Overlap Syndromes

ROBERT BENNETT

KEY POINTS

Diffuse connective tissue diseases (DCTDs) are usually associated with autoimmunity to spliceosomal components (U-RNPs, heterogeneous RNPs), nucleosomal components (nucleosomes, DNA, histones), and proteosomal components (HC9, LMP2).

Apoptotic modification of molecules often renders them more antigenic.

The evolution of symptoms may be associated with molecular mimicry and epitope spreading.

In their early stages most autoimmune connective tissue diseases are not clinically well differentiated; this stage of disease progression is called undifferentiated connective tissue disease (UCTD).

About 50% of UCTDs remain undifferentiated.

Important clues about the eventual direction of differentiation can be obtained from nail-fold capillary microscopy and the type of autoantibody profile combined with regular clinical evaluations.

Mixed connective tissue disease (MCTD) is the prototypical overlap disease with features of lupus, scleroderma, and inflammatory myositis. This overlap is not seen at the outset of MCTD; rather it often takes several years to develop.

The most common presentation of MCTD is Raynaud’s phenomenon.

MCTD is most commonly associated with antibodies to U1-RNP; in general this antibody predicts lack of severe renal and central nervous system (CNS) involvement.

The major cause of death in MCTD is pulmonary hypertension, and all MCTD patients should have regular echocardiograms to determine its evolution.

The management of overlap syndromes is based on the usual treatment of the constituent features of its clinical components (i.e., systemic lupus erythematosus [SLE], scleroderma, and inflammatory muscle disease).

4. Dermatomyositis (DM)
5. Rheumatoid arthritis (RA)
6. Sjögren’s syndrome

All six classic AICTDs are descriptive syndromes without a “gold standard” for diagnosis. The diagnosis of a well-differentiated AICTD is usually readily apparent without recourse to extensive investigations. However, in the early stages, there are often common features such as Raynaud’s phenomenon, arthralgias, myalgias, esophageal dysfunction, and positive tests for antinuclear antibodies (ANA). In such cases the diagnosis is not always so obvious; this is often referred to as undifferentiated connective tissue disease (UCTD). About 35% of such patients have clinical overlap syndromes, whereas most differentiate into a clinical picture consistent with the traditional description of an AICTD. In some instances one AICTD evolves into another AICTD over time.

The propensity for differentiation into a classic AICTD or the maintenance of an overlap state is often associated with distinctive serologic profiles and major histocompatibility (MHC) linkages. Although most rheumatologists generally feel more comfortable thinking in terms of the classic AICTD paradigms, a case can be advanced for using serologic profiles and HLA typing to better understand the clinical features and prognoses. In this respect a careful analysis of the overlap syndromes and their serologic associations has provided insights for understanding the clinical heterogeneity of the AICTDs. Researchers have reported numerous clinical correlations of autoantibodies (Table 86-1).

EPIDEMIOLOGY

The reported prevalence of AICTDs is variable, depending on methodology, nature of referral bias, and ethnicity. It is generally accepted that Sjögren’s syndrome has the highest prevalence (0.5 to 3.6%), with SLE being much lower at about 15 to 50 per 100,000. Scleroderma, polymyositis, and dermatomyositis are relatively rare AICTDs, occurring in fewer than 10 per 100,000. Experts are increasingly realizing that overlap syndromes of scleroderma and myositis are more common than the “pure” forms of the disease. There are no epidemiology studies of overlap syndromes, apart from Japan, where the reported prevalence of mixed connective tissue disease (MCTD) was 2.7 per 100,000. The syndrome of MCTD usually occurs as an isolated finding, but there are reports of a familial occurrence. Unlike SLE, precipitation by sun exposure has not been described in patients with MCTD. Likewise, drug exposure has not been related to the onset of MCTD, although a transient appearance of anti-RNP antibodies has been seen at the initiation of
of procainamide therapy. Vinyl chloride and silica are the only environmental agents that have been associated with MCTD so far.

**AUTOIMMUNITY IN OVERLAP SYNDROMES**

Compelling evidence indicates that autoimmunity is often antigen driven by components of subcellular particles, in particular spliceosomes, nucleosomes, and proteasomes.

**Autoimmunity to Spliceosomal Components**

Certain components of the spliceosome are common targets of autoimmunity in the AICTDs. Furthermore, it appears that post-translational modifications of these molecules, as occurs during apoptosis, are often associated with increased immunogenicity. Spliceosomes are complex nuclear particles made up of some 300 distinct proteins and 5 RNAs, which are involved in the processing of preribosomal RNA (pre-mRNA) into mature “spliced RNA.” Two major spliceosomal subunits are antigenic targets in autoimmunity: (1) small nuclear ribonucleoprotein particle (snRNPs) and (2) heterogeneous nuclear RNP particles (hnRNPs).

The snRNPs contain small RNA species ranging in size from 80 to 350 nucleotides that are complexed with proteins. These RNAs contain a high content of uridine and are therefore called U-RNAs; 5 different U-RNAs were defined on the basis of immunoprecipitation (U1, U2, U4, U5, and U6). Autoantibodies to these complexes are mainly directed to the protein components. Anti-Sm antibodies precipitate five proteins with molecular weights of 28,000 (B’), 16,000 (D), 13,000 (E), 12,000 (F), and 11,000 (G); five of these polypeptides are common to the U1, U2, U4, U5, and U6 RNAs. Anti-RNP antibodies precipitate three proteins with molecular weights of 68,000 (70K), 33,000 (A’), and 22,000 (C); these polypeptides are uniquely associated with U1 RNA (Figure 86-1). The clinical correlates considered to be distinctive of MCTD are associated with the 70 kD specificity with an immunodominant epitope embracing amino acid residue 125 flanked by important conformational residues at positions 119-126 (see Figure 86-1). On the other hand, SLE is associated with anti-Sm antibodies.

The hnRNPs are among the most abundant proteins in the eukaryotic cell nucleus. They contain pre-mRNA associated with 30 small proteins that are all structurally related and have molecular weights of 33 to 43 kD. Nine hnRN core proteins have been designated A1, A2, B1a, B1b, B1c, B2, C1, C2, and C3. An antibody termed anti-RA33, which
targets the 33 kD hnRNPA2, is particularly interesting because it is found in about one-third of sera from patient with RA, SLE, and MCTD. It also has associations with patient subsets of erosive arthritis in SLE, scleroderma, and MCTD and predicts the eventual development of RA in patients with early polyarthritis. Importantly, this association with anti-RA33 is not seen in scleroderma (sine erosions), PM, or overlaps of PM/Scl or PM/DM. The antigenic epitopes of hnRNPA2 contain two RNA binding regions at the N-terminal end and a glycine-rich C-terminal region. Certain disease subsets target these two RNA binding regions differently. For instance, RA and SLE sera preferentially react with the complete second RNA binding domain, whereas MCTD sera target an epitope that spars both RNA binding domains.

Autoimmunity to Nucleosomal Components

Nucleosomes are the compact building blocks of chromatin and consist of an octamer of two copies of histones H2A, H2B, H3, and H4, wrapped approximately 146 base pairs of DNA (Figure 86-2). During apoptosis endonucleases cleave chromatin with the liberation of nucleosomal particles. Following the release into the cytoplasm, nucleosomes migrate to the surface of the dying cell and thus become accessible to B cell receptors. The development of autoimmunity has been linked to defective phagocytosis of apoptotically released constituents. Nucleosomal antibodies are directed to antigenic determinants on the intact nucleosome rather than its individual components, DNA and histones. In a study of 496 patients with 13 different AICTD and 100 patients with hepatitis C, anti-nucleosome antibodies were found in the sera of patients with SLE (71.7%), Scl (43.9%), and MCTD (45.0%).

