Idiopathic Inflammatory Myopathy: Autoantibody Update

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Several defined, specific autoantibodies have been associated with polymyositis and dermatomyositis. These include autoantibodies to at least six of the aminoacyl–transfer-ribonucleic-acid synthetases; to the signal recognition particle; to the protein complexes labeled Mi-2 and PM-Scl; and several autoantibodies, such as anti-U1nRNP and anti-Ro/SSA, that have recognized associations with other conditions. These autoantibodies are a continuing area of interest. Recent studies have involved the clinical implications of these autoantibodies, and their potential significance for etiology and pathogenesis of the disease. This report will review recent studies of myositis autoantibodies and their clinical associations, both extramuscular features, such as interstitial lung disease and aspects of the myositis itself. New myositis autoantibodies continue to emerge, which may have clinical utility. Several have been associated with dermatomyositis, including juvenile dermatomyositis, which has a low frequency of traditional myositis autoantibodies. There is also new information regarding the antigenic targets of anti-Mi-2 and anti-PM-Scl, two of the earliest recognized myositis autoantibodies. New evidence over the past few years has challenged old concepts of the relationship of autoantibodies to the pathogenesis of myositis, and has suggested potential new mechanisms for the origin of the associated autoantibodies. Despite this progress, the reason for production of the autoantibodies and their role in tissue injury remain unknown.

Introduction

Screening tests, such as indirect immunofluorescence, Ouchterlony immunodiffusion, or protein A-assisted immunoprecipitation (IPP), shows that autoantibodies to nuclear or cytoplasmic antigens occur in a high proportion of patients with polymyositis (PM) and dermatomyositis (DM). Approximately 80% to 90% of patients with PM and DM have autoantibodies when combinations of tests are used. Inclusion body myositis (IBM) has shown a modestly higher frequency of positive anti-nuclear antibody tests than the general population, approximately 20% [1]. Such screening tests can direct attention toward autoimmune disease in patients with myopathies, but are of reduced clinical utility as a result of their lack of disease specificity and the frequency of positives in the normal population. Several autoantibodies to specific nuclear or cytoplasmic antigens have been associated with PM and DM and have been studied in detail. Most of these occur in only a relatively small percentage of patients with myositis. Together, established, defined autoantibodies occur in only about 50% of patients with myositis. These may nevertheless have more clinical significance, because of their disease specificity. Progress is being made in defining additional autoantibodies and narrowing this gap.

The association of autoantibodies to specific cellular antigens with some cases of autoimmune myositis has been recognized since the 1970s, with the description of myositis overlap syndromes with anti–nuclear-ribonucleoprotein (nRNP) and the identification of anti-Mi and anti-PM-1 (now anti-PM-Scl). Since then, studies have demonstrated several important concepts about defined myositis autoantibodies. Myositis autoantibodies have been divided into "myositis-specific autoantibodies" (MSAs) and "myositis-associated autoantibodies" (MAAs). MSAs occur almost exclusively in patients who have myositis at some point in their disease, while MAAs can occur in myositis but also often occur in patients without myositis. Myositis autoantibodies are usually present from the earliest stages of observed disease (with rare exceptions), and they usually persist over time even when disease is controlled or in remission, although the titer may change and they occasionally disappear [2–4].

The most common established MSA is anti-Jo-1, present in approximately 20% of patients with myositis in most studies [1,5]. Anti-Jo-1 reacts with histidyl–transfer-ribonucleic-acid [–tRNA] synthetase (hisRS), which catalyzes the binding of histidine to its tRNA ($tRNA^{his}$) [6]. Other autoantibodies react with aminoacyl-tRNA synthetases for threonine (PL-7), alanine (PL-12), isoleucine (OJ), glycine (EJ), and asparagine (KS), which bind those amino acids to their tRNAs [7]. These are much less frequent than anti-Jo-1, each present in less than 1% to 3% of patients with myositis. Generally patients react only with a

single aminoacyl-tRNA synthetase antigen, with rare exceptions [8]. Other MSAs include antibody to the signal recognition particle (anti-SRP), seen in 4% of patients myositis [9], and anti-Mi-2 in 5% to 10% [10]. MAAs are often associated with overlap syndromes. Anti-PM-Scl, for example, is associated with an overlap syndrome of myositis and scleroderma [11]. Other MAAs include anti-U1RNP, anti-Ro/SSA (both anti-Ro60 and anti-Ro52 [12]), and anti-Ku [13].

