UPDATE ARTICLE

Recent Advances in Idiopathic Inflammatory Myopathies (IIM) – Rapid Discoveries of Myositis-specific Antibodies (MSAS) and Myositis-Associated Antibodies (MAAS) – Moving Towards 'Precision Medicine'

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Abstract

The progress in the understanding of inflammatory muscle diseases over the past several decades has been slow but steady. The classification given by Bohan and Peter's in 1975 was based on clinical features. It served well, but inadequacies were also obvious. The increasing discoveries of autoantibodies in this group of disorders have helped in refining the classification of Bohan and Peter's to a large extent. At the present state of knowledge, it is now possible to classify and sub-classify this group of diseases using distinct clinical features combined with the type of autoantibodies in well-defined subsets. Not only the subsets help predicting the type of organ involvement and comorbidities but may also help choose a specific drug for a particular subclass. This approach may lead to the practice of precision medicine for inflammatory myositis.

Introduction

Inflammatory disease of the striated muscles were given different names in the past including *dermatomyositis* (if there was a typical skin rash), *polymyositis* (if there was only muscle weakness without skin rash), *amyopathic myositis* (if typical skin rash was present without muscle weakness), *childhood myositis*, *malignancy-related myositis*, *connective-tissue-related myositis* and *inclusion-body myositis*. However, considering the varying amount of chronic non-suppurative inflammation observed in the pathology of the affected muscles, in the last few decades, all-encompassing name Idiopathic Inflammatory Myopathies (IIMs) has become more acceptable. The clinical features of IIM are characterized by painless proximal muscle weakness with or without typical skin rash.[1] The rash is called Gottron's papules when present over the skin of the knuckles. If the similar rash is present at other parts of the body (mostly on the extensor surfaces of the other joints), then it is often called Gottron's sign. Broadly IIM-group of diseases is characterised by:

i. Proximal muscle weakness (limbs, neck flexors, and trunk muscles)
ii. Typical Gottron's papules or Gottron's sign in the skin
iii. Frequent association with clinical features that are usually seen in other connective-tissue diseases (CTDs, e.g. systemic lupus erythematosus {SLE}, systemic sclerosis {SSc}, Sjögren's syndrome, or undifferentiated connective tissue disease {UCTD})
iv. Raised muscle enzymes in the blood
v. Electromyographic (EMG) abnormalities that are characteristic for IIM (e.g. spontaneous electrical activities with myopathic pattern)
vi. Magnetic resonance imaging (MRI) that shows characteristic inflammatory changes in the affected muscles
vii. Characteristic chronic inflammatory pathology in the striated muscles.

With so many variables, clinically IIM has a broad spectrum of clinical presentations. Thus, there could be a typical patient with Gottron's papules-and-sign (Figure 1); heliotrope rash with periorbital swelling (Figure 2), photosensitive facial rash (Figure 2, 4a), 'Mechanic's hands' (Figure 3), necrotic skin lesions (Figure 4b), neck, trunk, proximal limb muscle weakness with high muscle enzymes, typical EMG, typical inflammatory muscle pathology and the patient shows good response to glucocorticoids (GCs) and steroid-sparing agents like methotrexate (MTX) or azathioprine (AZA). There could be another patient with minimal muscle involvement but only with the typical skin lesions and rapidly progressive interstitial lung disease (Figure 5a and b); a subset often called 'clinically amyopathic dermatomyositis' (CADM). Then, there could be another patient with similar serious lung disease with little skin or muscle involvement presenting to a pulmonologist; often seen in a subgroup of IIM called anti-synthetase syndrome (ASA), described below. At the other extreme, there could be a patient with severe rapidly progressive respiratory and pharyngeal muscle involvement with imminent death. Even the muscle enzymes may vary from 'normal' to very high levels and EMG changes from 'subtle' to 'severe' myopathic pattern. However, the main heterogeneity is demonstrated in the histopathology of muscles from 'almost normal' to 'severe inflammatory infiltrates with muscle fibre necrosis but little inflammation'.[2] Because of the heterogeneity, the classification of IIMs becomes difficult. This is also reflected in the response to drugs; some of them respond well to GC,[3] others may require the addition of MTX[3] or

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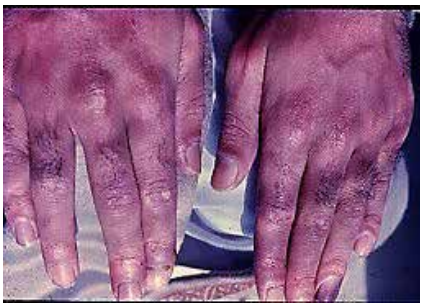

