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Review

Idiopathic inflammatory myopathies and the anti-synthetase syndrome: A comprehensive review

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ABSTRACT

Autoantibodies are a hallmark in the diagnosis of many systemic autoimmune rheumatic diseases (SARD) including idiopathic inflammatory myopathies (IIM). Based on their specificity, autoantibodies in IIM are grouped into myositis specific (MSA) and myositis associated autoantibodies (MAA). Among the MSA, autoantibodies against aminoacyl-tRNA synthetases (ARS) represent the most common antibodies and can be detected in 25–35% of patients. The presence of ARS and other autoantibodies has become a key feature for classification and diagnosis of IIM and is increasingly used to define clinically distinguishable IIM subsets. For example, anti-ARS autoantibodies are the key features of what has become known as anti-synthetase syndrome (aSS), characterized by multiple organ involvement, primarily interstitial lung disease, often accompanied by myositis, non-erosive arthritis, Raynaud's phenomenon, fever, and "mechanic's hands". Autoantibodies directed to eight different ARS have been described: Jo-1 (histidyl), PL-7 (threonyl), PL-12 (alanyl), OJ (isoleucyl), EJ (glycyl), KS (asparaginyl), Zo (phenylalanyl) and Ha (tyrosyl). Each anti-ARS antibody seems to define a distinctive clinical phenotype. Although several research methods and commercial tests are available, routine testing for anti-ARS autoantibodies (other than anti-Jo-1/histidyl-tRNA synthetase) is not widely available, sometimes leading to delays in diagnosis and poor disease outcomes.

Contents

1. Introduction

Autoantibodies are a hallmark in the diagnosis of many systemic autoimmune rheumatic diseases (SARD) including idiopathic inflammatory myopathies (IIM) [1,2]. These autoantibodies are typically directed to intracellular proteins, including nuclear and cytoplasmic antigens, and based on their specificity, autoantibodies in IIM can be grouped into myositis specific (MSA) and myositis associated autoantibodies (MAA) [3,4]. The presence of MSA and MAA has become a key feature for classification and diagnosis of IIM and is increasingly used to define clinically distinguishable IIM subsets. Among the MSA, autoantibodies against aminoacyl-tRNA

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synthetases (ARS) were detected in 25–35% of IIM patients [5]. Other autoantibodies in IIM are directed to the signal recognition particle (SRP), 3-hydroxy-3-methylglutaryl coenzyme (HMGCR), chromodomain helicase DNA binding protein 4 (Mi-2), SAE/small ubiquitin-related modifier (SUMO-1), MJ/nuclear matrix protein 2 (NXP2), melanoma differentiation-associated gene 5 (MDA5)/clinically amyopathic dermatomyositis p140 (CADM-140), and transcription intermediary factor (TIF)1-gamma (p155/140) [1,2]. The nomenclature of anti-ARS, like many other autoantibodies, is primarily based on the initials or the name of the index patient [6]. Anti-Jo-1 antibody is the most common, predominantly found in 15–30% of patients with polymyositis (PM) and in 60–70% of those with interstitial lung disease (ILD) [6]. Autoantibodies directed towards other ARS are less common, each reaching less than 5% prevalence in IIM. This chapter on the clinical and serological aspects of IIM is focused on ARS, including the biochemical properties and the current detection methods.

2. Clinical aspects of the anti-synthetase syndrome

Earlier studies only found anti-ARS autoantibodies in patients with IIM, but not in other SARD, and it was concluded that anti-ARS autoantibodies are myositis specific. Later on, it became evident that anti-ARS autoantibodies characterize their own clinical IIM phenotype that has become known as the anti-synthetase syndrome (aSS) and can sometimes occur as an overlap syndrome with other autoimmune diseases. Histological studies suggested that the aSS is a separate disease entity within the spectrum of IIM (reviewed in [4]). Myopathological changes in the aSS including perimysial connective tissue fragmentation and inflammation and muscle fiber pathology in neighboring perifascicular regions have been documented.