Myositis Autoantibodies and Their Clinical Associations

New studies of the occurrence of myositis autoantibodies

Recent studies have confirmed many of the general trends regarding the frequency of the traditional myositis autoantibodies and their subgroup associations that had previously been observed. However, some studies have suggested that the antibodies may not be as specific as they appeared. Among the most significant recent studies was that of Brouwer *et al.* [14••], who tested European patients with myositis for MSAs and MAAs. This study was distinctive not only in the size of its study population, with 417 total patients, but also in the sophisticated methods employed to detect the autoantibodies, including dot-blots using anti-sense RNA probes, and a new recombinant enzyme-linked immunosorbent assay (ELISA) for anti-Mi-2. ELISAs were also used to study antibodies to the 100 kd and the 75 kd proteins of PM-Scl, and Ro60 and Ro52. They found defined autoantibodies in 56% of patients, confirming the general impression that defined autoantibodies were found in about half of patients with idiopathic inflammatory myopathies (IIM) [1,5]. MSAs were found in 38% [14], with a similar proportion of MSAs in PM (38%) and in DM (41%), consistent with previous findings [1].

MSAs are usually found to be very rare in IBM. Love *et al.* [1] found defined autoantibodies in 12% of patients with IBM, all with anti-Ro/SSA (8% with anti-La/SSB), and none with MSAs. Brouwer *et al.* [14••] found a higher than expected frequency of defined autoantibodies (32%) and MSAs (18%) in IBM, including three anti-synthetases, one anti-SRP, and three anti-Mi-2. One previous study [15] had also reported anti-Jo-1 in IBM. The significance of the anti-Mi-2 found by Brouwer *et al.* [14••] in IBM is uncertain as a result of the lack of previous studies to establish the disease specificity of the new ELISA, which can detect anti-Mi-2 autoantibodies in patients who were negative with previous techniques [16].

The occurrence of anti-synthetases in IBM is surprising, because IBM differs clinically and histologically from the myositis usually associated with anti-synthetases, and patients with IBM do not usually show the extramuscular anti-synthetase syndrome [1,17]. Hengstman *et al.* [18•] described a patient with biopsy proven IBM and a consistent clinical presentation, whose serum had anti-Jo-1 detected by multiple techniques. Of interest is that the patient responded to prednisone treatment with marked improvement in strength, a response expected more with anti-Jo-1-associated PM than with IBM. This single case cannot exclude co-existence of diseases, but it indicates that the antibody may carry clinical significance even if IBM is seen by biopsy. If further studies confirm these observations, it may even point to potential etiologic or pathogenetic relationships between some cases of IBM and PM. The authors have not detected MSAs as part of IBM, and the authors consider them very rare. If traditional autoantibody tests in IBM reveal confirmed MSAs, the diagnosis should be reviewed.

Anti-synthetases

Specific MSAs have been associated with particular clinical features and syndromes. The best studied of these is the syndrome associated with anti-Jo-1 and other anti-synthetases [1,17]. Numerous studies have documented the high frequency of myositis in patients with anti-Jo-1, and the very low frequency of anti-Jo-1 in connective tissue disease patients without myositis [6,19]. However, case reports and some series have shown that a small percentage of anti-Jo-1 patients do not have myositis during their observed course. The frequency of myositis in studies can depend on how sera were chosen for testing and other factors, but is usually over 90% for anti-Jo-1, at some point in the course [17]. Some non-Jo-1 anti-synthetases have had a lower frequency of myositis. In a recent preliminary report studying anti-synthetases in Japanese patients [20], 100% of 25 anti-Jo-1 patients had myositis, but it was seen in only 13% of those with anti-PL-12, questioning its designation as an "MSA." Myositis is more common in US and UK anti-PL-12 patients [17,21] but is less frequent than in anti-Jo-1 patients [5,22]. The most recently described anti-synthetase, anti-KS, has also been associated with a lower frequency of myositis in the small number of patients studied [20,23•].

