

## REVIEW ARTICLE

## 'Overlap' syndromes

Ricard Cervera, Munther A Khamashta, Graham R V Hughes

Many of us at the end of a weekly lupus clinic are tempted to reflect that almost all shades of connective tissue 'overlap' occur, and that it is perhaps pointless to attempt too precise a definition in individual cases. The introduction of the concept of overlap syndromes was a pragmatic way to resolve an imprecise compromise. It represented an attempt to categorise various groups of disorders having in common some clinical and serological features, but failing to fulfil the established or proposed criteria for the classification of a distinct and separate entity, such as rheumatoid arthritis, progressive systemic sclerosis, systemic lupus erythematosus, or dermatomyositis. Some claim that as many as 25% of patients with connective tissue disease fall into one or other overlap group.<sup>1-5</sup>

In the past few years there has been limited success with attempts to describe distinct clinical entities, generally using serological markers. These include polemic entities such as mixed connective tissue disease,<sup>6-10</sup> subacute cutaneous lupus erythematosus,<sup>11 12</sup> or the recently described 'primary' antiphospholipid syndrome,<sup>13-16</sup> among others.

Following the observation by Sharp *et al*<sup>6</sup> that an overlap syndrome consisting of Raynaud's phenomenon, swollen hands, arthritis, and myositis was strongly associated with the presence of antibodies to nuclear ribonucleoprotein (RNP), the concept of mixed connective tissue disease has been useful. The serological specificity of these antibodies has been defined to epitopes on a 68 kD phosphoprotein uniquely associated with the RNP containing uridylic acid-rich small nuclear RNA (U-snRNP). At least 12 U-snRNPs have been identified, which account for about 1% of the total cellular RNA. The U1 to U6-snRNPs, with the exception of U3-snRNP, are known to play an important part in messenger RNA processing. In addition, a number of core DNAs coding for these antigens have been cloned and some specific characteristics of the deduced amino acid sequences are known.<sup>17</sup>

As the years go by clinical perception of mixed connective tissue disease has evolved considerably. For instance, patients with this disorder may have many other overlap and non-specific features, including pulmonary disease,<sup>18-21</sup> Sjögren's syndrome,<sup>22</sup> and even, renal<sup>23</sup> and cerebral disease.<sup>24</sup> Therefore, diagnosis of this entity must be based both on clinical and serological criteria. Although some attempts at classification have been made,<sup>25-27</sup> no definite agreement has been achieved.<sup>28 29</sup> In addition, it has been seen that the pattern of this

disease often changes to one of progressive systemic sclerosis. Interestingly, in such patients, it is common to see a gradual reduction of the hyperglobulinaemia and disappearance of the antibodies to U-snRNP.<sup>1</sup> Finally, there have been no major advances in identifying the aetiopathogenesis of this condition or in explaining the apparent association with antibodies to U-snRNP.<sup>29</sup> This has led to a protracted debate about the specificity or otherwise of mixed connective tissue disease.<sup>24</sup>

The title subacute cutaneous lupus erythematosus has been given to an overlap syndrome whose main clinical feature is the appearance of florid cutaneous lesions, often extremely photosensitive, sometimes with a characteristic serpiginous border. This disorder may include other systemic features such as Sjögren's syndrome, pericarditis, arthritis, and the occasional case of congenital heart block in the offspring (neonatal lupus). The serological association is with antibodies to SSA/Ro.<sup>11 12</sup> Recent knowledge of the structures that bear the SSA/Ro antigens has enabled definition of biochemical differences among patients with these antibodies. The first major antigen component of SSA/Ro to be described and cloned was a polypeptide of 60kD. Immunoblot techniques have been used recently to identify two other polypeptides as 52 and 48 kD species. Antibodies against the newly recognised 52 kD SSA/Ro peptide component have been found to be predominant in the sera from mothers of infants with neonatal lupus, whereas antibodies against the 60 kD antigens were not related.<sup>30</sup>

The term antiphospholipid syndrome has been recently proposed for a group of patients who have antiphospholipid antibodies—for example, anticardiolipin antibodies or the lupus anticoagulant, and in whom multiple venous and arterial thrombosis, recurrent fetal loss, and thrombocytopenia are common. These patients may also develop other features, including heart valve lesions, livedo reticularis, chorea, and haemolytic anaemia.<sup>31-33</sup> Whereas early studies concentrated on systemic lupus erythematosus or 'lupus-like' diseases,<sup>32</sup> it is now recognised that these manifestations may occur without any other feature of lupus being present, leading to the definition of the primary antiphospholipid syndrome.<sup>13-16</sup> Nevertheless, long term follow up of these patients has shown that some of them develop other connective tissue disease, such as systemic lupus erythematosus.<sup>34</sup> On the other hand, it is surprising that patients with high titres of antiphospholipid antibodies do not necessarily develop any of these clinical manifestations.

Lupus Research Unit,  
The Rayne Institute,  
St Thomas's Hospital,  
London SE1 7EH, UK  
R Cervera  
M A Khamashta  
G R V Hughes

Correspondence to:  
Dr Hughes.

