

ORIGINAL

Immune-mediated necrotizing myopathy: an emerging disorder



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KEYWORDS

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Anti-HMGCR
antibodies;
Statins

Abstract

Objectives: To describe the main features and the clinical management of a cohort of patients with immune-mediated necrotizing myopathy (IMNM).

Methods: We conducted an observational, monocentric, retrospective study of IMNM patients diagnosed in the Neuromuscular Unit of a tertiary hospital in Madrid (Spain) between 2013 and 2021.

Results: Sixteen IMNM cases were diagnosed, with a median age of 71.5 years (range 36–80), nine of whom (56.3%) were female. Thirteen (81.3%) patients had previously been treated with statins. The time from symptom onset to diagnosis was less than six months in eleven (68.8%) patients and the most common clinical symptoms were proximal weakness and myalgia. The only myositis specific autoantibodies detected were anti-3-hydroxy-3-methyl-coenzyme A reductase in thirteen patients. The treatment strategy was based on prednisone, although a combination with other immunosuppressive drugs was required in eight (50%) patients.

Conclusions: There has been an increase in the diagnosis of immune-mediated necrotizing myopathies in the last few years. The anti-HMGCR antibodies were the only detected in this sample showing their key role in the diagnosis. Early recognition of the disease facilitate to start treatment as soon as possible, which should be based on the initial response to corticosteroids and usually requires a combination of several drugs.

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PALABRAS CLAVE

Miopatía necrotizante
inmunomediada;
Miopatías
inflamatorias;
Anticuerpos
anti-HMGCR

Miopatía necrotizante inmunomediada: Experiencia en una unidad de Neuromuscular**Resumen**

Objetivos: Describir las características principales y el manejo clínico de una cohorte de pacientes con miopatía necrotizante inmunomediada (MNIM).

Métodos: Estudio observacional, unicéntrico y retrospectivo en el que se incluyeron los casos de MNIM diagnosticados en la Unidad de Neuromuscular de un hospital terciario en Madrid (España) entre los años 2013 y 2021.

Resultados: Dieciséis pacientes con MNIM se incluyeron en el estudio, con una mediana de edad de 71,5 (rango, 36–80) años, de los cuales 9 (56,3%) eran mujeres y trece (81,3%) pacientes habían sido tratados previamente con estatinas. El tiempo transcurrido desde el inicio de síntomas al diagnóstico fue menor de seis meses en once (68,8%) casos, y en todos, la forma de debut fue la aparición de debilidad proximal en miembros inferiores, seguido de mialgias como segundo síntoma más frecuente. En trece pacientes los anticuerpos anti-3-hidroxi-3-metilglutaril coenzima A reductasa (HMGCR) fueron positivos, siendo estos los únicos autoanticuerpos asociados a miositis detectados en la muestra. El abordaje terapéutico inicial se basó en el uso de corticoides, aunque la combinación con otros inmunosupresores fue necesaria desde el inicio en ocho (50%) casos.

Conclusiones: El diagnóstico de MNIM dentro de las miopatías inflamatorias ha aumentado en los últimos años. En nuestra muestra los únicos anticuerpos detectados fueron los anti-HMGCR, una pieza clave en el diagnóstico diferencial con otras miopatías inflamatorias. El tratamiento de la enfermedad debe ser individualizado teniendo en cuenta la respuesta inicial a corticoides y puede requerir la combinación de varios fármacos.

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Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of diseases characterised by inflammation of the muscles accompanied by extra-muscular symptoms affecting the skin, lungs, heart, and joints. Incidence varies between types of IIM.¹ Laboratory tests include the determination of specific antibodies, which manifest in approximately 60%-70% of the patients with IIM and are very useful in diagnosis and for identifying different groups with their own characteristics.^{2,3}

Another fundamental test for the diagnosis of IIM is muscle biopsy, as the different histological characteristics together with clinical data and the presence of antibodies have enabled researchers to develop a system to classify the different IIMs into 4 main subgroups: dermatomyositis, myositis associated with anti-synthetase syndrome, inclusion body myositis, and immune-mediated necrotizing myopathy (IMNM).⁴

Of these subgroups, IMNM was the most recently described, and it is characterised by more severe muscle weakness, higher levels of creatine kinase (CK), and rarely present with extra-muscular manifestations.⁵ The first milestone in the description of IMNM was the description of antibodies against the signal recognition particle (anti-SRP).^{6–8} After the publication of several studies, the designation “anti-SRP myositis” began to be used to refer to a group of IIMs associated with these antibodies. Soon after, the main histological characteristics were defined, with necrotic fibres and scarce inflammatory infiltrates,

which led to the recognition of IMNM as a separate entity within the group of IIMs in 2003.⁹ In 2010, a new antibody was detected, whose target is the enzyme 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGCR) in patients diagnosed with IMNM.¹⁰ This enzyme catalyses key reactions in cholesterol biosynthesis, and its expression in the cell membrane is increased in patients treated with statins, which may be a significant mechanism in the pathophysiology of the disease; however, the same antibodies have also been detected in patients who have never received lipid-lowering drugs.¹¹ Lastly, there is a third subgroup within the group of patients with IMNM that represents approximately 40% of cases, in which no antibody is detected.¹²