Fig. 1: Gottron's papules pathognomonic of dermatomyositis

Fig. 2: Periorbital heliotrope rah pathognomonic of dermatomyositis; photosensitive facial rash also seen in patients with dermatomyositis

Fig. 3: Classical 'Mechanics hands' in a patient with Jo-1 syndrome

AZA while some of them may be totally resistant to these treatments where intravenous immunoglobulins (IVIG) or newer (biologicals) drugs may be required. However, predicting response in a given patient to any of these modalities remains a major 'unmet need'. Because of the heterogeneity of the patients with IIM, proper drug trials are also difficult. A drug that may be highly effective in a certain subset of IIM may be perceived 'ineffective' in a heterogeneous population of patients that are unresponsive to the same

Fig. 4: (a and b) Photosensitive facial rash; necrotic skin lesions typical of MDA-5 associated IIM

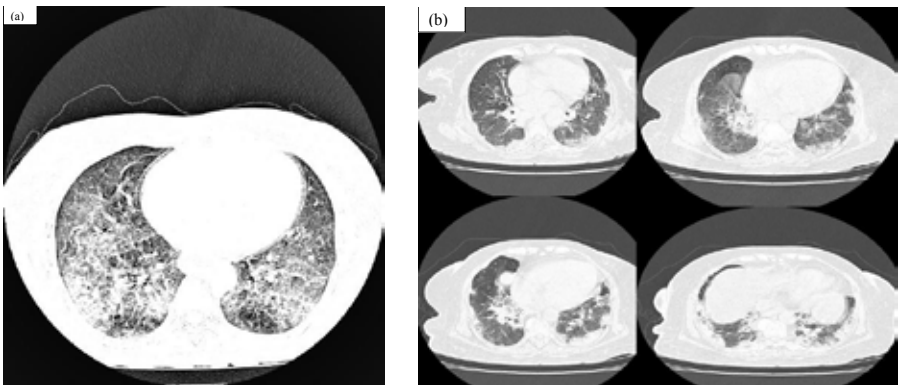

Fig. 5: Types of lung disease in IIM (a) HRCT chest showing bilateral diffuse ground-glass appearance with consolidative opacities suggestive of diffuse alveolar hemorrhage (DAH); (b) Interstitial lung disease (bronchiolitis obliterans with organizing pneumonia) common pattern seen with IIM

drug. Therefore, a better classification system with well-defined subsets based upon well-defined (histopathological, immunological) features is urgently needed. The bourgeoning discoveries of a large number of antibodies in patients with IIM in the recent past and using advanced immunohistopathological methods it is imminent that in the near future IIM subcategories would be better understood with clear idea of the type of treatment response and which drug would be best suited for that subset leading to the practice of 'precision medicine'.[3]

Progress in classifying IIMs – Recent advances

Over the last several decades a number of attempts have been made for classifying IIM. Starting from Medsger in 1970,[3] there have been more than 12 classification systems the latest being that by Lundberg and her colleagues.[4,5] Although differing in details, all of them have been aimed at achieving homogeneity of the subsets with better mechanistic pathobiology that would help in the specific drug use for a given subset aiming towards precision medicine. Despite many classifications systems including the most recent efforts by European League Against Rheumatism (EULAR),[5] the classification difficulties persist.[6] Therefore, till the development of an ideal classification system, the time-honoured system suggested by Bohan and Peter in 1975 would remain popular.[3] However, it is predicted that the rapid discoveries of a large number of IIM-specific and IIM-related autoantibodies

Table 1: Associations of certain specific clinical manifestations with Myositis Specific Antibodies

Myositis Specific Antibodies	Specific clinical association
Anti-TIFγ antibody	Very high association with malignancy – careful evaluation of malignancy (even occult) required
NXP-2 antibody	• In adults – high association with malignancy • In children – severe calcinosis cutis
ASA (syndrome) – 2 subgroups: Anti-Jo-1; anti-non-Jo-1 antibodies	Severe progressive interstitial lung disease; little muscle involvement (amyopathic), trivial skin rash or CADM
MDA5 antibodies	Severe progressive interstitial lung disease; little muscle involvement (amyopathic), skin rash atypical or CADM
Anti-HMGCR (subgroup not associated with statin exposure) antibodies	Association with malignancy?
Autoantibody-negative NAM	High association with malignancy

