Idiopathic Inflammatory Myopathies: A Comprehensive Review of Pathogenesis, Diagnosis, and Management

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ABSTRACT

Introduction: Idiopathic Inflammatory Myopathies (IIM) are a heterogeneous group of rare autoimmune disorders characterized by muscle inflammation. The classic presentation involves proximal and symmetrical muscle weakness, with the exception of Inclusion Body Myositis (IBM), which typically presents with distal and asymmetric weakness. This review aims to provide a comprehensive update on the clinical features, diagnosis, and management of IIM.
Discussion: The diagnosis of IIM is established through a combination of clinical examination, laboratory findings (elevated creatine kinase and specific autoantibodies), electromyography (EMG), and muscle histopathology. Extramuscular manifestations are common and may include Interstitial Lung Disease (ILD), pathognomonic skin rashes in Dermatomyositis (DM), and systemic or articular involvement. Furthermore, certain subtypes, particularly DM, are associated with an increased risk of malignancy. Treatment strategies predominantly rely on immunosuppressive therapy. First-line agents often include corticosteroids combined with methotrexate or azathioprine, while resistant cases may require mycophenolate mofetil, rituximab, or cyclophosphamide.
Conclusion: IIM can be distinctively classified into Dermatomyositis (DM), Polymyositis (PM), Necrotizing Autoimmune Myopathy (NAM), and IBM. While immunosuppression is effective for most forms, IBM remains a therapeutic challenge due to its complex pathogenesis and resistance to standard treatments. Continued research into novel therapeutic agents is justified to improve patient outcomes.

Keywords: Idiopathic Inflammatory Myopathy, Myositis

INTRODUCTION

Idiopathic Inflammatory Myopathies (IIM), collectively known as myositis, constitute a heterogeneous group of rare autoimmune disorders characterized by chronic muscle inflammation and systemic involvement. Clinically, IIM is distinguished by proximal and symmetrical muscle weakness, with the notable exception of Inclusion Body Myositis (IBM), which typically presents with distal and asymmetric weakness [1, 5].

The diagnosis of IIM is established through a combination of clinical assessment (distribution of paresis), laboratory markers such as elevated creatine kinase (CK) and specific autoantibodies, electromyography (EMG), and muscle histopathology. Magnetic Resonance Imaging (MRI) is valuable not only for identifying suitable biopsy sites but also for visualizing muscle edema patterns, which help differentiate IIM from other conditions such as muscular dystrophy [18]. While CK elevation is a hallmark of the disease, EMG is crucial for confirming the presence of irritable myopathy [1].

Extramuscular manifestations are frequent and significantly impact the clinical course; these include Interstitial Lung Disease (ILD), the pathognomonic cutaneous features of Dermatomyositis (DM), and articular involvement. Furthermore, IIM, particularly DM, is associated with an increased risk of malignancy [1, 7]. Myositis-specific autoantibodies play a pivotal role in defining clinical phenotypes. For instance, anti-Jo-1 antibodies are strongly associated with ILD (Antisynthetase Syndrome), while anti-HMG-CoA reductase antibodies are characteristic of Immune-Mediated Necrotizing Myopathy (IMNM or NAM) [13]. Histopathologically, muscle findings range from inflammatory exudates with varying distributions to the invasion of non-necrotic muscle fibers, necrosis, phagocytosis, and, in the case of IBM, rimmed vacuoles and protein deposits [1, 5].

Immunosuppressive therapy remains the cornerstone of management for active disease in DM, Polymyositis (PM), and NAM [18]. However, NAM is often more resistant to standard immunosuppression compared to DM and PM, especially in cases associated with malignancy or statin use. The majority of NAM cases require more than one immunosuppressive agent, with a high recurrence rate upon tapering [13]. As with DM and PM, first-line therapy typically consists of corticosteroids combined with methotrexate (MTX) or azathioprine (AZA). In refractory or severe cases, Intravenous Immunoglobulin (IVIG) may be beneficial. Second- and third-line agents include mycophenolate mofetil, cyclosporine, tacrolimus, rituximab, etanercept, and cyclophosphamide [18, 20].

This review aims to provide comprehensive information on the clinical signs, diagnostic criteria, and management strategies for myositis, serving as a learning resource for clinicians.

DEFINITION

Idiopathic Inflammatory Myopathies (IIM) constitute a heterogeneous group of autoimmune disorders primarily characterized by muscle inflammation (myositis). Historically, IIMs were classified into three main subtypes: Polymyositis (PM), Dermatomyositis (DM), and Inclusion Body Myositis (IBM). However, recent classifications have identified additional distinct subgroups, such as Necrotizing Autoimmune Myopathy (NAM) and Antisynthetase Syndrome.

In addition to the hallmark clinical finding of muscle weakness, the definition is supported by laboratory evidence of elevated creatine kinase (CK) and electromyography (EMG) findings confirming the diagnosis of irritable myopathy. Extramuscular involvement is a significant feature of these conditions, often manifesting as Interstitial Lung Disease (ILD), characteristic cutaneous rashes in Dermatomyositis (DM), and systemic or articular symptoms. Furthermore, DM is notably associated with an increased risk of malignancy.

Myositis-specific autoantibodies play a critical role in defining the clinical phenotype. For instance, anti-Jo-1 antibodies are frequently associated with ILD (Antisynthetase Syndrome), whereas anti-HMG-CoA reductase antibodies are characteristic of NAM. Muscle histopathology varies across subtypes, ranging from inflammatory exudates and necrosis to the invasion of non-necrotic muscle fibers, phagocytosis, and, in the specific case of IBM, rimmed vacuoles and protein deposits.

EPIDEMIOLOGY

Idiopathic Inflammatory Myopathies (IIM) constitute a heterogeneous group of autoimmune disorders primarily characterized by muscle inflammation (myositis). Historically, IIMs were classified into three main subtypes: Polymyositis (PM), Dermatomyositis (DM), and Inclusion Body Myositis (IBM). However, recent classifications have identified additional distinct subgroups, such as Necrotizing Autoimmune Myopathy (NAM) and Antisynthetase Syndrome.

In addition to the frequent elevation of Creatine Kinase (CK), electromyography (EMG) confirms the presence of irritable myopathy. Extramuscular involvement affects a significant number of cases, manifesting as Interstitial Lung Disease (ILD), typical cutaneous changes in Dermatomyositis (DM), and systemic or articular symptoms. Furthermore, there is an increased risk of malignancy, particularly in patients with DM.