The anti-synthetase syndrome is characterized by several extramuscular manifestations. Interstitial lung disease is the most important because of its clinical impact and effects on mortality [1]. It occurs in 50% to 80% of anti-synthetase patients. It can range in severity and course from asymptomatic to fulminant acute respiratory distress syndrome [24–27]. In a recent retrospective analysis of interstitial lung disease in patients with PM and DM seen over a 9-year period by Douglas *et al.* [28•], the most common pattern in those with biopsies was that of nonspecific interstitial pneumonia (NSIP) (81.8%). However, less than one third of patients were biopsied, which may have introduced a selection bias. The prognosis was better than for idiopathic pulmonary fibrosis (more often usual interstitial pneumonia), and was similar to that of NSIP in other settings. Anti-Jo-1was found in 38% of those tested, a lower frequency than in some previous studies. Anti-Jo-1 patients had a similar prognosis to that of the overall group, but the histology in anti-Jo-1 patients was not

specified. There have been numerous case reports of bronchiolitis obliterans organizing pneumonia (BOOP) in association with anti-Jo-1 or other anti-synthetases [29]. This pattern also has a relatively good prognosis and responsiveness compared with idiopathic disease.

Arthritis is also more common in the anti-synthetase syndrome than in others with PM or DM, observed in 50% to 90% of patients. It is sometimes deforming [30] but usually non-erosive, although erosive arthritis can occur [31••]. Other extramuscular features are considered to be part of the syndrome. Love *et al.* [1] found Raynaud's phenomenon in 60%, and mechanic's hands in 70%. Mechanic's hands, a hyperkeratotic rash along the edges of the fingers, was found in only 17% by Schmidt *et al.* [31••]. It can occur in association with other autoantibodies and, like other features of the syndrome, is not specific for anti-synthetase patients. Some, but not all, studies have also found an increased frequency of Sjögren's syndrome and sclerodactyly [17,31••]. Other features have been observed in anti-synthetase patients in low frequency in these studies, but it is unknown if they are part of the syndrome or occurred incidentally. The DM rash is usually found in a minority of anti-Jo-1 patients, but the rash was more frequent with other anti-synthetases [4].

In a recent extensive review of anti-Jo-1 clinical associations, Schmidt *et al.* [31••] noted that for most patients in their series and in the literature, the first symptom was not from the myositis, but from an extramuscular feature. Most of their patients did have signs of myositis at diagnosis, but they also saw patients with anti-Jo-1 who did not develop myositis, including a small number who did not have interstitial lung disease either. Most of these had a compatible arthritis, another common and often prominent feature of the syndrome. Myositis could be suppressed by treatment of other features, but this does not seem to explain all cases. These findings provide further support for the impression that anti-synthetase autoantibodies are more specific for the "anti-synthetase syndrome," which may not be fully expressed, than for myositis itself [22]. They also suggest that testing for these antibodies may be helpful in evaluating patients with interstitial lung disease, and some patients with arthritis (such as those with negative rheumatoid factor or non-erosive disease), even if myositis is not evident.

Original studies indicated that anti-Jo-1 patient sera reacted with the histidyl-tRNA synthetase enzyme but not the tRNA for histidine ($tRNA^{his}$) [6]. This was also true for patient sera with antibodies to other aminoacyl-tRNA synthetases with the exception of anti-PL-12 sera [21], which almost all reacted with alanyl-tRNA synthetase and $tRNA^{ala}$. However, in a more recent study [32] about one third of anti-Jo-1 sera reacted with a conformational epitope of $tRNA^{his}$. Further study is needed to determine if there is any additional clinical significance to the presence of anti-$tRNA^{his}$ autoantibodies, beyond that conferred by anti-Jo-1.

Other myositis-specific autoantibodies

The signal recognition particle is a ribonucleoprotein complex containing six proteins (of molecular weights 72, 68, 54, 19, 14, and 9 kd) and an RNA labeled 7SL. Early studies indicated that the 54 kd protein was the major antigen for most patients [9], but subsequent studies have indicated that the 72 kd protein is also an important antigen [33]. No clinical differences have yet been found between patients recognizing different components. The antibody can be detected by immunoprecipitation of the complex and identification of the 7SL RNA [9,14••], but the autoantibodies do not react directly with the 7SL RNA.

