Acute manifestations of autoimmune connective tissue diseases

Autoimmune connective tissue diseases are common conditions that often present non-specifically. Clinicians in emergency departments and acute medical assessment units may face these patients. This article provides an overview for the non-specialist clinician on the acute manifestations that may occur in these patients.

Connective tissue diseases (CTDs) are autoimmune diseases characterized by multisystem involvement often with musculoskeletal and cutaneous manifestations. Connective tissue is present throughout the body and may be classified into connective tissue, cartilage, bone and blood. In 1942 Klemperer et al coined the term 'collagen disease', which evolved to 'connective tissue diseases' (*Table 1*), also known as 'collagen vascular diseases' and 'autoimmune connective tissue disease'.

Clinical and laboratory features

The diagnosis of specific CTDs is often difficult because the presenting non-specific clinical manifestations can overlap and routine laboratory tests are not specific.

The pathophysiology of most CTDs remains unclear. The common histological feature of CTDs is the presence of inflammation in connective tissues characterized by mononuclear cell infiltration and necrosis associated with deposition of fibrinoid material. CTDs are characterized by their heterogeneous multisystem clinical manifestations. Common presenting features include weight loss, fever, malaise and fatigue, Raynaud's phenomenon, dry eyes and mouth, skin rashes or tightness, photosensitivity, arthritis or arthralgia, anaemia, bruising, oral ulcers, headaches or migraines. Given this multiplicity of symptoms, a careful and thorough clinical evaluation and a high degree of suspicion are essential when considering the differential diagnoses.

Laboratory tests may identify markers of systemic disease, autoimmune disorder, or specific organ involvement. Screening tests should include full blood count, erythrocyte sedimentation rate (ESR), biochemistry panel including C-reactive protein (CRP), urinalysis, and autoantibodies such as rheumatoid factor (RF), and antinuclear (ANA), anti-DNA and antiphospholipid antibodies. Further investigations include creatine kinase (CK), complement C3, C4 and anti-extractable nuclear antigens (ENA), such as antibodies to SS-A (Ro), SS-B (La), ribonucleoprotein (RNP) and Sm, Jo-1 antibody and anti-DNA topoisomerase (Scl-70) antibody.

Development of autoantibodies such as ANA, anti-Ro, anti-La, and antiphospholipid antibodies may precede the onset of clinical disease in systemic lupus erythematosus (SLE), often by many years (Vasoo and Hughes, 2004). This production of autoantibodies years before the onset of diseases may also be seen in limited scleroderma (anticentromere antibodies) (Weiner et al, 1991), myositis (autoantibodies against tRNA synthetases), and rheumatoid arthritis (RF). By contrast, the appearance of anti-Sm and anti-nRNP antibodies are associated with the clinical onset of disease (Arbuckle et al, 2003). It is especially important to make an early diagnosis since the prognosis depends on the extent of organ involvement, disease activity, damage and complications of therapy, especially infections. Treatment options include antimalarials, corticosteroids, and immunosuppressive agents including mycophenolate mofetil (MMF). Accelerated atherosclerosis is increasingly recognized as a contributor to late mortality.

Systemic lupus erythematosus

SLE is a common multisystem autoimmune inflammatory disease characterized by autoantibodies and associated with complement-mediated tissue damage. The typical disease course consists of remissions and relapses with an often unpredictable pattern and prognosis.

Table 1. Classification of connective diseases

Systemic lupus erythematosus	
Rheumatoid arthritis	
Sjögren's syndrome	
Systemic sclerosis (scleroderma)	
Dermatomyositis or polymyositis	
Antiphospholipid syndrome	
Mixed connective tissue diseases (overlap syndrome)	
Heritable disorders of connective tissue	Ehlers–Danlos syndrome
	Epidermolysis bullosa
	Marfan syndrome
	Osteogenesis imperfecta

From Moore and Richardson (1998); Jablonska and Blaszczyk (2001)