Myositis-specific autoantibodies significantly influence the clinical phenotype. For instance, Jo-1 antibodies are frequently associated with ILD, while anti-HMG-CoA reductase antibodies are characteristic of NAM. Muscle pathology ranges from inflammatory exudates with varying distributions to the invasion of non-necrotic muscle fibers, necrosis, phagocytosis, and, specifically in IBM, rimmed vacuoles and protein deposits.

GENERAL CLINICAL MANIFESTATIONS

Patients with Idiopathic Inflammatory Myopathies (IIM) typically present with weakness in the proximal muscles, manifesting as difficulty rising from a chair, climbing stairs, or lifting objects. While tasks requiring distal muscle strength, such as buttoning shirts or gripping objects, are often affected early in Inclusion Body Myositis (IBM), they are generally spared in the early stages of Polymyositis (PM), Dermatomyositis (DM), and Necrotizing Autoimmune Myopathy (NAM).

Ocular muscles are preserved across all subtypes; however, facial muscle weakness is frequently observed in IBM. In all subtypes, neck extensor and pharyngeal muscle involvement may occur, leading to difficulty lifting the head ("head drop") or dysphagia. Respiratory muscle involvement is rare but can occur in advanced disease or acute cases.

Muscle atrophy is a prominent feature in the early phases of IBM, specifically affecting the quadriceps and forearm muscles, but may progress in all subtypes if weakness becomes severe and chronic. Myalgia and muscle tenderness can occur, particularly in patients with antisynthetase syndrome [5].

Extramuscular manifestations may develop in all IIM subtypes, although they are less common in IBM. These include: Systemic symptoms: Fever, arthralgia, and Raynaud's phenomenon, which are characteristically seen in antisynthetase syndrome; Cardiac involvement: Arrhythmias or ventricular dysfunction may occur, though they rarely present with overt clinical symptoms, and Pulmonary involvement: Pulmonary complications, primarily Interstitial Lung Disease (ILD), are reported in 10% to 40% of patients. The prevalence of ILD reaches up to 70% in 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 presentation of Dermatomyositis (DM) involves cutaneous manifestations, muscle inflammation, or both, typically characterized by acute or subacute progressive proximal muscle weakness. Similar to Polymyositis (PM) and Necrotizing Autoimmune Myopathy (NAM), patients often experience difficulty raising their arms above their heads, rising from a chair, or climbing stairs. While distal strength is usually preserved early on, grip strength may be reduced in chronic DM and PM compared to controls. Muscle weakness is generally painless, except in patients with an acute onset or subcutaneous calcifications. DM can also cause bulbar muscle weakness, manifesting

as dysphagia, difficulty chewing, and occasionally dysarthria. Systemic involvement is particularly common in Juvenile Dermatomyositis (JDM), which often presents with muscle weakness and pain following episodes of fever and skin rash [5].

Characteristic skin rashes typically precede or occur simultaneously with the onset of muscle weakness, providing a critical clue for the diagnosis of classic DM. Amyopathic DM is a distinct subtype presenting with hallmark cutaneous features but without clinical muscle weakness, although minor inflammation may be detectable on biopsy. Conversely, DM sine dermatitis is challenging to recognize as it presents with histopathologically proven DM features in the absence of skin rashes.

The classic cutaneous manifestations include:

a. Heliotrope rash: A violaceous discoloration of the eyelids, often associated with periorbital edema.
b. Gottron's papules: Pathognomonic purple, lichenoid, scaly papules found on the extensor surfaces of the knuckles (metacarpophalangeal and interphalangeal joints), elbows, and knees. When located on the volar aspect, they are referred to as Inverse Gottron's Papules.
c. Erythematous rashes: Macular erythema may appear on the anterior chest ("V-sign"), upper back and shoulders ("Shawl sign"), or extensor surfaces (Gottron's sign).
d. Periungual changes: Dilated capillaries and hyperemia at the nail beds are common. In JDM, reduced nailfold capillary density correlates inversely with disease activity [8, 9].

Additional cutaneous features include subcutaneous calcinosis, which is frequent in JDM but rare in adult DM. "Mechanic's hands," characterized by hyperkeratotic, fissured skin on the dorsal and ventral aspects of the hands, are typically found in patients with Antisynthetase Syndrome. Cutaneous symptoms, particularly prominent pruritus, have a significant negative impact on the patient's quality of life [8, 9].

Diagnostic Criteria Bohan and Peter originally described five criteria for definitive DM: (1) proximal muscle weakness, (2) elevated serum Creatine Kinase (CK), (3) myopathic changes on EMG, (4) muscle biopsy showing inflammatory changes, and (5) characteristic skin rash. Targoff and colleagues later modified these by introducing myositis-specific autoantibodies as a sixth criterion, allowing a diagnosis if 4 of the 6 criteria are met.

To improve diagnostic specificity, the ENMC 2004 classification proposed criteria based on clinical features, laboratory data, and defined muscle biopsy findings. Under this system, Definitive DM requires pathological evidence of perifascicular atrophy. Probable DM is indicated by perivascular inflammatory cell infiltration, Membrane Attack Complex (MAC) deposition in small vessels, reduced capillary density, tubuloreticular inclusions in endothelial cells, or MHC-1 expression in perifascicular fibers. These pathological findings, even in the absence of a rash, are sufficient for a diagnosis of Probable DM sine dermatitis. More recently, the 2017 EULAR/ACR classification criteria introduced a weighted scoring system combining clinical variables (age of onset, weakness pattern, skin manifestations) and laboratory data (anti-Jo-1 antibodies, muscle enzymes) to determine the probability of II [5].

