What is New in Idiopathic Inflammatory Myopathies: Mechanisms and Therapies

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Abstract

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of disorders that cause muscle weakness and also have extramuscular manifestations involving various organ systems; namely the lung, skin, heart, and joints. Previously classified broadly as dermatomyositis (DM) and polymyositis now the spectrum of the disease has evolved into more clinical subtypes. There are now five clinicoserological subtypes recognized worldwide DM, antisynthetase syndrome (AS), overlap myositis (OM), immune mediated necrotizing myopathy (IMNM), and inclusion body myositis. Each of these subtypes has a unique phenotype and specific antibodies associated. With the evolving treatment options from the use of immunosuppressive medications to the use of targeted therapy with biologic agents, and further understanding of the pathogenesis of inflammatory myositis, we may have more effective treatment options. We discuss in this review, various myositis-associated antibodies associated with each clinicoserological subtype of IIM and their role. We also describe the evolving therapies and the evidence for the newer biologic therapies in the treatment of IIMs.

Keywords: Dermatomyositis, idiopathic Inflammatory Myopathies, immune mediated necrotizing myopathy, inclusion body myositis, muscle specific antibodies in India, polymyositis

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of disorders characterized by muscle weakness and inflammation. The prevalence of IIMs is 9-14 cases per 100,000 individuals.[1] Patients present with muscle weakness and extramuscular manifestations involving the lung, heart, skin, and musculoskeletal systems. Some patients have no obvious clinical muscle weakness but skin lesions alone (clinically amyopathic dermatomyositis/CADM), or interstitial lung disease (ILD) alone. Occasionally, a patient with an underlying hereditary muscle disease may be misdiagnosed as inflammatory myositis and subjected to heavy doses of immunosuppressants if not correctly diagnosed. In the recent years, immune-mediated necrotizing myopathy (IMNM) has been identified as a separate entity.[2] With the advent of newer myositis-specific antibodies and treatment with biologic agents, identification of clinicoserological subtypes may guide us to make wise treatment choices. This review will focus on the recent advances in the classification of IIMs and their management.

CLASSIFICATION OF IDIOPATHIC INFLAMMATORY MYOPATHIES (IIMS)

IIMs have been traditionally classified as dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) based on clinical and myopathological features.[3] Patients present with proximal muscle weakness, elevated muscle enzymes, electromyography (EMG) showing abnormal spontaneous activity in the form of fibrillation potentials or positive sharp waves and presence of inflammatory infiltrates on muscle biopsy. Clinically, IBM differs from other inflammatory myositis by asymmetric weakness involving the proximal lower extremity muscles (quadriceps, tibialis anterior muscles) and long finger flexors. Since Peter and Bohan first described the criteria for PM and DM, there has been a remarkable progress in understanding the disease pathogenesis, identification of newer and separate entities like immune mediated necrotizing myopathy, clinically amyopathic dermatomyositis, overlap myositis (OM), and cancer-associated myositis.[4,5] The earlier classification systems fail to capture the complexity of these diseases [Figure 1]. Previous myositis classification relied on muscle biopsy findings consistent with necrosis to define IMNM.[6] However, features of muscle necrosis

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have been reported in 16% with DM, 15% anti-Jo1 positive anti- synthetase syndrome (AS), and 21% of scleroderma-myositis.[7] Necrosis was also seen in some patients with hereditary myopathy.[8] On the contrary, 15--20% patients with IMNM associated with anti-SRP and anti-HMGCR myopathy had perivascular infiltrates in the muscle biopsy.[9,10] The recent 2017 EUCLAR (European League Against Rheumatism) classification of IIMs is based on a scoring system that includes age of onset of the disease, clinical, and laboratory features of myositis, anti-Jo 1 antibody, and muscle biopsy parameters and has a high sensitivity and specificity for diagnosing IIMs and their subtypes.[11] However, with the limitations in the muscle biopsy and evolving array of muscle-specific and muscle-associated antibodies that define a specific clinical syndrome, there is a need to reclassify the IIMs based on the specific autoantibody identified.[3]

Over the recent years, myositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs) have been identified in patients with idiopathic inflammatory myositis subtypes. MSAs are only seen in IIMs and each of these antibodies is associated with a unique phenotype and muscle biopsy features. On the contrary, MAAs are not specific for IIM; they are often seen in other connective tissue diseases (systemic lupus erythematosus {SLE}, systemic sclerosis {SSc}, undifferentiated connective tissue disorder {UCTD}, and Sjogren's syndrome. A total of five major entities are now recognized under the umbrella of idiopathic inflammatory myopathies: antisynthetase syndrome, dermatomyositis, immune mediated necrotizing myopathy, overlap myositis, and sporadic inclusion body myositis. Pure or classic PM is therefore a rare entity as these cases are now recognized as anti-synthetase syndrome and overlap myositis, or immune-mediated necrotizing myositis.[3]

SUBTYPES OF IDIOPATHIC INFLAMMATORY MYOPATHIES

Anti-synthetase syndrome (AS)

A clinical syndrome of myositis, ILD, arthritis, Raynaud's phenomenon, fever, and mechanic's hands is defined as anti-synthetase syndrome. The earliest report of AS with fulminant interstitial pneumonitis in a patient with arthritis of small joints of the hands, minimal skin erythema, and severe myalgias but no overt muscle weakness was reported by Mills and Mathews in 1956.[12] The clinical presentation of AS is variable and partly depends on the underlying antibody.[13] The group of antibodies that define the syndrome are aminoacyl t-RNA synthetase antibodies. Anti-AS antibodies can be detected in 30--40% of patients with inflammatory myositis and in 7--10% of patients with idiopathic interstitial pneumonia. The most common antibody in AS is anti-Jo 1 antibody (histidyl t-RNA synthetase antibody) in 60%. Other antibodies detected rarely are anti-PL7 (threonyl t-RNA synthetase) and anti-PL 12 (alanyl t-RNA synthetase) (10--15% cases of AS).[14] Anti-EJ (glycyl t-RNA synthetase), anti-OJ (isoleucyl t-RNA synthetase), anti-KS (asparaginyl t-RNA synthetase), anti-YRS (tyrosyl

t-RNA synthetase), anti-Zo (phenylalanyl t-RNA synthetase), and anti-Wa (directed against nucleobindin-2 (NEFA), a t-RNA-related protein) antibodies are extremely rare [Figure 2].