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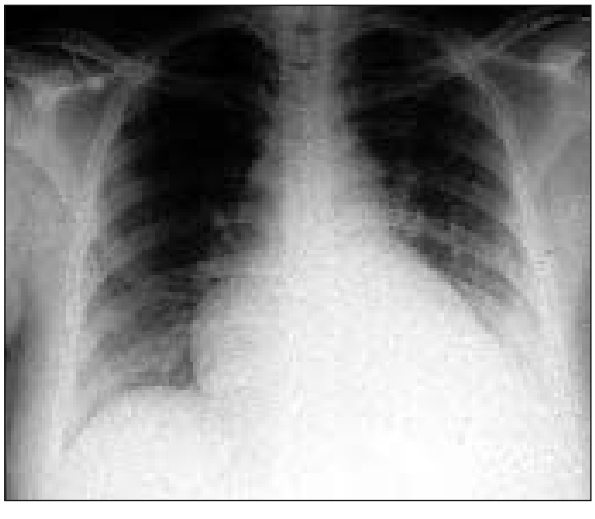
The term 'lupus' represents a cluster of autoimmune diseases separated into discoid lupus erythematosus (LE) (or chronic cutaneous LE), subacute cutaneous LE and SLE. It affects women of reproductive age, with a female: male ratio of about 9–10:1 and the peak incidence between 15 and 40 years of age, and is more common in those of African and oriental Asian ancestry than caucasians (Gladman and Urowitz, 1997). Factors such as pregnancy, menstruation, exogenous oestrogens, ultraviolet light (295–305 nm range), sunlight and steroid reduction or withdrawal can trigger a flare. Procainamide, hydralazine, hydantoins, penicillin, sulfonamides, minocycline and many other drugs including anticonvulsants may lead to lupus-like reactions which usually improve on withdrawal of the drug. The aetiopathogenesis of SLE is poorly understood although defects in immune complex clearance, B-cell tolerance, and T-cell function have all been seen. Abnormalities in apoptosis may be a component and may explain how autoantibodies to predominantly intracellular antigens arise in SLE (Munoz et al, 2005).

Classically, patients may have recurrent minor flares with fever, fatigue, serositis, photosensitivity (*Figures 1* and *2*) and thrombocytopenia. Acute lupus flares can be life-threatening as a result of the involvement of internal organs; e.g. CNS disease with psychosis, seizures and organic brain syndrome, cardiac and pulmonary disease, cutaneous and digital vasculitis (*Figure 3*) and glomerulonephritis may have a poor prognosis if not treated.

There are gender differences in the acute manifestations of SLE – males with lupus are more likely to have atypical cutaneous lesions, pleuritis and pericarditis at onset (*Figure 1*) and thrombosis during disease flares (Azizah et al, 2001). Males are also more at risk of neurological disease, vasculitis, nephritis, hepatosplenomegaly and seizures. However, alopecia, photosensitivity and thrombocytopenia are more frequent in women. Lupus flares during pregnancy are usually mild, mostly with arthritis and cutaneous manifestations. The risk of flares during and after pregnancy is controversial – some studies describe flares during the second trimester but others described most flares in the first trimester and yet other studies suggest that the risk of flares is not necessarily increased. If SLE is active at conception, the risk of a disease flare and poor pregnancy outcome is greatly increased.

Figure 1. Acute serositis in systemic lupus erythematosus with left pleural and pericardial effusions.



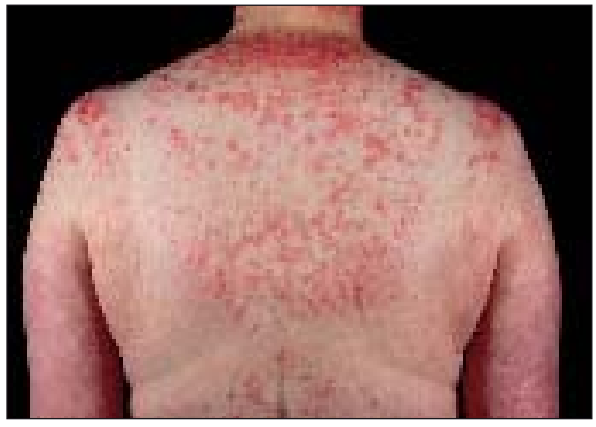


Figure 2. Severe photosensitive rash (subacute cutaneous lupus erythematosus) in a Ro positive systemic lupus erythematosus patient.