Autoimmunity to Proteosomal Components

The 26S proteasome is a large subcellular particle involved in the degradation of proteins that have been tagged with ubiquitin, resulting in the generation of peptides for presentation by the MHC class I molecules (Figure 86-3). There is good evidence that it is the target of an autoimmune response in AICTD. Antibodies to proteosomal subunits have been reported in patients with autoimmune myocarditis, systemic lupus erythematosus, and primary Sjögren’s syndrome. Circulating 20S proteasomes (c20S) subunits appear to have an association with disease activity in MCTD and SLE.

Generation of Autoimmunity

The antibody response to just one component of an intracellular structure such as a spliceosome will result in the uptake of the entire particle by antigen processing cells.
The nucleosome is the fundamental repeating unit of chromatin. The central part of the nucleosome is composed of a tetramer of two molecules of histones H3 and H4, flanked by two dimers of histones H2A and H2B. This central core is surrounded by two super-helical turns, consisting of 146 base pairs of histone-free DNA. Histone H1 is located at the point where DNA enters and exits the nucleosome. Antibodies to the nucleosome arise early in the evolution of systemic lupus erythematosus—before anti-DNA and antihistone antibodies. Thus the nucleosome is thought to be an important early autoantigen in the development of epitope spreading. Nucleosome antibodies are also found in scleroderma and mixed connective tissue disease. (From Amoura Z, Koutouzov S, Piette C, et al: The role of nucleosomes in lupus. Curr Opin Rheumatol 12:369–373, 2000.)

Disorders are characterized by differential degrees of epitope spreading. The widest range of antibodies, to both snRNP and hnRNP, is seen in SLE; a more restricted antispliceosomal antibody repertoire to snRNP and hnRNP is seen in MCTD; and in RA the antispliceosomal antibody repertoire is restricted to hnRNP. In general the autoimmune rheumatic diseases are characterized by the production of autoantibodies that recognize evolutionarily conserved molecules. The mechanism whereby these “hidden” intracellular molecules become autoantigens is an area of ongoing research. The two main theories are apoptotic modification and molecular mimicry.

Figures 86-2 and 86-3 illustrate the role of nucleosomes in lupus.

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The initial stimulus for a first antibody response may be a non-self-epitope possessing a peptide region that mimics a self-epitope—so-called molecular mimicry. Environmental stressors such as infection, toxins, drugs, and ultraviolet light may, under some circumstances, induce accelerated apoptosis. A critical limitation to molecular mimicry is the necessity for the antigenic sequence to undergo TCR recognition. Helper T lymphocytes (CD4+) usually recognize peptides of 12 to 16 amino acids in the context of HLA class II molecules. However, in some instances smaller peptides may be recognized. They can be more immunostimulatory than the parent ligand. Thus antigen recognition by T cells is highly degenerate and expands the potential for molecular mimicry. The universe of molecules containing a pentapeptide, for example, is much greater than for 12 amino residue peptide. Once an immune response to one component of an immunogenic molecular complex has been elicited, other proteins/epitopes of the complex may become antigenic by the same process of epitope spreading.15

**UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE**

**KEY POINTS**

Nearly all patients with a UCTD have Raynaud’s phenomenon in combination with an unexplained synovitis.

Nail-fold capillary microscopy is useful in evaluating the potential pathology.

Antibody profiles are useful in predicting the eventual clinical features: U1 RNP antibodies predict the differentiation into MCTD. DNA antibodies predict the differentiation into SLE. Nucleolar antibodies predict the differentiation into systemic sclerosis (SSc). Synthetase and PM/ScI antibodies predict the differentiation into a myositis overlap syndrome.

Rheumatologists frequently see patients who present with a weakly positive ANA and nonspecific symptoms such as arthralgias, fatigue, and cold sensitivity. The critical question in such patients is “will they develop a connective tissue disease?” or “do they have fibromyalgia?”

The answer to this question is not always straightforward because fibromyalgia is not a diagnosis of exclusion22; it is a common comorbidity with the well-defined CTDs and is often associated with cold-induced vasospasm.23 An algorithm for diagnosing UCTDs is given in Figure 86-4. In the early stages of a CTD, there may be just one or two suspicious clinical and laboratory features, but a definitive diagnosis cannot always be made. In such cases a working diagnosis of undifferentiated connective tissue disease (UCTD) may be appropriate.23 Most patients with this UCTD have Raynaud’s phenomena with or without an unexplained polyarthritis and a positive ANA with usually just a single autoantibody specificity, often anti-Ro and anti-RNP.24 A 5-year follow-up study of 665 patients with UCTD reported that only 34% developed a well-defined CTD (RA—13.1%, Sjögren’s—6.8%, SLE—4.2%, MCTD—4%, Scl—2.8%, systemic vasculitis—3.3%, and PM/DM—0.5%).25 Certain combinations of features are predictive for the development of an established CTD: Polyarthritis plus U1RNP antibodies predict MCTD, sicca symptoms plus anti-SSA/SSB antibodies predict Sjögren’s syndrome, Raynaud’s phenomenon plus a nucleolar ANA pattern predict Scl, polyarthritis plus high levels of rheumatoid factor (RF) predict RA, and fever/serositis plus a homogeneous ANA pattern or anti-dsDNA antibodies predict progression into SLE (Table 86-2). The identification of a pathologic nail-fold capillary pattern can provide some early indication that the UCTD may progress to systemic sclerosis (SSc) or MCTD (Figure 86-5).26 Low levels of vitamin D are also reported to be a risk factor for the development of UCTDs and should be evaluated and corrected in all such patients.27

**SCLERODERMA OVERLAPS**

**KEY POINTS**

Scleroderma overlap syndromes include scleroderma variants such as calcinosis, Raynaud phenomenon, esophageal involvement, sclerodactyly, and telangiectasia (CREST), myositis associated with sclerodactyly, and MCTD.

Raynaud’s phenomenon is often the first clinical feature of SSc overlaps and must be distinguished from primary cold Raynaud’s (i.e., cold-induced vasospasm).

The finding of thickened and dilated capillaries on nail-fold microscopy and pathologic autoantibodies (e.g., Scl-70, anticientromere, PM/ScI, U1-RNP) are important clues about the development of an overlap syndrome.

CREST has a common overlap with primary biliary cirrhosis.

Pulmonary fibrosis and pulmonary hypertension are the main causes of morbidity/mortality.

Scleroderma-like disorders (e.g., eosinophilic fasciitis, scleromyxedema, nephrogenic fibrosis, scleredema) need to be considered in the differential diagnosis of scleroderma overlaps.

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**Table 86-2 Disorders Associated with Increased Fibrosis**

<table>
<thead>
<tr>
<th>Localized</th>
<th>Morphea</th>
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<tbody>
<tr>
<td>Scleroderma</td>
<td>Scleromyxedema</td>
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<tr>
<td>Eosinophilic fasciitis</td>
<td>Peyronie’s disease</td>
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<tr>
<td>Dupuytren’s contracture</td>
<td>Pachydermoperiostitis</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>Sclerosing cholangitis</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Cryptogenic fibrosis</td>
</tr>
</tbody>
</table>

**Systemic**

| Scleroderma | Metastatic carcinoma |
| Retropertioneal fibrosis | Graft-versus-host disease |
| Nephrogenic systemic fibrosis | Amyloidosis |
Several fibrotic conditions may mimic scleroderma (see Table 86-2). Scleroderma itself has a widespread heterogeneity of disease expression ranging from a diffuse cutaneous disease, with a poor prognosis, to a limited cutaneous involvement, with generally a good prognosis. Furthermore, some patients with Scl have a prominent overlap with other connective tissue diseases. In many cases, these overlaps occur in patients who do not have prominent skin involvement (sine scleroderma) or with the limited form of the disease—CREST. Approximately 90% of patients with Scl have a positive ANA. Scleroderma-related antibodies include topoisomerase 1 (Scl-70), anticientromere (ACA),
A German registry for scleroderma has reported on patterns of organ involvement in two subsets of 1483 SSc patients. Limited distal skin involvement (distal to the knee and elbows) was seen in 46% (the lcSSc group), and 33% had progressive widespread scleroderma (rapid involvement of trunk, face, and extremities—the dcSSc group). An overlap syndrome was seen in 11%, and 8% were undifferentiated. The extent of organ involvement varied between subgroups. For instance, musculoskeletal involvement was seen in 68% of the overlap group compared with 57% of the dcSSc group. Pulmonary fibrosis (56%) and pulmonary hypertension (19%) were most common in the dcSSc group, but pulmonary hypertension was seen in 15% of the dcSSc group.