Anti-ARS autoantibodies are the hallmarks of the aSS, which is characterized by multiple organ involvement, primarily ILD, and is often accompanied by myositis, non-erosive arthritis, Raynaud's phenomenon, “mechanic's hands”, skin rashes, sicca syndrome and constitutional symptoms, such as fever. Besides the clear nosographic classification, diagnosis and management of aSS are still challenging due to often masked and/or non-specific symptoms at the disease onset [7]. Each anti-ARS seems to be associated with heterogeneous disease expression and severity [8], in which lung and joint involvement could be prominent at early disease stages. Disease progression and prognosis are predominantly affected by lung involvement and myositis may remain on a subclinical level in a significant number of patients in the non-Jo-1 groups [4]. In idiopathic interstitial pneumonias, anti-ARS autoantibodies have been reported in about 7% of patients, thus contributing to the definition of “idiopathic” ILD. Whether such autoantibodies could also have a predictive value for immune mediated ILD it has to be further elucidated [9]. The vast majority of anti-ARS patients have ILD, whereas it is estimated that one- to two-thirds of patients with myositis and ILD are positive for any anti-ARS antibody. Anti-ARS autoantibodies are rarer in dermatomyositis (DM) and juvenile PM, DM and in other SARD [4]. Anti-ARS can also be associated with necrotizing myopathy (anti-PL-12 autoantibodies) or pericarditis (anti-PL-7 autoantibodies) [10,11]. Recently studies have indicated that patients with anti-ARS autoantibodies other than those directed to Jo-1 have a different clinical outcome [8,12–14]. Patients with anti-PL-7 and anti-PL-12 autoantibodies frequently have ILD [15], gastrointestinal manifestations and less frequently have myositis compared to anti-Jo-1 positive patients [16]. It has been speculated that this might be attributed to the delayed detection due to lack of routine testing for those autoantibodies [4]. Recently, the importance of making a diagnosis based on anti-ARS serology has been illustrated by a comprehensive case report describing a 21-year-old man with fever, arthralgia and pulmonary infiltrates [17]. Since another recent case report of two anti-OJ positive patients did not confirm the poor prognosis of these patients [18], future studies are needed to verify these observations.

Autoantibodies have been shown to be present in the pre-clinical phase and can predict the outcome of certain diseases [19] and this is true for the anti-ARS as well [20]. Larger studies are needed to understand the utility of anti-ARS autoantibodies for patient stratification and risk management of those patients. As shown for systemic sclerosis [21], autoantibodies have the potential to classify patients with a specific clinical phenotype, which might support personalized medicine.

A recent international study of 430 juvenile idiopathic inflammatory myopathy (JIIM) patients emphasized that the clinical and serological spectrum of IIM in children is not a mirror image of adult disease [3]. Like adult IIM, JIIM is also characterized by skeletal muscle weakness, characteristic rashes, and other systemic features. In this study, 68% had a single myositis autoantibody and 32% had no identified myositis autoantibodies. Anti-p155/140 autoantibodies were the most frequent serological subgroup, present in 32% of patients with juvenile dermatomyositis (JDM) or overlap myositis with JDM, followed by anti-MJ autoantibodies, which were seen in 20% of JIIM patients, primarily in JDM. And unlike adult IIM, other MSAs, including anti-synthetase, anti-signal recognition particle (SRP), and anti-Mi-2, were present in only 10% of JIIM. The key conclusion of the study was that juvenile myositis is a heterogeneous group of illnesses that can be classified on the basis of distinct autoantibody phenotypes.

3. Classification criteria

Classification criteria for IIM date back almost 35 years to initial publications by Medsger et al. [22] to more current criteria proposed by Dalakas and Hohlfeld [23] and Hoogendijk et al. [24] (Table 1). Each set of proposed criteria have advantages and disadvantages, but the emphasis in establishing clinically valid criteria has more recently incorporated MSAs, starting with anti-Jo-1 and the aSS nomenclature (reviewed in [8,25]) and progressing to a wider spectrum of MSA as the basis for meaningful clinical phenotypes, particularly in JIIM [3].

For many years, the Bohan & Peter criteria [26] were the touchstone, but it was known that this schema had limitations because it was observer dependent (subjective), based on experience in a single institution, the rashes of DM were not specified, and no direction was provided on how to rule out other myopathies. In a study where the specialist consultant diagnosis was considered the gold standard, the 2003 criteria of Dalakas agreed best with specialist consultant diagnosis and the criteria of Bohan and Peter demonstrated very poor specificity [27]. Prospective studies are required to develop improved classification of criteria. Q7

4. Biological function and biochemical properties of synthetases

Aminoacyl-tRNA synthetases catalyze the ATP-dependent binding of a single amino acid to its specific tRNA during protein synthesis. Autoantibodies to Jo-1 (histidyl), PL-7 (threonyl), PL-12 (alanyl), OJ (isoleucyl), EJ (glycyl), KS (asparaginyl), Zo (phenylalanyl) and Ha (tyrosyl) have been described [4]. Although the biological significance remains unknown, many of the anti-ARS autoantibodies have been shown to inhibit the function of their target autoantigen in vitro [28].

5. Co-existence of anti-ARS and anti-Ro52 autoantibodies

Of high interest, the majority of IIM patients, especially those with aSS also have anti-Ro52/TRIM21 autoantibodies [29]. Ro52, also known as TRIM21, is an E3 ligase that interacts with many proteins [29]. Patients with both anti-Ro52/TRIM21 and anti-ARS displayed a different clinical phenotype characterized by severe myositis and joint impairment. Moreover, the coexistence of anti-Ro52/TRIM21 autoantibodies seems to be associated with an increased risk of cancer [30].

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