In the original studies, almost all patients with anti-SRP had PM. Although the total number of patients with this antibody has been described as small, many have had incomplete response to treatment or a need for continuing treatment with immunosuppressive agents, or acute and severe disease [9,33]. In one study [1], the mortality was higher than in other antibody-defined groups. That study also found a higher frequency of cardiac involvement. In a recent preliminary report, Hengstman *et al.* [34] also found incomplete responses and a need for continuing treatment, but were unable to confirm the higher frequency of cardiac involvement.

Brouwer *et al.* [14••] studied anti-SRP in myositis using a dot-blot with antisense RNA to identify 7SL in immunoprecipitates. Although the majority of anti-SRP patients (14 of 20 patients) had PM, more patients with DM were found than in previous studies (5 of 20). This was probably caused by the sensitive antibody detection method, but diagnostic criteria or population differences may have contributed. The occurrence of anti-SRP outside of PM has significance for assessing its potential etiologic and pathogenetic implications, as discussed in this report.

Anti-Mi-2 autoantibodies have had very high myositis specificity, and most patients (90%–95%) have had the DM rash. It is found in 10% to 20% of patients with DM in most studies [1,10] but may be more frequent in some ethnic groups or geographic locations [35]. It has been seen in children and adults with DM [36], and the subgroup with anti-Mi-2 has not been clinically distinguishable from other patients with DM.

Brouwer *et al.* [14••] found anti-Mi-2 outside the usual associated clinical group more frequently than expected. Their new anti-Mi-2 ELISA, using four overlapping recombinant fragments that span the length of the Mi-2β protein, found anti-Mi-2 in 58 patients, of which 17 (29%) had PM (9% of PM). There appeared to be differences in epitope reactivity between patients with PM and DM, as judged by the frequency of sera reacting with the different antigen fragments, but there was overlap between PM and DM. Previously, an ELISA using a single fragment (similar to "NM") was extensively tested for reaction with autoimmune sera, and it had the expected DM specificity, similar to other tests [37]. The epitopes were not localized further. Ge *et al.* [38] had previously found that a conformational

epitope reacted with all anti-Mi-2 sera that were positive by immunoprecipitation and immunodiffusion, but it is unknown whether this epitope was expressed in the recombinant ELISA.

False-positive results could have contributed because only eight of 17 ELISA-positive PM patient sera were confirmed by Western blotting. Studying anti-Jo-1, Schmidt *et al.* [31••] noted that low-level positive ELISA tests without confirmatory blotting were often not associated with the expected clinical manifestations. However, Brouwer *et al.* [14••] did not note differences in the levels of anti-Mi-2 in PM and DM sera. The increased sensitivity of antibody detection also resulted in an increase in the coexistence of MSAs, which are usually mutually exclusive. The myositis specificity of the new ELISA requires further testing, but if equal to that of other anti-Mi-2 tests, then the ELISA would be a valuable addition in view of its increased sensitivity. It is clear that in interpretation of autoantibody tests clinically, it is important to consider the technique used for detection.

Anti-Mi-2 was originally identified by immunodiffusion (anti-Mi-1 was a different precipitin line made by the prototype serum that proved to be unrelated) and showed a nuclear pattern by indirect immunofluorescence. By immunoprecipitation, anti-Mi-2 sera showed a series of proteins, the strongest of which migrated at 240 kd, and represented the major antigen. Two forms of the protein were identified, labeled anti-Mi-2α and anti-Mi-2β [39], which are 75% identical and react with anti-Mi-2 sera. The protein sequences contain a series of motifs, including a DEAH box, that indicate a role as a helicase and zinc finger motifs of the "PHD" type [37]. Mi-2α and Mi-2β were officially designated "CHD4" and "CHD3" based on the presence of a "chromo" domain, a "helicase" domain, and a "DNA-binding" domain [40]. These characteristics suggested a role in chromosomally-mediated regulation of transcription. This has since been demonstrated more directly. Mi-2β was shown to be part of a multi-subunit protein complex labeled "nucleosome remodelling deacetylase" (NuRD) [41]. This complex also contains histone deacetylases, which modify chromatin by affecting histone binding to DNA. Mi-2 modifies chromatin by an active, ATP-dependent mechanism. Thus NuRD can modify chromatin by at least two different mechanisms. In a recent study [42•], recombinant Mi-2 was shown to have nucleosome remodelling activity. The NuRD complex may also have a role in gene regulation through DNA methylation [43]. In the past few years, evidence has suggested a role for Mi-2 in transcriptional regulation in several cellular processes and has been the subject of significant scientific interest.

