

New Autoantibodies in Inflammatory Myopathies: Diagnostic Value and Relationship with Clinical Phenotypes

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Classification of idiopathic inflammatory myopathies (i.e., myositis) has always been difficult. In their seminal work on polymyositis and dermatomyositis in 1975, Bohan and Peter [1] were the first to establish a rational classification. Although still useful today, it has some limitations. Certain inflammatory myopathies, such as the recently described inclusion body myositis, are not included, and dystrophies such as dysferlinopathy might be misdiagnosed as polymyositis using these criteria. In 1991, Dalakas [2] proposed a new classification that focuses on pathological criteria and enables classification of patients with dermatomyositis, polymyositis, or inclusion body myositis. The main limitation of this system is that polymyositis, which is now considered a diagnosis of exclusion [3], is likely to be over-diagnosed. In fact, some authors suggest it may be as rare as unicorns, dragons and other mythological beasts [4,5].

Love et al. [6], also in the 1990s, reported that the presence of specific autoantibodies (anti-Mi2, anti-Jo1, anti-SRP) or associated autoantibodies (e.g., anti-Ro60/52, anti-La, anti-RNP, anti-PM/Scl) could be of help for subclassifying myositis, with each antibody being ascribed to a characteristic clinical phenotype. Such is the case of antisynthetase syndrome, characterized by the presence of myositis,

arthritis, fever, Raynaud's phenomenon, and interstitial lung disease, associated with anti-Jo1 antibodies.

Since Love's publication and particularly in the last 5 years, several new autoantibodies have been described and related to specific clinical phenotypes, and this has often implied the use of specific diagnostic or therapeutic approaches. For example, anti-TIF1 γ (formerly known as *anti-p155* based on its molecular weight on protein immunoprecipitation analysis), has proved to be a good marker of cancer-associated myositis [7,8]. Anti-MDA5 antibodies, which are strongly associated with rapidly progressive interstitial lung disease in patients with clinical amyopathic dermatomyositis [9], and the recently described autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme reductase (anti-HMGCR), which identify a subset of patients with statin-related myopathy and histological findings of immune mediated necrotizing myopathy [10], are other examples of the utility of these myositis-specific or -associated antibodies in diagnosing and classifying the various myositis groups.

The last member of the network is the recently described anticortactin antibody [11-13]. At present, anticortactin seems to be only a myositis-associated autoantibody, but a specific related phenotype may emerge as additional myositis cohorts are analyzed. According to recently published data [11, 12], anticortactin antibody can be used as a marker only of autoimmune myositis, which is important because other myopathies such as dystrophies or metabolic muscle diseases can mimic true autoimmune polymyositis. Nonetheless, cortactin is a ubiquitous protein that plays several roles in our organism.

It acts in the assembly of actin filament in muscle as well as in adhesion and migration of non-muscle cells, particularly neoplastic cells. Furthermore, cortactin seems to be implicated in tumor cell motility and metastasis, and it has been recognized for its association with cancer progression [14]. Therefore, anticortactin antibodies could also be relevant in patients with cancer-associated myositis.

As often occurs in science, the discovery of this autoantibody was a matter of chance, a serendipitous phenomenon. Researchers found an unexpected band on blot studies performed to confirm the results of enzyme-linked immunosorbent assay (ELISA)-positive anti-MDA5 and anti-HMGCR antibodies. On further analysis by mass spectrometry, the band was found to be cortactin. In parallel, other researchers found the same autoantibody in seronegative myasthenia gravis patients. The next logical step would be to investigate whether these antibodies are directed against the same or different epitopes of the molecule in myositis and myasthenia gravis patients, and to identify them.

Considering the emerging data, it seems that the diagnosis and classification of myositis will rely not only on clinical grounds and muscle pathology but also on the presence of myositis-specific and associated autoantibodies [15]. As occurred with anticortactin antibodies, identification of new autoantibodies will further help clinicians in the task of diagnosing and treating patients with inflammatory myopathy.

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