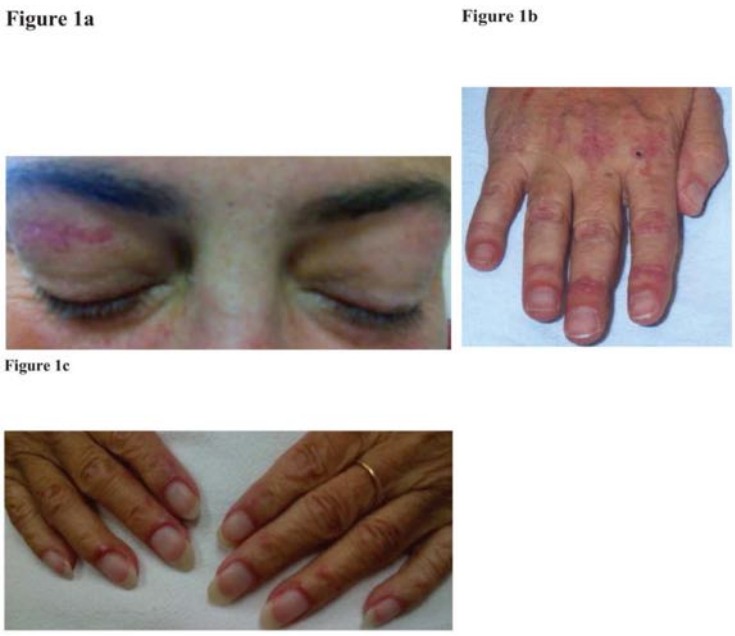

Figure 1. Manifestation DM clinical. Figure 1a. Heliotrope rash and periorbital edema and erythema in DM; Figure 1b. Papular rash scaly erythematous colored purple on DM - Gottron's papules, with ulceration of the skin and hyperemia perinungal.; Figure 1c. Hyperemia periungal in DM

Bohan and Peter described 5 criteria favoring the diagnosis of definitive DM, including proximal weakness, elevated CK, EMG myopathy, inflammatory pathology, and a characteristic rash that distinguishes 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 diagnostic specificity. 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 DM, 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 without 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 delayed in PM compared with 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, they do 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].

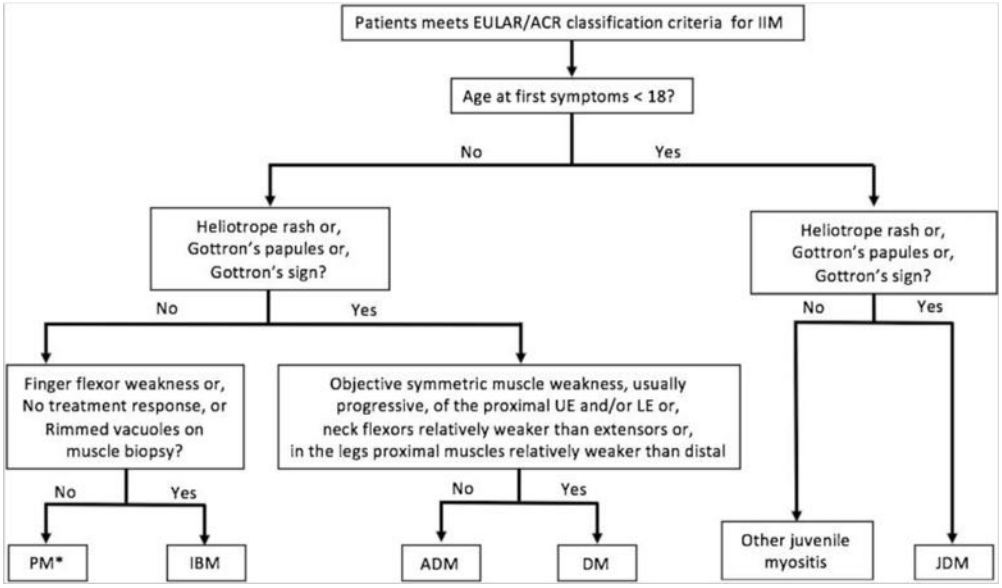

Figure 2. Eular IMM Classification

Overlap myositis (OM)

Overlap myositis (OM) is known as the largest myositis subgroup. Individual forms of myositis are heterogeneous and encompass the largest myositis subgroup. Patient with OM coming with weakness I or subacute in the arms and legs, similar to type myositis mentioned above. Usually, there is an enhancement enzyme in the muscle, including CK. OM can be diagnosed concurrently with abnormalities in other collagens, such as Sjögren's syndrome, systemic sclerosis, or systemic lupus erythematosus (SLE). The most common condition in OM is antisynthetase syndrome (ASS), which can be considered as different subforms of myositis. ASS consists of gathering symptoms typical of clinical conditions, including myositis, Raynaud's phenomenon, joint inflammation, hand mechanics, ILD, and the presence of anti-transfer RNA synthetase autoantibodies [10].

Inclusion body myositis (IBM)

IBM is inflammation of the muscle, especially in the idiopathic attack, in men with white skin who are over 50 years old. Onset of onset is slower and can attack the proximal or distal muscles. Weakness muscle usually

bilateral, but often No symmetrical. Limbs are more often attacked compared to arms, especially the muscles of the anterior thigh, with atrophic muscles prominent. Muscle axial, possibly affected, which causes camptocormia (bone behind bow to front) or head falls. 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 Creatinine kinase <15x ULN Onset age < 45 years Weakness of finger flexion > weakness shoulder abduction And/ or Weakness extension knee > hip flexor weakness	All matter following : Infiltrate inflammation endomysial Vacuoles walled Protein accumulation or 15-18nm filament
IBM based clinical	Duration weakness >12 months Creatinine kinase <15x ULN Onset age < 45 years Weakness of finger flexion > weakness shoulder abduction And Weakness extension knee > hip flexor weakness	One or more, however No all, from : infiltrate inflammation endomysial Upregulation of MHC class I Vacuoles walled Protein accumulation or 15-18nm filament
Probable IMM	Duration weakness >12 months Creatinine kinase <15x ULN Onset age < 45 years Weakness of finger flexion > weakness shoulder abduction Or Weakness extension knee > hip flexor weakness	One or more, however No all, from : infiltrate inflammation endomysial Upregulation of MHC class I Vacuoles walled 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 happen to everyone at any age, but is especially seen in adults; a disease that starts acutely, reaching a peak within a few days or weeks, or subacutely, developing gradually and causing malaise and very high levels of creatine kinase. NAM happened alone or after viral infections, related to cancer, in patients with abnormal connective tissue like scleroderma, or in patients taking statins, whose myopathy kept worsening after statin discontinuation (if myopathy improved in time 4 to 6 weeks after statin discontinuation, p This is possibly caused by the toxic medicine and not because of myopathy's immune nature. Most patients with NAM have antibodies against the signal recognition particle (SRP) or 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) [13].

