IDIOPATHIC INFLAMMATORY MYOPATHIES: ASSOCIATION WITH OVERLAP MYOSITIS AND SYNDROMES: CLASSIFICATION, CLINICAL CHARACTERISTICS, AND ASSOCIATED AUTOANTIBODIES

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ABSTRACT

Idiopathic inflammatory myopathies (IIM) are traditionally identified as a group of disorders that target skeletal muscle due to autoimmune dysfunction. The IIM can be divided into subtypes based on certain clinical characteristics, and several classification schemes have been proposed. The predominant diagnostic criteria for IIM is the Bohan and Peter criteria, which subdivides IIM into primary polymyositis (PM), primary dermatomyositis (DM), myositis with another connective tissue disease, and myositis associated with cancer. However, this measure has been criticised for several reasons including lack of specific criteria to help distinguish between muscle biopsy findings of PM, DM, and immune-mediated necrotising myopathy, as well as the lack of identification of cases of overlap myositis (OM). Because of this issue, other classification criteria for IIM have been proposed, which include utilising myositis-associated antibodies and myositis-specific antibodies, as well as overlap features such as Raynaud's phenomenon, polyarthritis, oesophageal abnormalities, interstitial lung disease, small bowel abnormalities such as hypomotility and malabsorption, and renal crises, amongst others. Indeed, the identification of autoantibodies associated with certain clinical phenotypes of myositis, in particular connective tissue disease-myositis overlap, has further helped divide IIM into distinct clinical subsets, which include OM and overlap syndromes (OS). This paper reviews the concepts of OM and OS as they pertain to IIM, including definitions in the literature, clinical characteristics, and overlap autoantibodies.

Keywords: Polymyositis (PM), dermatomyositis (DM), overlap myositis (OM), overlap syndromes (OS), scleroderma.

OVERVIEW OF IDIOPATHIC INFLAMMATORY MYOPATHIES

Idiopathic inflammatory myopathies (IIM) are traditionally identified as a group of disorders that target skeletal muscle due to autoimmune dysfunction. The IIMs can be divided into subtypes based on certain clinical characteristics, and several classification schemes have been proposed. Overall, the IIMs are characterised by common laboratory and clinical features including: proximal muscle weakness, elevation of muscle enzymes, characteristic muscle biopsy pathology, electromyography findings of inflammatory myopathy, and insertional irritability. Typical skin rashes, including heliotrope rash and Gottron's papules, are associated with dermatomyositis (DM). The predominant diagnostic criteria for IIM is the Bohan and Peter (B and P) criteria, which subdivides IIM into primary polymyositis (PM), primary DM, myositis with another connective tissue disease (CTM), and myositis associated

with cancer (CAM).[1,2] This criteria has however been criticised for several reasons including lack of specific criteria to help distinguish between muscle biopsy findings of PM, DM, and immune-mediated necrotising myopathy,[3] as well as the lack of identification of cases of overlap myositis (OM). As a result of this issue, other classification criteria for IIM have been proposed, including a clinico-serologic classification put forward by Troyanov et al.,[2] which utilises myositis-associated antibodies (MAA) and myositis-specific antibodies (MSA), and also includes overlap features.

According to this criteria, subsets of IIM are divided into PM, DM, and OM, which includes features such as Raynaud's phenomenon, polyarthritis, oesophageal abnormalities, interstitial lung disease (ILD), small bowel abnormalities such as hypomotility and malabsorption, and renal crises, among others. Indeed, the identification of autoantibodies associated with certain clinical phenotypes of myositis, in particular CTM overlap, has further helped divide IIM into distinct clinical subsets. For example, there are now >15 CTM overlap auto antibodies that have been identified.[4] In general, OM has been described as having features of myositis overlapping with clinical features of systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).[5] Certain autoantibodies in particular may be more significant in association with OM, including anti-PM/Scl, anti-U3RNP, anti-Ku, and the anti-synthetase antibodies.[4-10] In addition, certain end-organ associations, including cardiac, lung, and kidney involvement, are more likely to be relevant clinical manifestations of OM. However, despite the widespread use of the term OM, there appears to be no set consensus as to how this entity is optimally defined.