The therapeutic management of patients with IMNM is based on case series and expert consensus statements, and includes, in addition to corticosteroids, various immunosuppressants and immunomodulators, which are used in combination to control the disease.¹³ Furthermore, it would be necessary to screen for a possible underlying cancer, which has been associated with seronegative forms, and more controversially, with IMNM associated with anti-HMGCR antibodies.¹⁴

Methods

We performed a retrospective review of the database of the neuromuscular diseases unit at Hospital General Universitario Gregorio Marañón (Madrid), which identified cases of IMNM diagnosed between 2013 and 2021. The inclu-

sion criteria were adapted from the last consensus on the clinico-sero-pathological classification of IMNM of the European Neuromuscular Centre (ENMC).¹³ In addition to muscle biopsy findings compatible with necrotic or regenerative fibres in the absence of inflammatory infiltrates or with scarce inflammatory infiltrates, high levels of CK and recent onset of muscle weakness were required.¹³

The exclusion criteria were not meeting all inclusion criteria, family history of hereditary myopathy with a known genetic cause, and findings in the muscle biopsy or the remaining complementary tests suggestive of another alternative cause.

In each case, we reviewed the patient's clinical history and collected demographic and clinical data and the date of diagnosis. Based on the time since symptom onset, patients were classified as: acute onset (less than 4 weeks), subacute onset (between 4 weeks and 6 months), or chronic onset (more than 6 months from onset). We assessed the pattern of muscle weakness (lower limbs vs upper limbs, proximal vs distal, symmetrical vs asymmetrical) and measured the degree of severity using the Medical Research Council (MRC) scale, considering weakness severe when the MRC scale score was $\leq 3/5$ in any of the muscle groups analysed.

We subsequently analysed the complementary tests performed after the first examination at the neurology consultation and gathered CK values and the results of the autoimmune study. Immunoglobulin G-type myositis-specific antibodies were analysed in serum using the dot-blot technique (MYO12D-24, D-tek, Mons, Belgium), which detects and semiquantitatively measures 12 autoantibodies: anti-histidyl-tRNA synthetase (Jo1), anti-threonyl-tRNA synthetase (PL7), anti-alanyl-tRNA synthetase (PL-12), anti-glycyl-tRNA synthetase (EJ), anti-SRP, anti-nucleosome remodelling deacetylase (Mi2), anti-melanoma differentiation-associated protein 5 (MDA5), anti-transcription intermediary factor 1 γ (TIF1- γ), anti-HMGCR, anti-Sjögren's-syndrome-related antigen A autoantibodies (SSA/Ro52 kD), small ubiquitin-like modifier activating enzyme 1/2 (SAE 1/2), and anti-nuclear matrix protein 2 (NXP2).

An electromyography study was performed in all cases. The study was conducted by the neurophysiology department, and included an assessment of both activity at rest, to evaluate the presence of spontaneous activity, and activity during mild and maximal contraction, for the analysis of motor unit potentials (MUP). The number of muscles assessed in each patient was determined according to the physician's clinical judgement, including proximal and distal muscles of the upper limbs (trapezius, deltoids, flexor carpi radialis, biceps brachii, first dorsal interosseous, flexor digitorum longus) and lower limbs (iliopsoas, gluteus medius, tensor fasciae latae, rectus femoris, vastus lateralis, biceps femoris, tibialis anterior, and lateral gastrocnemius). No follow-up neurophysiological studies were performed.

When available, we reviewed whole-body muscle MRI studies, including T1-weighted turbo spin echo (TSE) sequences, and T2-weighted short tau inversion recovery (STIR) sequences.

Muscle biopsies, obtained at the time of diagnosis, were processed and assessed by the Department of Anatomical Pathology. First, samples were obtained and cryopreserved at -80°C , whereas a small fragment was preserved

in glutaraldehyde for the ultrastructural analysis. Routine staining included: haematoxylin-eosin (HE), Gomori trichrome stain, periodic acid–Schiff stain (PAS), Oil-Red O, ATPase 42, ATPase 46, ATPase 94, NADH 30, succinate, and COX-succinate. Immunohistochemistry studies were subsequently performed to complete the inflammatory myopathy study, including CD3, CD20, CD68, p62, and HLA-I labelling. The antibodies used were: anti-CD3 (Agilent, polyclonal rabbit anti-human), anti-CD20 (Agilent, monoclonal mouse anti-human clone L26), anti-CD68 (Agilent, monoclonal mouse anti-human clone PG-M1), anti-p62 (BD Transduction Laboratories, purified mouse anti-human clone 45/p62 [dok]), and anti-HLA-I (Agilent, monoclonal mouse anti-human clone W6/32); the manufacturers' staining protocols were followed in all cases.

