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Clinical features of immune mediated necrotizing myopathy patients in Viet Nam

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ABSTRACT

Introduction and Aims: Immune mediated necrotizing myopathy (IMNM) is a sub-type of inflammatory myopathies (IIM) that presents with significant muscle weakness, elevated creatine kinase (CK) levels and histopathological features of muscle fiber necrosis, with and without myositis specific antibodies. The aims of this study was to clarify clinical characteristics and autoimmune antibodies (Ab) of patients with immune-mediated necrotizing myopathy (IMNM) in Vietnamese patients.

Methods: A retrospective, single centre, case-series, describing the clinical manifestations and laboratory profile, including types of muscle specific antibodies in patients with IMNM.

Results: 12 consecutive patients with IMNM, 2 male and 10 female were studied. All of our patients had symmetric, predominantly proximal muscle weakness. 10 patients (83.3%) had severe weakness (MRC≤3/5) and mRS ≥ 3. 8 patients (66.7%) had elevated CK levels of more than 1000UI/L. 33.3% had anti- SRP (signal recognition particle) Ab and 25% had anti- HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) Ab. The proportion of patients with muscle atrophy, neck weakness, dysphagia and dyspnea between anti-SRP and anti-HMGCR groups did not differ significantly (p> 0.05). Severe muscle atrophy was seen in 1 seronegative patient (25%) and 6 seropositive patients (87.5%), p<0.05. No evidence of an underlying malignancy was found in any patient. Half the patients with anti-SRP Ab (n=2) and 66.7% of those with anti-HMGCR Ab (n=2) had severe weakness, with mRS scores 3–5 (p>0.05) even after treatment. 100% (n=4) of seronegative IMNM and 37.5% (n=3) of seropositive IMNM had significant improvement, with mRS scores 1-2 (p<0.05) after treatment.

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Discussions: Immune-mediated necrotizing myopathy in our series, is associated with SRP Ab in one third and HMGCR Ab in one quarter of patients. We did not find significant difference between these two groups with regards to clinical features, risk of malignancy and lung involvement and response to immunotherapy. Muscle atrophy was more common in seropositive patients and they appeared to respond less well compared to the 4 seronegative patients to immunotherapy.

Key words: idiopathic inflammatory myopathy, immune mediated necrotizing myopathy, serum autoantibodies, anti-SRP antibodies, anti-HMGCR antibodies.

I. INTRODUCTION

Immune mediated necrotizing myopathy (IMNM) is characterized by acute or subacute progressive proximal muscle weakness, raised creatine kinase (CK) level, and histopathological features of muscle fiber necrosis, with or without inflammatory cell infiltrates[1]. IMNM can be broadly defined based on the presence of serum autoantibodies, namely against anti-signal recognition particle, 3-hydroxy-3-methylglutaryl-coenzyme A reductase and seronegative.[2,3] The purpose of this study was to clarify clinical characteristics and laboratory features, including antibodies profile of patients with IMNM in Vietnamese patients.

II. METHODS

2.1. Study design

A retrospective single centre, case – series of consecutive patients with immune-mediated necrotizing myopathy over a period of 36 months.

2.2. Case definition

We used the criteria of Bohan and Peter[4] to screen the cases of myositis and IMNM was defined using the criteria delineated by the 2017 European League Against Rheumatism/ American College of Rheumatology Classification Criteria[5] and consensus derived at the Clinico-sero-pathological classification of IMNM in 224th European Neuromuscular Center (ENMC) International Workshop[3].

The diagnosis of IMNM was confirmed by a combination of electrodiagnosis (EDX), antibody testing, muscle biopsy, and imaging. The clinical deficits and disability were measured using Medical Research Council (MRC) Scale sum score[6] and Modified Rankin Scale (mRS).

The histopathological results of biopsy samples were evaluated by two experts and discussion with physician in charge of patient. Magnetic resonance imaging (MRI) with T1, T2 and STIR sequences for muscles in pelvic, thigh and upper calf areas were evaluated by two radiologists.

2.3. The autoimmune antibody (ab) tests

The panel of 18 autoantibodies to autoimmune myopathies (including Mi-2a, Mi-2b, TIF1g, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro52, cN-1A, HMGCR) were detected by immunoblot assays at the Center for Molecular Biomedicine of Ho Chi Minh City Medicine and Pharmacy University.

III. RESULTS

12 consecutive patients with IMNM, 2 males and 10 females were studied. The age at disease onset ranged 7 to 68 years (median: 46, mean: 42.9) and at diagnosis, 8 to 70 years (median:46, mean:42). The duration from symptom onset to diagnosis was 4 to 18 months (median: 11, mean:10.5).