HISTORICAL EVOLUTION OF IDIOPATHIC INFLAMMATORY MYOPATHIES CLASSIFICATION OVER TIME

Bronner et al.[11] have nicely summarised the history of the presentation, classification, as well as investigations into IIM over time. IIM was recognised as a clinical entity as early as the late 1800s. However, as noted by this study, it was not until the 1950s that PM was recognised as a stand-alone diagnosis.[11] At that point, Walton[12] noted that PM can occur without skin involvement and that inflammatory infiltrates may not always be present on muscle biopsy histopathology. He also noted that some subgroups of PM have features of collagen disease, or an association with malignancies. In addition, Walton characterised DM with predominant muscle and minimal skin findings, and defined a separate subgroup of collagen vascular disease with some muscle features.

The features of PM were further characterised by Walton and Adams[13] and included symptoms of limb-girdle muscular dystrophies, weakness, pain, arthralgias, and fevers. They also noted an association of PM with connective tissue diseases (CTD) such as SLE, SSc, and RA. These clinical observations of IIM were further clarified and formalised by B and P in 1975.[1]

As time went on, the important findings of muscle biopsy histology were included in the classification criteria. For example, in 1984 Arahata and Engel[11,14] looked at the role of T cells in the pathophysiology of IIM. In 1991, Dalakas[15] suggested diagnostic criteria for IIM based on similar principles of B and P which included muscle biopsy histopathology, as well as addressing the diagnosis of sporadic inclusion body myositis (IBM). However, necrotising autoimmune myopathy (NAM) was not identified as a unique subgroup.

MSA were taken into account in later criteria. For example, Targoff et al.,[16] in 1997, employed the original B and P criteria and classifications, but added the criterion of myositis-related autoantibodies. This was further expanded upon by Troyanov et al.[2] in 2005, with the addition of the subgroup of OM to their classification criteria. However, this classification does not include IBM or NAM.

In 2003, muscle biopsy findings and autoantibodies were both taken into account as part of a proposed classification scheme based on muscle biopsy findings[4,17] Under this classification scheme, the IIMs were divided into DM, PM, sporadic IBM, and nonspecific myositis. In addition, NAM was recognised as a distinct form of autoimmune muscle disease. However, the concept of OM as a stand-alone entity was not directly addressed.

DEFINITION OF OVERLAP MYOSITIS

As previously mentioned, the B and P criteria do not take into account autoantibodies or clear overlap syndrome (OS) symptoms, which would

more clearly define OM as a stand-alone entity. In an attempt to overcome these deficiencies, Troyanov et al.[2] developed two new classification systems of IIM which focus on overlap disease manifestations. The first classification scheme, named 'the modified B and P classification', added to the original B and P criteria and divided IIM into pure PM, pure DM, OM with at least one clear overlap clinical feature, and CAM with clear paraneoplastic features. The overlap features include polyarthritis, Raynaud's phenomenon, features of SSc such as sclerodactyly, calcinosis, gastrointestinal (GI) abnormalities, ILD, and features of SLE, amongst others.[2]

Their second classification scheme adds, along with the previously mentioned features, autoantibodies associated with OM. These autoantibodies can be subdivided into MSA and MAA categories. Under this scheme, OM would be defined as myositis with at least one clinicaloverlap feature and/or a myositis overlap antibody. These antibodies include anti-synthetase autoantibodies (ASS) as well as SSc-associated autoantibodies, amongst others.[2] However, not all patients with these autoantibodies may actually go on to develop myositis. Alternative labelling has been proposed, including nomenclature such as 'CTM-overlap' and/or ILD autoantibodies.[4]