Regarding the clinical management of patients with IMNM, we collected all data on the administration of different immunosuppressants, including the details of different treatment regimens, and whether or not they were used in combination. Treatment strategies were classified in accordance with the number of treatments administered: monotherapy (one single drug), bitherapy (2 drugs), or polytherapy (3 or more drugs).

Clinical response to treatment was reassessed at 6 months of follow-up, both subjectively (improvement, worsening, or stabilisation of symptoms) and objectively (muscle strength according to the MRC scale). CK levels were measured at 6 months, as well as the level of disability (modified Rankin Scale).¹⁵ All relapses were reported during the study follow-up period, and the diagnosis of cancer associated with myositis was considered in patients whose cancer diagnosis was established in the 3 years following the diagnosis of IMNM, in accordance with the criteria for the diagnosis of cancer-associated myositis.¹⁶

This study was approved by the medication research ethics committee of the Institute of Health Research at Hospital General Universitario Gregorio Marañón.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS) software, version 21. Categorical variables are expressed as the number of cases and percentages, and continuous variables as ranges and medians.

Results

Sixteen patients met all selection criteria and were included in the study. The first noteworthy finding was the upward trend in the diagnosis of IMNM in our sample, with the number of patients diagnosed per year progressively increasing from 2013 to 2021 (Fig. 1).

Demographic characteristics and clinical data

The median age at symptom onset was 71.5 years (range, 36–80); 9 patients (56.3%) were women. Before symptom onset, 13 patients (80.3%) had received treatment with

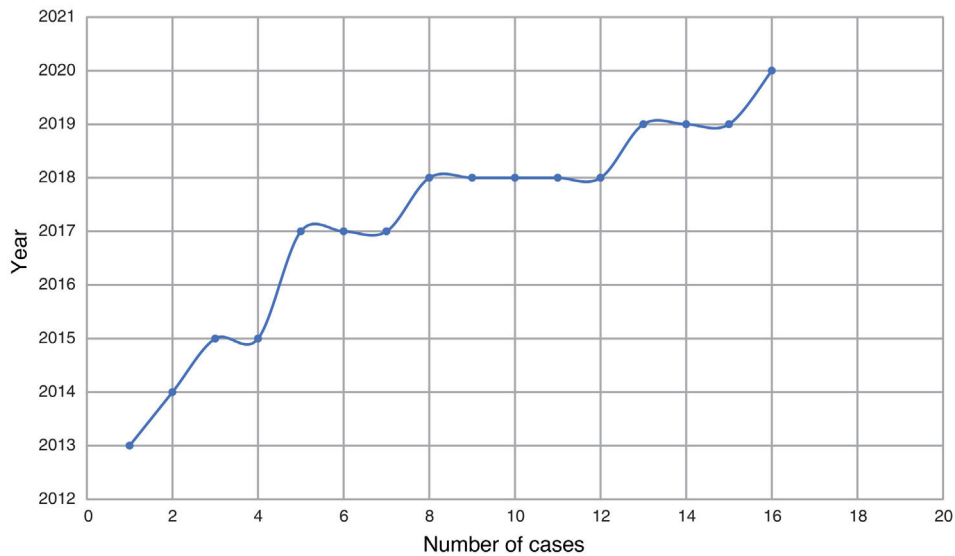


Figure 1 Graph showing the increasing number of cumulative cases of IMNM.

statins, with atorvastatin being the most frequently administered (used in 9 patients; 62.5%), followed by simvastatin and rosuvastatin (in 2 patients [12.5%] each).

The time elapsed from symptom onset to diagnosis was shorter than 6 months in 11 patients (68.8%); the most frequent type of presentation was subacute, in 9 cases (56.3%).

Proximal muscle weakness in the limbs was the initial symptom in all patients, and was considered severe in 10 (62.5%). Involvement was symmetrical in 15 patients (93.8%) and more pronounced in the lower limbs in 11 patients (68.8%), whereas the upper and lower limbs were similarly affected in the remaining 5 (31.2%). The second most frequent symptom was myalgia (12 patients; 75%), followed by neck weakness and dysphagia, observed in 4 patients (25%) each.

In 2 cases (11.8%), muscle weakness was accompanied by other extra-muscular manifestations associated with existing diagnoses of immune-mediated diseases: membranous nephropathy with antiphospholipid syndrome secondary to an autoimmune disease of unknown origin in one case and systemic vasculitis in the other.

Complementary laboratory tests

Median CK value was 4746 IU/L (range, 1001–9856 IU/L).