The diagnosis of lupus is based on clinical grounds, and supported by laboratory investigations. Classification criteria (*Table 2*) have been devised for research and should not be used to establish a diagnosis of SLE. Laboratory features characteristically include a high ESR with a normal CRP (almost unique to lupus and related disorders),

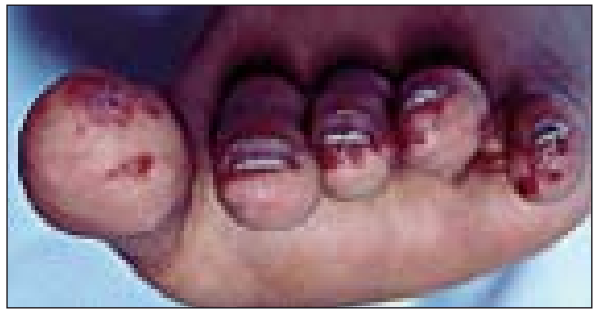


Figure 3. Digital vasculitis in systemic lupus erythematosus.

Table 2. American College of Rheumatology classification criteria for systemic lupus erythematosus

Malar rash
Discoid rash
Photosensitivity (by history or observation)
Oral ulcers (oral or nasopharyngeal, usually painless)
Arthritis (in two or more peripheral joints with tenderness, swelling, or effusion)
Serositis: pleuritis or pericarditis
Renal disorders (proteinuria ≥0.5 g/cells, ≥3+) and/or cellular casts
Neurological disorder: seizure or psychosis
Haematological disorder: haemolytic anaemia, leucopenia ≤4000/mm, lymphopenia ≤1500/mm, or thrombocytopenia
Immunological disorder: anti-DNA, anti-Sm, anticardiolipin, positive lupus erythematosus cell, false positive serological tests for syphylis
Positive results of fluorescent antinuclear antibody

From Tan et al (1982)

pancytopenia and low complement C3 and/or C4. ANAs are sensitive (present in 95% of patients) but not specific. High-affinity antibodies to dsDNA are characteristic hallmarks of human SLE, although negative anti-dsDNA antibodies do not exclude the diagnosis. Infection must be included in differential diagnosis in febrile lupus patients before attributing fever to SLE, although a normal CRP usually makes serious infection less likely.

Lupus flares are best treated by removal of precipitating factors, e.g. sunlight or drugs. Corticosteroids and immunosuppressive drugs – azathioprine, methotrexate, and cyclophosphamide – are indicated for severe flares, especially where there is major organ involvement. The 5-year survival is approximately 90% and death may occur from renal and cerebral complications, thrombosis, infections and accelerated atherosclerosis.

Antiphospholipid (Hughes) syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by recurrent arterial or venous thrombosis, pregnancy loss, and/or thrombocytopenia associated with persistently positive results of anticardiolipin (aCL) or lupus anticoagulant (LA) tests (Wilson et al, 1999). It was first described in 1983 by Professor Graham Hughes as primary APS (53%) or in association with other disorders – most commonly SLE (36%) (Cervera et al, 2002). Classification of APS is based on the Sapporo criteria (*Table 3*). Antiphospholipid antibodies, particularly LA and aCL, are the serological hallmarks of APS. Antibodies to a co-factor Beta-2 glycoprotein 1 are useful markers for the syndrome, but do not add any specificity over and above LA or aCL.

The hallmark of APS pathology is vascular thrombosis which can appear in any vascular bed. APS occurs most commonly in young to middle-aged adults but can present in children and the elderly. Venous thromboses are more common than arterial events in APS and the clinical course varies from asymptomatic positive antiphospholipid antibodies to the frequently fatal catastrophic antiphospholipid syndrome (CAPS) (Cervera et al, 2002). Deep vein thrombosis and pulmonary embolism are the most common venous events, whereas in the arterial system, the cerebral arteries are commonly affected, although coronary, renal and mesenteric arteries have also frequently been involved.

