

OVERLAP SYNDROMES

INTRODUCTION

The etiologies of all autoimmune connective tissue diseases are unknown and diagnosis has had to depend on patterns of symptoms and signs. The problem is heightened by the tendency for one disease type to merge with another, resulting in a continuous spectrum of clinical features among the rheumatic diseases, with the traditionally accepted entities such as systemic lupus erythematosus (SLE) or systemic sclerosis occupying only part of the continuum with the overlap syndromes lying between. To identify an overlap syndrome it is necessary to identify a constellation of distinctive features which constitute a true syndrome. Historically, this has been achieved in two ways; (i) on the basis of clinical involvement and (ii) by the detection of autoantibodies.

Overlap syndromes based on clinical features

Raynaud's phenomenon, sclerodactyly and alveolitis are common features of a number of autoimmune rheumatic diseases and cannot be used on their own to define a syndrome. Other features, such as thickening of the skin proximal to the fingers in scleroderma or the articular erosions in rheumatoid arthritis (RA) are sufficiently disease-specific to suggest that a patient having a combination of both have a true overlap. This may be the basis of the early descriptions of RA/systemic sclerosis overlaps and RA/SLE overlaps or 'rupus'. Before regarding these as distinctive syndromes it must be remembered that RA is a common disease and could occur by chance in a patient with systemic sclerosis or SLE.

Some studies have highlighted a second consideration; namely that erosive arthritis may occur in SLE and systemic sclerosis, thus suggesting that RA-like features can, in some patients, be a feature of the disease itself.

Overlap syndromes defined by autoantibodies

A remarkable feature of autoimmune connective tissue diseases is that serum from the majority of patients contain non-organ specific autoantibodies to DNA or to nucleic acid (both DNA and RNA) binding proteins. Dissection of the antigenic specificity of these antibodies has done much to justify the distinctiveness of the traditionally recognized entities, particularly when the antibodies segregate precisely with them. Such antibodies are the 'markers', such as anti-double-stranded (ds)DNA or anti-Sm, which are virtually restricted to SLE, or antibodies to the two DNA binding proteins, Scl-70 and centromere, which are found only in patients with clinical features which most clinicians would recognize as systemic sclerosis. However, antibody types may coincide with parts of the spectrum where diseases overlap with each other. The best known examples are antibodies which react mainly with U1- RNP. These are found in patients with overlapping features of SLE, systemic sclerosis and polymyositis. There are other syndromes which are also associated with myositis and specific antibodies; they include the polymyositis/fibrosing alveolitis overlaps found in patients with antibodies to Jo-I and the other tRNA synthetases, and the polymyositis/scleroderma overlap associated with anti-PM/Scl.

Although previously not regarded as markers of an overlap, it is now generally thought that antibodies to the nuclear and cytoplasmic complexes involved in RNA polymerase III transcription, **Ro(SS-A) and La(SS-B)**, occur in patients with Sjogren's syndrome who also have features of SLE; i.e. Sjogren's/SLE overlap syndromes. Other antibodies have also been described inappropriately in the view of some as markers of overlaps. They include the association of anti-Ro with subacute cutaneous lupus erythematosus (SCLE) and anticardiolipin antibodies with the primary antiphospholipid syndrome. It is arguable that the clinical features of these diseases are not overlapping, more that they represent disease subsets or distinctive syndromes in their own right.

1. MIXED CONNECTIVE TISSUE DISEASE (MCTD)

MCTD is an overlap syndrome combining features of SLE, systemic sclerosis and polymyositis together with the presence of antibodies to U1 RNP. The prevalence of MCTD is unknown. In most studies the number of patients with clinical and serologic features of the syndrome are about four-fold less frequent than patients with SLE, suggesting an overall prevalence in the region of 10 per 100,000. The female to male ratio is about 9:1.

No particular environmental agents have been associated with the disease although it is of interest that occupational exposure to vinyl chloride has been described in four patients. Several studies have described an association with DR4, one suggesting that the link could be accounted for by the MCTD patients who had erosive arthritis. A significantly increased frequency of the Gm phenotypes 1.3 and 3 have also been described.

Clinical Features

Being an overlap syndrome, MCTD lacks any distinctive clinical features. Raynaud's phenomenon is very common and is often associated with **edema of the hands**. This feature is often (wrongly) regarded as peculiar to MCTD, although it should be remembered that swollen hands occur in early scleroderma, eosinophilic fasciitis and the anti-tRNA synthetase antibody associated overlap syndromes. The appearance of the hands in MCTD may also reflect the overlapping diseases which constitute the syndrome and combine features of scleroderma, SLE and dermatomyositis. Arthritis and atthralgias are also common but again lack any unique pattern. Joint disease ranging from a relatively mild SLE-like peripheral synovitis through to erosive disease typical of RA and even arthritis mutilans have been described.