The autoimmunity studies performed to analyse the presence of myositis-specific autoantibodies detected anti-HMGCR antibodies in 13 patients (81.3%), 11 of whom (84.6%) were receiving treatment with statins before symptom onset; in the group of 3 seronegative patients, 2 (66.7%) were also receiving statins. No patient presented anti-SRP antibodies associated with IMNM. The seronegative group included 2 patients with extra-muscular manifestations associated with a systemic autoimmune disease and one patient who presented the typical symptoms of the disease.

Regarding the remaining analytical studies, we should underscore that antinuclear antibodies were positive in 2 cases (12.5%), associated with systemic vasculitis in one

Table 1 Main demographic characteristics, clinical data, and laboratory test results in 16 patients with immune-mediated necrotizing myopathy.

	Total (N = 16)
Age in years, median (range)	71.5 (36–80)
Women, n (%)	9 (56.3)
Previous statin treatment, n (%)	13 (81.3)
Atorvastatin	9
Simvastatin	2
Rosuvastatin	2
Clinical course, n (%)	
Acute (< 4 weeks)	2 (12.5)
Subacute (4 weeks–6 months)	9 (56.3)
Chronic (> 6 months)	5 (31.3)
Clinical symptoms, n (%)	
Proximal muscle weakness	16 (100)
Myalgia	12 (75)
Dysphagia	4 (25)
Neck weakness	4 (25)
Extra-muscular manifestations	2 (12.5)
Proximal muscle weakness pattern	
Symmetrical weakness, n (%)	15 (93.8)
Predominance in the lower limbs, n (%)	16 (100)
Severe weakness (MRC $\leq$ 3/5), n (%)	10 (62.5)
CK levels (IU/L), median (range)	4746 (1001–9856)
Positive anti-HMGCR antibodies, n (%)	13 (81.3)
Previous statin treatment, n (%)	11 (84.6)
Seronegative forms, n (%)	3 (18.7)
Previous statin treatment, n (%)	2 (66.7)

CK: creatine kinase; MRC: Medical Research Council scale.

patient and concomitantly with anti-HMGCR antibodies in the other.

Results of the main laboratory tests are summarised in [Table 1](#), together with the main demographic and clinical characteristics.

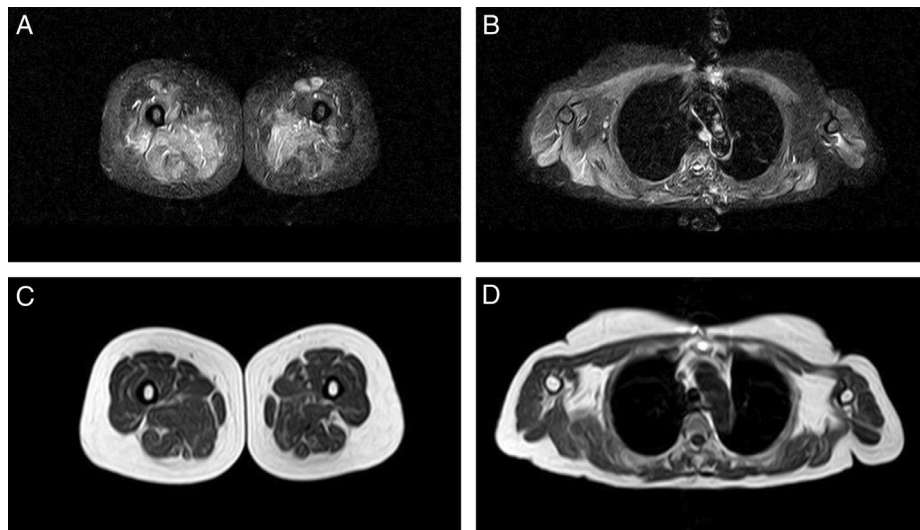


Figure 2 Whole-body muscle MRI study. In the thighs, T2-weighted STIR sequences (A) showed increased signal intensity in the adductor muscles in the medial compartment, vastus lateralis, and rectus femoris in the anterior compartment and biceps femoris in the posterior compartment, more predominantly on the right side. At the shoulder girdle level, increased signal intensity is observed in the periscapular and deltoid muscles, and less markedly in the pectoral muscles, with greater involvement on the right side (B). These changes were not accompanied by fatty replacement in T1-weighted turbo spin echo sequences (C and D).

Neurophysiology studies

An electromyography study revealed myopathic MUPs (short duration, with low amplitude and polyphasia) in proximal muscles in 15 patients (93.8%). This myopathic pattern was accompanied by the presence of spontaneous activity at rest in 12 cases (75%), with recordings showing fibrillations, positive waves, and complex repetitive discharges.

Myotonic discharges were detected in the absence of myotonic symptoms in 3 patients (18.8%); in 2, these discharges were exclusively detected in the vastus lateralis, whereas in the remaining patient, they were diffusely detected in the biceps brachii, gluteus medius, rectus femoris, and iliopsoas.