Anti-PM-Scl has been considered a MAA because some patients have scleroderma without myositis, and most patients have an overlap syndrome with features of the two conditions ("scleromyositis") [11,44]. However, unlike MAAs, anti-PM-Scl is mutually exclusive with other MSAs, and myositis is seen in the majority of patients (75%) [11]. Arthritis is also common, as is the DM rash, but there is usually limited cutaneous scleroderma. The myositis tends to be relatively responsive to treatment [13].

The antibody reacts with a complex of at least 11 proteins whose cellular role had previously been unknown. The major antigenic components of PM-Scl are the 100 kd protein, which reacts with most sera, and the 75 kd protein, which reacts with about half of sera [14••]. The reactive epitopes have been extensively characterized [45,46•].

Sequencing and analysis of these proteins eventually led to the recognition that the PM-Scl complex was the human homologue of the "exosome" that had been identified in yeast [47••,48•]. The complex is composed of exoribonucleases [49•] and is involved in RNA processing and degradation. Patient sera show nuclear and nucleolar staining by indirect immunofluorescence, but the complex was also found in the cytoplasm.

Significance of myositis-specific autoantibodies

Such studies raise the issue of whether antibody-defined subgroups represent distinct diseases, with aspects of etiology or pathogenesis that differ from patients with antibody-negative PM or DM, or represent a response in some patients to a more general process that can also occur in the absence of antibodies. This relates to the question of whether the antibodies are involved in pathogenesis, but the antibodies could alternatively be markers of another process. Studies in the past few years have provided interesting new information relevant to these issues.

Mozaffar and Pestronk [50••] compared the muscle histopathology of 11 patients with anti-Jo-1 with that of other patients with PM and DM. Although only three patients were considered to have a skin rash, all 11 showed perifascicular atrophy, usually associated with DM. In DM, this is accompanied by a vasculopathy and capillary loss, with reduced capillary index (here 0.55), but the capillary index in the anti-Jo-1 patients was not significantly reduced (0.88) compared with the patients with PM (0.95). The anti-Jo-1 patients all showed permysical connective tissue fragmentation, a finding that was uncommon in PM and DM, but was also seen in all of their patients with fasciitis. This suggests a fundamental difference in the pathogenetic mechanisms of myositis in the anti-Jo-1-defined group, favoring a distinct condition. Preliminary studies have also suggested distinctive features of muscle histology in anti-SRP-associated myositis [33], with some patients showing necrosis without inflammation.

A contrary impression derives from the report of Nagaraju *et al.* [51••], describing an interesting mouse model of myositis, based on observations that major histocompatibility complex Class 1 molecules are abnormally overexpressed on muscle fibers in myositis. Transgenic mice were developed in which expression of MHC Class I molecules on muscle could be controlled by addition or removal of tetracycline. When MHC expression was

induced, the mice developed progressive weakness over several months, with elevation of creatine kinase and histologic myositis. Eight of 23 transgenic mice with myositis developed anti-Jo-1 antibodies. There was no difference in disease expression noted between mice with antibody positive and antibody-negative myositis mice. In this model, anti-Jo-1 production appeared to be a secondary event, that was not required for, or evidently contributing to, development of myositis. Anti-Jo-1 arose in myositis without a specific stimulus for reaction to Jo-1 protein, arguing against molecular mimicry with a virus, a hypothesis that had been previously suggested. However, it is unknown whether human anti- Jo-1 arises in the same manner.

