Investigating idiopathic inflammatory myopathy; initial cross speciality experience with use of the extended myositis antibody panel

Antoinette O'Connor,[1] Jennifer Mulhall,[1] Sinead M.J. Harney,[2] John G. Ryan,[2] Grainne Murphy,[2] Michael T. Henry,[3] Peter Annis,[4] Vincent Tormey,[5] Aisling M. Ryan[1]

[1]Department of Neurology, Cork University Hospital, Cork; [2]Department of Rheumatology, Cork University Hospital, Cork; [3]Department of Respiratory Medicine, Cork University Hospital, Cork; [4]Department of Immunology, Cork University Hospital, Cork; [5]Department of Immunology, University Hospital, Galway, Ireland

Abstract

The discovery of unique autoantibodies has informed and altered our approach to the diagnosis and management of the inflammatory myopathies. This study reports the initial clinical experience of use of the Extended Myositis Antibody (EMA) panel in the largest university teaching hospital in Ireland. We conducted a retrospective review of all patients who had serum samples tested for myositis specific antibodies and myositis associated antibodies from April 2014 to March 2015. A positive EMA panel was of significant clinical utility in facilitating decisions on appropriate investigations, and need for onward referral to other physicians. Furthermore, this paper highlights the diversity of possible presentations of idiopathic inflammatory myopathy with subsequent need for multi-speciality involvement, and serves to heighten awareness among clinicians of the diagnostic use of extended myositis antibody testing in these cases.

Introduction

A subset of patients with myositis have unique autoantibodies.[1] This has informed and altered our approach to the diagnosis and management of the inflammatory myopathies.[2] The identification of myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA) is important because they are associated with specific clinical phenotypes, and may guide the physician in terms of treatment planning.[3] Myositis can have a diverse presentation. This study reports the experience and clinical utility of the Extended Myositis Antibody (EMA) panel across a range of specialties in a large teaching hospital.

Materials and Methods

Cork University Hospital (CUH) is the largest university teaching hospital in Ireland, and is a multi-specialty tertiary referral centre serving a population of 1.1 million. We conducted a retrospective review of the electronic and paper records of all patients who had serum samples tested for MSA and MAA from April 2014 -Mar 2015. *Euroline Autoimmune Inflammatory Myopathies immunoblot* was performed at University Hospital Galway. This assay uses membrane strip antigen testing to detect anti-: Mi2, TIF1 gamma, MDA3, NXP2, SAE1, Ku, PM- SCL 100, PM-SCL 75, OJ, EJ, Jo-1, PL-7, PL-12, Scl 70, centromere A, centromere B, RNA Pol III, Fibrillarin, Nor 90, Th/To, Ku, PDGFR and Ro-52. Demographic details, clinical presentation and requesting department were recorded. The use of additional investigations (electromyography, MRI, muscle biopsy, CT Thorax) and laboratory results, including creatine kinase and autoantibody profile, were documented.

We reviewed the utility of the assay in clarifying diagnosis, directing the investigative pathway and selecting the appropriate treatment.

Results

Twenty two patients (mean age: 55, SD:15) had an EMA panel sent during the study period. Thirteen (59%) were female. Referring departments across the hospital included respiratory medicine (n=8, 36%), rheumatology (n=5, 23%), neurology (n=4, 18%), and other (n=5, 23%). The assay cost €26.41 per sample analysed.

Clinical features at the time of presentation are displayed in Table 1. Additional investigations performed depended on the clinical picture but included cardiac or musculoskeletal MRI (n=8, 36%), CT Thorax (n=14,64 %), muscle biopsy (n=7, 32%) and EMG (n=6, 27%). Ten (45%) had other positive autoantibodies. These autoantibodies were ANA (n= 10, 45%), ENA (n=4, 18%), anti-Ro (n=3, 14%), anti-LA (n=1, 5%), anti-dsDNA (n=1, 5%) and p- ANCA (n=1, 5%). Of the 17 patients who had a CK recorded, six (27%) were elevated.

Correspondence: Antoinette O' Connor, Department of Neurology, Cork University Hospital, Wilton, Cork, Ireland.
Tel.: +353860876322 - Fax: +3534922667.
E-mail: antoinetteoconnor.aoc@gmail.com

Key words: Idiopathic inflammatory myopathy; myositis specific autoantibodies; myositis-associated autoantibodies.