It is also important to note that IIMs are a subtype of CTD in general. The term mixed CTD (MCTD) is an umbrella term, which includes PM, SSc, RA, and SLE, in association with the presence of a high autoantibody titre to U1 ribonucleoprotein (RNP). It was first described as a distinct entity by Sharp et al.[18] in 1972.[19] While classification criteria for each exist, it is widely recognised that some patients have features of more than one CTD and do not clearly fit into one category. For example, undifferentiated connective tissue disease is considered a unique clinical entity and is characterised by clinical symptoms including but not limited to Raynaud's phenomenon, serositis, fever, arthritis, vasculitis, lung involvement, and myositis.[20] It is thought that an OS occurs when two or more diagnoses of CTD occur in the same patient.[5,11] It has been recognised, however, that in some cases, MSA or MAA may be identified, which would again point towards the idea that the OS are in fact distinct clinical entities.[11]

Bronner et al.[11] summarised two approaches in categorising OS. One approach is the detection of a particular antibody in addition to expected clinical findings; for example, the anti-synthetase syndrome.[12] The second classification encompasses a constellation of clinical findings in the absence of an antibody; for example, RA and SLE overlap, which is known as rhupus syndrome.[11]

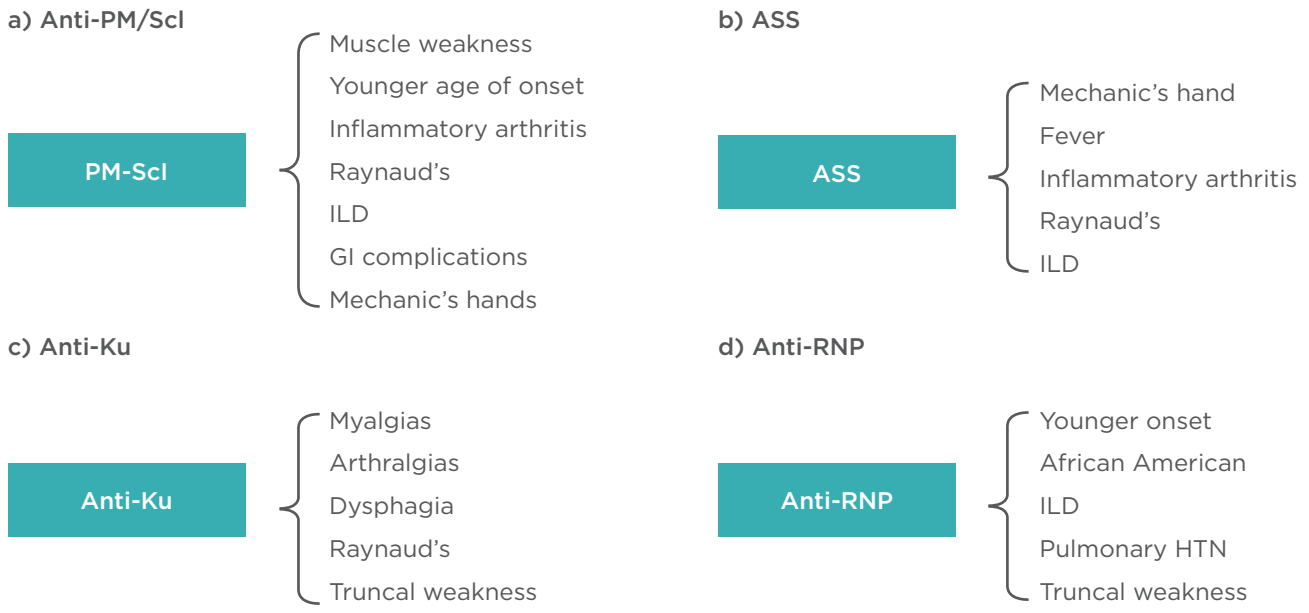

Figure 1: Autoantibodies associated with overlap myositis/overlap syndrome and associated clinical characteristics.