Specific antibody profiles tend to be associated with distinctive patterns of morbidity and mortality. Patients possessing anticientromere, anti U3 snRNP, and anti Th/To antibodies tend to have the limited form of Scl, whereas anti-Scl-70, ACA, and anti-RNAP are associated with diffuse skin involvement and systemic disease. Anti-PM/Scl antibodies are associated with a myositis/Scl overlap and a tendency to develop pulmonary interstitial disease. About 60% of patients with scleroderma have obvious synovitis, and 35% are positive for RF. Erosive arthritis in Scl has an association with anti-RA33; the Scl component in such overlap patients is often an incomplete form of CREST. The limited form of scleroderma has a well-documented overlap with primary biliary cirrhosis. The distinctive antibody association of scleroderma with PBC is antimitochondrial antibodies. Conversely, anticientromere antibodies have been found in 10% to 29% of patients with PBC; approximately half developed some features of the CREST syndrome. Hence a serologic overlap between the two syndromes is more prevalent in the clinical overlap. Low-grade muscle involvement is not uncommon in scleroderma, being described in between 50% and 80% of patients. A European review of 114 scleroderma overlap patients reported a 95% PM-Scl antibody positivity with 80% having an inflammatory myositis. This “scleromyositis” differed from MCTD by coexistent features of dermatomyositis (myalgia, myositis, Gottron sign, heliotrope rash,}

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**Figure 86-5** Nail-fold capillaroscopy in patients with systemic sclerosis and mixed connective tissue disease (MCTD). A, Normal capillaries. B, MCTD patient showing dilated and thickened capillary loops. C, Early scleroderma with irregular capillaries and mild dropout. D, Advanced scleroderma with capillary dropout and neoangiogenesis. (Modified from Cutolo M, Sulli A, Pizzorni C, Smith V: Capillaroscopy as an outcome measure for clinical trials on the peripheral vasculopathy in SSc—is it useful? Int J Rheumatol pii:784947, 2010.)
calcinosi), but no overlap SLE features, as is characteristic of classic MCTD. Many of these patients had a deforming arthritis of the hands. In general they had a chronic benign course, and most were steroid responsive. Scleroderma lupus overlaps are less common. However, Scl patients often have antinuclear other than ACA and Scl-70.

Nonscleroderma fibrotic disorder may be mistaken for a scleroderma overlap at initial presentation (see Table 86-2); although these disorders may have some systemic involvement, they seldom exhibit overlap features with other AICTDs.

Nephrogenic systemic fibrosis (NSF) is a fibrotic disorder that develops in some patients following exposure to gadolinium-containing contrast agents; most patients have pre-existing renal disease. Histologically there is fibroblast proliferation, thickened collagen bundles, and deposits of mucin, similar to those observed in scleromyxedema. The clinical presentation is a rapid progression with confluence of initially focal areas of indurated skin (Figure 86-6). The face is usually spared, but joint contractures may occur at the elbows and knees, and systemic involvement with pulmonary and neurologic symptoms can develop in refractory cases. NSF is usually nonresponsive to corticosteroids and immunosuppressive therapy.

Eosinophilic fascitis presents with limited scleroderma-like skin changes involving the extremities (see Figure 86-6). The correct diagnosis is suggested by finding a peripheral eosinophilia and a hyper-gammaglobulinemia. The definitive diagnosis is established by a full-thickness skin biopsy that shows a diffuse inflammation of the fascia. Initial treatment is with corticosteroids (prednisone 0.5 to 1 mg/kg) tapering according to the clinical response; some patients need to continue moderate-dose corticosteroids for up to 2 years. Methotrexate and mycophenolate may be used in refractory cases.

Scleromyxedema is characterized by cutaneous mucinosi and is often associated with a gammapathy, usually IgM and light chains. The mucinous skin lesions appear as waxy papules on the face, neck, and limbs. If the papules coalesce, it may be mistaken for scleroderma (see Figure 86-6). Systemic involvement may occur with dysphagia, proximal muscle weakness, pulmonary, cardiac, and renal complications. It is difficult to manage; corticosteroids are usually tried initially, in refractory cases some benefit has

been reported for intravenous immunoglobulin and thalidomide.

Scleredema is a cutaneous mucinosis that often starts with a febrile episode and resolves spontaneously.\(^{46}\) More chronic scleredema has been associated with paraproteinemia including multiple myeloma and diabetes mellitus. The dermis is thickened with increased collagen glycosylation, as in diabetic stiff skin syndrome. The face and neck are commonly involved, and there is relative sparing of the hands and feet (see Figure 86-6). Systemic organ involvement is rare, but a monoclonal gamopathy is sometimes seen. Such cases need to be worked up for lymphoma. Refractory cases have been helped by local radiotherapy.

**MYOSITIS OVERLAPS**

**KEY POINTS**

- Myositis overlap syndromes are more common than the classic descriptions of PM or DM.
- Amino-acyl trRNA synthetase antibodies (ARS) are associated with myositis, arthritis, and interstitial lung disease.
- Arthritis and interstitial lung disease may antedate the appearance of myositis in patients with ARS.
- Antibodies to synthetases, signal recognition particle (SRP), and nucleoporins tend to be associated with corticosteroid unresponsiveness.
- Antibodies to U1RNP, Pm-Scl, or Ku are associated with corticosteroid responsiveness.
- Antibodies to 155 kDa and 140 kDa proteins have been associated with an increased risk of myositis-associated malignancy.

Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) are the classic idiopathic inflammatory myopathies (IIM), yet the same clinical picture and investigational findings may be found in patients with SLE, Scl, MCTD, and Sjögren’s syndrome. Such overlaps, especially with scleredema, have been reported as being more common in the classic description of polymyositis.\(^{4}\) When clinical overlaps emerge, they are most commonly associated with specific autoantibodies, namely anti-PM-Scl, anti-Ku, U1 RNP, Jo-1, SRP, and ARS.\(^ {16}\) The arthropathy associated with polymyositis is characterized by deforming subluxations (particularly of the distal interphalangeals and thumbs) with only minor erosive changes. Another myositis overlap syndrome is seen in patients with amino-acyl trRNA synthetase antibodies (ARS).\(^ {45}\) This is a family of enzymes that catalyze the transfer of a specific amino acid to its cognate transfer RNA—the commonest association is with anti-Jo-1 (histidine-trRNA synthetase). The clinical syndromes associated with the various antisynthetase antibodies are similar, with remissions and exacerbations characterized by inflammatory myositis, fever, Raynaud’s syndrome, and skin problems (mechanic’s hands).\(^ {46}\) The arthritis of ARS may initially mimic RA with an inflammatory arthritis and nodules; erosions, however, do not occur.\(^ {47}\) Interstitial lung disease may be a presenting clinical feature of patients with ARS antibodies, with myopathy occurring much later. The association of myositis in patients with anti-U1-RNP antibodies is usually seen in the context of MCTD.\(^ {10}\) Antibodies to the signal recognition particle (SRP) have been reported in 4% of patients with Scl/PM overlap; these patients usually have a severe, rapidly progressive myositis with prominent muscle fiber necrosis without much inflammatory cell infiltration.\(^ {15}\)