PATHOGENESIS

Immunopathology

Although IIM is not well-known, the pathogenesis of autoimmune involvement in the IIM journey remains unclear. In DM, C5b-9, a membranolytic complex of complement, is activated more quickly (before damage to the muscle fibers is clearly visible) and is stored in endothelial cells, causing necrosis, a decline in capillary density, endomysial ischemia, and muscle damage. - Destruction of fibers resembles microinfarction; remaining capillaries have a widened lumen to compensate for ischemia. Residual perifascicular atrophy is described as hypoperfusion endofascicular, most prominent at the periphery of fascicles. Activation of the Membranolytic attack complex triggers the release of proinflammatory cytokines, increases the adhesion of regulatory molecules to cells and the endothelium, and facilitates the migration of activated lymphocytes, including B cells, CD4+ T cells, and plasmacytoid dendritic cells, to the perimysial and endomysial regions. 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 may contribute to disease pathogenesis [14, 15].

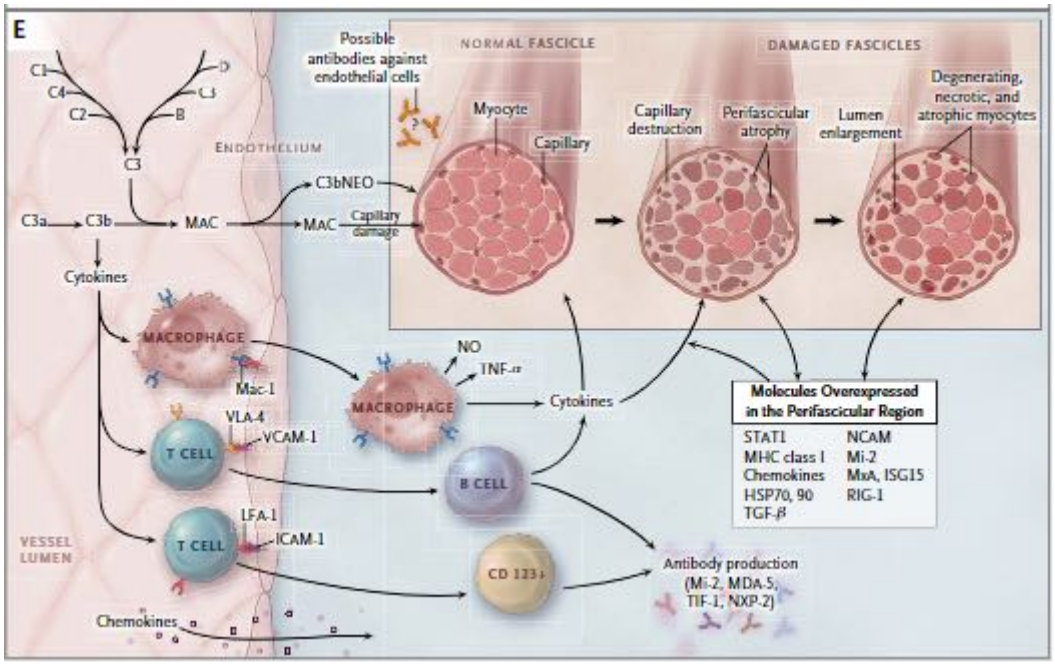

Figure 3. Schematic diagram immunopathogenesis of DM

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.

