Idiopathic inflammatory myopathies: An update

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ABSTRACT

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disease with complex clinical features. It has been sub-classified as: (1) Dermatomyositis, (2) Polymyositis, and (3) Inclusion body myositis (IBM). Nowadays, there are some studies in literature suggest necrotizing autoimmune myopathy and immune-mediated necrotizing myopathy should also be added to this group of disease. There is a debate in the diagnosis of IIM and up until now, about 12 criteria systems have been proposed. Some of the criteria systems have been used widely such as Griggs et al.’s proposal for IBM. Clinical findings, autoantibodies, enzymes, electrophysiological, and muscle biopsy findings are diagnostic tools. Because of diseases’ complexity, none of the findings are diagnostic alone. In this study, we discussed the diagnostic criteria of IIMs and described detailed morphological features.

KEY WORDS: Dermatomyositis, idiopathic inflammatory myopathies, inclusion body myositis, polymyositis

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disease with complex clinical features. The histological features of them usually include various degrees of degenerative changes and inflammatory (usually lymphocytic) infiltrates [1]. Histopathological evaluation is one of the key tools for the diagnosis of IIM. Because of the complexity of clinical, morphological and laboratory findings of this group of disease, none of the findings are diagnostic for any kind of IIM. Diagnosis needs to include a combination of all findings [2].

Clinically, the most frequent finding is proximal and symmetrical weakness, but it can also be non-proximal and non-symmetrical [3]. Disease usually starts as weakness in shoulders and hip muscle, acutely or subacutely. Dysphagia can accompany [3].

Histopathologically, muscle fiber degeneration, regeneration, and mononuclear inflammatory cell infiltration have been determined in all kinds of IIM [4]. These are common histopathological findings for IIM. However, IIM subtypes have also some specific morphological findings. For example, perifascicular changes (like atrophy) are specific for dermatomyositis (DM) and lymphocytic infiltration of normal appearing (non-necrotic) muscle fibers for PM [4].

In IBM, amyloid accumulation and mitochondrial changes can be demonstrated. Although, endomysial inflammation is an important finding in the diagnosis of IMM, absence of inflammatory infiltrate does not exclude disease, especially in the situation of increased MHC-1 expression [4]. In spite of exceptions, increased MHC-1 expression is a common finding in most of IIM. The types of lymphocytes are different in DM and IBM/PM.

Laboratory studies show increased muscle related enzymes such as creatine phosphokinase (CPK), lactate dehydrogenase (LDH), or aldolase [5]. Autoantibodies may also increase. The most frequent autoantibody increased in IMM is Jo-1, which is an anti-tRNA synthetase antibody [6].

In this review, we discussed all aspects of IIMs from initial clinical features to treatment, and we presented detailed data with figures about pathological diagnosis of IMM.

REVIEW

Pathogenesis

Studies have shown that two main factors are important in the pathogenesis of IIMs: Genetics and immunological factors.
There are many papers about pathogenic mechanism of IMM in literature. There is a clear relationship between some HLA subgroups and IMMs. HLA-DRB1-0301 and HLA-DQA1-0501 alleles have been reported as risk factors for IIM in Western populations [7]. It has been shown that DRB1-0803 related with increases PM susceptibility among the Japanese population [7]. Sugiu[8] et al. has shown that among Caucasians, the allele of DRB1-0301 has linked to the production of anti-Jo1, whereas in the Japanese population the DRB1-0803 has associated with susceptibility to IIM and to the production of anti-aminoacyl-tRNA synthetases (ARS) [8]. These findings have shown a clear relationship genetic factors and IMMs and these examples can be extended.

There are some immunological differences between subgroups of IMMs, too. In DM, inflammatory infiltrate has been seen mostly at the interfascicular area around vessels and most of them are CD4+ T-cells [4]. However, in PM and IBM, inflammatory infiltrate are mostly at endomyosial area and non-necrotic muscle fiber infiltration by CD8+ T-cells are an important diagnostic clue [4]. In all of these three diseases, increased MHC-1 expression on muscle fiber has been seen which is negative in normal muscle. Taken together these features strongly suggest that a cell-mediated cytotoxicity plays a key role in the pathogenesis of PM, according with this interpretation, clonally expanded CD8+ T-cells invade muscle fibers expressing antigen-presenting MHC Class I molecules and release cytotoxic granules, thus leading to myofiber necrosis [4].