Author contributions: AOC, collection of data, drafting the work and revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved; JM, data acquisition, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved; SMJH, JGR, GM, MTH, PA, VT, AMR, drafting the work and revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

Conference presentations: Platform: UK Neuromuscular Translational Research Meeting 2015. Poster: American Academy of Neurology Annual Meeting 2016.

Received for publication: 23 October 2016.
Accepted for publication: 6 February 2017.

Licensee PAGEPress, Italy
Clinics and Practice 2017; 7:922
doi:10.4081/cp.2017.922

A positive EMA panel was identified in six (27%). Investigations and outcomes of patients with a positive EMA panel are shown in Table 2.

A positive panel influenced the diagnostic and treatment pathway of all six patients.

Patient 3 was a 35-year-old woman who presented in acute heart failure, NYHA II. She had an elevated troponin (600s) and CK (1787), yet had a normal cardiac MRI and transthoracic echocardiogram. EMA panel was positive for Anti PM-Scl 75 and Anti PM-Scl 100 antibodies, providing evidence that her cardiac failure was secondary to an autoimmune process. Her antibody profile resulted in first line treatment with rituximab, avoiding use of cyclophosphamide in

a young woman who intended to start a family. One-month post rituximab infusion her dyspnoea had resolved and both her CK and troponin levels had normalised.

Patient 4 presented with a parietal stroke, and had a CK of 1539 on admission. Muscle biopsy was non-specific. CT cerebral angiogram did not show evidence of a segmental vasculopathy. EMA panel was positive for anti-pl7, resulting in a diagnosis of anti-synthetase syndrome. Consequently, CT Thorax and pulmonary function tests were performed, as well as onward referral to a respiratory physician.

Patient 5 presented with progressive dyspnoea, arthralgia and weakness. She had a normal CK (145). CT Thorax and lung biopsy were non-diagnostic. EMA panel was positive for anti-pl 12, precluding the need for muscle biopsy. Treatment with a combination of rituximab and steroids has halted the progression of her dyspnoea, and has lead to a resolution of her weakness.

Patient 6 tested positive for anti-TIF1 gamma, and as a result has an annual CT-Thorax Abdomen and Pelvis screening for an occult malignancy.

Table 1. Clinical features at the time of presentation.

Clinical features	Present no. (%)
Dyspnoea	12 (55%)
Weakness	11 (50%)
Myalgia	11 (50%)
Skin changes	8 (36%)
Arthralgia	7 (32%)
Dysphagia	4 (18%)
Raynauds	2 (9%)
Weight loss	2(9%)
Pyrexia of unknown origin	1 (5%)

All six patients received immunosuppression following EMA results. Two were treated with steroids alone, three received steroids in combination with rituximab, and one received steroids followed by azathioprine and then mycophenylate mofetil. All six patients had documented subjective improvement in symptoms on receiving immunosuppression.

Discussion and Conclusions

EMA panel is entering standard clinical practice but is not yet a routine tool in the investigation of Idiopathic Inflammatory Myopathy (IIM) in all centres.[3] Diagnosis of autoimmune myopathy was previously dependent on muscle biopsy, EMG and radiological investigations. With the advent of the EMA panel, these tests may no longer be mandatory.[4] Use of the panel avoided an invasive procedure (muscle biopsy) in two patients. Antibodies are detectable early in the disease course, and are specific for autoimmune myopathy.[3] The EMA panel was diagnostic in 27% of patients, when traditional testing had not been definitive.

A positive EMA panel is of significant clinical utility in facilitating decisions on appropriate investigations.[5] Patient 6 in our study has entered a cancer surveillance programme after testing positive for anti-TIF1 gamma; an antibody associated with a significantly increased risk of malignancy.[3] In anti-synthetase syndrome pulmonary involvement is the major determinant of patient prognosis.[4] Patients 4 and 5 in our study had dyspnoea on presentation, and features of ILD on imaging. All patients diagnosed with anti-synthetase syndrome should have a high resolution CT Thorax and pulmonary function tests performed.[6] Onward referral to a respiratory physician, as was the case for patients 4 and 5 in our study, should be considered.