A 2006 clinical and longitudinal study of 100 consecutively treated French Canadian patients with idiopathic IIM concluded that the original Bohan and Peter classification of inflammatory myopathies should be abandoned because 60% of patients with IIM were found to have an overlap syndrome.\(^ {4}\) In this study an overlap syndrome was based on the presence of an inflammatory myopathy as per the Bohan and Peter classification,\(^ {47}\) plus at least one clinical overlap feature (Table 86-3), or one of the following autoantibodies: synthetases, centromere, topo I, RNA-polymerases I or III, Th, U1RNP, U2RNP, U3RNP, U5RNP, Pm-Scl, Ku, SRP and nucleoporins (see Table 86-3). The distinction between classic PM/DM and an overlap syndrome was reported to be of prognostic/therapeutic significance because classic PM nearly always pursued chronic course with 50% of patients being initially unresponsive to corticosteroid therapy. Pure dermatomyositis was almost always chronic, but most had an initial response to corticosteroids. On the other hand, myositis overlap syndromes (usually with scleredema features) were almost always responsive to corticosteroids (+90% response rate). When overlap patients were divided according to antibody subsets, antisynthetase, SRP, and nucleoprotein aAbs were markers for treatment-resistant myositis, whereas aAbs to U1RNP, Pm-Scl, or Ku were markers for corticosteroid responsiveness. Patients with autoimmune myositis, especially dermatomyositis, are at risk of developing cancer,\(^ {17}\) and it has been problematic as to how far and how often one should pursue a malignancy workup. It is now apparent that the finding of an antibody against 155 kDa and 140 kDa protein specificities (anti-155/140 antibody) signifies a significant risk for the co-occurrence of a malignancy and points to the need for a thorough cancer workup.\(^ {18}\)

**MIXED CONNECTIVE TISSUE DISEASE**

**KEY POINTS**

- The clinical overlap features of MCTD (i.e., Scl, SLE, and IIM) seldom occur concurrently but develop sequentially over the course of months or years.
- Raynaud’s phenomenon is seen in nearly all patients with MCTD; if Raynaud’s syndrome is absent, the diagnosis should be reconsidered.
- About 25% of MCTD patients develop renal involvement—usually membranous glomerulonephritis. Proliferative glomerulonephritis is uncommon in MCTD.
- Serious CNS involvement is rare in MCTD; the commonest findings are trigeminal neuropathy and sensorineural hearing loss.
- Pulmonary HTN is the commonest cause of death in MCTD patients and should be screened for on an ongoing basis.
Table 86-3  Suggested Classification for Inflammatory Myopathies

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>PM</td>
<td>Pure polymyositis</td>
</tr>
<tr>
<td>DM</td>
<td>Pure dermatomyositis</td>
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<tr>
<td>OM</td>
<td>Overlap myositis: myositis with at least 1 clinical overlap feature and/or an overlap autoantibody</td>
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<tr>
<td>CAM</td>
<td>Cancer-associated myositis: with clinical paraneoplastic features and without an overlap autoantibody or anti-Mi-2</td>
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Bohan and Peter’s\textsuperscript{a} Definition of Myositis

1. Symmetric proximal muscle weakness.
2. Elevation of serum skeletal muscle enzymes.
3. Electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges.
4. Muscle biopsy abnormalities of degeneration, regeneration, necrosis, phagocytosis, and an interstitial mononuclear infiltrate.
5. Typical skin rash of DM including the heliotrope rash, Gottron sign, and Gottron papules.

Definite myositis: 4 criteria (without the rash) for PM, 3 or 4 criteria (plus the rash) for DM.
Possible myositis: 2 criteria (without the rash) for PM, 2 criteria (plus the rash) for DM.

Definition of Clinical Overlap Features

Inflammatory myopathy plus at least 1 or more of the following clinical findings: polyarthritis, Raynaud's phenomenon, sclerodactyly, scleroderma proximal to metacarpophalangeal joints, typical SSC-type calcinosis in the fingers, lower esophageal or small-bowel hypomotility, DLCO lower than 70% of the normal predicted value, interstitial lung disease on chest radiogram or computed tomography scan, discoid lupus, anti-native DNA antibodies plus hypocomplementemia, 4 or more of 11 American College of Rheumatology criteria for systemic lupus erythematosus, antiphospholipid syndrome.

Definition of Overlap Autoantibodies

Antisynthetases (Jo-1, PL-7, PL-12, OJ, EJ, KS); scleroderma-associated autoantibodies (scleroderma-specific antibodies: centromeres, topoisomerase I, RNA polymerases I or III, Th; and antibodies associated with scleroderma overlap: U1-RNP, U2-RNP, U3-RNP, U5-RNP, Pm-Scl, Ku, and other autoantibodies (signal recognition particle, nucleopilins)).

Definition of Clinical Paraneoplastic Features

Cancer within 3 yr of myositis diagnosis, plus absence of multiple clinical overlap features; plus, if cancer was cured, myositis was cured as well.

MCTD was described by Sharp and colleagues\textsuperscript{a} in a 1972 paper reporting an overlap of SLE, Scl, and PM. This was the first overlap syndrome defined in terms of a specific antibody—namely antibodies to a ribonuclease-sensitive extractable nuclear antigen (ENA). Over the past 38 years, many studies have explored the clinical correlates of this antibody system (now called U1 RNP).

Serologic Features

The basic premise of the MCTD concept is that the presence of high-titer anti-U1 RNP antibodies modifies the expression of an AICTD in ways that are relevant to prognosis and treatment.\textsuperscript{c} The first clue to diagnosing MCTD is usually a positive ANA with a high-titer speckled pattern. The titer is often greater than 1:1000 and sometimes greater than 1:10,000. This finding should prompt the measurement of antibodies to U1-RNP, Sm, Ro, and La. It is also pertinent to note whether the serum contains antibodies to dsDNA and histones because patients destined to follow a course most consistent with MCTD have sera with predominant U1-RNP reactivity. Antibodies to dsDNA, Sm, and Ro are occasionally seen as a transient phenomenon in patients with MCTD. But when they are found consistently, as the predominant antibody system, the clinical picture is usually more consistent with classic SLE. Antibodies to the 70 kD antigen, especially in its apoptotic form, are most closely associated with the clinical correlates of MCTD.\textsuperscript{c}

Clinical Features

Diagnosis

MCTD is an overlap syndrome that embraces features of SLE, Scl, and PM/DM.\textsuperscript{57} These overlap features seldom occur concurrently; it usually takes several years before enough overlapping features have appeared to be confident that MCTD is the most appropriate diagnosis.\textsuperscript{38} The commonest clinical associations with U1 RNP antibodies in the early phase of the disease are hand edema, arthritis, Raynaud’s phenomenon, inflammatory muscle disease, and sclerodactyly. No American College of Rheumatology (ACR) criteria are available for the diagnosis of MCTD, but a comparative study reported that two criteria sets, those of Alarcon-Segovia and Kahn, had the best sensitivity and specificity (62.5% and 86.2%, respectively)\textsuperscript{39} (Table 86-4). The sensitivity could be improved to 81.3% if the term “myalgia” was substituted for “myositis.”\textsuperscript{59} Some patients initially diagnosed as MCTD will evolve into a clinical picture most consistent with SLE or RA; in one long-term follow-up, more than half of the subjects continued to satisfy criteria for MCTD.\textsuperscript{41} A comparison of the clinical and serologic features of MCTD with SLE, RA, Scl, and PM/DM is given in Table 86-5.

