Immune-mediated necrotizing myopathy (IMNM) is a group of inflammatory myopathies showing necrotic and regenerating fibers without noteworthy inflammatory cell infiltration on pathology. The pathologic findings are different from those of dermatomyositis or sporadic inclusion body myositis. Furthermore, the discovery of myositis-specific antibodies in patients with IMNM, such as anti-signal recognition particle or anti-3-hydroxy-3-methylglutaryl-CoA reductase antibodies, has enabled us to expand our knowledge of IMNM. However, the phenotype and pathological findings of IMNM are unremarkable; therefore, it is difficult to diagnose, and IMNM has been relatively unrecognized. In this review, we introduce the clinical features, diagnosis, pathomechanism, and treatment of IMNM for clinicians.

Keywords: Myositis; Dermatomyositis; Myositis, inclusion body

Introduction

Idiopathic inflammatory myopathy (IIM) is a heterogeneous disease group characterized by muscle weakness, elevated serum levels of creatine kinase (CK), and inflammatory features of muscle pathology. Dermatomyositis (DM) and polymyositis (PM) were introduced by Bohan and Peter [1], and this classification was then widely recognized until sporadic inclusion body myositis (sIBM) was proposed in the 1990s. Starting in the 2000s, debate ensued regarding the existence of PM, because many patients diagnosed with PM were later considered to have sIBM, DM, overlap syndrome with connective tissue disease, or immune-mediated necrotizing myopathy (IMNM) [2,3]. DM, sIBM, and anti-synthetase syndrome have been well recognized as subtypes of IIM showing prominent lymphocytic infiltration on muscle biopsy [4]. However, in the last two decades, muscle pathologic findings showing many necrotic fibers without significant lymphocyte infiltration have been reported; this presentation is now widely recognized as IMNM [5].

To date, two different myositis-specific antibodies (MSAs) have been associated with IMNM: anti-signal recognition particle (SRP) and hydroxy-3-methylglutaryl-CoA reductase (HMGCR) antibodies. The SRP complex comprises a 7S RNA and six protein subunits with molecular weights of 9, 14, 19, 54, 68, and 72 kDa [4]. SRP is essential for the translocation of nascent polypeptides into the endoplasmic reticulum and was first identified in the 1980s by RNA immunoprecipitation (RNA-IP) [6]. The anti-HMGCR antibody was first recognized in 2010 from necrotizing myositis as anti-200 kD/100 kD [7]. The 100 kDa protein was later identified as a monomer of HMGCR [8]. Furthermore, IMNM patients with anti-HMGCR antibodies were reported to show a homogeneous phenotype, and 63% of patients had been exposed to statins [7].

Distinct muscle pathology findings and the involvement of MSAs separated IMNM as a subtype of IIM. Here, we review how IMNM differs from other subtypes of IIM from a clinical standpoint.
Epidemiology

The incidence of IMNM has not been analyzed. The global incidence of IIM ranges from 1.16 to 19 per 1 million person-years [9]. In Korea, the incidence of IIM was estimated at 2.9 to 5.2 per 1 million person-years [10].

Anti-SRP IMNM accounts for 5% to 15% of patients with IIM [11]. Anti-SRP IMNM is common in patients in the fifth or sixth decades of life and is more frequent in women than in men [11]. Anti-HMGCR IMNM is present in 6%-10% of IIM cases, and it occurs more frequently in women older than 40 years [11]. The target of the anti-HMGCR antibody is also the target of statins, and exposure to a statin may be a trigger of the disease. However, anti-HMGCR IMNM in childhood has also been reported [12], and statin exposure is not frequent in Asia [13]. Therefore, other factors may be able to provoke anti-HMGCR IMNM besides statin exposure.

Clinical Features

1) Muscular phenotype

The main feature of IMNM is limb weakness. Most patients with IMNM exhibit limb weakness of subacute onset from several weeks to months. A few cases have been reported with a slowly progressive onset for several years [14]. The distribution of muscle weakness in IMNM is similar to that in other idiopathic inflammatory myopathies, except for sIBM. Bilateral proximal limb weakness is notable, in which lower limb weakness precedes upper limb weakness [15]. Patients with anti-SRP antibody tend to have concomitant dysphagia (30%-70%), unlike those with anti-HMGCR antibody (Table 1) [11,15–17]. Patients with anti-SRP IMNM also show more severe muscle weakness and atrophy than those with anti-HMGCR IMNM [15,16]. The level of serum CK is high in both types of IMNM, ranging from 1,000 to 10,000 IU/L, which is higher than in other IIM groups [11]. The serum level of lactate dehydrogenase is also elevated, ranging from 350 to 840 IU/L (normal range, 100-250 IU/L), but it is not as high as in patients with metabolic myopathy [18].