Muscle magnetic resonance imaging

A whole-body muscle MRI study was only performed in a patient due to diagnostic uncertainty related to an atypical presentation with mild symptoms. STIR sequences displayed increased signal intensity compatible with muscle edema, with no fatty replacement on T1-weighted sequences (Fig. 2). The most affected muscles were the glutei in the pelvic girdle, the adductor muscles in the medial compartment of the thigh, the biceps femoris in the posterior compartment, and the vastus lateralis and intermedius, as well as the rectus femoris in the anterior compartment. Less strikingly, we also observed edema in the periscapular muscles and deltoids.

Muscle biopsy

The anatomical pathology study of 16 patients (100%) of our sample revealed the necrotic and regenerative fibres typical of the disease.

Fibres were accompanied by inflammatory infiltrate in 8 cases (50%); 6 patients (37.5%) presented less prominent lymphocytic inflammatory infiltrates, whereas in 3 cases (18.7%), necrotic fibres were associated with macrophagic infiltrates. HLA-I immunostaining was performed in 14 patients, and yielded positive results in the sarcolemma and cytoplasm of non-necrotic fibres of 9 patients (64.3%).

Fig. 3 shows examples of the main histological characteristics of the patients in our sample.

Therapeutic management and prognosis

Pharmacological treatment was started after diagnosis of IMNM in all patients. The initial approach was based on the use of prednisone at 1 mg/kg. During the first stage of induction treatment, prednisone at 1 mg/kg was the first drug to be used in all cases, with the exception of one patient with multiple comorbidities, including poorly controlled diabetes mellitus and poor previous functional status, who started treatment with azathioprine.

Based on the initial response to prednisone and the severity of clinical symptoms, other drugs were needed during the first 6 weeks after diagnosis: 6 patients required bitherapy (31.3%) and 3 patients (18.8%) required polytherapy with 3 drugs. The treatments most frequently used in combination therapy were intravenous immunoglobulins (IVIG) (in 5 patients) and other immunosuppressants, such as methotrexate (in 5 patients), azathioprine (in 2 patients), and mycophenolate mofetil (in one patient). Plasma exchange was performed in one patient, who received 8 plasmapheresis sessions on alternating days, due to symptom severity and a lack of improvement after starting treatment with prednisone at 1 mg/kg and adding methotrexate. The patient, a 71-year-old man with positive anti-HMGCR antibodies and muscle biopsy results showing a small inflammatory lymphocytic and macrophagic infiltra-

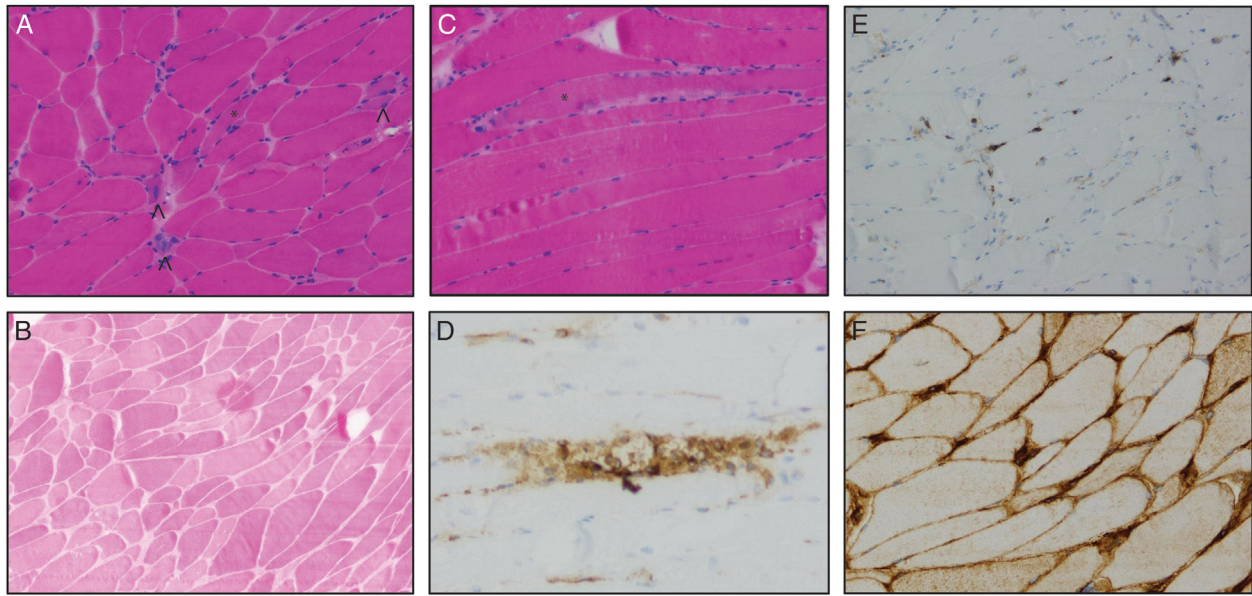


Figure 3 Muscle biopsy. Slices of striated muscle showing moderate variability in fibre size (A) with groups of atrophic angular fibres (asterisks), regenerative fibres (arrowheads), and occasional myophagocytosis (B; asterisks). Haematoxylin and eosin staining. ATPase 42 staining revealed presence of fibres of different types (B). Immunostaining showed positive CD-68 macrophages in the endomysium and inside muscle fibres (D), disperse positive CD-3 lymphocytes (E), and positive HLA-I labelling with deep staining of the membrane and small extension to the sarcoplasm (F).