Autoimmune myopathies are important to identify as they often respond to immunosuppression.[7] In our study all patients with a positive EMA panel (n=6, 27%) experienced symptomatic improvement on receiving immunosuppressants. A positive panel in patient 3 provided evidence for use of rituximab, as opposed to cyclophosphamide. This resulted in preservation of fertility, in addition to a clinical improvement.[8]

In addition to myositis, a constellation of clinical features have been described in inflammatory myopathies, including dyspnoea, Raynaud's phenomenon, polyarthritis, fever and weight loss.[5] Four of our six positive cases had feature of ILD on imaging. ILD may precede the occurrence of overt myositis in up to 20% of cases, and is estimated to result in an excess mortality of up to 50%.[6] The multisystem nature of autoimmune myopathy means patients need collaborative input from different medical specialities. EMA panels were performed by respiratory physicians, rheumatologists and neurologists in our study. Ongoing involvement of these physicians is particularly important; all of whom need to be familiar with the diverse clinical presentation of IIM.

This study illustrates the value of the EMA panel in defining a heterogeneous patient population into clinicoserological phenotypes, thus guiding treatment pathways. Furthermore, it highlights the diversity of these presentations, the need for multispeciality input and serves to heighten awareness among clinicians of the diagnos-

Table 2 Investigations, treatments and outcomes of patients with a positive EMA panel.

	Ab	CK*	Other Ab	MRI	Muscle biopsy	EMG	CT Thx	Immunosuppressed Improvement	Symptom
1	RNA Pol III, Ro 52	390	Yes: ANA	MSK: Fatty Infiltrate	Non Specific	Myopathic	NP	Yes (steroid, Azathioprine, MMF)	Yes, improved muscle strength
2	Anti-Mi2 Beta	72	No	MSK: Normal	Normal	Myopathic	NP	Yes (steroid)	Yes, improved muscle strength
3	Anti PM-Scl 75, Anti PM-Scl 100	1787	Yes ANA	Cardiac: Normal	NP	NP	Yes, ILD	Yes (steroid, rituximab)	Yes, dyspnoea improved
4	Anti Pl7	1539	Yes: ANA, Ro	NP	Necrotising vs. immune mediated	NP	Yes, ILD	Yes (steroid)	Yes, muscle strength and dyspnoea improved
5	Anti Pl 12	145	Yes: ANA, dsDNA	NP	NP	NP	Yes, ILD	Yes (steroid, rituximab)	Yes, dyspnoea improved
6	Anti TIF1 gamma	141	No	MSK: Atrophy	Inflammatory myopathy	Myopathic	Yes, ILD present	Yes (steroid, rituximab)	Yes, improved muscle strength

Ab, antibody; MRI, magentic resonance imaging; either cardiac or musculoskeletal (MSK); Thx, thorax; NP, not performed; ILD, interstitial lung disease. *CK, measure in mmol/l, normal range 40-180.

tic use of extended myositis antibody testing in these cases.

References

1. Hengstman GJD, Van Engelen BGM, Vree Egberts WTM, et al. Myositis specific autoantibodies: overview and recent developments. Curr Opin Rheumatol 2001;13:476-8.
2. Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology 2009;48:607-12.
3. Ghirdello A, Bassi N, Palna L, et al. Autoantibodies in polymyositis and dermatomyositis. Curr Rheumatol Rep 2013;15:335.
4. Jouneau S, Hervier B, Jutant EM, et al. Pulmonary manifestations of antisynthetase syndrome. Rev Mal Respir 2015;32:618-28.
5. Hervier B, Benveniste O. Clinical phenotypes and prognosis of antisynthetase syndrome. Rev Med Intern 2014;35: 453-608.
6. Lega JC, Reynaud Q, Belot A, et al. Idiopathic inflammatory myopathies and the lung. Eur Respir Rev 2015;24: 545.
7. Tansley S, Gunawardena H. The evolving spectrum of polymyositis and dermatomyositis - moving towards clinicoserological syndromes: a critical review. Clin Rev Allergy Immunol 2014;47: 264-73.
8. Muñoz-Beamud F, Isenberg DA. Rituximab as an effective alternative therapy in refractory idiopathic inflammatory myopathies. Clin Exp Rheumatol 2013;31:896-903.