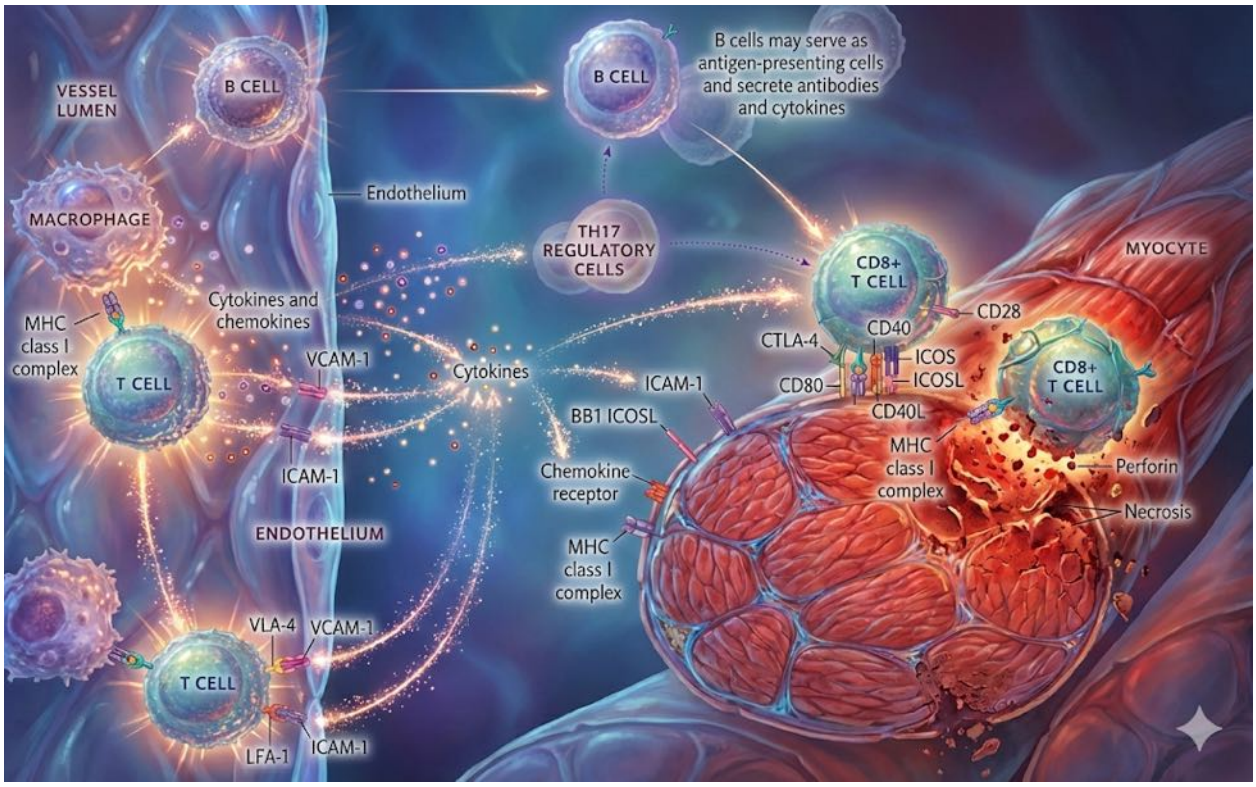

Figure 4. Mechanism damage mediated by muscles T cells in PM and IBM

Triggering factors include disease inflammation, muscle, and an unknown factor. Risk factors, genetic control response, immunity to the agent, and the environment have been proposed as factors that have not been defined. Interaction genetics 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 may be responsible for the body's tolerance to immunity; however, efforts to amplify viruses, including coxsackievirus, influenza virus, paramyxovirus, cytomegalovirus, and Epstein-Barr virus, have failed in muscle tissue. The best evidence for the viral link involves retroviruses, as PM or IBM develops in infected people, including the human immunodeficiency virus (HIV) or a lymphotropic virus in human T cells. However, retroviral antigens are only

detected in macrophages endomysium and not in skeletal muscle. Autoinvasive T cells moved in a clonal way, and some of them were specific against retroviruses. HIV -related PM and HIV -related IBM must be differentiated from myopathy mitochondria toxicities caused by antiretroviral drugs, which improved when the drug was stopped [14, 15].

Component IBM Degenerative

IBM is a complex disorder because, in addition to components of autoimmune disorders, it includes components of important degenerative diseases, marked by the presence of amyloid congophilic precipitates within a number of fibers. Similar to what is seen in Alzheimer's disease, deposits of this react with immune to precursor proteins amyloid, amyloid -ß42, apolipoprotein E, a-synuclein, presenilin, ubiquitin, and phosphorylated tau, indicating the existence of protein aggregation. Deposition of TDP43, a translocated DNA- binding protein in a way deviates from nuclei to cytoplasm, and p62, a transport protein that transports polyubiquitinated proteins, was detected in fiber muscle using immunostaining, has recommended as a diagnostic marker [16,17]

In vitro evidence suggests that amyloid - ß42 and its oligomers are involved in intracellular toxicity, however, it is 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 fibers that don't invade, or divacuole, has shown different regulatory signals for inflammation, for example, interferon-receptor signals. Strong evidence shows that aging, abnormal proteostasis (network that controls proteins), disorders autophagy, stress cells caused by MHC class I or oxide, long-lasting inflammation, and proinflammatory cytokines such as interferon-γ and interleukin-1ß can in a way, cumulatively trigger or increase degeneration, which leads to the accumulation of more carry on molecule trigger stress and misfolded proteins [16,17].

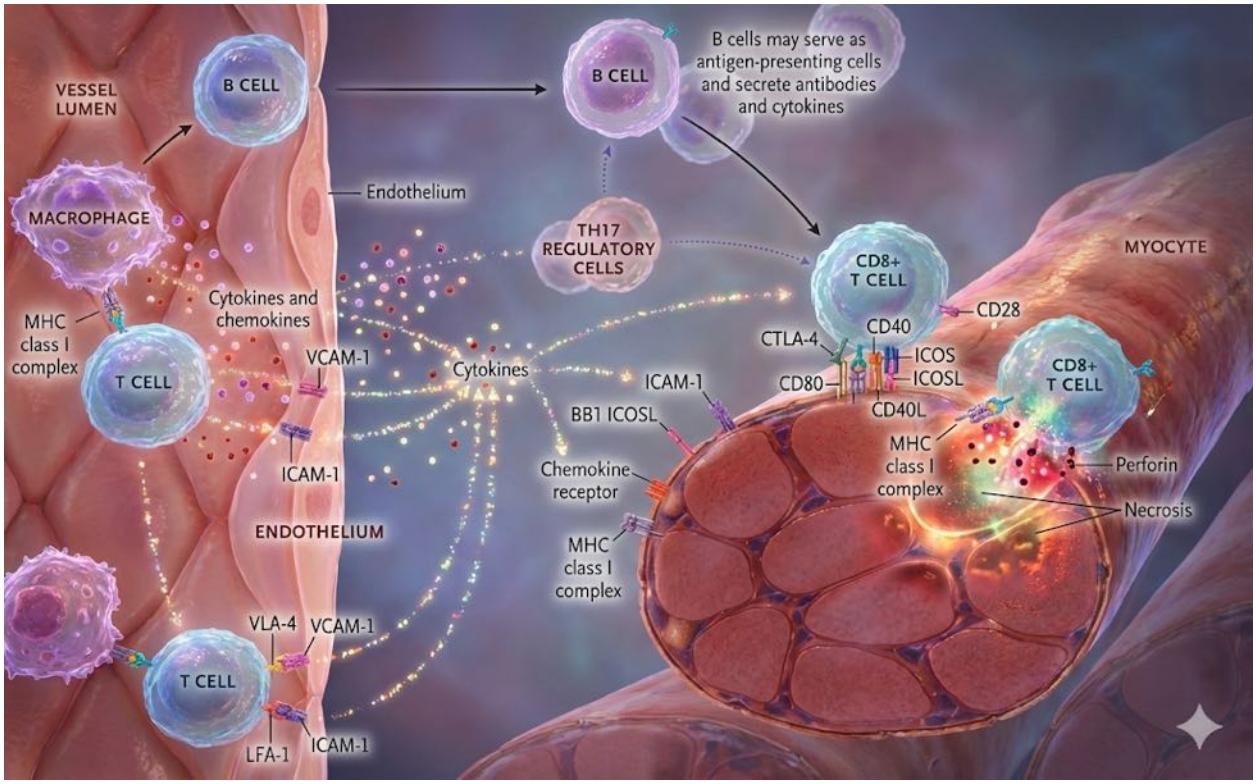

Figure 5. Mechanism Pathogenesis in IBM

DIAGNOSIS

Inspection

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, exceeding 50 times the upper limit of normal, were observed in patients with NAM, and the lowest (less than 10 times the upper limit of normal) were observed 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 myoglobin 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 guide the selection of muscles with the greatest inflammation for biopsy [18].

