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

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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 MSA and MAA from April 2014 -March 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-50. 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.

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-50. 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.

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

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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-pl12, 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.**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Present no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>12 (55%)</td>
</tr>
<tr>
<td>Weakness</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Skin changes</td>
<td>8 (36%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Raynauds</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Pyrexia of unknown origin</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

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 program 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, polyarthritides, 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 specialties. 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-
tic use of extended myositis antibody testing in these cases.

References