Myositis and fibrosing alveolitis are the two most important common features of the syndrome. There is little evidence to suggest that the pattern of muscle or lung involvement in MCTD differs from that of other diseases, although studies of patients selected purely on the basis of myositis or fibrosing alveolitis suggest that the prognosis in patients with anti-U1 RNP may be marginally better than those without. Nevertheless, both myositis and fibrosing alveolitis are potentially fatal and pulmonary hypertension, in particular, is a lethal complication.

Other clinical features of MCTD simply reflect those of the diseases which it overlaps. Skin manifestations include sclerodactyly, scleroderma (usually relatively restricted), calcinosis, telangectasia, photosensitivity, malar rash and the rash of dermatomyositis. Pleurisy, pericarditis

occur in about 60% of patients. Radiological evidence of esophageal dysmotility has long been recognized as a feature in more than half the patients. One recent study has emphasized a high frequency of heartburn (48%) and dysphagia (38%) in MCTD patients, as well as rarer gastrointestinal features including malabsorption syndromes and bowel perforations due to vasculitis. Sjogren's syndrome occurs in about 50% of MCTD patients, although the sicca symptoms are usually less prominent than those with anti-La (SS-B) antibodies. Trigeminal neuralgia, although a recognized feature of SLE, is a striking feature of MCTD in about 25%.

When first described, MCTD was thought to be characterized by good prognosis and a low frequency of cerebral and renal disease (compared to SLE). This opinion has now been revised, after longer follow-up studies, to the view that prognosis of MCTD is in fact worse than lupus, most of the deaths being attributable to pulmonary hypertension. The low frequency of cerebral disease appears to have stood the test of time although there is no agreement about renal disease. When it occurs, renal involvement is either membranous nephritis, or less commonly, the renal vasculopathy characteristic of scleroderma leading to malignant hypertension.

INVESTIGATIONS

The diagnosis of MCTD is critically dependent on the demonstration of high titer anti-UI RNP antibodies. The presence of anti-U 1 RNP antibodies in the serum means that all MCTD sera will give a speckled nuclear staining pattern on indirect immunofluorescence .

Other investigations show features common to connective tissue diseases in general. The most frequent hematologic findings are leukopenia, thrombocytopenia and a high ESR. Serum immunoglobulins may be extremely high with IgG levels reaching over 40g/l in some patients. In contrast to SLE, complement levels are usually normal or high. Rheumatoid factors are elevated in approximately 70%. Important negative findings are tests for anti-Sm and anti-DNA antibodies. These if present represent exclusion criteria for the diagnosis of MCTD and suggest that the disease lies more firmly in the SLE part of the spectrum.

ETIOLOGY

Molecular mimicry with retroviral antigens has been proposed on the basis of sequence similarities between the 33kDa polypeptide of UI RNP and a consensus sequence common to a number of animal retroviruses.

PATHOGENESIS

It is difficult to envisage how autoimmunity to a ubiquitous nuclear ribonucleoprotein complex such as the U 1 RNA particle could give rise to the variety of vascular and tissue lesions found in MCTD. One theory is that anti-RNP antibodies penetrate cells via Fc receptors and destroy them. It was suggested that the cells bearing these receptors were predominantly T-suppressor cells and that their destruction resulted in the proliferation of uncontrolled autoreactive T-helper (TH) cells.

MANAGEMENT

There is no specific treatment for MCTD. Treatment depends entirely on the pattern of clinical involvement. Mild disease such as arthralgias require symptomatic treatment only, whereas severe complications such as myositis or fibrosing alveolitis need high-dose steroids, often in combination with immunosuppressive drugs. It should also be borne in mind that MCTD can also differentiate into SLE and that potentially lethal complications, particularly fibrosing alveolitis, can be occult at the time of presentation.

All patients with MCTD require careful, long-term follow-up. As in SLE, management is based on clinical assessment and laboratory tests for specific organ involvement. At each visit every patient should be examined clinically, including blood pressure, their urine tested for protein, and laboratory tests including complete blood count and muscle enzymes measured routinely. There is no single laboratory test which can be used for monitoring disease activity and progression, although several studies have suggested that a rise in anti-U1 RNP antibodies measured by a quantitative ELISA may be helpful in the short term for predicting flares of the disease. In some patients a fall in total white count (particularly the lymphocyte count) or rise in ESR and total immunoglobulin levels may be helpful in assessing overall disease activity, although these should never be relied on for dictating treatment options. At intervals, depending on the severity of the disease, a full survey of autoantibodies, including anti-Sm and anti-dsDNA, should be performed as an early warning of those differentiating into SLE.