Histopathology

In DM, inflammation is perivascular and most prominently located in the interfascicular septa or fascicle edges. Muscle fibers undergo necrosis and phagocytosis, often at the periphery of the fascicle, 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 (the MHC-CD8 complex) are useful for confirming the diagnosis and ruling out disorders caused by nonimmune inflammation, as seen in some forms of muscular dystrophy [20, 22]

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

In NAM, many necrotic fibers 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, and is often accompanied by complement deposition in capillaries [20, 22]

IBM has all the inflammatory features of polymyositis, including CD8-MHC complexes, and, in addition, chronic myopathic changes with increased connective tissue and fiber size variability, and 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 absent from muscle biopsy samples, leaving only inflammation, 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 non-necrotic 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].

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 most common antibody in DM, found in about one-third of cases, is the anti-TIF-1a/B/y antibody. TIF-1 antibodies are associated with malignancy in 75% of adult patients; in children, they are 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 NXP2, 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. A patient with an antibody often shows an amyopathic course and presents with dysphagia and mild to moderate ILD [23].

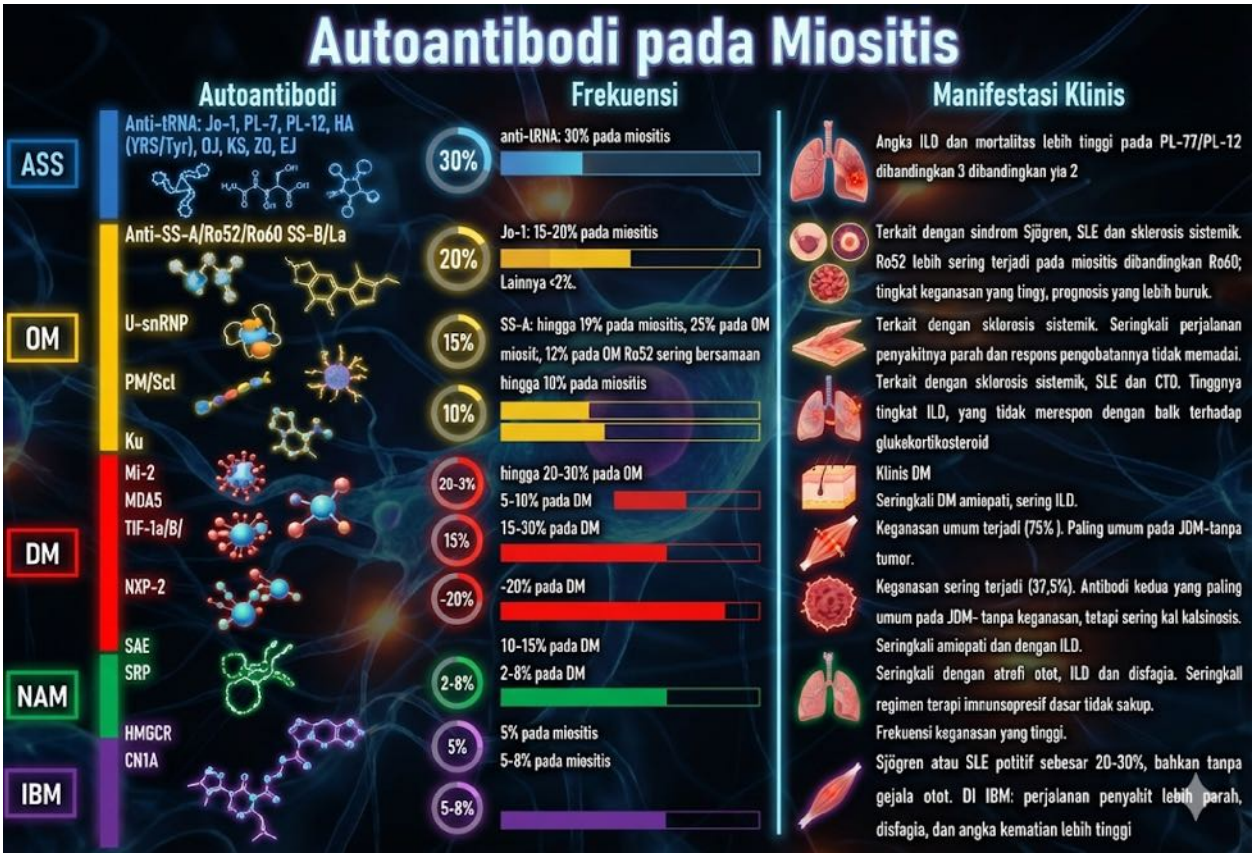

Figure 6. Overview of autoantibodies in IIM and clinical manifestations

Two auto-antibodies have been proven relate to NAM. Anti-SRP antibodies are present in approximately 10 to 20% of patients with NAM, though the level of detection varies widely (from 0% to 54%). Anti-SRP can be linked with cardiomyopathy and travel to serious illness with atrophic muscles, ILD, and dysphagia. Autoantibodies have been identified in up to 60% of certain NAM groups, and these are anti-HMGCR. At varying levels, 30-60% of patients have had prior exposure to statins. A connection with malignancy has been shown to be higher in patients with anti-HMGCR and without autoantibodies than in patients with anti-SRP [24].

The most common antibody anti-synthetase is Jo-1 antibodies, which are observed in ~30% of patients with myositis according to the latest meta-analysis. Anti-PL-7 and anti-PL-12 were found in 3-4% of cases, and all other anti-synthetase antibodies were not common enough (<2%): anti-EJ, anti-ZO, anti-OJ, anti -KS, anti-HA(YRS/Tyr). Apart from antibodies anti-synthetase, five other antibodies relate to OM and other connective tissue abnormalities. They can cause a syndrome clinically identical to ASS or a number of images, for example. ILD and myositis, plus individual connective tissue abnormalities. The most common antibodies are anti-PM/ Scl (targeting two subunits, 75 kDa and 100 kDa complex exosomes, nuclear), which is commonly linked with systemic sclerosis and occurs in 12% of cases of myositis. Anti-U-snRNP antibodies are observed in 3-8% of patients with myositis and are related to mixed connective tissue disease (CTD). Temporary patient with anti-U-snRNP often has a good prognosis, anti-PM/ Scl shows a more severe disease and requires a more responsive treatment that is not adequate. Anti-Ku antibodies are associated with systemic sclerosis, SLE, and mixed CTD and do not differentiate among them. In myositis, the occurrence. This occurs at a frequency of 1-3%, but in overlapping syndromes, it occurs in 19% of cases. This has high levels of ILD, which do not respond well to glucocorticosteroids; meanwhile, muscle symptoms usually respond. Anti-SS-A/Ro52/R060 and anti-SS-B/La are usually found in Sjögren's syndrome, SLE, and systemic sclerosis. This occurs in patients with myositis with a 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 are found in patients with myositis than in those with Ro60, and both are found in CTD. Anti-Ro52 antibodies often appear simultaneously with anti-synthetase antibodies, for example. In 56-72% of patients, there was a positive result for anti-Jo-1. Patient with results positive double This own risk more violence high and a worse prognosis [25,26].