3.1. Clinical and laboratory characteristics of the patients with IMNM

Patient	Age	Time to diagnosis (month)	MRC ≤3/5	mRS	CK (U/L)	Abs	Therapy	**Refractory
1	70	18	+	5	1600	TIF1g,Ro	Steroid, AZT	+
2	67	14	+	5	834	SRP	Steroid, MTX	+
3	58	6	+	4	2166	SRP,Ro,PM/Scl	Steroid, MPM, MTX	+
4	58	10	+	3	4154	SRP	Steroid, MTX, AZT	+
5	52	12	-	2	752	-	Steroid, MTX	-
6	49	4	-	2	11965	-	Steroid, MTX	-
7	43	6	+	4	14332	-	Steroid, MTX, AZT	-
8	43	4	+	4	2779	SRP, Ro	Steroid, AZT	+
9	30	12	+	3	2517	-	Steroid, MTX	-
10	23	15	+	4	407	HMGCR	Steroid, MPM, MTX	+
11	14	18	+	4	132	HMGCR	Steroid, AZT	+
12	8	7	+	4	2345	HMGCR,Ro,Jo1	Steroid, Tofacitinib	-

**Refractory: poor response to treatment after 6 months of steroid and immunosuppressants. MTX: Methotrexate, AZT: azathioprine, MPM: mycophenolate mofetil

All of our patients had symmetric and predominantly proximal muscle weakness, 83.3% (10) had severe weakness, MRC≤3/5 and mRS ≥ 3. Two had mRS = 2 at admission. Muscle atrophy was found in 8 (66.7%). One patient, with anti HMGCR Ab, had an erythematous skin rashes on the abdomen of uncertain etiology. No specific signs of dermatomyositis eg heliotrope, V-sign, shawl sign, Gottron's papules and Gottron's signs were found. None had cardiopulmonary complications.

The serum creatine kinase (CK) level was elevated more than 1000 UI/l in 8 patients (66.7%). All patients had normal NCS, but myopathic patterns in EMG. All patients had normal chest, abdominal findings on chest X-ray, chest-abdominal CT scan and/or ultrasound, and negative tumor markers.

Anti-SRP Ab were found in 4 patients (33.3%) and anti- HMGCR Ab in 3 patients (25%). 1 patient had anti TIF1g and anti Ro antibodies. These eight cases were grouped into the seropositive group.

Three in the anti-SRP group (75%), 2 in the anti-HMGCR group (66.7%) had severe muscle atrophy, p>0.05. Six (75%) in the seropositive group had severe muscle atrophy (p<0.05). Severe muscle weakness (MRC≤3/5) was found in 4 patients with anti SRP (100%) and 3 patients with anti HMGCR (100%). Two seronegative patients had severe muscle weakness (p>0.05).

Three anti-SRP Ab patients (75%) and 1 anti-HMGCR Ab patient (33.3%), and 5 seronegative patients had significant neck weakness (p>0.05). Among 3 patients with dysphagia, 1 had anti TIF1g and anti Ro antibodies and 2 had anti-SRP Ab (50%). None of anti HMGCR Ab patients and seronegative patients had dysphagia (p>0.05). Only 1 anti-SRP ab patient (25%) had dyspnea (p>0.05).

Ten patients were ordered muscle MRI and

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there were 7 patients (70%) with the presence of muscle atrophy, 5 patients (50%) with the presence of fat infiltration and 5 patients (50%) with the presence of muscle edema.

In muscle biopsy, necrosis and regeneration of muscle fibers and inflammatory cell infiltration were seen in 83.3% and 66.7%, respectively. Increased expression of MHC class I on sarcolemma of muscle fibers was observed in 90.9%, deposition of MAC on sarcolemma of muscle fibers was seen in 81.8% and infiltration of $CD4^+$ T cells was seen in 66.7%. Two patient has neither significant necrosis or inflammatory infiltrates. One was a patient with anti SRP ab and with raised CK, suggesting that the absence of necrosis in the sections studied was likely a sampling error. The sarcolemma was, however positive for MHC class 1 antigen. Another patient with anti HMGCR ab had no necrosis or inflammation, normal creatine kinase and MHC class I antigen staining was not increased, highlighting the additional diagnostic value of antibody.

All of 12 patients were treated with steroid and immunosuppressants therapy, including azathioprine, methotrexate, mycophenolate mofetil. Seven patients did not respond to the combination of steroid and immunosuppressant therapy and experienced a reduction less than 2 points in mRS after 6 months. Of these cases, five were treated with Rituximab and one with IVIG. After 6 months with treatment, two patients of anti-SRP group (50%) and two patients of anti-HMGCR group (66.7%) still had significant weakness and functional deficits with mRS scores 3–5 ($p>0.05$). Overall, all four of seronegative patients and 37.5% (n=3) of seropositive, including 2 SRP (50% of SRP group) and 1 HMGCR (33.3% of HMGCR group), had significant improvement, with mRS scores 1-2 ($p<0.05$), after 6 months of immunosuppressive treatment.