tion associated with necrotic fibres, in the absence of HLA-1, showed no improvement during plasma exchange nor over the 10 following days. Therefore, IVIG were added, achieving a slow improvement in the following weeks.

The different treatment regimens used as induction treatment are detailed in Fig. 4.

After the induction treatment, 6 months after diagnosis, 13 patients (81.3%) reported subjective clinical improvement, with the median CK value decreasing to 420 IU/L (range: 27–1719 IU/L); 7 patients (43.8%) achieved complete resolution of weakness, 4 (25%) experienced a significant clinical improvement of muscle strength, and symptoms remained unchanged in 2 (12.5%). The degree of weakness was still severe in 3 patients (18.7%).

In the analysis of factors potentially associated with the initial clinical response to treatment, the clinical response was considered good when complete resolution or significant clinical improvement was achieved. Regarding neurophysiological studies, we observed a slightly higher proportion of patients (9 cases; 75%) achieving symptom resolution or significant improvement in the group of patients with spontaneous activity than among those without this activity (2 cases; 50%). Regarding anatomical pathology findings, good responses were more frequently achieved in the HLA-I–positive group (8 patients; 88.9%) than in the HLA-I–negative group (3; 60%); whereas the association with the presence or absence of inflammatory infiltrate was similar, with good responses in 5 patients (62.5%) in the group with inflammatory infiltrates and 6 patients (75%) in the group with no inflammatory infiltrates.

Two of the 3 seronegative patients, the 2 presenting extra-muscular manifestations, presented severe weakness at diagnosis and achieved a good initial response to monotherapy. In the remaining seronegative case,

although the level of weakness was not severe at diagnosis, methotrexate had to be added during the induction treatment, achieving a good clinical response at 6 months.

Maintenance treatment differed according to clinical progression. Patients showing no improvement or insufficient improvement required a more aggressive treatment approach; therefore, at that time, 4 patients (25%) were receiving polytherapy with 3 drugs. In the case of a 36-year-old woman with anti-HMGCR antibodies and no previous treatment with statins, who presented slow progression but no improvement despite treatment with prednisone and methotrexate, treatment with rituximab was started.

The degree of severity, as measured with the modified Rankin Scale at 6 months, amounted to a median of 1 (range, 0–4) (Fig. 5).

During the follow-up period, 2 patients (12.5%) experienced relapses; in the case of the patient treated with rituximab, symptoms did not improve: progression was very slow despite having used several lines of treatment.

Lastly, we detected a case of cancer associated with IMNM in a 73-year-old man with anti-HMGCR antibodies who was diagnosed with liposarcoma and a squamous cell carcinoma of the tongue concomitantly to myositis. The patient underwent surgery for both tumours and received treatment with 3 drugs (prednisone, methotrexate, and IVIG), despite which muscular symptoms did not improve and the patient died 9 months after symptom onset.

Discussion

This retrospective study describes the main characteristics of a cohort of patients diagnosed with IMNM, including clin-