Anti-TIFγ = Anti-transcriptional intermediary factor 1-gamma; Anti-nuclear matrix protein 2 = NXP-2; ASA = anti-synthetase antibody; Anti-Jo-1 and anti-non-Jo-1 = autoantibodies against aminoacyl-tRNA synthetases; CADM = clinically amyopathic dermatomyositis; MDA5 = Anti-melanoma differentiation-associated gene 5

Table 2: Pure dermatomyositis: The patients in this group have classical dermatomyositis with pathognomonic and characteristic skin lesions that precede onset of myositis. *This subset is not associated with ILD. The association with cancer* (within the 3 yrs. from the *onset of the disease) depends upon the associated MSA*, as follows

Common characteristics
- Typical classical rash of DM includes Heliotrope rash, Gottron's papules and sign, V-shawl sign, holster sign
- Skin rash precedes the myositis
- Typical proximal muscle weakness affecting the neck flexors, muscles of the trunk and the proximal muscles in the limbs.
- Not associated with ILD

Anti- Mi-2 disease[16]	• Characteristic skin rash of DM • Typical muscle weakness • Increased muscle enzymes • Not associated with ILD	Autoantibodies targets nucleosome remodelling deacetylase complex*	Not associated with malignancy	Responds well to GC, immune-modulators (e.g. MTX and AZA)
Anti-SAE disease	• Characteristic skin rash of DM • Typical muscle weakness • Increased muscle enzymes[16] • Not associated with ILD	Antibody targets a small ubiquitin like modifier activating enzyme (SAE ab)[9,21$]	Not associated with malignancy	Responds well to GC, immune-modulators (e.g. MTX and AZA)
Anti-TIFγdisease	Skin rash-Same as Mi-2 disease, may have psoriasiform rash , red on white skin , hyperkeratotic verruca like papules Often clinically amyopathic.[22]	Antibody react with transcription intermediary factor **γ (TIF γ)**	**High association with malignancy within 3 years of onset in adults but not in children**[9,3,13,23] PET-Scan is recommended in those where associated malignancy is not known	Improves with the treatment of the underlying malignancy
Anti-NXP-2 disease	*Clinical features depend on age of onset.* **In paediatric age** - Skin rash may not be classical, severe calcinosis cutis, muscle atrophy and contractures. - Usually amyopathic may involve distal muscles **In adults** Skin rash is severe with minimal calcification and occasionally very high muscle enzymes.	Autoantibody reacts with nuclear matrix protein 2 (NXP-2)	**High association with malignancy in adults but not in children**[9,24]	For severe calcinosis (ectopic calcium tumours), surgical enucleation may be required

*Reichlin and Mattioli discovered it for the 1st time in 19763 and later confirmed by Targoff and Reichlin in 1985.[3] It was the 1st MSA antibody to be discovered; $Small ubiquitin like modifier activating enzyme (SAE ab) was first described by Betteridge□ this has association with HLADQB1*03.[25]

combined with advancements in immunohistopathological studies of the affected muscles, is likely to lead to a better and improved classification system of IIM which will help to practice precision medicine.[4,7-12] A Canadian group of workers has suggested a way of grouping IIM subsets that takes into account a number of newly identified MSAs and MAAs, but it may not be exactly a classification system.[7]

Newer Autoantibodies in IIM – Towards Better Classification and personalised treatment

Historically, Reichlin and Mattioli reported the first 'Myositis Specific Antibody'(MSA) in 1976.[13] It was named anti-Mi-2 antibody, found almost entirely in the 'garden-variety' of DM with typical rash, muscle weakness, high muscle enzymes and good response to GC with good prognosis, the finding repeatedly confirmed over time.[3] It also proved that MSAs could predict the disease course as well as the response to certain specific drugs. The discovery of the anti-Mi-2 antibody also firmly placed IIMs in the category of systemic inflammatory rheumatic diseases within the field of Rheumatology.[13] Additionally, it persuaded specialists in the field to put in serious efforts in discovering autoantibodies in IIM, which may help proper classification and appropriate treatment, a prediction that seems to be getting proven with rapid discoveries of a large number of Myositis-Specific Antibodies (MSAs) and Myositis-Associated Antibodies (MAAs).[9] MSAs are seen specifically and *only* in patients with IIM. On the other hand, MAAs are not specific for IIM; they are also often seen in other connective tissue diseases (e.g. systemic lupus erythematosus {SLE}, systemic sclerosis {SSc}, undifferentiated connective tissue disease {UCTD}, and Sjögren's syndrome). Thus, profiling for autoantibodies in patients with IIM has now become almost mandatory for determining prognosis, likely disease course, complications, and the precise treatment for that subset. Table 1 gives a summary of the associations of certain specific clinical manifestations with MSAs.