Clinically, patients with anti-Jo 1 AS present with symmetric proximal muscle weakness. Predominant lung involvement with ILD is seen in 80--90%, myositis seen in 30--60%, arthritis in 94%, and mechanics hands in 71%. Patients have a high risk for ILD but not cancer. Pulmonary involvement is the cause of morbidity as well as mortality, hence requiring aggressive immunosuppressive therapies.

Jo 1 negative AS may present with ILD alone without clinical or overt muscle weakness (clinically amyopathic), myositis or DM. In clinically amyopathic patients, AS as the cause of underlying ILD may be missed or delayed in diagnosis. Often, ANA is negative. Aggarwal *et al.* showed anticytoplasmic antibody positivity in these patients and suggested it as a screening test for AS along with Jo-1 antibody.[15] Anti-OJ, anti-KS, and anti-PL-12 present with ILD alone.[16] Due to the delay in diagnosis, anti-Jo 1 negative AS has worse outcomes with low survival rates than Jo-1 AS. A classic DM rash, a rash with papules on palmar surface of the hands, or necrotizing skin lesions are seen in the recently described clinically amyopathic anti-MDA5 DM associated with AS.

Dermatomyositis (DM)

DM presents with a characteristic skin rash with muscle weakness. Peak age of onset is 40--50 years; however, the disease manifests in children as well. Females are affected more than males. Muscle weakness in DM involves the proximal muscles symmetrically in a limb--girdle distribution. Neck flexors are weak. Distal muscles are involved only late in the course of the disease. Patients may have dysphagia as in other inflammatory myopathy subtypes. Muscle atrophy is not seen early in the course, unless the disease is long standing. CADM may present with prominent skin rash typical of DM with minimal or no muscle disease. Skin rash in DM precedes or accompanies the proximal muscle weakness. Gottron's papules and heliotrope rash are pathognomonic for DM. Gottron's papules are violaceous papules seen over the dorsum of knuckles (metacarpophalangeal and interphalangeal joints) symmetrically. When present over the extensor surface of joints this is referred to as Gottren's sign [Figure 3]. Heliotrope rash is a violaceous rash over the upper eyelids. This may be accompanied with eyelid edema. Some patients have hyperpigmented or hypopigmented skin lesions (poikiloderma) in the upper back, upper chest, and the neck in a "V" shape. This is seen classically in the sun exposed areas and is referred to as the "shawl sign" on the back and "V sign" on the chest. Poikiloderma may be seen on the lateral aspect of the thighs. Some patients have facial or generalized erythema. Psoriasiform lesions may be seen in the scalp. Calcinosis cutis (deposition of calcium underneath the skin) is commonly seen in juvenile DM, overlap syndrome, and anti-nuclear matrix protein 2 (anti-NXP2) myopathy. Vasculitic skin lesions may be seen with anti-NXP2 DM. Nail findings, such as periungual erythema, erythematous capillary nail bed,
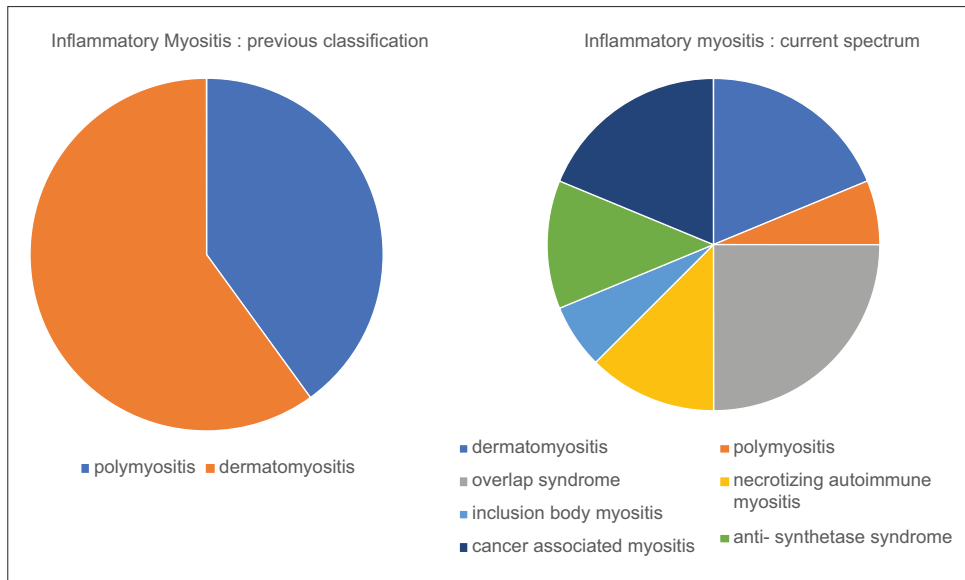
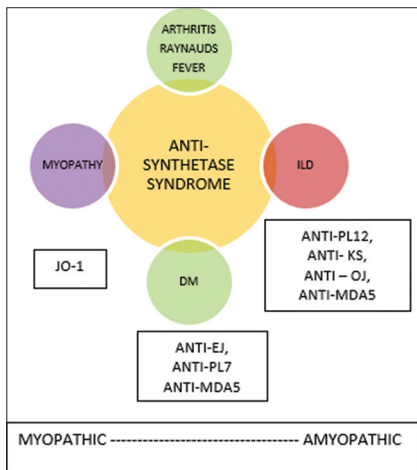**Figure 1:** Changing spectrum of idiopathic inflammatory myopathy

