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EDITORIALS

POLYMYOSITIS-ASSOCIATED OVERLAP SYNDROMES

THE diagnosis of a disease depends on knowledge of its cause or on the recognition of clinical or laboratory features unique to that disease. The aetiology of the autoimmune connective tissue diseases is unknown and many of the clinical features, such as arthritis or Raynaud's phenomenon, are common to most of them. The diagnosis of the traditionally recognized entities, such as systemic lupus erythematosus (SLE), is therefore based on pattern recognition which has become formalized by the generation of diagnostic criteria which include autoantibodies. These antibodies do not always respect traditionally held diagnostic boundaries and many segregate with overlap syndromes rather than with what have been thought to be distinct diseases. It has been claimed that the clinical features of some overlap syndromes are distinctive enough to suggest that they may be diseases in their own right. One area which has developed rapidly in the last few years is that of overlap syndromes in which polymyositis, fibrosing alveolitis, arthritis and Raynaud's phenomenon are common clinical features. This group comprises patients with mixed connective tissue disease (MCTD) associated with antibodies to U1 ribonucleoprotein (U1RNP), and two other clinically similar syndromes associated with antibodies to Jo-1 and PM/Scl (Table I).

Mixed connective tissue disease is an overlap syndrome combining features of SLE, systemic sclerosis and polymyositis combined with the presence of antibodies to U1RNP. The debate as to whether MCTD is a 'distinct entity' or even justifies the term 'disease' [1] has now waned, although some studies have noted that patients with MCTD differentiate into typical SLE or scleroderma and have proposed the term undifferentiated CTD (UCTD) [2–4]. The problem with UCTD is that it may be applicable to conditions associated with other autoantibodies.

TABLE I
Clinical features (%) of patients with MCTD, anti-aminoacyl-tRNA antibodies and PM/Scl antibodies

	Anti-U1RNP antibodies	Anti-Jo-1 antibodies	Anti-PM/Scl antibodies
Raynaud's	85	93	100
Arthritis/algia	95	90	97
Myositis	63	83	88
Lung fibrosis	67	79	78
Sclerodactyly	67	72	97
Sjögren's syndrome	50	59	34
Dermatomyositis rash	–	38	38
Dysphagia	67	31	78
Calcinosis	–	24	47

Modified from refs 5, 8, 9 and 10.
–, reported but not enumerated.

Whatever name is used, the clinical features associated with anti-U1RNP have not changed significantly since a large series in 1976 [5]. The prevalence of MCTD is in the region of 10/100 000. The male to female ratio is ~1:9 and the disease does not appear to show the relative preponderance of Afro-Caribbeans seen in SLE. An association with DR4 or DR1 has been described [4].

Being an overlap syndrome, MCTD lacks any distinctive clinical features. Raynaud's phenomenon is very common and is often associated with oedema of the hands, although this feature may also occur in early scleroderma, eosinophilic fasciitis and the anti-tRNA synthetase antibody-associated overlap syndromes [4]. Joint disease, ranging from a relatively mild SLE-like peripheral synovitis through to erosive disease typical of rheumatoid arthritis (RA), has been described [6]. Myositis and fibrosing alveolitis are the two most important features of the syndrome, both originally being described in >60% of patients. With the increasing use of more refined serological techniques, milder forms of MCTD are being recognized and it is likely that myositis is less common but still an important feature. Other clinical features of MCTD simply reflect those of the diseases which it overlaps. Skin manifestations include sclerodactyly, scleroderma, calcinosis, telangiectasia, photosensitivity, malar rash and the rash of dermatomyositis. Pleurisy and pericarditis occur in ~60% of patients. There is also a high frequency of heartburn and dysphagia in MCTD patients, as well as rarer gastrointestinal features including malabsorption syndromes and bowel perforations due to vasculitis [7].

When first described, MCTD was thought to be characterized by a good response to steroids, a low frequency of cerebral and renal disease, and a favourable prognosis (compared to SLE). The opinion about prognosis has now been revised, after longer follow-up studies, to the universally held view that the prognosis of MCTD is in fact worse than that of lupus, most of the deaths being attributable to pulmonary hypertension or, less commonly, the renal vasculopathy leading to malignant hypertension characteristic of scleroderma [8].

The Jo-1 antibody/antigen system was originally named after a patient, and the antibody was thought to be a marker for myositis, being detected in patients with polymyositis and rarely in dermatomyositis. It is often thought of as a myositis-specific antibody, even though it is now known that patients with anti-Jo-1 antibodies have other features of systemic connective tissue diseases, sometimes without myositis, but including Raynaud's phenomenon, arthritis (often

RA-like and erosive) and fibrosing alveolitis (reviewed in [9]). One feature of the syndrome is said to be 'mechanic's hands' which consists of hyperkeratosis of the fingers associated with cracking and fissuring of the skin overlying the finger pulp. When it was definitively demonstrated that the Jo-1 antigen was histidyl-tRNA synthetase, other tRNA synthetases, including alanyl- and threonyl-tRNA synthetase, were also described as less common autoantigens in polymyositis-associated overlap syndromes. The clinical features of all of these syndromes are similar so that they are often grouped together as the tRNA synthetase syndromes.