**Clinical Features**

IMMs are a heterogeneous group of disease which mostly affects skeletal muscle. Clinical features can include muscle weakness, skin disease, and internal organ involvement [9]. Onset is usually over 18 years old. However, DM may start in childhood. Weakness is usually proximal and symmetrical. Head flexors are affected more than extensors. Heliotrope rash and Gottron’s signs/papules can be seen in DM [9].

**Laboratory Findings**

There are two important group of a target for laboratory investigation of IMM: Muscle enzymes and autoantibodies. Muscle enzymes are CPK, LDH and aldolase [3]. All of these tree enzymes elevate almost every time in IMM, but normal levels of enzymes do not exclude the disease [3]. Autoantibodies are very important in the diagnosis of IMM. They are present in over 80% of patients with immunomediated myositis [10]. There are two main groups of autoantibodies: Myositis specific autoantibodies (MSA) or myositis-associated antibodies [10]. MSA include antibodies directed against aminoacyl-tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ, JS, and KS), signal recognition particle, nuclear helicase Mi-2, and p155. Troyanov et al. has been compared the overall frequency of MSA in IMM and investigated the relationship between serology and pathological findings. According to their study, overall frequency of MSA was 42% and anti-Jo1 was the most common overlap autoantibodies. Muscle biopsy by itself was not able to distinguish the different serologic subgroups as clinic/serologic classification cannot fully predict the pathological findings [11]. Patients with non-Jo-1 anti-ARS Abs have a worse survival rate than those with anti-Jo1. In recent years, anti-cN1A autoantibodies have been found greatly expressed in patients with IBM [12]. In some case series of patients, anti-cN1A was present in up to 60% of IBM patients. It is believed that cN1A has a role in the pathogenesis of IBM and it has value in the diagnosis of IBM.

**Histopathological Findings**

The most important histopathological finding of PM is lymphocytic infiltration of non-necrotic muscle fiber [Figure 1]. Lymphocytes are mostly CD8+ T-cells. Inflammatory infiltrate is usually endomyosial area; interfascicular connective tissue is affected lesser degree. There are usually necrotic and regenerative muscle fibers [4]. In almost all PM, MHC-1 overexpression is seen [Figure 2].

In DM, inflammatory infiltrate are mostly CD4+ T-cells and it is mostly at interfascicular connective tissue, around vessels. The most diagnostic clue is perifascicular changes [Figure 3] even in the absence of inflammation. Single muscle fibers or clusters of muscle fibers in various stages of necrosis and/or regeneration are frequently observed [4]. An early histological feature is the involvement of intramuscular blood vessels; the angiopathy is characterized by: (1) The deposition of
immunoglobulins and complement, including the C5b-C9 membrane attack complex, on endomysial capillaries and small blood vessels and (2). The reduction in a number of capillaries with endothelial hyperplasia and enlargement of the lumen of the remaining capillaries [13]. Another important clue of disease is the presence of tubuloreticular inclusions within the endothelial cytoplasm on electron microscopic examination. To support the diagnosis, EM can be made in the absence of specific findings of DM.

In analogy to PM, non-necrotic muscle fiber infiltration by CD8+ T-lymphocytes and endomysial lymphocytic infiltration may also be seen in IBM. In addition, IBM has following features: (1) Vacuoles in muscle fibers [Figure 4], (2) eosinophilic cytoplasmic globules, (3) Amyloid deposition [Figure 5], (4) mitochondrial dysfunction findings (Ragged red, ragged blue and COX-negative fibers) [Figure 6] [4]. Nowadays, TDP43 and cN1A proteins have been also showed in muscle fiber of patient with IBM [14]. Interestingly, muscle tissue with IBM may have small angulated muscle fibers, which are considered indicative of a neurogenic process.

Immune-mediated necrotising myopathy is a new entity has a specific histological pattern [15]. Characteristic findings are randomly distributed necrotic muscle fibers along with fibers in various stages of regeneration but in the absence of or sparse mononuclear cell infiltrates [15]. There were no T or B cells. Myophagocytic fiber can be seen. MHC class I antigen does not show increased expression, if show, its expression is weak and focal [15].