Early Symptoms

In the early stages most patients destined to develop MCTD cannot be differentiated from the other classic AICTDs.
The assumption that a diagnosis of MCTD implies a simultaneous presence of features usually seen in SLE, ScI, and PM is erroneous. It is unusual to see such an overlap during the early course of MCTD, but with the progress of time the overlapping features usually occur sequentially. Early in the course of the disease most patients complain of easy fatigability, poorly defined myalgias, arthralgias, and Raynaud’s phenomenon; at this point in time a diagnosis of RA, SLE, or undifferentiated connective tissue disease (UCTD) seems most appropriate. If such a patient is found to have swollen hands or puffy fingers (Figure 86-7) in association with a high-titer speckled ANA, he or she should be carefully followed for the evolution of overlap features (see Table 86-3). A high titer of anti-RNP antibodies in a patient with UCTD is a powerful predictor for a later evolution into MCTD. Less commonly there is an acute onset of MCTD, which gives little clue to the subsequent course; such presentations have included polymyositis, acute arthritis, aseptic meningitis, digital gangrene, high fever, acute abdomen, and trigeminal neuropathy.

**Table 86-4 Diagnostic Criteria for Mixed Connective Tissue Disease**

<table>
<thead>
<tr>
<th>Alarcón-Segovia Criteria</th>
<th>Kahn Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serologic criteria</td>
<td>Anti-RNP at hemagglutination titer of 21:1600</td>
</tr>
<tr>
<td></td>
<td>High-titer anti-RNP corresponding to a speckled</td>
</tr>
<tr>
<td></td>
<td>ANA of 21:1200</td>
</tr>
<tr>
<td>Clinical criteria</td>
<td>1. Swollen hands</td>
</tr>
<tr>
<td></td>
<td>2. Synovitis</td>
</tr>
<tr>
<td></td>
<td>3. Myositis (biologically proven)</td>
</tr>
<tr>
<td></td>
<td>4. Raynaud’s phenomenon</td>
</tr>
<tr>
<td></td>
<td>5. Acrosclerosis</td>
</tr>
<tr>
<td>MCTD present if</td>
<td>Serologic criterion accompanied by 3 or more clinical criteria,</td>
</tr>
<tr>
<td></td>
<td>one of which must include synovitis or myositis</td>
</tr>
<tr>
<td></td>
<td>Serologic criterion accompanied by Raynaud’s</td>
</tr>
<tr>
<td></td>
<td>phenomenon and 2 or more the 3 remaining</td>
</tr>
<tr>
<td></td>
<td>clinical criteria</td>
</tr>
</tbody>
</table>


**Fever**

Fever may be a prominent feature of MCTD in the absence of an obvious cause. Fever of unknown origin has been the initial presentation of MCTD; after careful evaluation, fever in MCTD can usually be traced to a coexistent myositis, aseptic meningitis, serositis, lymph adenopathy, or intercurrent infection.

**Joints**

Joint pain and stiffness is an early symptom in nearly all patients who develop the MCTD syndrome. Over the past 2 decades it has become increasingly apparent that joint involvement in MCTD is more common and more severe than in classic SLE. About 60% of patients eventually develop an obvious arthritis, often with deformities commonly seen in RA such as ulnar deviation, swan neck, and boutonnière changes. Radiographs usually show a characteristic absence of severe erosive changes; they often

**Table 86-5 Differential Features of the Classic Autoimmune Connective Tissue Diseases**

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>SLE</th>
<th>RA</th>
<th>ScI</th>
<th>PM</th>
<th>MCTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleurisy/pericarditis</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Erosive joint disease</td>
<td>±</td>
<td>+++</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>+</td>
<td>–</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Inflammatory myositis</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>±</td>
<td>–</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Nonacral skin thickening</td>
<td>–</td>
<td>–</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Interstitial pulmonary fibrosis</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>++</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Butterfly rash</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Seizures/psychosis</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Trigeminal neuropathy</td>
<td>+</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>++</td>
<td>+</td>
<td>±</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Transverse myelopathy</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Diffuse proliferative glomerulonephritis</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Renovascular hypertension</td>
<td>+</td>
<td>–</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Inflammatory vasculitis</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Noninflammatory vasculopathy</td>
<td>–</td>
<td>–</td>
<td>+++</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Esophageal dysmotility</td>
<td>+</td>
<td>±</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

MCTD, mixed connective tissue disease; PM, polymyositis; RA, rheumatoid arthritis; ScI, scleroderma; SLE, systemic lupus erythematosus.
develop a flexor tenosynovitis, bone edema, and pericapsular inflammation reminiscent of a seronegative spondyloarthropathy (Figure 86-8). A positive RF is found in 50% to 70% of patients; indeed, patients may be diagnosed as having RA and fulfill ACR criteria for RA.

**Skin and Mucous Membranes**

Most patients with MCTD develop mucocutaneous changes sometime during the course of the syndrome. Raynaud’s phenomenon is the commonest problem and one of the earliest manifestations of MCTD. It may be accompanied by puffy, swollen digits and sometimes total hand edema. In some patients, skin changes commonly associated with classic SLE are prominent findings, particularly malar rash and discoid plaques. Other problems have included buccal ulceration, sicca complex, orogenital ulceration, livedo vasculitis, subcutaneous nodules, and nasal septal perforation.

**Muscle**

Myalgia is a common symptom in patients with the MCTD syndrome. In most patients there is no demonstrable weakness, EMG abnormalities, or muscle enzyme changes. It is often unclear whether the symptom represents a low-grade myositis, physical deconditioning, or an associated

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**Figure 86-7** The hand of a man with mixed connective tissue disease. The fingers have a generally puffy appearance with a fusiform proximal interphalangeal swelling of the third finger from an inflammatory arthritis. There is a periungual infarct at the nail fold of the third finger. (Modified from Pape JE: Other manifestations of mixed connective tissue disease, Rheum Dis Clin North Am 31:519–533, 2005.)

**Figure 86-8** Hand magnetic resonance images of two females aged 25 and 32 with mixed connective tissue disease and hand arthritis. A, Patient 1 has synovitis/effusion around the ulnar styloid (asterisk) and tenosynovitis of the flexor and extensor tendons (arrows) (T1-weighted gadolinium-enhanced sequence on axial plane). B, Patient 2 has intense synovitis of the radioulnar joint (asterisk) and extensor tenosynovitis (arrows) causing thickening of the dorsum of the hand (T1-weighted short tau inversion recovery [STIR] sequence on axial plane). C, Patient 1 has synovitis/effusion, and pericapsular edema is seen in the second proximal interphalangeal joint. The distended capsule is indicated by arrows. D, Patient 2 has intracapsular synovial effusion or synovitis of the third and fourth metacarpophalangeal joints (arrows). (Both C and D are T1-weighted STIR sequences in the coronal plane.) (From Cimmino MA, Lozzelli A, Garlaschi G, et al: Magnetic resonance imaging of the hand in mixed connective tissue disease, Ann Rheum Dis 62:380–381, 2003.)
fibromyalgia syndrome. The inflammatory myopathy associated with MCTD is similar histologically to IIM, with features of both the vascular involvement of DM and the cell-mediated changes of PM.80 In most patients myositis occurs as an acute flare against a background of general disease activity. Such patients usually respond well to a short course of high-dose corticosteroid therapy. Another scenario is that of a low-grade inflammatory myopathy, which is often insidious in its onset; these patients often have a poor therapeutic response to corticosteroids. Some patients with PM associated with MCTD develop an impressive fever82; other patients may give a history of febrile myalgias that were diagnosed as "flu..."