2) Extramuscular phenotype

Interrstitial lung disease has been reported to be present in 23% to 38% of patients with anti-SRP IMNM [11]. However, these patients did not complain of dyspnea. Myocarditis can also be seen in 2%-40% of these patients, presenting as chest pain, palpitations, congestive heart failure, and electrocardiographic abnormalities [11]. The risk of malignancy is unclear, but was reported to be slightly increased in anti-HMGCR IMNM (Table 1) [19,20]. In seronegative IMNM, a high incidence of associated cancer was observed, with an incidence ratio of 8.35 (95% confidence interval, 1.68-24.41; p < 0.01) [19]. Anti-SRP IMNM is not associated with cancer [15].

Table 1. Comparison Between Anti-SRP and Anti-HMGCR IMNM

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<th>Anti-SRP</th>
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<td>MAC deposition on sarcolemma on histology</td>
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SRP, signal recognition particle; HMGCR, anti-3-hydroxy-3-methylglutaryl-coA reductase; IMNM, immune-mediated necrotizing myopathy; +, ++, ++++, less common to more common; -, none; MAC, membrane attack complex. Modified from [15–17].

Diagnosis

1) Myositis-specific antibody

The identification of MSA is necessary to classify the subtype of IMNM. However, a uniform method to test MSA for IMNM has not been established. For anti-SRP IMNM, an anti-SRP antibody is screened by an enzyme-linked immunosorbent assay (ELISA) or the line blot technique, which detects only the 54-kDa SRP subunit in the commercial kit [4]. Many patients with anti-SRP IMNM do not have reactivity against this protein. Thus, false negatives can result [14]. The presence of anti-SRP antibody can be confirmed by RNA-IP, the immunoprecipitation of radioactively labeled whole-cell extracts, or the in vitro transcription and translation protein products, which enable the detection of other subunits. However, RNA-IP is laborious, limiting its clinical applications. The anti-HMGCR antibody is screened by ELISA, the false positivity rate of which is only 0.7% [21]. Thus, ELISA is recommended to be performed when the probability of anti-HMGCR IMNM is high. In a research setting, immunoprecipitation of purified HMGCR protein is required for confirmation [4].

2) Muscle magnetic resonance imaging

Muscle magnetic resonance imaging (MRI) is an excellent non-invasive tool for measuring the extension of muscle damage. However, the MRI findings in patients with IMNM are not specific enough for diagnosis compared with the detection of MSA...
or the findings of muscle biopsy [11]. Despite the limitation of muscle MRI in diagnosing IMNM, several studies have shown distinctive findings in IMNM compared to other types of IIM [22,23]. Muscle damage showed a tendency to affect the gluteus minimus, gluteus maximus, lumbar extensor, and subscapularis in patients with IMNM compared to those with sIBM [22]. In thigh muscle MRI, atrophy and fatty replacement were identified in the lateral rotators, glutei, and medial and lateral compartments of IMNM patients [23]. Among IMNM patients, patients with anti-SRP IMNM showed more extensive edema, atrophy, and fatty replacement than those with anti-HMGCR IMNM [23].

3) Pathology

On light microscopy, one of the features distinguishing IMNM from other types of IIM is the presence of necrotic and regenerating fibers without definite endomysial inflammatory cell infiltration on hematoxylin and eosin (H&E) staining (Fig. 1A). Those fibers are randomly scattered. Necrotic and regenerating fibers can exhibit different phases of necrosis, with paleness, coarseness, and phagocytosis [11]. The presence of perifascicular atrophy or lymphocytes surrounding non-necrotic fibers is uncommon [4]. On modified Gomori-trichrome (mGT) staining, necrotic and regenerating fibers can be seen in accordance with the findings of H&E staining [11]. However, rods or ragged-red fibers are not evident on mGT staining.