The only antibody associated with IBM was CNIA (5NTIA/5NTCIA, originally called "Mup44"). Observation latest shows 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 of other conditions such as Sjögren's syndrome and SLE were also positive by ~20-30%, even without exists symptom muscle weakness. Latest data in the IBM group pointed out that the presence of CN1A is associated with a more severe disease, dysphagia, and higher mortality [27].

TREATMENT

Non Pharmacological

In the acute phase, the sufferer is recommended to rest. Passive movement must be done during the acute period to prevent contracture. Contracture often Happened to JDM. After phase I is resolved, the sufferer must engage in active exercise, such as fine exercise, isometric, or isotonic. The role of a physiotherapist is very important, not only for helping test muscle strength, but also to make a deep training program planning for strengthening muscles. Exercises are very important for preventing muscle atrophy and contractures [18].

Apart from improving muscle strength and maximizing oxygen uptake, training exercise resistance in myositis patients results in a decline in gene expression, reflecting reduced proinflammatory and profibrotic gene networks and decreased tissue fibrosis. In severe cases, therapy starts with exercise range-of-motion, passive during the first month, and CK starts responding to pharmacotherapy before beginning an exercise program. Strict strengthening of very weak muscles. In patients with light to moderate weakness, the program starts with strengthening after initiation of steroids. Because of pain, arthralgia, and possible consequences, arthritis is reduced with early joint flexion and mobilization, which is important for preventing contracture of joints, both large and small, especially in JDM. Supplementation with creatine monohydrate may also play a role, as it improves functional performance with minimal side effects [28].

Pharmacology

Corticosteroids

Corticosteroids is drug line First to PM/DM with dose 60 mg/ day up to 2 mg/ kgBB prednisone. The repair clinic will be seen on Sunday, the first treatment, or gradually over time, 3-6 months. Evaluation of strength muscles and CPK levels should be done every 3 weeks. At week 6, the decision steroid dose should be determined. If the patient's circumstances improved, the initial steroid dose was maintained until the patient's muscle strength and CPK levels returned to normal. Does the Still must be maintained up to 4-8 weeks, then new levels are lowered slowly, namely 10 mg/ day every month. After a dose of prednisone up to 10 mg/ day for 1 month, the dose was lowered again to 5 mg/day and maintained up to 1 year. If during the decline the steroid dose rises again, it is increased back to the previously prescribed dose.

If in the 6th week after steroids are given, no show improvements are expected, then azathioprine can be added with a dose of 2-3 mg/ kgBW, started with a dose of 50 mg, 1 time/ day. If after 3 weeks, No There is no improvement, dosage of azathioprine is raised to 100 mg/ day, and can be raised again until the maximum dose is achieved, 150 mg/ day. When giving azathioprine, one must be careful of the possibility of side effects on the marrow, bones, and disorders function.

Methotrexate

Methotrexate, combined with azathioprine, is considered the agent of choice for immunotherapy in the first-line treatment of muscle involvement in IIM. Methotrexate has also been successfully used to treat skin manifestations in DM patients. Methotrexate can be given to adults or children, with a dose initially 7.5 mg/ week, and can be raised up to 15 mg/ week after 4-6 weeks. No expected improvements were obtained.

The most common side effects of methotrexate are infection, hepatotoxicity (increased liver enzymes and cirrhosis), and changes in blood cell counts, as well as transaminases, which must be tested routinely in treated patients with methotrexate. Methotrexate must be used with caution in people with functional disturbances and in patients who were also treated with nonsteroidal anti-inflammatory drugs. Toxicity to the lungs in treated patients with methotrexate shows serious side effects and cannot be predicted.

Azathioprine

Azathioprine (AZA) is a purine analogue that acts as an antimetabolite, blocking purine synthesis 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 to subtract the daily prednisone dose and is associated with better functional results. AZA is usually given orally at 50 mg/day and then gradually increased by 25-50 mg every 1-2 weeks up to 2 mg/kg/day. Complete blood count, cell blood count, heart enzymes, and kidney function must be checked routinely in patients receiving AZA.

General side effects include vomiting, liver toxicity, and marrow suppression. The effect next to the last one is very common in people with a deficiency of the genetic enzyme thiopurine S-methyltransferase before AZA therapy.

Calcineurin inhibitor

Cyclophosphamide and cyclosporine-A are rarely given to PM/DM, though they can have a good effect. Cyclosporine A provides good results in myositis with positive anti-Jo-1 antibodies and in polymyositis refractory to other treatments. Dose cyclosporine -A for myositis is 2.5-5 mg/ kgBW / day. While giving cyclosporine-A, blood pressure and kidney function must be closely monitored. When blood pressure and creatine levels increase by 20% since starting to give, the cyclosporine-A dose should be tapered [18].

Intravenous immunoglobulin (IVIG)

IVIG, a product derived from thousands of blood donors, has a complex immunomodulatory mechanism. Estimated involves modulation production of autoantibodies, pathogenic and inhibitory binding, emphasis on pro-inflammatory cytokines, blockade of Fc receptors, stimulant factors for colony macrophages, and increased chemotactic protein-1 monocytes, changes in T cell function, and decreased circulation of CD54 lymphocytes and cell inhibition. transmigration to the muscle. Trials controlled in a way that was random, with cross-over optional, showed that IVIG 2 gm/kg given every month for 3 months is very effective in 9/12 patients with resistant DM to treatment. Even though it's a randomized controlled trial, IVIG is also felt to be effective for DM, PM, and NAM. Guidelines: The American Academy of Neurology 2012 recommended that IVIG be effective and considered for treating DM cases that are not responsive. There isn't enough evidence to support or refute the use of IVIG in 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 to the disease or lower compared to the control. The initial dose is 2 g/kg, given over two to five days, and then the infusion is repeated every two to four weeks, with a total dose of 0.4 g/kg to 2 g/kg monthly [29].