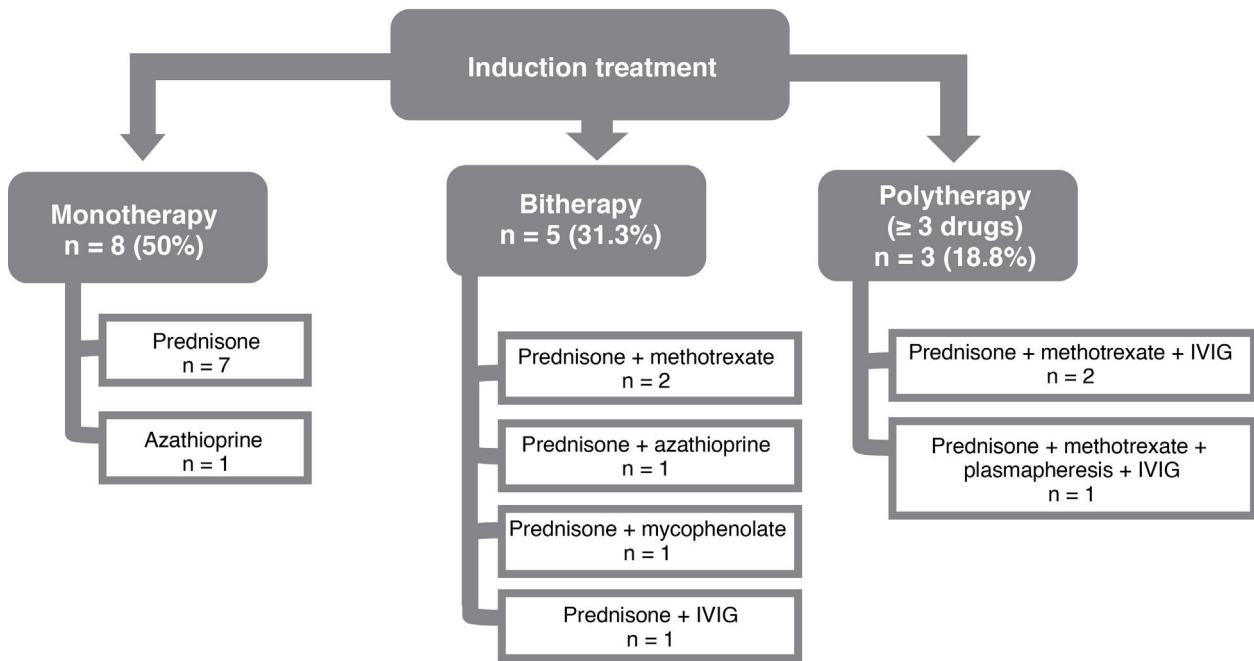


Figure 4 Schematic representation of the induction treatment in 16 patients with immune-mediated necrotizing myopathy. IVIG: intravenous immunoglobulins.

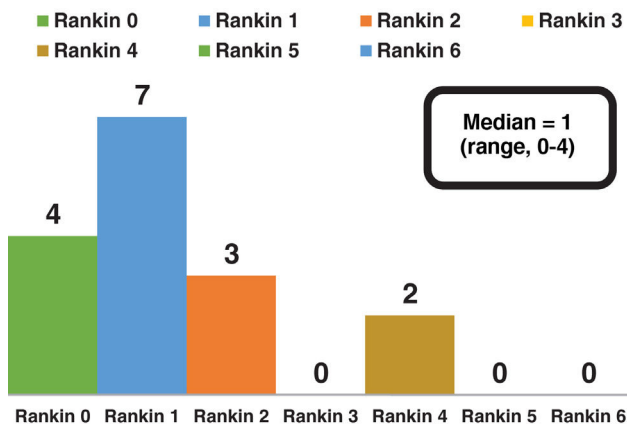


Figure 5 Distribution of modified Rankin Scale scores at 6 months after diagnosis.

ical data, autoantibodies, histological pattern, treatment strategy, and progression, with particular focus on the first 6 months after diagnosis.

The first significant finding of our study is the fact that the diagnosis of IMNM became more frequent over the study period (Fig. 1), which makes this subtype of IIM an emerging disease.

In line with previous reports,^{5,12,13,17–19} the prevalence of the disease was slightly higher among women (56.3%), although the age of onset in our sample (median: 71.5 years) was slightly higher than in other series. A possible reason for this is the high prevalence in this cohort of cases with positive anti-HMGCR antibodies and the absence of patients with anti-SRP antibodies (who are typically younger), and the high prevalence of cases with previous exposure to statins, which are habitually prescribed to older adults.^{5,20}

Regarding clinical data, the most frequent form of presentation was acute-subacute, with proximal and symmetrical limb muscle weakness, and very high CK levels.^{5,18} However, it is worth highlighting a case with positive anti-HMGCR antibodies that progressed slowly, mimicking limb-girdle muscular dystrophy, similarly to other reported cases. This underscores the relevance of requesting anti-HMGCR antibody determination in cases of probable diagnosis of limb-girdle muscular dystrophy in which no genetic cause or family history is identified.^{21,22} Another relevant clinical finding is the fact that, similarly to previous studies, extra-muscular manifestations were infrequent; cases included systemic vasculitis and antiphospholipid syndrome secondary to another autoimmune disease, which supports the association between some types of IMNM and other immune-mediated systemic diseases that may represent a risk factor for the development of IMNM.²³ These patients progressed favourably.

Regarding myositis-associated autoantibodies, noteworthy observations were the absence of cases with anti-SRP antibodies and the high prevalence of forms associated with anti-HMGCR antibodies (81.3%). A possible explanation may be the high number of patients receiving treatment with statins in our setting.^{11,24–27} However, history of treatment with statins in patients with IMNM associated with anti-HMGCR antibodies varies between series; in our sample, history of treatment with statins was also reported in 2 seronegative patients (66.7%), which suggests that other immunogenetic and environmental factors are involved in the pathophysiology of the disease.^{28–30}