Fibrosing alveolitis, often complicated by pulmonary hypertension, is the most frequent cause of death directly attributable to MCTD. This should always be anticipated by examining patients for basal rales and by performing regular chest radiographs. Because the many patients with early pulmonary involvement have no abnormal physical signs and normal radiographs it is advisable to perform pulmonary function tests, including diffusion capacity at presentation and at subsequent intervals to assess progression. If there is evidence of deterioration, bronchial alveolar lavage or biopsy can be used to assess disease activity prior to treatment.

Drug treatment for MCTD depends on symptoms or the pattern of organ involvement. About one-third of patients are adequately controlled by analgesics or NSAIDs. Raynaud's phenomenon can be particularly troublesome and is characteristically unresponsive to corticosteroids. Most patients derive some benefit from simple conservative treatment with electrically heated gloves and a minority respond to calcium channel antagonists such as nifedipine. Arthritis and SLE-like skin involvement is often treated successfully with antimalarials such as hydroxychloroquine. Low-dose corticosteroids are effective for controlling cutaneous edema, arthritis and pleurisy. High-dose corticosteroids are indicated for the treatment of severe systemic disease such as vasculitis, myositis or fibrosing alveolitis. Myositis is a particularly important complication requiring the correct use of corticosteroids. Because of the mistaken belief that MCTD is peculiarly corticosteroid-responsive, patients may be given inadequate treatment. In addition, the apparent lack of an early response may drive the physician into the unnecessary use of cytotoxic drugs. Myositis in MCTD should be treated like myositis occurring in any other context

Immunosuppressive drugs are used in two contexts in MCTD. For the induction of remission or for their corticosteroid-sparing effects. The commonest indication for induction of remission is fibrosing alveolitis, although any SLE-like manifestation such as nephritis, systemic vasculitis may also require immunosuppression. The commonest drug used in this context is cyclophosphamide in a daily dose of 1-2mg/kg/day in combination with high-dose corticosteroids. Cyclophosphamide may also be given as pulse therapy either as single intravenous (i.v.) infusions of 500mg-1g spaced at intervals of two to four weeks depending on the complete blood count or as weekly oral pulses of 300mg; both regimes to a total dose of 3-6g.

2. tRNA SYNTHETASE ASSOCIATED OVERLAP SYNDROMES

The tRNA synthetases are a series of cytoplasmic enzymes which take part in protein synthesis by adding specific amino acids encoded by transfer RNA (tRNA) during the assembly of polypeptides. A number have been described as autoantigens although histidyl tRNA synthetase is by far the commonest target for autoimmunity. This antigen, like other soluble cellular antigens, was initially defined as a precipitin reaction obtained with a prototype serum. The antigen was named after the patient, Jo-1. When it was definitively demonstrated that the Jo-1 antigen was histidyl-tRNA synthetase, other tRNA synthetases, including alanyl and threonyl-tRNA synthetases, were also described as less common autoantigens in polymyositis associated overlap syndromes.

Clinical Features

The clinical features of patients with antibodies to histidyl-tRNA synthetase (Jo-1) are very similar to those with antibodies to other tRNA synthetases and are therefore presented together. Overall, the clinical features of patients with anti-tRNA synthetase antibodies are strikingly similar to those with MCTD, such that it would be difficult to predict whether an individual patient with Raynaud's phenomenon, arthritis, myositis and alveolitis would have anti-Jo-1 or anti-U1 RNP antibodies. On the other hand, there are differences between the patients analyzed as groups. Patients with anti-Jo-1 antibodies have myositis and fibrosing alveolitis more frequently and both are more likely to give rise to the presenting symptoms. In addition, there is some evidence to suggest that the prognosis of the alveolitis is worse in patients with tRNA synthetase antibodies compared to those with anti-U1 RNP. Patients with anti-U1 RNP tend to have more SLE-like features, and may be more likely to differentiate into SLE. It is noteworthy that patients with anti-Jo-1 antibodies may have erosive, deforming arthritis and are often diagnosed as suffering from RA.