**Heart**

All three layers of the heart may be involved in MCTD.86 An abnormal electrocardiogram (ECG) is noted in about 20% of patients. The most common ECG changes are right ventricular hypertrophy, right atrial enlargement, and interventricular conduction defects. Pericarditis is the commonest clinical manifestation of cardiac involvement, reported in 10% to 30% of patients. Pericardial tamponade is rare. Involvement of the myocardium is increasingly recognized. In some patients myocaridal involvement is secondary to pulmonary hypertension (PAH); this occurs in some 20% of patients and is often asymptomatic in its early stages.69 The early detection of pulmonary hypertension is increasingly important because there are now more effective therapeutic options. PAH is probably underdiagnosed in its early stages; in a community rheumatology practice setting an elevation of the estimated right ventricular systolic pressure (ERVSP), consistent with the diagnosis of PAH, was found in 13% of previously undiagnosed subjects.52 This diagnosis should be suspected in patients with increasing exertional dyspnea. Two-dimensional echocardiography with Doppler flow studies is the most useful screening test, with a definitive diagnosis requiring cardiac catheterization showing a mean resting pulmonary artery pressure greater than 25 mm Hg at rest. The development of pulmonary hypertension has been correlated with a nail-fold capillary pattern similar to that seen in Scl, antiendothelial cell antibodies, anticardiolipin antibodies, and anti-U1-RNP antibodies.13 Both left and right ventricular dysfunction appears to be a common finding that is not always associated with PAH; regular echocardiographic evaluations are recommended for all MCTD patients, especially those with PAH. Elevated levels of anti-U1RNP antibodies, antiendothelial cell antibodies, serum thrombomodulin, and Willebrand factor are prognostic clues to the development of PAH.12

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**Figure 86-9** Muscle biopsy from the biceps brachii of a mixed connective tissue disease patient [H&E stain, ×300]. **A**, Moderate variation of fiber size and degenerated fibers (→) with mononuclear cell infiltration. **B** and **C** show perivascular inflammatory infiltration and thickening of vessel walls. (Modified from Vianna M, Borges MT, Borba EF, et al: Myositis in mixed connective tissue disease: a unique syndrome characterized by immuno-histopathologic elements of both polymyositis and dermatomyositis, Arq Neuro-Psiquiatr 62:923–934, 2004.)
Lung involvement occurs in up to 75% of patients. Early symptoms that should prompt further investigations are dry cough, dyspnea, and pleuritic chest pain. Interstitial lung disease (ILD) occurs in up to 50% of subjects. High-resolution computed tomography (HRCT) is the most sensitive test to determine the presence of ILD (Figure 86-10). The commonest HRCT findings are septal thickening and ground-glass opacities. Untreated ILD is usually progressive with the development of severe pulmonary fibrosis in 25% of subjects after 4 years of follow-up. Pulmonary hypertension (PAH) is prognostically the most severe form of pulmonary involvement in MCTD. Unlike Scl, where pulmonary hypertension is often secondary to an interstitial pulmonary fibrosis, PAH in MCTD is usually caused by a bland intimal proliferation and medial hypertrophy of pulmonary arterioles (Figure 86-11).

Kidney

In the initial description of MCTD, renal involvement was considered to be rare. After some 4 decades of observations, it is now evident that renal involvement occurs in about 25% of patients. However, high titers of anti-U1 RNP antibodies are relatively protective against the development of diffuse proliferative glomerulonephritis, irrespective of whether they occur in a setting of classic SLE or MCTD. When patients with MCTD do develop renal changes, it usually takes the form of a membranous glomerulonephritis. This is often asymptomatic but may sometimes cause an overt nephrotic syndrome. The development of diffuse proliferative glomerulonephritis or parenchymal interstitial disease has been rarely recorded in MCTD. There is increasing recognition that MCTD patients are at risk of developing a renovascular hypertensive crisis similar to the scleroderma kidney.

Gastrointestinal

Gastrointestinal involvement is a major feature of the overlap with scleroderma, occurring in about 60% to 80% of patients. The commonest abdominal problem in MCTD is disordered motility in the upper gastrointestinal tract. There have been case reports of hemoperitoneum, hemobilia, duodenal bleeding, megaloclon, pancreatitis, ascites, protein-losing enteropathy, primary biliary cirrhosis, portal hypertension, pneumatosis intestinalis, and autoimmune hepatitis. Abdominal pain in MCTD may result from bowel hypomotility, serositis, mesenteric vasculitis, colonic

Figure 86-10 Computed tomography scans of a patient with mixed connective tissue disease and pulmonary hypertension (A, upper zones; B, lower zones). There are bilateral pleural effusions and enlarged bilateral mediastinal lymph nodes in the right paratracheal region and left perivascular areas. The pulmonary artery has a diameter greater than that of the ascending aorta—consistent with the diagnosis of pulmonary hypertension. Both hilar pulmonary arteries are also enlarged. A fairly large pericardial effusion is present. The lungs show evidence of a diffuse abnormality with linear opacities and some areas of ground-glass attenuation in the upper zones. At the lung bases there are more confluent opacities, both reticular and ground glass, and some air-space consolidation. No honeycombing is identified, and there is no distortion of the lung architecture. (From Saito Y, Terada M, Ishida T, et al: Pulmonary involvement in mixed connective tissue disease: comparison with other collagen vascular diseases using high resolution CT, J Comput Assist Tomogr 26:349–357, 2002.)

Figure 86-11 Intimal hyperplasia and smooth muscle hypertrophy without accompanying inflammation are the characteristic features of the vasculopathy of mixed connective tissue disease. When it occurs in the lung, as shown here, it may give rise to severe pulmonary hypertension. (Note absence of pulmonary fibrosis.) The plexiform lesion (arrow) is a characteristic pathologic finding in this disease process. (From Bull TM, Fagan KA, Badesch DB: Pulmonary vascular manifestations of mixed connective tissue disease, Rheum Dis Clin North Am 31:451–464, 2005.)
perforation, and pancreatitis. Malabsorption syndrome can occur secondarily to small bowel dilation with bacterial overgrowth. Liver involvement in the form of chronic active hepatitis and Budd-Chiari syndrome has been described. Pseudodiverticulae, identical to those seen in SCC, may be seen along the antimesenteric border of the colon.

**Nervous System**

In keeping with Sharp's original description, CNS involvement has not been a conspicuous feature of MCTD. The commonest problem is a trigeminal neuropathy. In a review of 81 cases of trigeminal neuropathy seen in a neurologic clinic, the most frequently associated CTDs were undifferentiated connective tissue disease (47%), mixed connective tissue disease (26%), and scleroderma (19%). A sensorineural hearing loss has been reported in nearly 50% of MCTD patients. In contrast to CNS involvement in classic SLE, frank psychosis and convulsions have rarely been reported in MCTD. Headaches are a relatively common symptom; in the majority of patients they are vascular in origin with many of the components of classic migraine. In a subset of these patients, signs of meningeal irritation develop and examination of the cerebral spinal fluid reveals the changes of aseptic meningitis. Aseptic meningitis in MCTD has also been described as a hypersensitivity reaction to NSAIDs, in particular sulindac and ibuprofen. There are isolated reports of transverse myelitis, cauda equina syndrome, cerebral hemorrhage, retinal vasculitis, optic neuropathy, progressive multifocal leukoencephalopathy, cold-induced brain ischemia, myasthenia gravis, polyradiculopathy, demyelinating disorder, and peripheral neuropathy. Elevated CSF levels of anti-U1 RNP antibodies, with a predominance of anti-70 kD antibodies, have been reported in both SLE and MCTD patients with diffuse central neuropsychiatric involvement.