IV. DISCUSSION

We report a case- series of 12 patients with IMNM from a single centre in Viet Nam. Our study shows that characteristic clinical features of IMNM include severe weakness (83.3%) and severe muscle atrophy (66.7%). Most of the patients in our study had significantly elevated CK levels (66.7%). These features were similar to the data reported by Suzuki et al[7] and Tiniakou et al.[8] The number of patients who were negative for MSAs was 33.3%, similar to that reported by Yang et al[9] (32.7%). The proportions of patients with anti- SRP Ab and anti- HMGCR Ab in our study were 33.3% and 25%, similar to the 39% and 26%, respectively, by Watanabe et al.[10] We did not find increased risk of malignancy and lung involvement in the 12 patients.

In Watanabe's study[10], the average age of anti HMGCR group was 56.4±18.8,while in our study, all patients with anti HMGCR were younger, including 23, 14 and 8 years. Patients with anti- HMGCR antibodies had less severe illness compared to those with anti- SRP antibodies in Watanabe's study. However, in our study, the occurrence of severe symptoms such as neck muscle weakness, dysphagia, respiratory insufficiency, severe muscle weakness and severe muscle atrophy were not significantly different between the two groups. The explanation for this difference may be that younger anti HMGCR patients had more severe disease than older patients, which was also reported by Tiniakou et al[8]. Like Watanabe' et al[10], outcomes between the two groups were similar.

The proportion of neck muscle weakness, dysphagia, dyspnea, severe muscle weakness in seronegative and seropositive groups was not

significantly different and response to treatment of seronegative patients was significantly better than seropositive patients. This was similar to the report by Xu et al[11], however, unlike their study we found a difference in severe muscle atrophy between the two groups ($p<0.05$).

Conclusions: Most patients with IMNM had significant muscle weakness and remarkably elevated muscle enzymes level. The difference in the occurence of the severe symptoms between anti SRP and anti HMGCR groups is not significant. Seronegative patients and 50% of SRP ab patient and 33.3 % of HMGCR ab patient responded well to treatment. Our study is, limited by the small number of patients. We are continuing to prospectively recruit and study more patients so as to better under IMNM in our region.

REFERENCES

1. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Immune-mediated necrotizing myopathy. *Curr Rheumatol Rep.* 2018;20(4):21 PubMed PMID: 29582188; PubMed Central PMCID: PMCPMC6019613. doi:10.1007/s11926-018-0732-6.
2. Schmidt J. J. Current classification and management of inflammatory myopathies. *Neuromuscul Dis.* 2018;5:109–129.
3. Allenbach Y, Mammen AL, Benveniste O, Stenzel W. 224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. Immune-Mediated Necrotizing Myopathies Working Group. *Neuromuscul Disord.* 2018 Jan; 28(1):87-99.
4. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med.* 1975 Feb 13;292(7):344-7.
5. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis.* 2017 Dec;76(12):1955-1964.
6. Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve*. 1991 Nov;14(11):1103-9. doi: 10.1002/mus.880141111. PMID: 1745285.
7. Suzuki S, Nishikawa A, Kuwana M, et al. Inflammatory myopathy with anti-signal recognition particle antibodies: case series of 100 patients. *Orphanet J Rare Dis.* 2015; 10:61.
8. Tiniakou E, Pinal-Fernandez I, Lloyd TE, et al. More severe disease and slower recovery in younger patients with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. *Rheumatology (Oxford)*. 2017 May 1;56(5):787-794.
9. Yang H, Tian X, Zhang L, Li W, Liu Q, Jiang W, Peng Q, Wang G, Lu X. Clinical and pathological features of immune-mediated necrotising myopathies in a single-centre muscle biopsy cohort. *BMC Musculoskelet Disord*. 2022 May 6;23(1):425.doi: 10.1186/s12891-022-05372-z.
10. Watanabe Y, Uruha A, Suzuki S,et al. Clinical features and prognosis in anti - SRP and anti- HMGCR necrotising myopathy Journal of Neurology. *Neurosurgery & Psychiatry* 2016;87: 1038-1044.
11. Ma X, Xu L, Ji S, Li Y, Bu B. The Clinicopathological Distinction Between Seropositive and Seronegative Immune-Mediated Necrotizing Myopathy in China. *Front Neurol*. 2021 Jul 5;12:670784. doi: 10.3389/fneur.2021.670784. PMID: 34290662; PMCID: PMC8287052.