Antibodies to PM/Scl are part of a complex of precipitin reactions originally termed PM-1. Although the PM-1 antibody was originally regarded as a marker for polymyositis, anti-PM/Scl was found in ~15% and appeared to be associated with a polymyositis/scleroderma overlap syndrome [8]. The clinical features are very similar to those of other myositis-associated overlap syndromes with a high frequency of Raynaud's phenomenon, arthritis, myositis and interstitial lung disease [10]. Every patient studied to date is DR-3 positive. The PM/Scl antigen is nucleolar, and hence serum samples contain anti-nucleolar antibodies by immunofluorescence.

The clinical features of the three myositis-associated overlap syndromes are remarkably similar and would challenge the use of the word 'distinct' to describe MCTD. It would be difficult to guess the serology of an individual patient on clinical examination alone. However, there are subtle differences which can be appreciated when larger groups of patients are seen. All three are essentially SLE/scleroderma/polymyositis overlap syndromes with MCTD tending more to the SLE end of the spectrum. The PM/Scl syndrome veers towards scleroderma and the Jo-1 syndrome towards systemic sclerosis with more prominent lung disease and less skin involvement, although it may occasionally present as RA. Of the three, Jo-1 syndrome probably has the worst prognosis and requires the most aggressive treatment, and MCTD the least. Whether or not these syndromes can be classified as 'entities' awaits the demonstration of aetiology. If each antibody were shown to be induced by a different but specific aetiological agent, then the use of antibodies for diagnosis would be justified and the use of the word 'disease' substantiated. Until such time, it is probably best to maintain the term 'overlap syndrome' for all three, including MCTD.

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REFERENCES

1. Sharp GC, Irwin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease: an apparently distinct rheumatic disease syndrome associated with a specific antibody to extractable nuclear antigen. *Am J Med* 1972;**52**:148–59.
2. De Clerk LS, Meijers KA, Cats A. Is MCTD a distinct entity? Comparison of clinical and laboratory findings in MCTD, SLE, PSS and RA patients. *Clin Rheumatol* 1989;**8**:29–36.
3. Singsen BM, Bernstein HH, Kornreich HK, King KK, Hansen V, Tan EM. Mixed connective tissue disease in childhood. *J. Paediatr* 1971;**90**:893.
4. Maddison PJ. Overlap syndromes, mixed connective tissue disease and eosinophilic fasciitis. *Curr Opin Rheumatol* 1989;**1**:523–8.
5. Sharp GC, Irwin WS, May CM *et al.* Association of antibodies to ribonucleoprotein and Sm antigens with mixed connective tissue disease, systemic lupus erythematosus and other rheumatic diseases. *N Engl J Med* 1976;**295**:1149–54.
6. Bennet RM, O'Connel J. The arthritis of mixed connective tissue disease. *Ann Rheum Dis* 1978;**32**:397–403.
7. Marshall JB, Krertschmar JM, Gerhardt DC *et al.* Gastrointestinal manifestations of mixed connective tissue disease. *Gastroenterology* 1990;**98**:1232–8.
8. Venables PJW. Overlap syndromes. In: Klippel JH, Dieppe PA, eds. *Rheumatology*. London: Mosby, Mosby-Year Book, 1994;28.1–28.8.
9. Marguerie C, Bunn CC, Beynon HLC *et al.* Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl tRNA synthetases. *Q J Med* 1990;**77**:1019–38.
10. Marguerie C, Bunn CC, Copier J *et al.* The clinical and immunogenetic features of patients with antibodies to the nucleolar antigen PM-Scl. *Medicine* 1992;**71**:327–36.

THE DIAGNOSIS OF GOUT AND CPPD CRYSTAL ARTHROPATHY

GOUT generally presents to the clinician as an episodic, self-limited inflammatory arthritis. Identification of monosodium urate (MSU) crystals in a synovial fluid sample obtained from the inflamed joints during an attack, or from tophi at any time, is pathognomonic of the disease, providing a precise and simple diagnostic test. When the relationship between MSU crystals and gouty inflammation was originally established, it was assumed that crystal seeding in the joint cavity, or perhaps their *de novo* formation, was the cause of the gouty attacks, which tend to subside spontaneously in a few days or weeks. It was then supposed, despite occasional observations suggesting the contrary, that crystals were absent from the joint cavity between attacks, thus the clinician would have to wait for a new attack to make a diagnosis through crystal identification. During the last 15 yr, it has become apparent that crystals can be found in synovial fluid samples obtained from asymptomatic metatarsophalangeal [1] and knee joints [2] of these patients. The presence of MSU crystals in the synovial fluid is very regular in those joints previously inflamed in patients whose serum uric acid has not been lowered by treatment [3]. MSU crystals were also found in