Figure 2: Spectrum of antisynthetase syndrome and antibodies. Jo-1 antibody is the commonest antibody associated with antisynthetase syndrome. Anti-EJ and PL-7 may present with classic DM. 60-70% of anti- OJ and anti-KS present as ILD alone. Anti-MDA5 is associated with severe necrotizing skin lesions and rapidly progressive ILD. Abbreviations: ILD: interstitial lung disease, DM: dermatomyositis, CADM: clinically amyopathic dermatomyositis

and cuticle overgrowth with hemorrhagic infarcts within it is also very characteristic of DM. Necrotizing skin lesions with palmar papules are the disease defining features of CADM associated with anti-MDA5 and carries a high mortality. The risk of cancer remains high for the first 3--5 years after the onset of DM.[17] The most common cancers are breast, ovary, lung, colon, nasopharyngeal cancer in Asians and non-Hodgkin's lymphoma [Figure 4].

Antibodies define novel subgroups in pure DM
Myositis-specific antibodies have been recently identified in patients with DM. We discuss the specific clinical features associated with each of them in detail [Table 1].

Anti--Mi2 (nucleosome remodeling deacetylase complex)
Anti-Mi2 autoantibody accounts for 10--30% of DM and is highly specific for it. Patients present with a characteristic DM rash, mild, or minimal muscle weakness, no ILD and no risk of cancer with an excellent response to steroids and good prognosis.[18]

Anti-small ubiquitin-like modifier activating enzyme (SAE)
Antibodies to SAE were first identified in two DM patients from UK by Betteridge *et al.* in 2007.[19] Anti-SAE is found in 8-10% of the adult DM patients. Clinically, patients present similar to anti-Mi2 DM with a mild disease and favorable prognosis. However, patients may have dysphagia and severe skin disease with periungual lesions. ILD is mild in the form of limited nonspecific interstitial pneumonia.

Anti-transcriptional intermediary factor 1 gamma (TIF 1 gamma)/anti-155/140 autoantibody
Targoff and Reichlin in 2006 identified a new DM-specific autoantibody, anti-TIF 1 gamma antibody that immunoprecipitated a group of proteins with a molecular weight of 155 and 140 kD, hence called anti-155/140 antibody.[20] TIF1 gamma was found in 75% (6/8) of patients with cancer-associated DM, 29% of juvenile DM, 33% OM, and 21% adult DM. As compared to AS, fever, Raynaud's phenomenon, mechanics hand, arthritis, or ILD was lower in anti-TIF1 gamma associated DM. The antibody is found in 20--30% of adult and juvenile cases of DM. Skin lesions are aggressive with low prevalence of ILD. Presence of TIF1 gamma in cancer associated DM is 22--100%. Positive anti-155 antibody was shown to be 96% specific for cancer-associated myositis and had a negative predictive value of 97% for ruling out cancer in patients with DM.[21] The risk of cancer remains high for 3 years after the diagnosis of DM. Anti-TIF 1 gamma is expressed in solid tumors. Cancers of the breast, ovary, and

Table 1: Myositis-specific antibodies associated with DM

	Prevalence (%)	DM	Other clinical features	Anti-synthetase syndrome	Cancer	Prognosis	Treatment response
Anti-Mi 2	10	DM rash	Mild myositis	No ILD	No cancer risk	Good prognosis	Excellent treatment response
Anti-SAE	1	DM rash--severe Periungual lesions	Dysphagia	Mild ILD	No cancer risk	Good prognosis	Excellent response to treatment
Anti-TIF 1 gamma	10--15	Aggressive skin lesions		Low prevalence of ILD	High association with cancer in adults	Poor prognosis	Poor response due to underlying malignancy
Anti - NXP2	1--5	Adult and juvenile DM Calcinosis cutis	Muscle contracture, atrophy	Joint contractures Arthritis ILD	High association with cancer	Poor prognosis	Poor response to treatment due to underlying malignancy
Anti - MDA5/CADM 140	15-20	Severe necrotizing skin rash with vasculopathy Tender papules over palms	Amyopathic	Anti- synthetase syndrome with rapidly progressive ILD	Risk of cancer	Poor prognosis	High morbidity and mortality due to rapidly progressive ILD

Abbreviations: DM: dermatomyositis, ILD: interstitial lung disease, CADM: clinically amyopathic dermatomyositis, Anti-Mi2: chromatin remodeling complex, anti-SAE: small ubiquitin-like modifier activating enzyme, anti-TIF1 gamma: TIF 1 gamma, anti-NXP2: nuclear matrix protein 2, anti – MDA5: melanoma differentiation associated protein

lymphoma are the three most common cancers associated. These findings suggest a specific cancer screening approach in anti-TIF 1 antibody positive patients. However, children and young adults <50 years do not carry the cancer risk.