An alternative to the molecular mimicry hypothesis as an explanation for autoantibodies is the hypothesis that they result from events occurring in the process of apoptosis [52••]. Proteins undergoing proteolytic cleavage during apoptosis may generate fragments with new epitopes, which may be presented on the cell surface in apoptotic blebs. Of particular interest was a report by Casciola-Rosen *et al.* [52••] that analyzes numerous cellular autoantigens associated with connective tissue diseases for cleavage by granzyme B, as could occur during cytotoxic lymphocyte granule-induced apoptosis. They found that autoantigens were much more likely than other proteins to be cleaved by granzyme B, seen with 80% of autoantigens, and this would account for cleavage of some autoantigens that are not cleaved by caspases. Myositis autoantigens were prominent among those which are cleaved, although there were exceptions.

New Antibodies

Newly identified antibodies

Myositis-specific autoantibodies can be helpful in establishing a diagnosis if present, but they are not useful in excluding a diagnosis because approximately half of patients with myositis do not have any of the established, defined autoantibodies. As noted, screening tests suggest the presence of additional antibodies, and there is interest in determining these additional specificities. In the past few years, several newly-defined autoantibodies with apparent myositis association have been identified, and established antibodies have been noted to have new myositis associations.

It was recently found that some patients with myositis react with human PMS-1, a DNA mismatch repair enzyme that is a member of the MutL family [53•]. The autoantibody was detected by immunoprecipitation of S35-labeled PMS-1, but patient autoantibody did not react by immunoblot. The antibody recognized the C-terminal fragment, the portion that varies in different MutL-family enzymes. Antibody was found in sera of 7.5% of 53 patients with myositis but not in sera from any of 94 patients with lupus or scleroderma or 39 normal subjects, although it was found in a patient with active herpes zoster. All four anti-PMS-1 myositis sera reacted with at least one other autoantibody, including one that also had anti-Mi-2. One anti-PMS-1 serum also had antibodies to other MutL family mismatch repair enzymes, PMS-2 and MLH-1. Anti-PMS-2 was also found in a second myositis serum, which also had anti-MLH-1, and in one lupus serum. Anti-MLH-1 alone was found in one myositis serum. The finding of patients with myositis independently reacting with different members of a related family of enzymes is reminiscent of the aminoacyl-tRNA synthetases, except that autoantibodies to more than one of these repair enzymes co-exist in the same individuals, and thus far no distinctive syndrome or clinical associations have emerged.

Two other new autoantibodies with an apparently strong myositis association have been described in recent preliminary reports. Both were identified by immunoprecipitation from human cultured cell extracts, and both appear to be predominantly associated with DM, including juvenile DM. Overall, children with myositis have a lower frequency of myositis autoantibodies, in part caused by the much lower frequency of anti-Jo-1 autoantibody compared with adults. In a preliminary study of the autoantibodies in 47 children with IIM, anti-PM-Scl was the most frequently encountered autoantibody, seen in 10 patients; anti-Mi-2 was seen in four, but anti-Jo-1 in only two patients [54]. However, five patients had a new autoantibody labeled anti-MJ. Further study in a wider population found the antibody in 14 patients (17.5%), including 13 with DM (more in juvenile than adult patients) and one with systemic-lupus-erythematosus–myositis overlap [55]. Seven had relatively severe disease, and eight had calcinosis. Anti-MJ autoantibody reacts with an unidentified protein of approximately 140 kd.

A second new autoantibody was later found in 31 patients, 29 of whom had DM, including 20 children and nine adults [56]. This was approximately 14% of those tested, but the autoantibody was more frequent in amyopathic dermatomyositis. Among these patients, with a characteristic DM rash for an extended period without development of clinically evident myositis, the authors have seen the anti-155kd antibody in approximately 80%, while MSAs and MAAs have been less frequent than in usual DM [57]. Some of the sera with anti-155kd autoantibodies have had an associated antibody reacting with a 95 kd protein labeled Se. The cellular role of the new antigens (MJ, 155kd, and Se) has not yet been determined, and it is unknown whether these apparently nuclear proteins have any functional relationship to PMS-1, Mi-2, or other known antigens. The presence of the new antibodies in some cases of adult and juvenile DM suggests that juvenile DM is not a separate condition distinct from adult DM, which has been suggested in the past based on the higher frequency of calcinosis and intestinal perforation.