Among other proposed overlap syndromes, a subset which seems to have clinical and serological specificity is the group of patients with polymyositis, pulmonary fibrosis, and antibodies against Jo-1 (histidyl-tRNA synthetase).<sup>35</sup> In addition, other overlap features are commonly associated, including Raynaud's phenomenon and Sjögren's syndrome.

It was obvious from the beginning that the occurrence of these overlap entities varied considerably from one centre to another. The reasons for these discrepancies may be multiple. Firstly, the clinical definitions of the major components of these syndromes—Raynaud's phenomenon, Sjögren's syndrome, myositis, lung disease, cutaneous rash, or thrombosis—are open to widely differing interpretation as well as to variation within individual patients over time. Secondly, the proposed serological 'markers'—anti-U-snRNP, anti-SSA/Ro, or antiphospholipid antibodies—are not specific for these syndromes and may be present in a variety of other autoimmune diseases.<sup>36</sup>

Clearly, the two reasons for attempts at subdivision concern treatment and prognosis. Some therapeutic generalisations are already possible. Mixed connective tissue disease in its florid form is often resistant to treatment (frequently more so than is 'classical' systemic lupus erythematosus), and the severity of joint inflammation may require treatment similar to that used in rheumatoid arthritis. The subset of patients with subacute cutaneous lupus erythematosus seems to be particularly amenable to antimalarial treatment.<sup>37</sup> Patients with the antiphospholipid syndrome are more prone to thrombosis than to inflammatory disease such as vasculitis and treatment is thus geared towards anticoagulation.<sup>38</sup> As to prognosis, only time will tell. Perhaps, some of the overlap syndromes may be better termed 'transitional' syndromes because they will progress to another connective tissue disease.

Identification of the antigens at molecular level provides important insights into the pathogenesis of connective tissue diseases. Although autoantibody 'fingerprinting' has contributed much to the definition of disease subsets, the whole movement has slightly run out of steam. Ignorance of prognosis of these overlap syndromes dictates that precise clinical descriptions are still central to definition.