Anti-NXP2/anti-MJ antibody/anti-140 antibody

Anti-NXP2 antibody recognizes a 140 kD nuclear protein called nuclear matrix protein 2. It was first described in juvenile DM patients who had refractory DM, polyarthritis with joint contractures, severe calcinosis, and intestinal vasculitis. Anti-NXP2 antibody is reported in 25% juvenile and adult DM cases, rarely in PM.[22] Typical DM rash is common with higher prevalence of ILD. Skin lesions are severe with vasculitis. Like anti-TIF 1 gamma DM, adult DM with anti-NXP2 has a high risk of underlying malignancy.

Anti–melanoma differentiation-associated protein (MDA5)/anti-CADM 140

Anti-MDA5 antibody was isolated in 20--30% of Asian patients with CADM, severe necrotizing skin lesions, and rapidly progressive ILD.[23] Patients have severe skin rash but little or no muscle involvement. Skin lesions in anti-MDA5 disease are severe with ulcerations and vasculopathy. Among cutaneous manifestations, panniculitis is highly associated with anti-MDA5/CADM140. Patients have unique skin ulceration with tender papules on the palms. A total of 50% (4/8) of anti-CADM140 positive DM described by Sato *et al.* had rapidly progressive ILD, while only 6% (2/34) in the anti-CADM140 negative group had ILD. Other studies from Japan showed similar strong association of rapidly progressive ILD with anti-CADM140 positive CADM resulting in poor prognosis. Anti-MDA5 was also reported in ILD in juvenile DM cases.[24] Patients have a low risk of cancer. Cervical, ovarian, breast, and lung cancer were seen in a few cases.[25,26] Majority of anti-MDA5 cases have been from Asian cohorts with CADM patients mainly from Japan and Korea. The disease was thought to be milder in the United States, with mild ILD, prominent muscle weakness, and sustained clinical remission even in the fulminant forms of ILD.[27] However, recent studies have shown that rapidly progressive ILD with clinically amyopathic DM forms do occur in the Western population as well.[28] The antibody levels correlate with the disease activity and the clinical course hence may be a useful biomarker predicting response to treatment. Anti-MDA5 antibodies are specific for DM, most have CADM and is predictive of poor survival across all age groups, sex, and ethnicity due to rapidly progressive ILD, despite aggressive immunosuppressive therapy.

Is there any difference between juvenile and adult DM?

Both juvenile and adult DM patients manifest the characteristic rash and proximal myopathy. Calcinosis cutis is a feature of juvenile DM skin manifestation. Anti-NXP2 with calcinosis cutis was described first in juvenile DM and has a favorable prognosis in children and young adults than in adults in whom the risk of malignancy is higher. Anti-TIF 1 gamma associated juvenile DM does not carry a high risk of an underlying malignancy. Overall, ILD and malignancy are less common among the younger adults and rarely seen in children. Possible explanations for the varying clinical presentations in the two age groups are due to influence of environmental factors. Internal factors may play a role as well. Children are rapidly growing, while adults may show a different response due to cellular ageing and differences in their immune response.[29]

Immune mediated necrotizing myopathy (IMNM) or necrotizing autoimmune myosis

IMNM is identified as an important and a separate disease entity in the recent years. A total of 10% of autoimmune inflammatory myopathies are necrotizing myopathies associated with either anti-SRP or anti-HMGCR antibodies.[9,30] 3 subgroups are described: anti-SRP myositis, anti-HMGCR myositis, and seronegative necrotizing myositis. The hallmark of IMNM is acute-subacute onset of severe proximal muscle weakness, elevated creatine kinase (CK) usually in 1000s

and muscle biopsy showing minimal inflammatory muscle infiltrate with prominent muscle necrosis. Slowly evolving disease may mimic muscular dystrophies.[7] If anti-SRP or anti-HMGCR antibodies are positive, a muscle biopsy may not be needed to provide evidence of muscle necrosis. Presence of extramuscular manifestations, such as skin, joints, lung or cardiac involvement suggests the possibility of another inflammatory myopathy, despite the presence of muscle necrosis in the muscle biopsy.[8] Children with slowly progressive muscle weakness with no family history of muscular dystrophy or a negative genetic test for myopathy should also be tested with these antibodies.

Anti-SRP myositis

SRP antigen is a complex of 7SL RNA and several proteins including 72, 68, 54, 19, 14, and 9 kD that regulate the translocation of proteins across the endoplasmic reticulum. Anti-SRP myositis was first recognized in 1980s. The disease is characterized by severe rapidly progressive proximal muscle weakness and disability, neck weakness, dysphagia, respiratory insufficiency, and muscle atrophy with an incomplete response to corticosteroids and no clinical signs of multiorgan involvement.[31] Skin rash is absent. Interstitial lung disease and cardiac involvement is less common. Serum creatine kinase levels may be very high (3000--25 000 IU/l). The age of onset ranges from 32 to 70 years. A seasonal pattern of disease onset in Autumn was noted by Miller *et al.*[32] Muscle biopsy shows an active myopathy, muscle fiber necrosis, and regeneration. There is prominent endomysial fibrosis but little or no inflammation. Deposition of membrane attack complex (C5b-9) in capillaries, reduction in the capillary density, and enlargement of endomysial capillaries is diffusely seen in anti-SRP myositis rather than patchy distribution in DM. Rarity or absence of foci of mononuclear inflammatory cells is another common feature of anti-SRP myopathies that differs from many immune or inflammatory myopathies. Clinically, anti-SRP myopathy should be considered a differential in rapidly progressive severe proximal muscle weakness with very high CK and characteristic muscle biopsy features. Anti-SRP myositis is not associated with cancer. The disease responds to early initiation of corticosteroids and may require aggressive immunosuppressive therapy.