Clinical phenotype groups based upon the MSAs and MAAs[7]

1. Classical dermatomyositis that presents with a pathognomonic skin rash that appears before the proximal muscle weakness affecting the neck flexors, muscle in the trunk and the proximal limb muscles associated with high levels of muscle enzymes, typical electromyographic and histopathological features. Lungs are not involved in this group. Association with malignancy depends upon the type of associated myositis-specific antibody (Table

Table 3: IIM with interstitial lung disease

Name of the phenotype	Clinical profile	Autoantibodies	Associated with malignancy	Treatment
ASA syndrome (anti-synthetase antibody syndrome of 2 subtypes)[15,26,27]				
Anti-Jo1 syndrome	- Transient skin rash - Raynaud's phenomenon (RP) - ***Severe progressive ILD*** - Mild muscle weakness - Mildly elevated muscle enzymes - Mechanic's hands	Anti-Jo1ab. (an MAA) Association with Anti-Ro ab. confers greater resistance to treatment	Not within 3 yrs of onset	GCs, Immunosuppressive drugs e.g. Methotrexate (MTX), Azathioprine (AZA), Rituximab (RTX)[36]
Anti-non Jo1 syndrome	- Skin rash minimal - Unresponsive ILD - Worse survival	PL-7, PL-12, OJ, EJ, Ha, Zo, KS	Not within 3 yrs of onset	Response to RTX, not yet established
MDA5 syndrome[7,9,26-28]				
	- Skin rash minimal - Cutaneous ulceration due to severe vasculopathy is a characteristic feature[29] - Clinically amyopathic DM - ILD is severe	MDA-5 (Anti – melanoma differentiation associated gene – 5) Anti-cytoplasmic pattern of ANA staining	Not within 3 yrs of onset	GCs, Immunosuppressive drugs e.g. MTX, AZA

2).

2. IIM associated with interstitial lung disease. This group of IIM is characterised with rapidly progressive interstitial lung disease with minimal muscle involvement, variable skin involvement from no rash to moderately severe rash and variable EMG findings and muscle enzyme levels. Based upon the presence of MSAs there are 2 major subgroups namely (i) Anti-synthetase syndrome (ASA) and (ii) MDA-5 (antibody against melanoma differentiation-associated gene 5) syndrome (Table 3).

   i. ASA syndrome: Characteristic clinical features of ASA syndrome is the absence or trivial skin rash and minimal or no features of muscle involvement called 'Clinically amyopathic dermatomyositis' (CADM). Such patients are likely to be misdiagnosed as idiopathic ILD and usually present to pulmonologists. The characteristic feature of this form of ILD is that it does not respond to the usual line of treatment. The pulmonologists may consider them as a form of 'resistant ILD'. However, in the subgroup analysis of the famous RIM trial, it was shown that the patients with anti-Jo-1 syndrome respond to treatment with rituximab.[14] In the second type of ASA namely 'anti-non-Jo-1' syndrome, the clinical features are similar to that of the anti-Jo-1 syndrome but the response to rituximab has not yet been confirmed.

   ii. MDA-5 syndrome: The main feature of patients with the MDA5 syndrome is rapidly progressive, severe, difficult-to-treat interstitial lung disease (ILD). Therefore, such patients may present to a pulmonologist. However, a careful physical examination would reveal skin rash pathognomonic of dermatomyositis. Another important feature of the rash is frequent ulceration of the Gottron's lesions and occasionally painful reddish lesions on the palm that are characteristic of the MDA5 syndrome.[15,16] A rheumatologist may confuse it with the typical garden-variety of dermatomyositis. However, the absence or only trivial muscle weakness with none or only minimal elevation of muscle weakness (i.e. CADM) and the pulmonary features (not seen in classical dermatomyositis) gives away the diagnosis. The seriousness of the lung involvement in this subset of IIM can be realised by the prognosis of the MDA5 syndrome that is considered even worse than IIM associated with malignancy.[16]