PM: polymyositis; ASS: anti-synthetase syndrome; RNP: ribonucleoprotein; ILD: interstitial lung disease; HTN: hypertension; GI: gastrointestinal.

In other studies, the definition of OS has not required the presence of an antibody, but rather clinical features of two different CTD. Moreover, OS has not only referred to a subtype of IIM, but rather a subtype of SSc as well. For instance, Pakozdi et al.[8] reviewed a cohort of patients with SSc. In this study, patients who fulfilled the American College of Rheumatology (ACR) criteria for SSc simultaneously with other CTD features were classified as having an OS. Troyanov et al.[2] noted that SSc is the most common CTD associated with IIM. In fact, Dalakas et al.[15] stated that only SSc and MCTD may truly overlap with DM, not PM.

However, OS/OM should be distinguished from MCTD. Patients with MCTD have features of three different disorders: SLE, SSc, and myositis. MCTD diagnosis also requires the presence of antibodies against a component of the spliceosome complex, the U1 RNP.[14-16] MCTD does not always have IIM as a feature. It has been suggested that up to 72% of patients with MCTD may exhibit a subclinical increase in muscle enzyme levels; however, only 2–3% of these patients present with myositis at first examination. Over half of these patients (51%) may eventually develop subclinical myositis.[17] Clinical presentation is often mild, and most patients respond well to low-dose corticosteroids.[18] However, there is controversy surrounding the concept of MCTD, in that some have considered it as a subset of SLE, and it has also been proposed that eventually MCTD patients will evolve into a definite CTD.[19]

SUBTYPES OF OVERLAP MYOSITIS ACCORDING TO AUTOANTIBODIES

There are several autoantibodies that have been linked with OM/OS (Figure 1), which may be associated with typical clinical manifestations.

Anti-Polymyositis/Scl Antibodies

Anti-PM/Scl antibodies are found in DM, PM, SSc, and OM/OS. The PM/Scl complex, also known as the human exosome complex, belongs to a class of antinucleolar antibodies, and is made up of 16 proteins.[9] The major proteins of this complex are named PM/Scl-100 and PM/Scl-75, for their apparent molecular weights.[9] Nakken et al.[20] defined the anti-PM/Scl antibody after describing a group of patients with IIM, in which half of them had features of scleroderma. Anti-PM/Scl antibodies have been found in up to 55% of patients with PM/DM who also presented with features of SLE and Sjögren's syndrome (SS),[9,21] 2–12% of patients with SSc alone,[9,22-24] and 21–24% of patients with PM/SSc overlap.[7,9,25] In the cohort studied by Pakozdi et al.[8] a group of patients with SSc/PM overlap were analysed and it was found that they were positive for anti-PM/Scl antibody in almost a third of cases (33.1%); however, in 17% of cases, this antibody was seen with another CTD or OS.

This antibody is often found in cases of OM or OS. Its main features are muscle weakness, younger age of onset of disease, inflammatory arthritis, Raynaud's phenomenon, ILD, and possible GI dysfunction, although the degree and severity of ILD and GI complications varies among studies. Mechanic's hands (cracking and hyperkeratosis of the radial aspects of the digits), nail-fold capillary changes, puffy fingers, and calcinosis have also been noted.[4]

Subclinical muscle weakness is a common feature in patients with PM/SSc OM. However, this antibody has also been found in individuals with SSc with no muscle involvement at all.[20] Patients tend to be younger at disease onset than typical SSc patients, with milder skin involvement as well as inflammatory arthritis.[4,7,9,26] Raynaud's phenomenon is common, but digital ulceration is rare. In the study by Guillen-Del Castillo et al.,[6] Raynaud's phenomenon and digital ulcerations were found to be less frequent in patients with SSc and ILD who were positive for the anti-PM/Scl antibody when compared with patients with SSc and ILD who were Scl-70 antibody positive; in addition, anti-PM/Scl patients had less GI dysfunction,[6] but there was no difference in the prevalence of calcinosis or inflammatory arthritis. However, myositis was more frequently seen in the patients who were positive for anti-PM/Scl antibodies. Cardiac involvement was similar in both groups. A German registry noted the frequency of PM/Scl antibodies to be 4.9% in their cohort of SSc patients; in these patients, there was a correlation with creatine kinase (CK) elevation, however there was less oesophageal involvement.[27]

