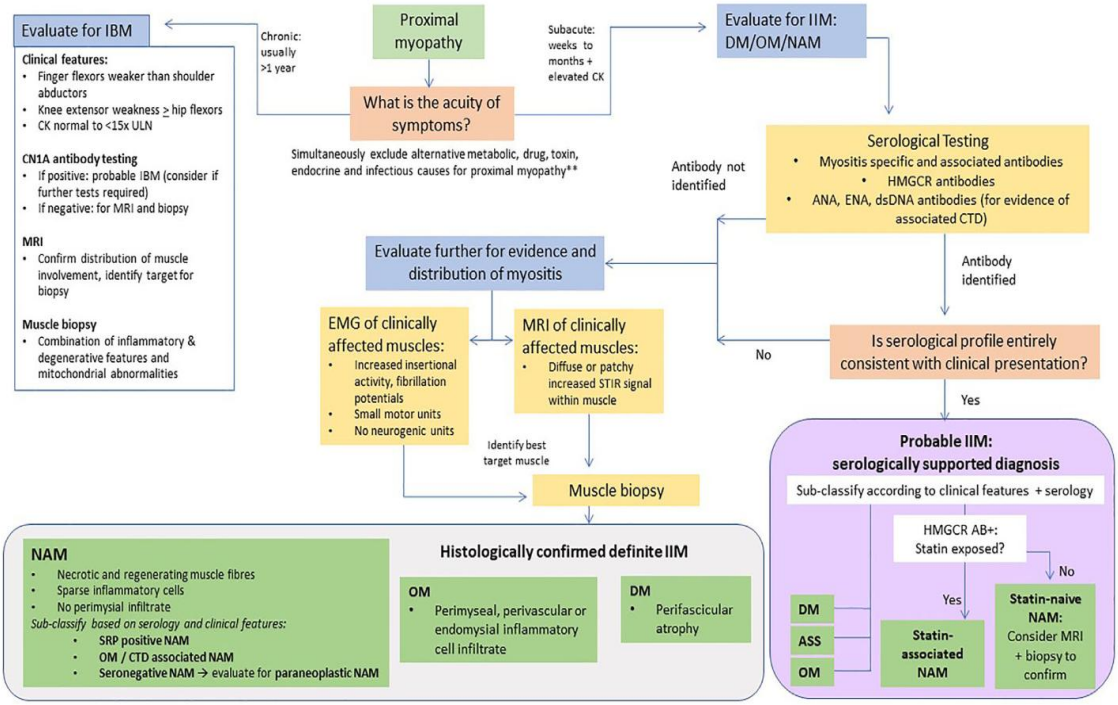


**Figure 7.** Algorithm for the diagnosis of proximal myopathy

## PROGNOSIS

The 5 year life expectancy of PM/DM sufferers is quite good, it can reach 85%; Meanwhile, in PM/DM sufferers who are associated with malignancy, it really depends on the prognosis of the malignancy. The 5 year life expectancy of patients who have positive anti-Mi-2 antibodies is even better, it can reach 90%. The worst prognosis is obtained in patients who have anti-SRP antibodies whose 5 year life expectancy is only 30%. [18]

Poor prognostic factors in PM/DM patients include older age, male sex, non-Caucasian ethnicity, longer duration of symptoms before diagnosis, ILD, cardiac involvement, dysphagia, cancer, and myositis-specific serum antibodies (including coexistence of anti-Ro52 and anti-

Ro52). anti-Jo1 antibody, SRP, anti-155/140 antibody, or anti-CADM-140). Complete remission of PM/DM occurred less frequently (13.6% versus 41.1%) and mortality (47.8% versus 7.3%) was higher in elderly patients compared to young patients. In a recent study, the co-presence of Ro52 and Jo1 antibodies was associated with more severe myositis/joint disorders, symptomatic ILD, increased risk of cancer, and higher mortality. Anti-SRP antibodies are associated with the acute onset of refractory necrotizing myositis and antibody titers correlate with CK levels and disease activity. Anti-155/140 antibodies are associated in adults with malignancy, whereas the presence of anti-CADM-140 antibodies is associated with amyopathic DM and rapidly progressive ILD. [33,34]

## CONCLUSION

Four different forms of myositis (DM, PM, N A M, IBM) can be differentiated based on certain clinical clues on examination and additional diagnostics, especially muscle biopsy. Despite many recent studies and growing knowledge about the pathogenesis of myositis, treatment of DM, PM and N A M is still based more on experience than on prospective double-blind studies with sufficient numbers of patients. IBM remains a challenge due to its complex pathogenesis and lack of effective treatment. Given the increasing interest in rare disorders and the development of new therapeutic approaches, including new biologic treatments, the hope of finding better treatments for these patients seems justified.

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## CONFLICT OF INTEREST

There is no conflict of interest in this study.

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