Anti-HMGCR myopathy

Patients with statin intolerance who develop muscle weakness or myalgia improve after discontinuation of the offending drug. Christopher-Stine *et al.* isolated an autoantibody from the sera of patients with IMNM that immunoprecipitated proteins with a molecular weight of 200 and 100 kDa. HMGCR has a molecular weight of 100 kDa and its isomer 200 kDa. Majority of these patients had prior history of statin exposure. Statin exposure was therefore thought to be linked to IMNM. Anti-HMGCR antibody was identified as a cause of IMNM in patients with prior statin exposure.[2] Patients have persistent muscle weakness or creatine kinase elevation long after discontinuing the statin, have positive anti-HMGCR antibody, and improve only with immunotherapy.

Statin exposure is a risk factor for anti-HMGCR myopathy. Mushroom a natural source of statin may be a risk factor as well. Class II major histocompatibility complex (MHC) allele DRB1 * 11:01 has been identified to be an immunogenetic risk for anti-HMGCR myopathy.[33] Varied clinical presentations have been identified in anti-HMGCR myositis. Adult onset anti-HMGCR myopathy presents as a subacute onset progressive proximal myopathy with dysphagia and high creatine kinase levels (1000--20,000). As in other autoimmune diseases, there is a slight female predominance. Extramuscular manifestations (arthritis, rash, Raynaud's phenomenon, or ILD that define the AS) are uncommon. Occasional atrial tachyarrhythmias have been documented however cardiac involvement has not been seen commonly. Cancer association is lower than that of DM. Adenocarcinomas of the gastrointestinal tract, cancer of breast, uterus, and ovaries has been reported. Rare cases of thyroid cancer, lymphoma, and melanoma are also reported.[34] Age appropriate cancer screening is recommended. Young onset anti-HMGCR myopathy has similar clinical phenotype but no prior history of statin exposure. Children with anti-HMGCR myopathy have a favorable outcome. Younger adults without statin exposure tend to have a more severe disease and poor response to immunotherapies than the statin exposed group.[33] A very small percentage may present with a chronic course mimicking limb girdle muscular dystrophy phenotype.[35] These patients may have had asymptomatic CK elevation for years before presenting with muscle weakness. Asymptomatic hyperCKemia may be the initial presentation in a few. Recognition of these patients is important as it has therapeutic implications. Creatine kinase levels correlate with disease activity in necrotizing myopathy, in contrast to other autoimmune inflammatory myopathy (DM, PM) where CK may even be normal and patients have significant muscle weakness. Elevation of muscle enzymes precedes the muscle weakness in immune-mediated necrotizing myopathy. Monitoring of creatine kinase levels is useful in long-term follow-up as the levels decline with treatment and increase with disease flares. Muscle biopsy characteristically shows pauciimmune inflammation with predominant necrosis in the majority (80%). Lymphocytic infiltration is rarely seen.

Anti-HMGCR autoantibodies have a specificity of 94--100% and a sensitivity of 95--99%.[36] With a false-positive rate of 0.7%, a positive report in a patient with high pretest probability points toward anti-HMGCR myopathy. If other phenotypes or asymptomatic patients have an incidental positive result, this should not be considered as an anti-HMGCR myopathy unless confirmed by more specific assays or patient has a necrotizing myopathy. Patients with statin intolerance or self-limited statin associated myopathy or genetically proven limb girdle muscular dystrophy have not shown positive anti-HMGCR antibody results. Coexisting other autoimmune diseases like myasthenia gravis, other MSA antibodies (anti-SRP), inclusion body myositis has been found. Overall, a positive anti-HMGCR in a right clinical setting is diagnostic of anti-HMGCR myopathy and warrants aggressive treatment.

Overlap myositis

"Overlap myositis" is a clinical term used when there is co-occurrence of inflammatory myopathy (PM or DM) and connective tissue disorders, SLE, systemic sclerosis, Sjogren's syndrome, or a mixed connective tissue disorder. The antibodies are seen in the connective tissue disorder and hence not specific for the myositis. This group of antibodies is therefore named as MAAs. Anti- Ro/SSA is the commonest (>30%). It is a marker of Sjogren's syndrome and is frequently associated with AS. Anti-Jo1 and anti-Ro/SSA positivity implies a high risk for ILD, myositis, arthritis, and cancer. All overlap syndromes have a higher risk of ILD. Other antibodies are anti-PM/Scl, anti-Ku, and anti-U1RNP.

A total of 5--17% of patients with scleroderma have myositis. Patients may show features of calcinosis, Raynaud's phenomena, esophageal dysmotility, sclerodactyly, and telangiectasia) or systemic sclerosis. Patients with CREST have anticentromere antibodies; those with progressive systemic sclerosis have anti-Scl-70, while some patients with scleroderma myositis are positive for anti-PM/Scl (also called anti-PM-1). Anti-Ku is seen in DM and systemic sclerosis, while anti-U1RNP is associated with DM and SLE.

Inclusion body myositis (IBM)

Sporadic inclusion body myositis was first described by Chou in 1967 in a 66-year-old man with chronic myositis. Muscle biopsy showed distinctive intranuclear and cytoplasmic filamentous inclusions and vacuoles.[37] The term inclusion body myositis was later coined by Yunis and Samaha in 1971.[38] Mendell *et al.* identified amyloid in muscle fibers by Congo red staining.[39] This is now recognized as a commonest cause of inflammatory myopathy in individuals above the age of 50 years in the United States. IBM is thought to be associated with ageing. Unlike other inflammatory myopathy subtypes, this disorder is unresponsive to treatment and has a slowly progressive clinical course. The slow progressive nature may result in delay in the diagnosis.