A cohort of 40 SSc patients with myopathy were observed in a study by Ranque et al.[28] These patients had muscle involvement, with CK of >5-times the upper limit. Each patient was matched by two control SSc patients for skin involvement, sex, age at SSc onset, and disease duration, without myopathy. The presence of

anti-PM/Scl antibody was significantly associated with myopathy.

ILD is also seen, but tends to be milder than that seen in other CTD or in ASS, and non-specific interstitial pneumoniae may predominate, with higher baseline forced vital capacity values as well as greater rates of improvement during the course of disease.[4] In patients with SSc and anti-PM/Scl antibodies, the prevalence of ILD has been quoted to be between 30–78%.[6] Vandergheynst et al.[29] retrospectively reviewed a cohort of 14 patients with anti-PM/Scl antibodies: 5 had SSc/DM OS, 4 had DM, 1 had PM, 3 had SSc, and 1 had SS. Asnoted in prior studies, the three main features identified in these patients were Raynaud's phenomenon, ILD, and inflammatory arthritis. Similarly, Oddis et al.[25] screened serum samples from 617 patients with various CTD for anti-PM/Scl antibody. Twenty-three patients had these antibodies present; of these, 16 had pure IIM or OM, 6 had SSc alone, and 1 had an overlap of SSc and RA. Overall, it was suggested that this antibody is associated with a subset of patients with CTD, in addition to SSc or myositis features, that present with inflammatory myopathy, arthritis, and limited cutaneous involvement. Troyanov et al.[2] also noted that patients with anti-PM/Scl antibodies had features of inflammatory arthritis, Raynaud's phenomenon, DM rashes, and mechanic's hands, as well as features of SSc.

This phenotype of features of SSc with IIM has been characterised by others; Torok et al.[30] described an entity known as scleromyositis, thought to be a SSc/PM OS with features of Raynaud's phenomenon, myositis, scleroderma, ILD, arthritis, calcinosis, mechanic's hands, and the presence of anti-PM/Scl antibodies. These findings were also noted by Selva-O'Callaghan et al.[31]

Regarding subtypes of anti-PM/Scl antibodies, a study by D'Aoust et al.[9] focussed on the PM-1α antibody, a major epitope of the PM/Scl complex, in patients with SSc. As previous studies have also noted, patients with this antibody were more likely to be younger at the onset of Raynaud's phenomenon, have skeletal muscle weakness, calcinosis, as well as inflammatory arthritis. As in prior studies, ILD and GI involvement was less frequent. Koschik et al.[7] found that the presence of the anti-PM-Scl antibody was associated with OS; namely, SSc associated with features of both PM/DM and SLE, as well as RA. Skeletal myopathy was higher in patients with the presence of anti-PM/Scl antibodies compared to those without. Interestingly, GI involvement was less common in the anti-PM/Scl positive group, and pulmonary fibrosis was more commonly found in patients positive for anti-PM/Scl; however, when detected, the fibrosis was less severe, and pulmonary arterial hypertension (PAH) was also less common. Calcinosis was more common in anti-PM/Scl antibody positive patients, but was not found as frequently in the OS group with anti-PM/Scl antibodies as in the DM group.