3. The syndrome of necrotising autoimmune myositis (NAM; often mimics pure polymyositis): This subset of IIM is characterized by rapidly increasing muscle weakness in the trunk and the proximal muscles in the limbs, associated with high to very high levels of muscle enzymes. Because the patients with NAM show minimal or no skin rash, they are often misdiagnosed as pure 'polymyositis'.[8,10] The diagnosis is established only with muscle biopsy that typically shows extensive necrosis of the muscle fibres with the occasional attempt to regeneration and little cellular infiltrates. This disease has certain subsets associated with specific MSAs as follows (Table 4).

   i. Patients with anti-3-hydroxy-3-methyl glutaryl-coenzyme A reductase (HMGCR) autoantibodies: Only a small proportion of such patients give a history of having taken statins. These patients have mild disease, do not have lung disease, no relationship with cancer and responds well to GC treatment if started early in its course.[17] In contrast, those with no statin-intake history could have a serious rapidly progressive muscle disease, resistance to treatment and a higher change of association with malignancy[18] (Table 4).

   ii. Patients with anti-signal recognition particle (SRP) antibodies: Clinically these patients have severe progressive muscle involvement in the inflammatory myositis distribution associated with minimal or no skin rash (thus resemble polymyositis).[19] Dysphagia (initiation of deglutination) may be present due to the involvement of the pharyngeal muscles. It is not associated with cancer or lung involvement. Such patients respond poorly to the standard line of treatment of

Table 4: The syndrome of Necrotizing Autoimmune Myositis (NAM)

Common characteristics:				
Rapidly progressive Muscle weakness High CK levels			Histopathology shows widespread necrosis of muscle fibres with some regenerations but no inflammatory cellular infiltrates. Generally unresponsive to GCs and other immunomodulatory drugs.	
Absence of DM rash as well as clinical features of CTD.[9,11]				
This is divided into four sub sets				
Anti-HMGCR antibody syndrome	It has two clinical variants a. H/o treatment with statins – it is less common and response well to GC and immunomodulatory drugs b. H/o statin treatment- it is more common and has rapidly progressive muscular weakness. It is resistant to standard treatment	HMGCR antibody (anti 3 hydroxy 3 methyl glutaryl coenzyme A reductase)	Patients with no h/o statin treatment- no association with malignancy Patients with h/o statin treatment – high chance of association with malignancy?	Responds well to GCs and immunomodulatory drugs if detected early.[30]
Anti-SRP antibody syndrome	- Progressive, sub-acute and severe necrotizing muscle disease - Minimal or no skin rash - Can be misdiagnosed as polymyositis[31] - Dysphagia could be a prominent symptoms - Cardiac involvement is controversial	Anti-SRP (signal recognition particle) antibody[8,32]	Associated with malignancy	Poor response to standard line of drugs
Anti-SMN antibody syndrome	- Severe rapidly progressive muscle weakness - High CK levels – histopathology is same as NAM group except that it shows minimal inflammatory infiltrates	Anti-SMN (survival of motor neuron complex) antibody**		Poor response to standard treatment
Auto-antibody negative NAM	Clinical feature are common to NAM group		Increased association with malignancy	Poor response to standard treatment

**Can be associated with several myositis associated antibodies (MAA)[33] which creates problem in its classification.

Table 5: 'Pure' polymyositis and Inclusion-Body Myositis

Pure polymyositis - immunologically silent disease		
This entity is extremely rare (accounts for only 5% of all IIM patients) and some cases of polymyositis could be the mimics of myositis (e.g. Familial myopathies due to genetic mutations, metabolic and endocrine myopathies, others)[6,11] rather than true pure polymyositis[7]		
Inclusion body myositis (IBM)[34,35]		
- Rarest form of IIM - Significant involvement of distal limb muscles - Diagnostic confirmation requires electron microscopy	Recently reports showed presence of Anti-cN1A (antibody against cytosolic 5 nucleotidase1A)	Till today no known treatment for this disease