Many patients with AICTDs have changes on brain magnetic resonance imaging that are referred to as unspecified bright objects (UBOs). In many instances UBOs occur in the absence of neurologic symptoms. However, there is a modest correlation between the density and positioning of UBOs; in MCTD these lesions tend to cluster at the corticomediulary junction and periventricular region.

**Blood Vessels**

Raynaud’s phenomenon is an early feature of nearly all patients who are eventually diagnosed as having MCTD. A bland intimal proliferation and medial hyper trophy affecting medium and small vessels is the characteristic vascular lesion of MCTD and other AICTDs (see Figure 86-5). Fingernail capillaroscopy is abnormal in most MCTD patients with the same pattern of capillary dilation and dropout that has been reported in Scl. An angiographic study reported a high prevalence of medium-size vessel occlusions (Figure 86-12). Endothelial cell and anticardiolipin antibodies have been reported to be associated with endothelial dysfunction and the development of atherosclerosis in MCTD.

![Figure 86-12](https://example.com/figure8612.jpg) **Figure 86-12** A, Digital angiogram showing multiple arterial occlusions with collateral formation. B, Digital angiogram showing ulnar artery occlusions. (From Pelter JS, Gabor GT, Porter JM, Bennett RM: Angiographic findings in mixed connective tissue disease: correlation with fingernail capillary photomicroscopy and digital photoplethysmography findings, Arthritis Rheum 28:768, 1985. Reprinted with permission of the American College of Rheumatology.)
Blood
Hematologic abnormalities are a common finding in MCTD. Anemia is found in 75% of patients, and the usual profile is most consistent with the anemia of chronic inflammation. A positive Coombs test is seen in about 60% of patients, but an overt hemolytic anemia is uncommon. As in SLE, a leukopenia affecting mainly the lymphocyte series is seen in about 75% of patients and tends to correlate with disease activity. Less common associations have been thrombocytopenia, thrombocytopenia purpura, and red cell aplasia. Hypocomplementemia has been described in several studies; it is not as prevalent as in classic SLE and has not been correlated with any particular clinical situation. Positive tests for RF have been found in about 50% of patients. The presence of RF is associated with more severe degrees of arthritis, especially if anti-A2/RA33 are also present. Anticardiolipin antibodies or lupus anticoagulants, or both, have also been reported. Unlike the anticardiolipin antibodies found in SLE, they are β2-glycoprotein independent and tend to be associated with thrombocytopenia rather than thrombotic events.

Pregnancy
Reports of maternal and fetal morbidity in MCTD are quite diverse. In a comparison study of patients with MCTD and SLE, the fertility rates in both and diseases were unaltered, whereas the parity and fetal wastage was increased in both. Some studies have reported an exacerbation of MCTD during pregnancy and postpartum flares, whereas others have not. Antiphospholipid antibodies have been linked to spontaneous abortion in MCTD. A single case of neonatal "lupus" has been reported, suggesting a pathogenic role for the transplacental passage of anti-U1 RNP antibodies.

Juvenile Mixed Connective Tissue Disease
MCTD may first become apparent in childhood. The average age of onset in one report was 10.7 years. Polyarthritis and Raynaud's phenomena are the most common presenting features. There tends to be a progression of organ involvement with 20% involvement at 5 years and 48% at 10 years. Significant myocarditis, glomerulonephritis, thrombocytopenia, seizures, hemolytic uremic syndrome, an acute coronary syndrome, and aseptic meningitis have been described in isolated cases.

MANAGEMENT OF CONNECTIVE TISSUE DISEASE OVERLAPS
The rational management of overlap CTDs is confounded by the absence of controlled trials. Recommendations for management are based on conventional treatments for SLE, PM/DM, RA, and Scl. General guidelines for treating specific features of the overlap CTDs are given in Table 86-6. Nearly all patients with CTDs experience Raynaud's phenomenon. Apart from advice as to minimizing cold exposure, most cases should be tried on calcium blockers (e.g., nifedipine). The use of topical nitrates, endothelin antagonists (e.g., bosentan), phosphodiesterase-5 inhibitors (e.g., tadalafil), and prostaglandin analogs (e.g., iloprost) should be considered in severe refractory cases. Pulmonary hypertension is the main cause of death in MCTD, and patients should be evaluated at regular intervals for the development of this complication because early intervention is the key to effective management. Recent advances in the treatment of pulmonary hypertension have led to reduced morbidity and mortality. Overall effective management requires anticoagulation and vasodilator therapy such as calcium channel blockers or prostacyclin analogues. Long-term treatment with intravenous epoprostenol or prostacyclin improves exercise capacity, hemodynamics, and survival in many patients, as does therapy with inhaled iloprost. Evidence indicates that some patients respond to a regimen of intravenous cyclophosphamide and corticosteroids. Bosentan, an oral endothelin-1 antagonist, has been reported to improve dyspnea and slow PAH progression in MCTD.

The management of overlap syndromes has not been the subject of controlled trials. Therefore management is based on an analysis of the clinical features and the application of management strategies used in the usual treatment presenting features in terms of inflammatory arthritis, Raynaud's, inflammatory muscle disease, serositis, interstitial lung disease, pulmonary hypertension, and the gastrointestinal features of scleroderma. By definition, the clinical features of an overlap syndrome will be quite diverse and often change over time. Thus a constant reappraisal of management strategies is necessary at each patient visit.

Many of the problems causing morbidity in overlap syndromes tend to be intermittent and responsive to corticosteroids (e.g., aseptic meningitis, myositis, pleurisy, pericarditis and myocarditis). On the other hand, nephrotic syndrome, Raynaud's phenomenon, deforming arthropathy, acrosclerosis, and peripheral neuropathies are usually steroid resistant. Many of the scleroderma-like gastrointestinal problems can be managed according to the usual practice in scleroderma such as management of renal crisis with ACE inhibitors, Raynaud's phenomenon with calcium channel blockers, and gastrointestinal reflux disease with proton pump inhibitors. Fibrotic lung disease is notoriously resistant to corticosteroids and immunosuppressives; there is some evidence that a new class of drugs, the tyrosine kinase inhibitors (e.g., imatinib), may be effective in some patients.

In patients with steroid-resistant thrombocytopenia, refractory myositis, or hemolytic anemia, it is worth considering the use of intravenous gammaglobulin or danazol. Successful autologous peripheral blood stem cell transplantation has been reported in a patient with refractory myositis and MCTD. Over the long term, concern usually mounts over the total corticosteroid burden and the possibility of inducing an iatrogenic steroid myopathy, nosocomial infection, aseptic necrosis of bone, or accelerated osteoporosis. Routine evaluation of bone mineral density is warranted to detect early presymptomatic osteoporosis and initiation of therapy with antiresorptive agents. Unless contraindicated, all patients should take supplementary calcium and vitamin D. In patients requiring long-term corticosteroids it would seem reasonable to use antimalarials or methotrexate in an attempt to minimize the cumulative
Table 86-6  Guidelines for Managing Overlap Syndromes