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

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

Therapy biology other

If the disease does not respond to glucocorticoids and immunoglobulins intravenously, the patient must be evaluated repeatedly, and if there is uncertainty in diagnostics, a muscle biopsy must be considered. If the diagnosis is confirmed, come back; approved agent biology for the treatment of the disease; other options can be considered as choice treatments, experimental. A number of choices, including rituximab (anti-CD20 antibody), which at a dose of 2 g (divided into 2 infusions over 2 weeks) is effective in some patients with DM, PM, or NAM. In a randomized, placebo-controlled study involving 200 patients, at week 8, there is no difference between the placebo groups. groups and rituximab groups, and based on design research, results No significant; however, on Sunday, 44, when all patients have received rituximab, 83% complied with the definition repair. Patients with anti-Jo-1, anti-Mi-2, or anti-SRP antibodies appear to have a higher likelihood of a good response. Inhibitor factors of tumor necrosis (infliximab, adalimumab, and etanercept) are ineffective and may worsen or trigger the 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). Overall, the impact period from IIM has improved substantially, with a level of continuity lasting 10 years longer, 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, an immunosuppressive agent immunosuppressive 5% has been tried as a treatment for the subtype disease. However, everything failed, maybe because the disease started far before

the patient looked for medical help, when the cascade of degeneration had already begun. Glucocorticoids, methotrexate, cyclosporine, azathioprine, and mycophenolate. There is no effective treatment, and although a number of patients initially experience subjective light when treated with one agent, there is no benefit in terms of the period length achieved. Immunoglobulin intravenous proven No effective in controlled trials, but may help a number of patients temporarily, especially those who suffer dysphagia. Alemtuzumab can give a short stabilization period; however, the required studies are controlled. Treatment with Anakinra has not yet succeeded. Targeted trials of inhibitory TGF-β molecules in muscle or factor growth muscle are currently taking place. Bimagrumab, an inhibitory antibody targeting the TGF-β superfamily signaling receptor, was shown in a small-scale study to increase muscle volume after 8 weeks.

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

Although hope life patients with normal IBM, some big patients with end-stage disease need tools like a stick, a tool help with walking, or a wheelchair.

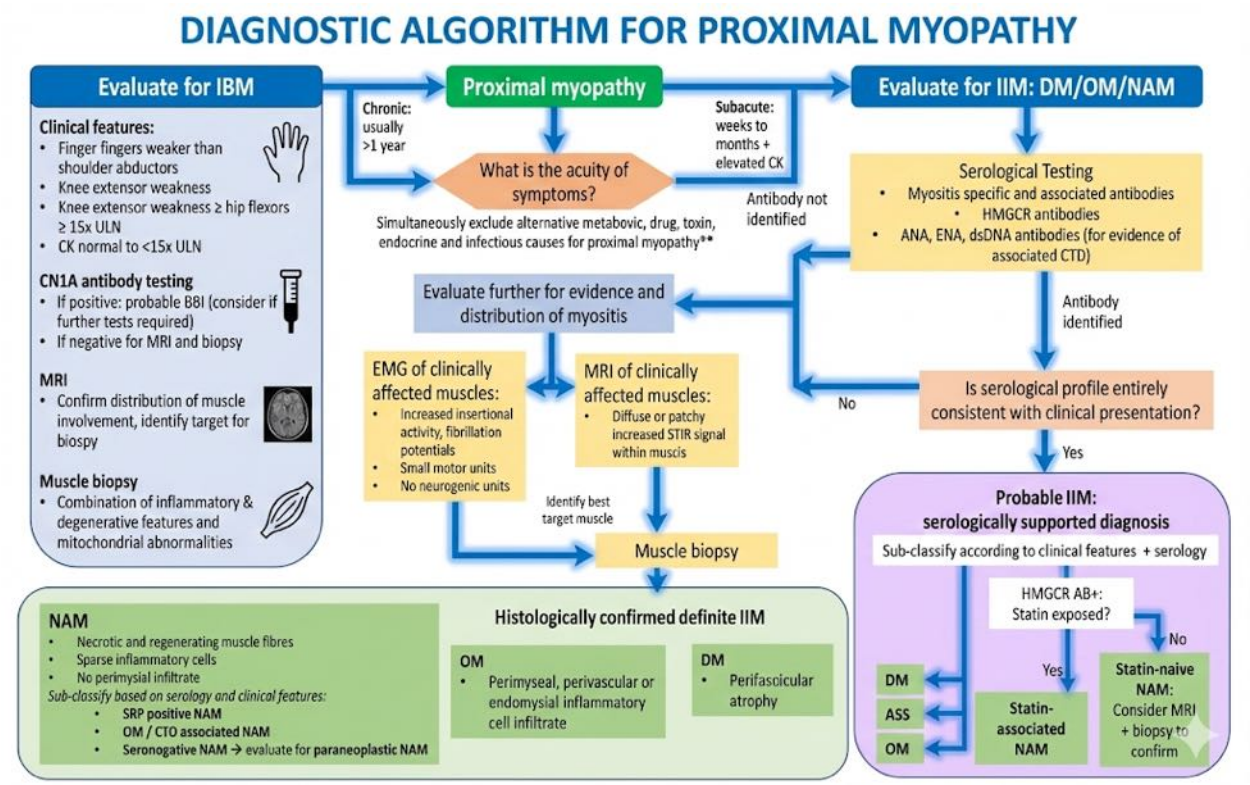

Figure 7. Algorithm for the diagnosis of proximal myopathy

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 with positive anti-Mi-2 antibodies is even better, reaching 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 with malignancy in adults, whereas anti-CADM-140 antibodies are associated with amyopathic DM and rapidly progressive ILD [33, 34].

CONCLUSION

Four forms of myositis (DM, PM, NAM, IBM) can be differentiated based on clinical clues on examination and additional diagnostic tests, especially muscle biopsy. Despite many recent studies and growing knowledge of the pathogenesis of myositis, treatment of DM, PM, and NAM is still largely based on experience rather 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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