The clinical hallmark is an asymmetric muscle weakness and atrophy of the quadriceps, forearm flexor muscles, and the ankle dorsiflexors. This pattern of weakness is present in two-thirds of patients with IBM. Forearm and wrist flexors are weaker than the shoulder abductors, while the knee extensors and ankle dorsiflexors are weaker than the hip flexors. This pattern of muscle weakness helps differentiate IBM from PM/DM in which weakness is predominantly proximal. Also, asymmetric weakness in IBM is in contrast with the symmetric muscle weakness in PM and DM. It may be misdiagnosed as ALS due to the asymmetric weakness; however, early involvement of finger flexors as opposed to intrinsic muscles of the hand differentiates IBM from ALS. Difficulty swallowing occurs in up to 60% IBM cases. Mild facial weakness is identified in 1/3rd. Sensory symptoms may be absent but 30% may have evidence of a generalized sensory neuropathy on clinical examination and electrophysiological studies. IBM is not associated with extramuscular features as in PM or DM.

Anti-cytosolic 5'-nucleoside 1A antibody (NT5C1A antibody), a serological marker of IBM was first identified by Larman *et al.* in 2013.[40] The antibody is detected in 34--44% patients with IBM, 4% of PM or DM cases, and <5% of overlap syndromes. It may also be found in 36% in Sjogren's and 27% in SLE.[41] IBM may be associated with other autoimmune diseases. In the right clinical scenario, anti-cytosolic 5'-nucleoside 1A antibody is supportive of a diagnosis of IBM. Muscle magnetic resonance imaging may be useful to identify the muscle groups involved.

Electrophysiologic studies show evidence of large fiber, length dependent sensorimotor axon loss polyneuropathy in 30% of patients. Electromyography (EMG) shows increased spontaneous activity and small duration small amplitude polyphasic myopathic motor units with early recruitment. In addition, neurogenic large polyphasic motor unit action potentials may be seen in about 1/3rd leading to a misdiagnosis of amyotrophic lateral sclerosis (ALS).

IBM is largely resistant to treatment with steroids and immunosuppression. Various experimental therapies with arimoclomol, intravenous immunoglobulin have not been successful. Dalakas *et al.* demonstrated that alemtuzumab, a humanized monoclonal anti-CD 52 antibody infusions in patients with IBM, slowed down the progression of the disease up to 6 months and improved muscle strength. A recent study of alemtuzumab showed marked long-term improvement in muscle strength after 12 weeks and that lasted for almost 3 years.[42]

Pure Polymyositis is a Rare Disease

With the concept of OM, IMNM, and AS, pure PM now seems to be a rarity. Those who were thought to be pure PM are now reclassified as one of the above subcategories of IIMs. PM now accounts for only 8% of IIM and remains a diagnosis of exclusion [Figure 5]. Antibodies are detected in up to 60--80% of patients with IIM using different methods. Inflammation on muscle biopsy may be seen in IBM which presents with distal asymmetric weakness and does not respond to immunotherapy. Inflammatory infiltrates in muscle biopsy may also be seen in hereditary muscle diseases (limb girdle muscular dystrophies such as dysferlinopathy) which can lead to inappropriate use of immunosuppressive medications if not correctly diagnosed. Refer to Table 2 for disorders that mimic PM. It is important to emphasize that not all myopathies with inflammation are classified as "inflammatory myopathies". Definitive histopathological diagnosis of PM requires presence of perimysial/perivascular inflammatory cell infiltrates or endomysial inflammatory cells with CD8 + T cells invading nonnecrotic muscle fibers that express MHC-1 antigens. This biopsy feature is however not diagnostic for PM as it is also seen in IBM and rarely in dystrophies.

Figure 3: The above picture shows characteristic skin rash of juvenile dermatomyositis in a young boy. Violaceous papules are seen classically over the dorsum of the knuckles of both hands (Gottren's papules) in panel A and over the extensor surfaces of the elbows and knees bilaterally (Gottren's sign) in panels B and C
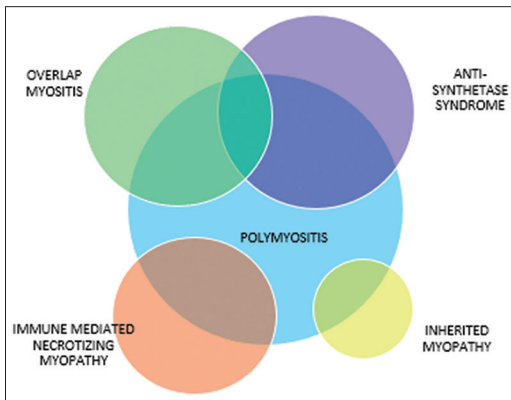

Figure 5: Pure polymyositis is a rare entity. It is recognized to be a part of overlap myositis, antisynthetase syndrome, immune-mediated necrotizing myopathy. Inherited myopathy may mimic polymyositis

Table 2: Disorders that mimic polymyositis

Inclusion body myositis

Immune-mediated necrotizing myopathy (IMNM)

Myotonic dystrophy type II

Limb girdle muscular dystrophy (dysferlinopathy, FSHD)

Late onset congenital myopathies

Late onset acid maltase deficiency (Pompe's disease)

Muscular dystrophies

Other myopathies (metabolic, endocrine myopathies, drug/toxin related, infectious, amyloid)

(Abbreviations: FSHD: facioscapulohumeral muscular dystrophy)