<table>
<thead>
<tr>
<th>Problems</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue, arthralgias, myalgias</td>
<td>NSAIDs, antimalarials, low-dose prednisone (&lt;10 mg/day); trial use of modafinil</td>
</tr>
<tr>
<td>Arthritis</td>
<td>NSAIDs, antimalarials, methotrexate, Consider TNF-inhibitor*</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Keep warm, avoid finger trauma, avoid β-blockers, stop smoking; dihydralpyridine calcium channel blocker (e.g., nifedipine); cs-sympatholytic (e.g., prazosin); consider endothelin receptor antagonist (e.g., bosentan) in recalcitrant cases</td>
</tr>
<tr>
<td>Acute-onset digital gangrene</td>
<td>Local chemical sympathectomy (infiltration of lidocaine at base of involved digit), anticoagulation, topical nitrates; consider hospitalization for intra-arterial prostacyclin; start endothelin receptor antagonist therapy</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>NSAID or short course of prednisone (~20 mg/day)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>NSAID or short course of prednisone (~20 mg/day); tamponade will require percutaneous or surgical drainage</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>Discontinue NSAIDs,* short course of high-dose prednisone, about 60 mg/day</td>
</tr>
<tr>
<td>Myositis</td>
<td>Acute onset, severe: prednisone 60-100 mg/day</td>
</tr>
<tr>
<td></td>
<td>Chronic, low grade: prednisone, 10-30 mg/day</td>
</tr>
<tr>
<td>Membranous glomerulonephropathy</td>
<td>Mild: no treatment required</td>
</tr>
<tr>
<td></td>
<td>Progressive proteinuria: trial of ACE inhibitor; trial of low-dose aspirin combined with dipyridamole</td>
</tr>
<tr>
<td></td>
<td>Severe: trial of prednisone 15-60 mg/day plus monthly pulse cyclophosphamide or daily chlorambucil</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Steroids alone are seldom effective. Low-dose aspirin combined with dipyridamole to prevent thrombotic complications; ACE inhibitor to reduce protein loss; trial of prednisone 15-60 mg/ day plus monthly pulse cyclophosphamide or daily chlorambucil; dialysis or transplantation may be required</td>
</tr>
<tr>
<td>Scleroderma-like renal crisis</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Trial of steroids and cyclophosphamide; avoid digoxin</td>
</tr>
<tr>
<td>Incomplete heart block</td>
<td>Avoid chloroquine</td>
</tr>
<tr>
<td>Asymptomatic pulmonary hypertension</td>
<td>Trial of steroids and cyclophosphamide, low-dose aspirin and angiotensin-converting enzyme inhibitors; consider endothelin receptor antagonist (oral bosentan)</td>
</tr>
<tr>
<td>Symptomatic pulmonary hypertension</td>
<td>Intravenous prostacyclin, angiotensin-converting enzyme inhibitors, anticoagulation, endothelin receptor antagonist (oral bosentan); trial of sildenafil; heart-lung transplantation</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>Discontinue NSAIDs and give short course of high-dose prednisone (~80 mg/day)</td>
</tr>
<tr>
<td>Vascular headache</td>
<td>Trial of propranolol and/or alternate-day aspirin, 350 mg</td>
</tr>
<tr>
<td>Autoimmune anemia/thrombocytopenia</td>
<td>Symptomatic use of a triptan (e.g., sumatriptin, eletriptan)</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>High-dose steroids (=prednisone 80 mg/day) with taper dependent on clinical course. Consider danazol, IVIG, and immunosuppression in recalcitrant cases</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Immediate infusion of fresh frozen plasma; may require plasma exchange and transfusion of platelet depleted RBCs; consider splenectomy in recalcitrant cases</td>
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<td>*Has been associated with flares in MCTD and SLE.</td>
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<td>+Sulindac and ibuprofen have been associated with a hypersensitivity aseptic meningitis.</td>
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<td>cCardiotoxic at high doses.</td>
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<td>3Predisposes to ventricular arrhythmias.</td>
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<tr>
<td>sPredisposes to complete heart block.</td>
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<tr>
<td>&amp;Cannot be used if esophagus is more than mildly involved.</td>
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Steroid burden. Antimalarials should be used with caution in overlap patients with a fascicular or bundle branch block due to the risk of causing a complete heart block[112] or an idiopathic hepatitis.[113] Digitalis is relatively contraindicated in patients with myocarditis due to the risk of inducing ventricular arrhythmias. As in SLE, the TNF inhibitor etanercept has been reported to exacerbate MCTD.[114] Rituximab has been beneficial in some patients with severe refractory antisyntethetate syndrome.[115] Patients with severe hand deformities may be helped by soft tissue release operations and selected joint fusions.

The management of pregnancy presents several special problems in patients with overlap CTDs. Doria and colleagues[116] have provided the following general advice:

1. Patients should be correctly informed about the risk of becoming pregnant.
2. Pregnancy should be planned when the disease is in remission because it increases the probability of successful maternal and fetal outcome.

3. Patients should be regularly monitored during gestation and postpartum by a multidisciplinary team including a rheumatologist, an obstetrician, and a neonatologist.

4. In the case of disease relapse an adequate treatment, even aggressive if necessary, should be recommended because active disease can be more detrimental for a fetus than drugs.

There is often a tendency to assume that all patients with overlap CTDs should be on long-term corticosteroids; this mistake is compounded by the assumption that all medical problems in these patients are related to their underlying overlap CTDs. For instance, apparent flares of discomfort and pain in overlap CTDs may be due to myofascial pain syndrome or fibromyalgia and are thus unresponsive to corticosteroids. Likewise, the feeling of malaise and easy fatigueability may be related to a reactive depression or the fact that the patient has become deconditioned. Premature atherosclerosis is now well recognized as a cause of increased morbidity and mortality in AICTDs, and all patients with overlap syndromes need ongoing evaluation for risk factors and appropriate advice and therapy for hypertension and hyperlipidemia. The management of patients with overlap CTDs requires continuing reassessment of an ever-changing pattern of clinical problems and a constant alertness to the iatrogenic disease. As with any disease of unknown etiology, effective management of patients with the overlap CTDs presents a constant and ever-evolving challenge.

PROGNOSIS

The prognosis for overlap syndromes is often better than the classic AICTDs. For instance, Troyanov reported on the follow-up of 100 patients with idiopathic inflammatory myopathy. It was found that the long-term course after treatment with prednisone, with a dose/duration that initially resulted in good symptomatic improvement, was strikingly different; all PM patients (100%) and most DM patients (92%) progressed to chronic myositis, whereas only 58% of overlap patients developed persistent muscle disease. The tendency for overlap patients to develop chronic disease was more common in those with antisynthetase and nucleolar antibodies and less with antibodies to U1-RNP, Pm-Scl, or Ku. Patients with three or four U1 snRNP antibodies (i.e., anti-70 kD, anti-A, anti-C, and anti-U1 snRNA) tended to have minimal renal disease compared with patients with just one or two reactivities. Antibodies to 155 kD and 140 kD proteins in myositis are a risk factor for the development of cancer. There is unequivocal evidence that patients with high-titer U1-RNPs antibodies have a low prevalence of serious renal disease and life-threatening neurologic problems; in this sense MCTD can be favorably compared with classic SLE. However, not all patients with MCTD have a favorable prognosis and death may occur from progressive pulmonary hypertension and its cardiac sequelae. A 38-year follow-up of 47 MCTD patients at the University of Missouri reported a favorable course in 62% and continuing active disease in 38%. Eleven (23%) patients had a fatal outcome related to pulmonary hypertension in nine patients and two deaths unrelated to MCTD. It is evident that the course of overlap syndromes is unpredictable; many patients do follow a relatively benign course, but it is major organ involvement that ultimately dictates the morbidity and mortality of the disease.

References

CHAPTER 86 | OVERLAP SYNDROMES


References


The references for this chapter can also be found on www.expertconsult.com.
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During the preparation of your manuscript for publication, the questions listed below have arisen. Please attend to these matters and return this form with your proof.

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