CAPS is seen in ≤1% of patients and is a commonly fatal manifestation characterized by multiple organ infarctions over a period of days to weeks (Cervera et al, 2002). The most common precipitating factors are infection or recent surgery and the clinical manifestations are those of multiorgan failure involving multiple vessels and organs (*Figure 4*).

Appropriate treatment of APS includes anticoagulant drugs and antiplatelet therapy. Anticoagulation with warfarin to an international normalized ratio (INR) of 2.5–4.0 offers some protection against recurrent thrombotic events although it has been suggested that in venous events an INR of 2.0–3.0 may be sufficient. Anticoagulation is usually lifelong. The management of CAPS, where severe widespread thrombosis occurs acutely despite anticoagulation, may include plasma exchange or intravenous immunoglobulin. Cyclophosphamide appears to increase the risk of mortality (Cervera et al, 2002).

Table 3. Sapporo classification criteria for antiphospholipid (Hughes) syndrome

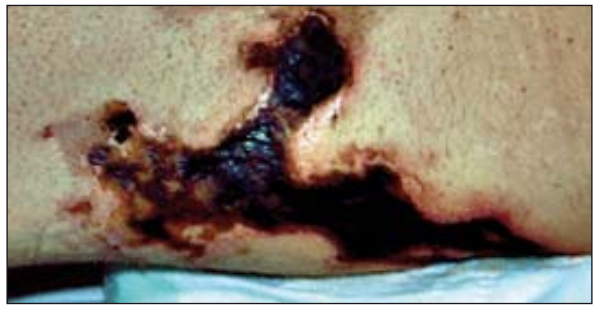
Clinical criteria	One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ confirmed by findings from imaging, Doppler studies, or histopathology
Pregnancy morbidity (frequent miscarriages or premature births)	One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation
	One or more premature births of a morphologically normal neonate at 34th week of gestation
	Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
Laboratory criteria	Anticardiolipin antibody of IgG and/or IgM isotype in blood, present in medium or high titre, on two or more occasions, at least 6 weeks apart
	Lupus anticoagulant present in plasma, detected according to the International Society on Thrombosis and Hemostasis guidelines. Lupus anticoagulant detected on two or more occasions, at least 6 weeks apart

Ig = immunoglobulin. From Wilson et al (1999)

Systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune systemic connective tissue disease distinguished by sclerotic skin changes that are often accompanied by multisystem disease of the joints, gastrointestinal tract, respiratory and renal systems. The predominant pathology is microvasculopathy, fibrotic destruction of the skin and internal organs (*Figure 5*). Autoantibodies include the presence of ANAs, Scl-70 (DNA topoisomerase I) (in 70%), anti-centromere (70–80% of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangieactasia (CREST), or limited cutaneous SSc and 25% in Raynaud's phenomenon), and anti-PM-Scl is associated with a polymyositis/scleroderma overlap (LeRoy et al, 1988). The most common presenting age is between the third and fifth decade, with a female:male ratio of 3–15:1; it is more common in women with African ancestry. There are four types of SSc:

Figure 4. Severe skin necrosis in catastrophic antiphospholipid (Hughes) syndrome.



1. Diffuse cutaneous – poor prognosis, earlier and more extensive systemic involvement
2. Limited cutaneous – (formerly CREST) more benign course fewer renal complications, but pulmonary hypertension a significant risk
3. SSc sine scleroderma – visceral manifestations of SSc without skin changes
4. SSc in overlap – concomitant SLE, polymyositis, rheumatoid arthritis (RA).

The American College of Rheumatology classification criteria for scleroderma (Beigelman et al, 1953) include one major criterion (sclerodermatous skin changes proximal to the metacarpophalangeal joints) and two of three minor criteria (sclerodactyly, digital pitting scars, and bibasilar pulmonary fibrosis on chest radiograph). Characteristic clinical manifestations include Raynaud's phenomenon, acute skin oedematous thickening or chronic skin tightening with sclerodactyly; non-deforming arthritis; dyspnoea and fine inspiratory basal lung crepitations; gut disorders and hypertension (hypertensive crisis). Anti-Scl70 antibodies are virtually pathognomonic of scleroderma and predict internal organ involvement, proximal scleroderma, and a poor outcome (Rothfield, 1992).