Pathogenesis

Evidence that host/virus interactions on the background of genetic susceptibility leads to autoantibody induction is possibly more compelling for the tRNA synthetase antibodies than any other pattern of autoimmunity in rheumatic disease. Genetic susceptibility is well established with an almost 100% association between anti-Jo-1 antibodies and the HLA tissue type DR3. Histidyl-tRNA synthetase is known to be involved in the aminoacylation of enteroviruses and it is conceivable that the interaction of host plus virus complex could lead to an anti-host response. Accumulating, but indirect, evidence for the involvement of Coxsackie B viruses in myositis

provides a further stimulus for the investigation of induction of anti-tRNA antibodies by a specific etiologic agent. Involvement of the idiotype network in the induction of autoimmunity has been proposed. This theory, suggests that autoantibodies are anti-idiotypes to antiviral antibodies, and that the antiviral antibody reacts with the viral RNA at its binding site to the host protein, and that the autoantibody (the anti-idiotype) reacts with the host protein at its RNA binding site.

Management

Having established the autoantibody specificity the treatment is as for any other multisystem autoimmune disease, except that the relatively poor prognosis of the fibrosing alveolitis should be borne in mind and should possibly suggest earlier intervention with corticosteroids and immunosuppressive drugs than would be used in MCTD.

3. THE PM/SCL ASSOCIATED OVERLAP SYNDROME

Antibodies to PM/Scl are part of a complex of precipitin reactions originally termed PM-1. Although PM-I antibody was regarded as a marker antibody for polymyositis occurring in 70% of patients, anti-PM/Scl was found in about 15% and appeared to be associated with a polymyositis/ scleroderma overlap syndrome with clinical features very similar to those of the anti-tRNA associated overlap syndromes. However, there are differences. Myositis and fibrosing alveolitis are described as less frequent, less severe and more likely to respond to treatment with corticosteroids or immunosuppressive drugs. The PM/Scl antigen is nucleolar, and hence serum samples contain antinucleolar antibodies by immunofluorescence.

4. THE SLE/SJOGREN'S SYNDROME OVERLAP DEFINED BY ANTI-LA(SS-B)

Clinical features

The La (SS-B) antigen is known to shuttle between nucleus and cytoplasm and its antibodies occur in both SLE and Sjo'gren's syndrome, particularly when there are overlapping features of both diseases. Patients with anti-La antibodies have Sjogren's syndrome with prominent systemic features. Most of the extraglandular features are SLE-like, with a high frequency of arthritis, rashes, Raynaud's phenomenon, leukopenia and thrombocytopenia. Characteristic of the anti-La associated overlap syndrome is a purpuric hyper-gammaglobulinemic rash in about 30% of patients and a relatively low frequency of nephritis compared to patients with typical SLE. However, renal tubular acidosis (often subclinical) may occur in up to 30% of patients.

Pathogenesis

The La antigen is involved in RNA polymerase III transcription and binds to both host and viral RNAs in infected cells. A clue to a mechanism for the induction of anti-La antibodies may lie in the observations that the La antigen is translocated from the nucleus to the cytoplasm and plasma membrane during virus infection and thus becomes available to the immune system. Its interaction with viral RNA and, possibly viral proteins, could induce anti-La antibodies by tolerance bypass, possibly occurring in the salivary gland itself. Support of this hypothesis is the demonstration that some viruses persist within salivary epithelium, although no one has

convincingly demonstrated La antigen presentation within the glands of patients with Sjogren's syndrome.

Management

The treatment of Sjogren's syndrome associated with anti-La is largely symptomatic with tear and saliva substitutes. Therapy for extraglandular manifestations depends on the pattern of clinical involvement. Arthritis and rashes respond to low doses of corticosteroids, sometimes in combination with azathioprine. Some studies suggest that antimalarials may be effective. Fibrosing alveolitis and myositis both occur, though less frequently than in MCTD, and may require high-dose corticosteroids and cytotoxic drugs. Similar treatment may be used for systemic vasculitis which is often manifest as mononeuritis multiplex. A recognized presentation in the elderly is fever, weight loss and lymphadenopathy, sometimes associated with polymyalgia. These patients often do well with a relatively modest dose of corticosteroids.

CONCLUSION

The concept of overlap syndromes makes many rheumatologists feel uneasy, although their distinctiveness is no longer the subject of the intense debate that it was in the past. In practice, the diagnosis of an overlap syndrome makes little difference to treatment although the detection of an autoantibody does help the clinician to anticipate particular complications. The description of overlap syndromes in terms of autoantibodies is based on the assumption that the pattern of autoimmunity reflects the underlying cause for the disease. If this proves to be the case the definition of disease by an antibody will be justified.