**Diagnostic Criteria**

There are plenty of diagnostic scales for IIM in literature. These can be summarized as Medsger et al., 1970 (for IIM); DeVere and Bradley, 1975 (for IIM) [16]; Bohan and Peter, 1975 (for PM/DM) [17]; Dalakas, 1991 (for PM/DM/IBM) [18]; Griggs et al., 1995 (for IBM) [19]; Tanimoto et al., 1995 (for PM/DM) [20]; Targoff et al., 1997 (for IIM) [21]; Mastaglia and Phillips, 2002 (for PM/DM/IBM) [22]; van der Meulen et al., 2003 (for PM/DM/other) [23]; Dalakas and Hohlfeld, 2003 (for PM/DM) [24]; Hoogendijk et al., 2003 (for PM/DM) [25]. The most known and commonly used ones are Griggs’s criteria for IBM and Bohan/Peter’s for PM/DM. Tables 1 and 2 have shown the details of criteria.

These scales usually sort the criteria (clinical, laboratory or muscle biopsy findings, etc.) and suggest some classifications like definite or possible according to criteria which patient has. Nowadays, it is needed new classification criteria because most of “diagnostic scales” do not include autoantibodies. Hence, they are mostly insufficient.
**Table 1: Bohan and Peter’s criteria for DM and PM**

<table>
<thead>
<tr>
<th>Symmetric proximal muscle weakness</th>
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<tr>
<td>Elevation of serum levels of skeletal-muscle enzymes including CPK, aldolase, AST, ALT or lactate dehydrogenase</td>
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<tr>
<td>Abnormal electromyogram with myopathic motor unit potentials, fibrillations, positive sharp waves, and increased insertional irritability</td>
</tr>
<tr>
<td>Muscle biopsy features of inflammatory infiltration and either degeneration/regeneration or perifascicular atrophy</td>
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<tr>
<td>Typical skin rash of DM that includes: Gottron’s sign, Gottron’s papules or heliotrope rash</td>
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**DMARDs** include rituximab, tumor necrosis factor inhibitors, one of most frequently used non-biological DMARDs. Biological modifying anti-rheumatic drugs (DMARDs). Cyclosporine A is a typical DMARD used in the treatment of inflammatory conditions. **Corticosteroids** are often used in conjunction with DMARDs to reduce inflammation and promote healing.

**Table 2: Griggs criteria for IBM diagnosis**

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<th>I. Characteristic features</th>
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<tr>
<td>A. Clinical features</td>
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<tr>
<td>1. Duration of illness &gt;6 months</td>
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<td>2. Age at onset &gt;30 years old</td>
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<td>3. Muscle weakness must affect proximal and distal muscles of arms and legs and must include one of the following: Finger flexor weakness, wrist extensor weakness or quadriiceps muscle weakness</td>
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<td>B. Laboratory features</td>
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<td>1. Serum creatine kinase &lt;12 times upper limit of normal</td>
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<td>2. Muscle biopsy</td>
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<tr>
<td>a. Mononuclear cell invasion of non-necrotic muscle fibers</td>
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<tr>
<td>b. Vacuolated muscle fibers</td>
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<tr>
<td>c. Either</td>
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<tr>
<td>i. Intracellular amyloid deposits or</td>
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<tr>
<td>ii. 15-18 nm tubulofilaments by electron microscopy</td>
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<td>3. Electromyography consistent with features of inflammatory myopathy</td>
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| II. Associated disorders - An associated disorder does not preclude IBM if diagnostic criteria are fulfilled |
| III. Diagnostic criteria for inclusion body myositis |
| A. Definite inclusion body myositis: Muscle biopsy with all the following features: invasion of non-necrotic fibers by mononuclear cells, vacuolated muscle fibers, and intracellular amyloid deposits or 15-18 nm tubulofilaments. None of the clinical or other laboratory features are mandatory if muscle biopsy features are diagnostic |
| B. Probable inclusion body myositis: Invasion of non-necrotic muscle fibers by mononuclear cells and vacuolated fibers together with the clinical features A1, 2, 3 and laboratory features B1, 3 |

**CONCLUSION**

Studies have been provided a better understanding of pathogenesis and biologic behavior of IMMs. Because of that patients’ management is better now. However, this rapid improvement in immunology is also needed a revised and/or new diagnostic criteria.

**REFERENCES**


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