One previously described antinuclear autoantibody, anti-56kd, has been an exception to generalizations about the established myositis autoantibodies. In the original

studies, sera from the majority of patients in all myositis clinical subgroups reacted with an unidentified 56 kd component of nuclear ribonucleoproteins by Western blot [58,59]. The antibody was relatively specific for myositis, with few exceptions. It was most common in juvenile DM (92%), but was even common in myositis with malignancy (75%) [60]. The titer seemed to vary with disease activity, which suggests the possibility of a role in pathogenesis. Of particular interest is a recent preliminary report confirming the frequent occurrence of this antibody in juvenile DM, although not quite as high a rate (62%) [61]. This difference may have related to population differences, because it was more common in association with DQA1*0501. The fact that the antibody has been found in such a high proportion of highly disparate clinical subgroups raises the possibility that it is a secondary response, such as a cross-reaction with a muscle protein. However, given the observed disease frequency and specificity, it would have potential clinical utility regardless of its role in disease. Alternatively, anti-56 kd may be related to the newer DM antibodies such as anti-MJ and anti-155kd, and may together account for many of the positive anti-nuclear antibodies, and have important implications for the disease.

New myositis associations

A recent report found that a previously described antibody to a tRNA-related protein antigen (Wa), that was found in scleroderma, can occur in myositis as well [62]. Of interest was that the two patients with anti-Wa had interstitial lung disease, suggesting a clinical similarity to patients with anti-synthetases. It has previously been suggested that the association of myositis with antibodies to tRNA-related antigens may extend further than the anti-synthetases alone. Antibodies to Fer (believed to be elongation factor 1α) and Mas [1,14••] immunoprecipitate tRNA and occur in myositis, but they are not myositis-specific [63]. Myositis antibodies to cytoplasmic antigens not associated with tRNA have also been noted (anti-KJ [5], anti-SRP), and the reason is still not understood. The cellular role of Wa antigen is unknown.

Several other autoantibodies that occur in myositis, but whose primary association is with other conditions, have been studied recently. In findings confirming those of a previous study in another population, Tormey *et al.* [64•] found that 54% of patients with scleroderma and anti-U3RNP (anti-fibrillarin) and diffuse cutaneous involvement had associated muscle involvement considerably higher than expected. Pulmonary hypertension is also increased in this group.

Rutjes *et al.* [12] had previously demonstrated an increase in anti-Ro52 in patients with myositis (20%), that was even stronger among patients with anti-Jo-1 (58%). The authors found a similar high frequency of anti-Ro52 in non-Jo-1 anti-synthetase patients [65] and in 47% of anti-PM-Scl patients. Anti-Ro52, at 25%, was the most common defined autoantibody in European patients with myositis [14••], compared with only 4% with anti-Ro60.

Anti-endothelial cell antibodies were recently found in 38% of patients with IIM [66]. They were found in two of three patients with interstitial lung disease, independent of anti-synthetases. Anti-histones were also recently found in patients with IIM, noted in 17%, predominantly reacting with histone H1 [67]. Antibodies to 20S proteasomes, cytoplasmic complexes involved in protein degradation, are common in myositis (63%), reacting with the αC9 component [68]. They are also common in systemic lupus erytemetosus (58%) and primary Sjögren's syndrome (39%) but not in rheumatoid arthritis or normals, suggesting a potentially meaningful, but not myositis-specific, response [69].

Conclusions

Myositis-related autoantibodies can be identified in an increasing proportion of patients with PM and DM. They can be helpful in diagnosis caused by their disease specificity, and in further characterization of a patient's disease caused by their clinical subgroup associations. It may be useful to consider MSAs as an additional criterion in the Bohan and Peter criteria set, as described in this report.

Major questions remain regarding these antibodies. The reasons for production of MSAs, for disease and subgroup specificity, and for the localization of tissue injury, are unknown. The reason autoantibodies to different anti-synthetases in different patients are associated with similar clinical syndromes is not understood. Finally, it is unknown if MSAs play a role in pathogenesis.

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