Other subtypes of the anti-PM/Scl antibody have also been studied. Hanke et al.[23] looked at the clinical manifestations of patients positive for anti-PM/Scl-75c and anti-PM/Scl-100 autoantibodies in patients with SSc. Muscle disease, pulmonary fibrosis, and digital ulceration were associated with both subtypes. Interestingly, the anti-PM/Scl-75 antibody was found in younger patients with higher activity levels of disease, less GI involvement, but increased joint contractures, and were also found to exist in a subset of patients positive for anti-PM/Scl-75 autoantibodies.[32] In addition, the anti-PM/Scl antibodies were more often seen in patients with diffuse SSc, as opposed to those with PM/SSc overlap; prior studies have shown a higher association in overlap patients.[33,34]

Compared to previous studies, which have looked at the implication of the anti-PM/Scl antibody in SSc, Marie et al.[35] analysed a series of patients with DM/PM based on the B and P criteria, as opposed to OM or OS, who were positive for anti-PM/Scl. None of these patients had evidence of another CTD. The presence of the anti-PM/Scl antibody had a stronger association with lung and oesophageal involvement, which was sometimes severe. Patients with the anti-PM/Scl antibody also presented with ASS symptoms, including mechanic's hands, Raynaud's phenomenon, arthritis, and ILD. The authors have suggested that the presence of mechanic's hands may be a unique distinguishing feature of anti-PM/Scl-positive PM/DM.

Anti-Synthetase Antibodies and the Anti-Synthetase Syndrome

There are eight autoantibodies that are associated with ASS (Table 1), which target the amino-acyl tRNA synthetase enzymes. ASS has classical clinical manifestations that include myositis, mechanic's hands, fever, non-erosive inflammatory arthritis,

Raynaud's phenomenon, and ILD.[4] However, heterogeneity in the presentation of ASS has been observed. This was demonstrated in a large series of Japanese patients positive for ASS antibodies, where there were variations regarding distribution and onset of manifestations of ASS.[36] Regarding typical systems of ASS, Bhansing et al.[10] noted features such as mechanic's hands, Raynaud's phenomenon, ILD, arthritis, and myositis in a subgroup of patients with SSc-PM OS who were positive for anti-Jo-1 antibodies. As previously mentioned, Troyanov et al's.[2] second classification system included ASS antibodies. They found that anti-Jo-1 was the most commonly seen antibody in OM, with clear features of ASS. Almost half of these patients presented with high initial CK levels (>9000 U/L). Other ASS autoantibodies were also identified, including anti-PL7 and anti-PL12; these patient groups presented with severe ILD. A single patient tested positive for anti-KS autoantibodies, and their presentation was unique for features of digital ischaemia as well as deep vein thrombosis. Interestingly, ASS autoantibodies were markers for a chronic myositis course.

The anti-Jo-1 autoantibody was noted to be the most frequently seen of all the ASS in the study by Love et al.[38] in 1991 in a population of patients with IIM. This study found that in the IIM patients who were studied, autoantibodies were present in all clinical groups; anti-nuclear antibodies (ANA) were significantly more frequently found in patients with another CTD than with PM, IBM, or CAM. After ANA, ASS were most commonly seen, with anti-Jo-1 being the most frequent. They also found that the majority of patients with anti-Jo-1 antibodies had PM. It is interesting to note that some features of the ASS, for example ILD and Raynaud's phenomenon, are also features of SSc. Troyanov et al.[2] raised the question as to whether the extra-muscular manifestations of ASS are actually more in keeping with SSc.

Regarding the issue of muscle biopsy, a recent international workshop on the pathological diagnosis of IIM noted a discussion of typical muscle biopsy findings in ASS. Findings on muscle biopsy include inflammatory perimysial fragmentation, sarcolemmal membrane attack complex deposit staining on fibres next to the perimysium, as well as fine filaments in myonuclei present on ultrastructural examination.[39]

Anti-Ku

When found in SSc patients, anti-Ku autoantibodies are often associated with SSc OS, namely features of SSc with muscular involvement.[10,27] Cavazzana et al.[40] found that patients with anti-Ku antibodies presented with undifferentiated CTD or OS, including PM and SSc.