On immunohistochemistry, major histocompatibility complex (MHC) class I positivity is noted on the sarcolemma of scattered fibers in IMNM, but MHC class II is absent from the sarcolemma [11]. Deposits of C5b-9 (membrane attack complex) on the sarcolemma can be observed, which is not unique for IMNM [11]. An autophagy marker, p62, can be highlighted in several fibers showing fine granular or homogeneous staining (Fig. 1B) [11]. These findings are different from those of sIBM, which harbors fibers stained as plaque-like by p62 [11].

Pathomechanism

The precise pathogenesis of IMNM is not fully understood [4]. However, several roles of anti-SRP and HMGCR antibodies have been clarified [4]. Clinically, the serum anti-SRP or HMGCR antibody titer correlates with disease activity. A previous study showed that the anti-SRP antibody level was reduced after plasma exchange [24]. Furthermore, the serum level of CK correlates with anti-SRP and HMGCR autoantibody titers [20,24]. In vitro, both anti-SRP and HMGCR antibodies have been proven to induce muscle fiber atrophy [25]. This study demonstrated that the transcription of genes encoding atrophic factors (muscle atrophy F-box protein and E3 ubiquitin-protein ligase TRIM63) increased [25]. Furthermore, the co-culture of muscle fibers with purified anti-SRP and HMGCR antibodies was associated with high levels of tumor necrosis factors and interleukin-6, resulting in muscle atrophy. Simultaneously, reduced levels of the anti-inflammatory cytokines interleukin-4 and interleukin-13 induced impaired muscle regeneration by myoblast fusion defects [25]. In a mouse model, Rag2-/- mice were injected with purified

Fig. 1. Light microscopic findings from a patient with anti-SRP antibody. (A) A few scattered necrotic (black arrows) and regenerating (white arrows) fibers are seen on hematoxylin and eosin staining. (B) A fiber showing fine granular staining is noted using antibody targeting p62 (sc-28359, 1:200 dilutions; Santa Cruz Biotechnology, Dallas, TX, USA). For the purpose of comparison, a plaque-like stain can be seen in sporadic inclusion body myositis (small box). Scale bar, 100 μm.
immunoglobulin G (IgG) from patients with anti-SRP and HMGCR IMNM for 21 days. Grip strength was evaluated on days 8, 14, and 21. The strength significantly decreased in both anti-SRP and HMGCR IgG-injected mice [26]. The pathology of mice receiving purified IgG from anti-SRP IMNM showed multiple necrotic fibers and complement C5b-9 deposits [26].

Treatment

No randomized, blinded, controlled trials of IMNM have been published. Most treatments rely on case reports or expert consensus. However, corticosteroids remain the first line. Intravenous methylprednisolone (1 g for 5 days) is followed by oral high-dose prednisone (1 mg/kg daily) [5]. Of note, oral corticosteroids must be tapered to the lowest dose as soon as possible [5,11]. Within 1 month after corticosteroid administration, oral methotrexate (0.3 mg/kg weekly, maximum dose 25 mg/week) or azathioprine (3 mg/kg daily) is highly recommended [5]. It is also necessary to monitor hepatic function and the blood count [5]. Many studies have warned against treatment with steroids alone. In pediatric patients with anti-HMGCR IMNM, no patients achieved clinical remission with only corticosteroid treatment [12]. In a literature review, a mean number of 1.5 different additional immunosuppressants were needed in patients with anti-HMGCR IMNM [27]. The European Neuromuscular Center guidelines recommend using rituximab as a second or third agent in patients with anti-SRP IMNM, which was also supported in other reports [5,17]. However, rituximab did not show notable efficacy in patients with anti-HMGCR IMNM [28]. Intravenous immunoglobulin was reported to be efficacious both in patients with anti-HMGCR IMNM and in those with anti-SRP IMNM [5,11,29]. The prognosis of patients with IMNM is poor. Despite 4 years of immunotherapy, one-third and half of anti-HMGCR and anti-SRP IMNM patients showed no recovery, respectively [11].

Conclusion

We summarized the clinical features, phenotype, pathomechanism, and treatment of IMNM. The phenotype and pathological findings of IMNM are not straightforward to diagnose, but some findings in the differential diagnosis for IMNM are evident, such as MSA specific to IMNM. Clinicians need to remain alert and should not overlook the diagnosis of IMNM.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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References