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4. 'Pure' polymyositis: In recent days, the concept of 'pure polymyositis' is being challenged. The reason is that most of the patients who are diagnosed with pure polymyositis are turning out to be one of the NAMs or mimics of myositis (rare forms of hereditary myopathies). Therefore, as a rule, the present advice is to carry out the advanced immunohistopathological study, including electron microscopy, of the muscle biopsy specimen before labelling patients as having pure polymyositis (Table 5).
5. Overlap myositis: Strictly speaking, this could be considered the largest and the most common group of IIMs. However, the clinical features of the other connective tissue diseases (e.g., systemic lupus erythematosus (SLE), systemic sclerosis (SSc), mixed connective tissue disease (MCTD), and Sjögren's syndrome) may dominate the clinical features to the extent that the clinical relevance of the muscle involvement becomes secondary in most cases. Certain clinical manifestations that could help recognising the 'overlap' myositis include inflammatory arthritis, Raynaud's phenomenon, dysmotility of the lower oesophagus, certain specific features of SLE (e.g. butterfly rash, to be distinguished from the photosensitive facial rash of DM crossing the nasolabial fold as opposed to that seen in SLE rash that does not cross the nasolabial fold), or sicca features of Sjögren's syndrome. An important clinical point of note is that in overlap myositis (as against "pure" DM) the muscle *weakness appears before the skin rash*. Overlap-myositis patients also show the presence of a variety autoantibodies that are often also seen in the different CTDs (Table 6).
6. Inclusion-body myositis (IBM): This is the rarest form of inflammatory myositis. It is characterized often by the presence of distal limb muscle involvement. Unfortunately, the confirmation of its diagnosis is difficult because that requires an electron microscopic examination of the muscle tissue to demonstrate the 'inclusions'. Recently a specific autoantibody has been described in this disease namely an antibody against cytosolic 5'nucleotidase 1A (anti-cN1A) thus firmly placing this entity under the 'umbrella' of autoimmune myositis group'. But, this antibody cannot be used as a marker of IBM because it is also found in about 1/3rd of the patients with Sjögren's syndrome and SLE. Till date, there is no known treatment for this disease.

A New Class of Autoimmune Muscle Disease – the confluence of myositis with hereditary myopathies

It may be noted that in all the above mentioned IIMs, and the autoantibodies associated with them are *not reactive against any anatomical/biochemical component of the striated muscles itself*. Most antigens are molecules involved in cell functions, found not only in most cells in the body but often across species. Therefore, mechanistically, it is difficult to implicate them in

Table 6: *Overlap Myositis* with the presence of autoantibodies that belong to the general category of routinely performed 'anti-nuclear antibody' test by immunofluorescence technique using Hep-2 cells as the antigen substrate. These are NOT specific for myositis but are often 'associated' with the clinical features of inflammatory myositis; these are called 'Myositis Associated Antibodies (MAA)'

Clinical features	Antibodies	Cancer association	Treatment
Inflammatory arthritis (usually of rheumatoid pattern) Fever RP Lower oesophageal dysmotility Sicca symptoms Muscle involvement appears before appearance of skin rash Overlap with CTDs may be subtle[7]	Ab to ENA associated with other CTDs e.g. SnRNP, Ro, La, Ku, PM-Scl	Not within 3 yrs. of the onset	Treat the dominant CTD

specific muscle disease. Thus, the above mentioned antibodies only remain as 'disease markers'. In contradistinction with the above scenario, very recently there has appeared a report of the detection of an autoantibody against a muscle-specific antigen where the disease resembles some form of AIM.[20] The target antigen of this antibody is a molecule called four-and-a-half LIM domain 1 (FHL1), a component of striated muscles; the antibody being called anti-FHL antibody. It is to be noted that FHL-1 mutations cause some varieties of X-linked hereditary myopathies (FHL1-related myopathies). This group of myopathies are characterized by severe muscle damage and dysfunction. In contrast, those with anti-FHL antibody the clinical features include muscle atrophy, dysphagia, and vasculitis. Histopathology shows severe muscle fibre damage. Till now there is no treatment described for this disease.

Conclusion

The discovery of the anti-Mi2 autoantibody, the first such antibody in IIM, was a landmark event, firmly establishing idiopathic inflammatory muscle diseases to have an autoimmune basis. Many workers would therefore, prefer to use the name 'Autoimmune Myositis' (AIM) for this group of diseases.[7] The discovery was also unique because it showed an autoimmune marker that could also predict a good response to drugs (GC, immunomodulatory drugs). Over the next several decades more and more antibodies have been identified in the IIM group of diseases. These discoveries have helped in classifying them in homogeneous groups where the clinical features (especially the skin, and the muscles disease course), response to different drugs, extra-pulmonary associations (especially malignancy and interstitial lung disease) are becoming better defined. The main excitement is because of the possibility of targeted treatment for these subsets with increasing practice of 'precision medicine'.[36]

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