- 1 Hughes G R V. Overlap syndromes. In: Jayson M I V, Black C M, eds. *Systemic sclerosis: scleroderma*. London: Wiley, 1988: 331-40.
- 2 Tuffanelli D L, Winkelmann R K. Systemic scleroderma. A clinical study of 727 cases. *Arch Dermatol* 1961; **84**: 359-71.
- 3 Dubois E L, Chandor S, Friou G J, Buschel M. Progressive systemic sclerosis (PSS) and localized scleroderma (morphea) with positive LE cell test and unusual systemic manifestations compatible with systemic lupus erythematosus (SLE). *Medicine (Baltimore)* 1971; **50**: 199-222.
- 4 Keil H. Dermatomyositis and systemic lupus erythematosus. *Arch Intern Med* 1969; **60**: 109-39.
- 5 Dubois E L. The relationship between systemic lupus erythematosus, progressive systemic sclerosis and mixed connective tissue disease. In: Dubois E L, ed. *Systemic lupus erythematosus*. Los Angeles: USC Press 1974: 477.
- 6 Sharp G E, Irving W, Tan E, Gould G, Holman H. Mixed connective tissue disease: An apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med* 1972; **52**: 148-59.
- 7 Bennet R, O'Connell D. Mixed connective tissue disease. A clinicopathological study of 20 cases. *Semin Arthritis Rheum* 1980; **10**: 25-52.
- 8 Bennet R. Mixed connective tissue disease and other overlap syndromes. In: Kelley W, Harris E D Jr, Ruddy S H, Sledge G. *Textbook of rheumatology*. Philadelphia: Saunders, 1985: 1115.
- 9 Ramos Niembro F, Alarcón-Segovia D, Hernández Orditz J. Articular manifestations of mixed connective tissue disease. *Arthritis Rheum* 1979; **22**: 43-51.
- 10 Sharp G, Singen B. Mixed connective tissue disease. In: McCarthy D, ed. *Arthritis and allied conditions*. Philadelphia: Lea and Febiger, 1985: 962-70.
- 11 Sontheimer R D, Thomas J R, Gilliam J N. Subacute cutaneous lupus erythematosus: a cutaneous marker for a distinct lupus erythematosus subset. *Arch Dermatol* 1979; **115**: 1409-15.
- 12 Herrero C, Bielsa I, Font J, et al. Subacute cutaneous lupus erythematosus. Clinicopathological findings in 13 cases. *J Am Acad Dermatol* 1988; **19**: 1057-62.
- 13 Asherson R A. A 'primary' antiphospholipid syndrome? *J Rheumatol* 1988; **15**: 1742-6.
- 14 Mackworth-Young C G, Loizou S, Walport M J. Primary antiphospholipid syndrome: features of patients with raised anticardiolipin antibodies and no other disorder. *Ann Rheum Dis* 1989; **48**: 362-7.
- 15 Alarcón-Segovia D, Sánchez-Guerrero J. Primary antiphospholipid syndrome. *J Rheumatol* 1989; **16**: 482-8.
- 16 Asherson R A, Khamashta M A, Ordi-Ros J, et al. The "primary" antiphospholipid syndrome: major clinical and serological features. *Medicine (Baltimore)* 1989; **68**: 366-74.
- 17 Van Venrooij W J, Sillekens P T G. Small nuclear RNA associated proteins: autoantigens in connective tissue diseases. *Clin Exp Rheumatol* 1989; **7**: 635-45.
- 18 Harman C, Wolfe J, Lillard S, Heed C, Cordon R, Sharp G. Pulmonary involvement in mixed connective tissue disease [Abstract]. *Arthritis Rheum* 1976; **19**: 801.
- 19 Weiner-Kronish J, Solinger A, Warnock M, Churg A, Ordonez N, Golden J. Severe pulmonary involvement in mixed connective tissue disease. *Am Rev Respir Dis* 1981; **124**: 499-503.
- 20 Sullivan W, Hurst D, Harmon C, et al. A prospective evaluation emphasizing pulmonary involvement in patients with connective tissue disease. *Medicine (Baltimore)* 1984; **63**: 92-107.
- 21 Derderian S, Tellis C, Abbrecht P, Welton R C, Rajagopal K R. Pulmonary involvement in mixed connective tissue disease. *Chest* 1985; **88**: 45-8.
- 22 Alarcón-Segovia D. Symptomatic Sjögren syndrome in mixed connective tissue disease. *J Rheumatol* 1976; **3**: 191-5.
- 23 Kitridou R, Akmal M, Ehresmann G, Quismorio F, Massry S. Nephropathy in mixed connective tissue disease [Abstract]. *Arthritis Rheum* 1980; **23**: 704.
- 24 Lázaro M A, Maldonado Cocco J A, Catoggio L J, Babini S M, Messina O D, García Morteo O. Clinical and serologic characteristics of patients with overlap syndrome: Is mixed connective tissue disease a distinct clinical entity? *Medicine (Baltimore)* 1989; **68**: 58-65.
- 25 Sharp G C. Diagnostic criteria for classification of MCTD. In: Kasukawa R, Sharp G C, eds. *Mixed connective tissue diseases and anti-nuclear antibodies*. Amsterdam: Elsevier, 1987: 23-32.
- 26 Alarcón-Segovia D, Villarreal M. Classification and diagnostic criteria for mixed connective tissue diseases. In: Kasukawa R, Sharp G C, eds. *Mixed connective tissue diseases and anti-nuclear antibodies*. Amsterdam: Elsevier, 1987: 33-40.
- 27 Kasukawa R, Tojo T, Miyawaki S, et al. Preliminary diagnostic criteria for classification of mixed connective tissue disease. In: Kasukawa R, Sharp G C, eds. *Mixed connective tissue diseases and anti-nuclear antibodies*. Amsterdam: Elsevier, 1987: 41-7.
- 28 Alarcón-Segovia D, Cardiel M H. Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients. *J Rheumatol* 1989; **16**: 328-34.
- 29 Maddison P J. Overlap syndromes, mixed connective tissue disease, and eosinophilic fasciitis. *Current Opinion in Rheumatology* 1989; **1**: 523-8.
- 30 Buyon J P, Ben-Chetrit E, Karp S, et al. Acquired congenital heart block. Pattern of maternal antibody response to biochemically defined antigens of the SSA/Ro-SSB/La system in neonatal lupus. *J Clin Invest* 1989; **84**: 627-34.
- 31 Asherson R A, Harris E N. Anticardiolipin antibodies. Clinical associations. *Postgrad Med J* 1986; **62**: 1081-7.
- 32 Boey M L, Colaço C B, Gharavi A E, Elkoni K B, Loizou S, Hughes G R V. Thrombosis in systemic lupus erythematosus: striking association with the presence of circulating lupus anticoagulant. *Br Med J* 1983; **287**: 1021-3.
- 33 Cervera R, Font J, López-Soto A, et al. Isotype distribution of anticardiolipin antibodies in systemic lupus erythematosus: prospective analysis of a series of 100 patients. *Ann Rheum Dis* 1990; **49**: 109-13.
- 34 Baguley E, Asherson R A, Pal C, Harris E N, Khamashta M, Hughes G R V. The antiphospholipid syndrome: treatment and five year follow-up [Abstract]. *Br J Rheumatol* 1989; **28** (suppl 2): 106.
- 35 Bernstein R M, Morgan S J, Chapman J, et al. Anti-Jo-1 antibody: a marker for myositis with interstitial lung disease. *Br Med J* 1984; **289**: 151-2.
- 36 Bernstein R M. Humoral autoimmunity in systemic rheumatic disease. *J R Coll Physicians Lond* 1990; **24**: 18-25.
- 37 Lanham J, Hughes G R V. Antimalarial therapy in SLE. *Clin Rheum Dis* 1982; **8**: 279-98.
- 38 Hughes G R V, Khamashta M A. Anticardiolipin antibody. A cause of a tendency to thrombosis. *Br Med J* 1989; **299**: 1414-5.