In patients with PM/SSc OS, the prevalence of anti-Ku antibodies in sera has been quoted to range between 2.3–55%.[27] A retrospective review by Pakozdi et al.[8] reported on a cohort of patients with SSc/myositis OS, and found that anti-Ku antibodies were uncommon. This autoantibody was detected in 2.3% of SSc/IIM and 1% of SSc/RA. Similar to their findings with the anti-PM/Scl autoantibody, Troyanov et al.[2] found that, in their cohort, patients with anti-Ku antibodies presented with features of RA and SLE. In terms of cutaneous involvement, Kaji et al.[41] studied a cohort of patients with SSc and myositis features; they found that the presence of the anti-Ku autoantibody was less associated with DM rashes than anti-PM/Scl.

Table 1: Antisynthetase autoantibodies and associated antigens.[37]

Antisynthetase Autoantibody	Antigen
Anti-Jo-1	Histidyl t-RNA synthetase
Anti-PL-7	Threonyl t-RNA synthetase
Anti-PL-12	Alanyl t-RNA synthetase
Anti-EJ	Glycyl t-RNA synthetase
Anti-OJ	Isoleucyl t-RNA synthetase
Anti-KS	Asparaginyl t-RNA synthetase
Anti-Zo	Phenylalanyl t-RNA synthetase
Anti-Ha	Tyrosyl t-RNA synthetase

Rigolet et al.[42] studied a cohort of patients who tested positive for anti-Ku antibodies. Thirty-seven percent of patients had IIM, the majority of these patients as part of an OS, with features of SSc, SS, and SLE. Patients with IIM OS had clinical features including myalgia, proximal muscle weakness, dysphagia, and increased CK. ILD was also noted, which in the majority of cases was corticosteroid resistant, as well as Raynaud's phenomenon and arthalgias.

An interesting phenotype of IIM, known as camptocormia, characterised by truncal weakness, has been described in association with anti-Ku antibodies. Zenone et al.[43] reported such a case of myositis with Raynaud's phenomenon, muscle necrosis, and sclerodactyly, leading to a PM/Scl OS diagnosis. Camptocormia has also been reported in other patients with IIM.[44,45]

Anti-Ribonucleoprotein

Anti-RNP antibodies are antibodies against the RNP complex, and include anti-U1-RNP and anti-U3-RNP. Antibodies to U3-RNP are most often seen in diffuse cutaneous SSc myositis OS.[41] Seen more frequently in African-Americans, patients may be younger at disease onset, and have consistent features of myositis, ILD, renal, and cardiac involvement. PAH is associated in particular with diffuse cutaneous involvement and the presence of anti-U3-RNP.[10] These findings were corroborated by Aggarwal et al.,[26] who also noted a poor prognosis in patients with SSc and anti-U3-RNP antibodies. In their cohort, almost all SSc patients positive for anti-U3-RNP antibodies had SSc alone (925), and 8% had an OS. The percentage of patients with OS was similar to that of patients negative for the anti-U3-RNP antibody. This antibody was not seen more frequently in patients with diffuse versus limited skin findings of cutaneous SSc; however, in the OS population, patients positive for anti-U3-RNP presented with predominantly diffuse SSc. Eight of the nine anti-U3-RNP positive patients with OS had myositis, and the remaining one had SLE. Patients with OS and IIM presented less frequently with CK elevation and had less inflammation on muscle biopsy.

Pakozdi et al.,[8] in their study of patients with SSc overlap syndromes, the presence of anti-U1-RNP was more frequently found in patients with SSc/SLE. In the study by Troyanov et al.,[2] anti-U1-RNP antibody was associated with a monophasic course of IIM. In their cohort of patients with OM, SSc-associated autoantibodies were present in 34% of the OM patients, with anti-U1-RNP being the most common antibody, being present in 13% of patients.

CONCLUSION

IIM may be associated with OM/OS, and include features of other CTD such as SSc, SLE, RA, or SS, apart from myositis seen in MCTD. Certain autoantibodies may be associated with phenotypical clinical presentations.

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