ISSUES IN THE DIFFERENTIAL DIAGNOSIS IN INDIA

Muscular dystrophies of various types are commonly seen in the Indian population. In particular, the limb girdle muscular dystrophies, as consanguinity and community marriages are prevalent in India.[43] Sporadic examples of muscular dystrophies pose a diagnostic challenge, particularly as the investigative facilities available to neurologists are limited in
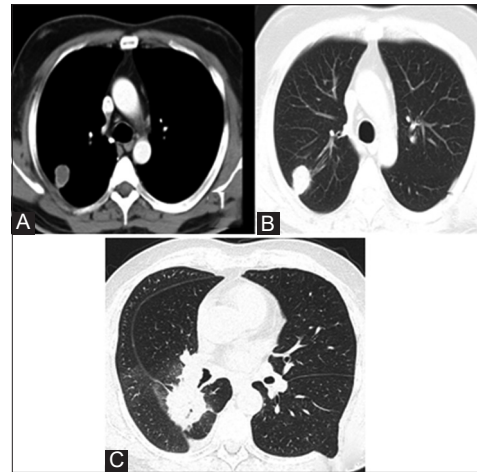

Figure 4: Ca bronchus in a patient with DM. Panels A and B show a focal peripheral nodular lesion in the upper lobe of the right lung suspicious for cancer in a patient with DM. Panel C shows a spiculated mass in the right lower lobe in another patient with DM. (Acknowledgement: Dr. Sunila Jaggi, Associate Professor, Department of Neuroradiology, BHIMS, Mumbai)
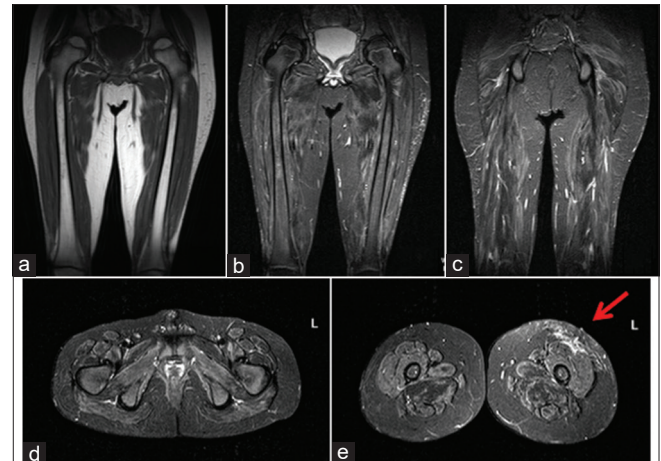

Figure 6: Muscle MRI with T1 W coronal (a) and T2/STIR coronal images (b and c) and T2 STIR axial images (d and e) of a patient with DM showing patchy edematous changes in the muscles in the T2 STIR coronal and axial images. The arrow points toward the subcutaneous edema. (Acknowledgement: Dr. Sunila Jaggi, Associate Professor, Department of Neuroradiology, BHIMS, Mumbai)

terms of pathology and genetic information. Dysferlinopathy, dystrophinopathies, facioscapulohumoral dystrophy (FSHD) are some examples of diagnostic difficulties. Patients with FSHD may have phases of rapid motor deterioration with elevation of CK and patients with dysferlinopathy can have cramps, aches, and pains with swelling of muscles and extreme elevation of CK. Biopsies from all the three dystrophies are known to show presence of inflammatory cells, adding to the confusion. In these situations, details of clinical examination to establish the phenotypic expression coupled with more details of the biopsy analysis with immunocytochemistry and western blotting help to clarify the diagnosis. A simple clinical score to different dystrophies and inflammatory myopathies can be utilized to form

a judgment, in the absence of advanced investigations.[44] Also, there is a general feeling that inclusion body myositis may be under recognized due to limitations of investigative facilities.

PREVALENCE OF MUSCLE-SPECIFIC ANTIBODIES IN INDIA

Indian data on muscle specific antibodies are limited for a few isolated case reports and series. These are largely from rheumatology journals. This may partly be due to the lack of awareness of muscle-specific antibodies as patients with myopathies are largely treated by physicians and pediatricians and may not be referred to a neurologist. Anti-HMGCR and anti-NT5C1A antibody testing is not available in India. Detection of MSAs requires specialized testing and is available only in major cities in India. Srivastava *et al.* reported myositis-specific antibodies in 61/125 IIMs (49.2%). Majority of MSA were anti-Mi 2 (20.9%), 23.4% were AS antibodies including anti-Jo-1, anti-PL7, anti-PL12, and anti-EJ and the remaining were anti-SRP (4.8%).[45] AS is still an underrecognized form of ILD in India. A single center experience of necrotizing autoimmune myopathy was reported from Nizam's Institute of Medical Sciences, Hyderabad by Ayesha *et al*.[46] Out of 15 patients with IMNM, two had connective tissue disorder, three had a previous history of statin exposure (2/3 had anti-HMGCR positivity), one was paraneoplastic and associated with anti-HMGCR antibodies, and nine were idiopathic (three were anti-SRP and one was positive for anti-HMGCR). In the pediatric IIMs, juvenile DM is commonly followed by OM. In a small series of nine patients with juvenile DM anti-SRP, anti-TIF 1 gamma, anti-MDA5 were identified as cause of IIM.[47]

ROLE OF MUSCLE MRI

Muscle MRI can objectively define the severity and the distribution of myopathy. MRI can delineate areas of muscle which are active (represented by edema on STIR images) or infiltrated by fatty tissue (hyperintensity on T1-weighted images) or presence of muscle atrophy [Figure 6]. MRI also can be used to choose the site of muscle biopsy. False-negative rate of blind biopsies is 10--45% even among patients with active IIM due to sampling error. Muscle MRI with STIR sequences has a sensitivity of 89--100% for detecting inflammatory changes. Van De Vlekkert *et al.*, 2015 suggested to use an approach of combining muscle MRI and muscle biopsy to yield the diagnostic accuracy of inflammatory myopathies. A muscle MRI, however, may not help differentiate between different inflammatory myopathies or inherited myopathies.[48] Other conditions in which STIR hyperintensity are seen in muscle MRI are denervation, myonecrosis, infection, trauma, and non-inflammatory myopathies. Many of these conditions mimic IIMs as CK is elevated. In long-standing IIMs, CK levels may be normal due to fatty infiltration and atrophy. Also, CK may not correlate with disease activity in IIMs. Muscle MRI may be helpful to monitor disease progression while on treatment. Whole body MRI has been used in some centers however not widely available. This has an advantage of detecting an occult malignancy. Newer imaging modalities such as functional imaging with phosphorus MRI, structural imaging with diffusion tensor imaging studies, magnetic resonance elastography that assess muscle stiffness are still research tools.