Neurophysiological studies showed the typical pattern, with myopathic MUPs and spontaneous activity³¹; the number of patients also presenting electrical myotonia (3; 18.8%) was lower than in other series. One possible explanation may be that we did not analyse the paraspinal muscles, in which

electrical myotonia is frequently detected in patients with IMNM and which in some cases are the only muscles affected. All 3 patients presented anti-HMGCR antibodies and history of exposure to statins; this is consistent with other studies indicating that, although the cause of myotonia is unknown, it may be favoured by previous treatment with statins.³²

In a single case, the study was complemented with a muscle MRI study due to scarce clinical symptoms; this study showed the presence of edema with no fatty replacement. Unlike other cases reported in the literature showing frequent presence of fatty replacement, it may not have been detected in this case as symptoms were mild within the IMNM severity spectrum, and the muscle MRI study was performed early in the course of the disease.³³

Although it has been suggested that a diagnosis of IMNM may be established without a muscle biopsy in patients with positive anti-HMGCR antibodies,^{34,35} in the light of the necessity of this study in seronegative patients and with the aim of preventing delays in treatment onset pending antibody results, biopsy specimens were taken routinely in all patients with clinical suspicion of IMNM.

Given the lack of controlled clinical trials and clinical guidelines, treatment was based on clinical experience and retrospective case series, in accordance with the recommendations of the latest consensus of the ENMC.¹³ As recommended in these guidelines, initial treatment consisted of corticosteroids in all patients, with one exception due to comorbidities. Based on the initial response, if no clinical improvement was achieved, a second or third drug^{5,12,18,20,36} was added; IVIG and methotrexate were the most frequently used options in our sample, indicated in 5 patients each and used in combination in 3. IVIG are recommended as part of the induction treatment for refractory disease, even in monotherapy if corticosteroids are contraindicated. In our series, IVIG were not used in monotherapy in any case, but were used as the second drug if sufficient improvement had not been achieved with corticosteroids, and were considered first after corticosteroids if no improvement was observed in patients with mild weakness, with the aim of achieving an earlier response than with other immunosuppressants.

Such other corticosteroid-sparing drugs as azathioprine, mycophenolate, and ciclosporin have been proposed as possible alternatives, whereas rituximab is considered a therapeutic option for refractory patients with poor response to previous treatments.^{5,12,13,18,20,28,36,37} In our sample, azathioprine was used in 2 cases: in monotherapy in an elderly woman due to its better safety profile, and as a second drug added to corticosteroids in another case, in which IVIG had to be added due to insufficient clinical response. In the case of mycophenolate, it was used in one patient, although it was soon switched to methotrexate due to poor tolerance. The patient showing a slowly progressive course was treated with rituximab due to the lack of response to other drugs, without achieving a significant clinical improvement. Lastly, the use of plasmapheresis has been suggested based on the potential pathogenic role of antibodies, although no clear consensus has been reached on recommending this treatment.^{17,28,38–40} In our series, the

patient with positive anti-HMGCR antibodies under treatment showed no benefit after 8 sessions.

The number of patients obtaining a good clinical response was slightly higher in the subgroup with spontaneous activity in the neurophysiological study than in the subgroup without activity (75% vs 50%) and the subgroup positive for HLA-I in the muscle biopsy (88.9%, vs 60% of HLA-I–negative patients).

At 6 months of follow-up, although more than half of patients achieved complete resolution or a significant symptom improvement, 8 patients still required combination therapy with several drugs. An important finding is the low rate of relapses (12.5%), possibly associated with a better prognosis of HMGCR-antibody–associated forms, which are highly prevalent in this cohort, versus SRP-antibody–associated forms.²⁰

Regarding cancer diagnosis, myositis-associated cancer in IMNM is controversial, and is particularly associated with seronegative forms of the disease.⁴¹ In our sample, on the contrary, the only case of cancer was reported in a patient with HMGCR-antibody–associated IMNM, which would support an increased risk of cancer in patients with forms of the disease associated with these antibodies.^{14,30,42,43}

Our study presents some limitations, as this is a small case series with a retrospective design. Furthermore, no functional scales were systematically applied during patient assessment and follow-up.

Further studies are needed to determine different patterns of progression in the different patient subgroups, which would help make early predictions of clinical response.

Conclusions

IMNM is the last entity within the group of IIMs to be recognised as a different subgroup, whose diagnosis has increased in recent years. In our sample, the only antibodies detected in association with myositis were anti-HMGCR antibodies, mostly in patients with previous treatment with statins. Determination of these autoantibodies and muscle biopsy are key to establishing an early, accurate diagnosis and for starting treatment as soon as possible, which should be customised in accordance to response to corticosteroids. Several drugs have to be combined to achieve a clinical response. The use of other therapies, such as plasmapheresis, is controversial.

Although the majority of patients presented a favourable prognosis at 6 months, and the relapse rate was low, it is important to consider that there are different patient subgroups, and some of these present an atypical clinical course with a poorer response to immunosuppressants. Furthermore, the possibility of a concealed cancer should not be considered exclusively in patients with seronegative forms of the disease.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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