TREATMENT OF AUTOIMMUNE INFLAMMATORY MYOSITIS: ROLE OF BIOLOGICS

The treatment of IIMs has been challenging. Due to the heterogeneous nature of the disease and a small number of randomized controlled clinical trials there is a lack of consensus data on how to utilize the available treatment strategies. Measures of disease activity such as manual muscle testing (MMT) and CK levels may not provide an accurate evaluation of response to treatment. MMT may be influenced by presence of muscle fibrosis, scaring, or atrophy rather than ongoing disease activity. MRI muscle may be useful in these cases to evaluate the degree of edema vs. muscle atrophy or fatty infiltration. Similarly, serum CK levels may be normal or decrease in patients with advanced IIM due to muscle fibrosis and atrophy and may be elevated in noninflammatory and hereditary myopathies. This makes monitoring of the treatment response challenging.

Traditionally, the treatment includes the use of immunosuppression with steroids, and steroid sparing agents; namely azathioprine, mycophenolate mofetil, methotrexate and immunomodulatory agent intravenous immunoglobulin. Intravenous immunoglobulin significantly improved muscle strength in 15 patients with refractory DM in a double-blind placebo-controlled trial.[49] Plasma exchange has not been found to be helpful as compared to sham plasma exchange in myositis.[50]

Unfortunately, many patients are refractory to corticosteroids and immunosuppressive agents. Calcineurin inhibitors, tacrolimus, and cyclosporine inhibit T cell-mediated immunity and have been used with success in refractory myositis complicated by ILD. Cyclophosphamide and chlorambucil use is limited to refractory myositis due to the greater toxicity of chlorambucil and risk of malignancy.

Therefore, newer modes of treatment are being studied. With the newer antibodies and their clinical subtypes being recognized, it may be possible to conduct clinical trials on specific myositis subtypes further guiding therapeutic strategies. Newer biologic agents that target different molecular pathways are being explored in the treatment of myositis. B cell depletion therapy with Rituximab which has been used to treat B cell lymphoma is gaining popularity in refracting myositis. It has been reported to be useful in several small case reports and case series in refractory IIMs. Small open labeled trials on rituximab in six treatment-resistant DM patients and another one in refractory PM patients demonstrated clinical improvement and decline in CK levels.[51,52] On the contrary, another small open labeled

trial of rituximab in eight DM patients failed to show significant clinical improvement.[53] The largest randomized double-blind placebo-controlled trial of rituximab in IIM, the Rituximab in myositis trial (RIM study) in adult and pediatric patients with refractory DM randomized 195 patients to receive early or late (8 weeks) rituximab. There was no significant difference between the two treatment arms but 83% of refractory adult and juvenile DM patients showed significant clinical improvement. Rituximab use was also associated with a steroid sparing effect. The initial responders to rituximab responded well to the disease flares with repeat rituximab dosing.[54] Use of these biologic agents can be expensive. Aggarwal *et al.* predicted that anti-Jo1 and anti-Mi-2 were strongly associated with a favorable response in rituximab treated myositis patients in the RIM trial. He also showed that those patients without a definable autoantibody had a worse outcome as compared to those with an underlying autoantibody.[55] Biomarkers such as interferon chemokine (IFNCK) scores may help identify rituximab responsiveness in refractory myositis.[56]

There are case reports of tumor necrosis factor (TNF) alpha inhibitors (etanercept, infliximab) in resistant DM. Small case series and case reports of the use of TNF alpha inhibitors in DM patients have mixed results; few suggested possible benefits, while others showed no improvement. Possible side effects are malignancies and connective tissue disease, SLE. The randomized controlled trial of etanercept (50 mg subcutaneous weekly for 52 weeks) in 16 DM patients failed to show significant treatment effect. However, they had a longer time to treatment failure as compared to the placebo group.[57] Rare cases of myositis developing after the use of TNF alpha inhibitor etanercept have recently been described.[58] Infliximab use in refractory myositis has mixed results in small series and case reports. Alemtuzumab (depletes both B and T cells through interfering with the T cell signaling pathways by recognition of CD52 on B and T lymphocytes and natural killer cells), abatacept (upregulates costimulatory molecules, CD28, and CTLA-4), sifalimumab (interferon (IFN) alpha/beta immune response) and tocilizumab (interleukin IL -6 antagonist) are being studied as therapeutic targets in refractory myositis.

Conclusion

IIMs have significant morbidity and mortality particularly those with AS with ILD and cancer-associated myositis. There has been a significant progress in the myositis specific antibodies and identification of their unique clinical subset of the broad spectrum of IIMs. The treatment of myositis remains a challenge due to the heterogeneous nature of the disease, refractoriness to corticosteroids, and its long-term side effects and the high cost of intravenous immunoglobulin. Newer biologic agents hold promise however awaits further research and studies.

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There are no conflicts of interest.

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