About 80% of the renal crises associated with this disease occur in patients with diffuse cutaneous SSc within the first 4–5 years of disease. Scleroderma renal crisis is defined by accelerated hypertension, rapidly progressive renal failure, increased plasma renin activity, microangiopathic haemolytic anaemia and thrombocytopenia. Risk factors for scleroderma renal crisis include diffuse skin disease, new anaemia, new cardiac events, high-dose steroids (≥20 mg daily of prednisolone), and the presence of anti-RNA polymerase III antibodies. However, pulmonary involvement is probably the most important visceral lesion in SSc. In many cases, patients may be asymptomatic despite evidence of fibrotic involvement of the lung parenchyma. The prevalence of pulmonary arterial hypertension (PAH) in patients with scleroderma is approximately 15% (Mukerjee et al, 2003) and fulminant pulmonary hypertension may rapidly lead to death (Coghlan and Mukerjee, 2001). Early detection of PAH by annual echocardiographic screening of patients at risk should lead to improved survival with the advent of new therapies.

A variety of therapies have been used to manage SSc with little or no benefit. Therapeutic options depend on the clinical manifestations. For example, anticoagulation is essential in scleroderma-related PAH (Sanchez et al, 1999) along with supportive oxygen therapy, diuretics and prostacyclin analogues (e.g. treprostinil, iloprost, beraprost). Data support the use of endothelin receptor antagonists in scleroderma-related PAH (Kim and Rubin, 2002). Bosentan is the first such agent approved in the European Union and USA for the treatment of primary PAH and PAH related to collagen vascular diseases such as scleroderma with World Health Organisation functional class grade III (Rubin et al, 2002).

The treatment of choice for scleroderma renal crisis is angiotensin-converting enzyme inhibitors and prostacyclin, which reverse underlying hyperreninaemia and control arterial hypertension (Steen et al, 1990). These patients need close monitoring as the risk of progression to severe renal impairment requiring dialysis is high. The prognosis is very variable and depends on the extent of renal, cardiac and pulmonary involvement.

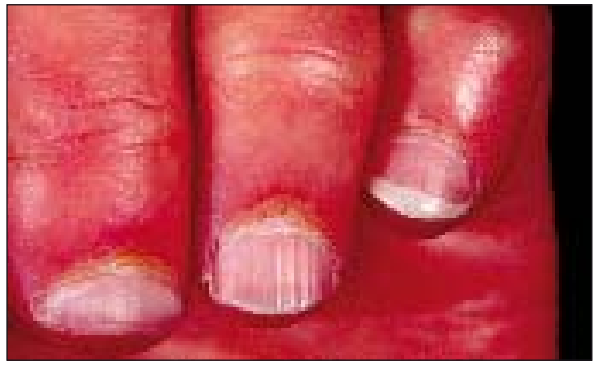


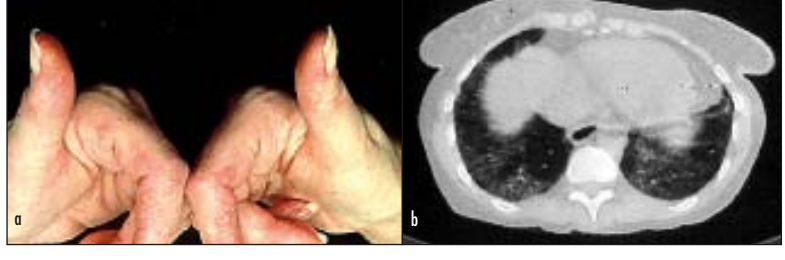
Figure 5. Sclerodactyly and macroscopic nailfold capillary loops in a patient with diffuse systemic sclerosis.

Polymyositis or dermatomyositis

Polymyositis or dermatomyositis (PM/DM) has an incidence of 2–10 cases per million, with a bimodal age distribution at 10–15 and 45–60 years of age. The female:male ratio is 3:1. The five possible criteria for diagnosis are symmetrical muscle weakness, dermatological features, elevation of muscle enzymes, electromyography abnormalities and muscle biopsy confirmation. The diagnosis of PM includes four criteria without a rash, and DM is diagnosed when three criteria are present plus the typical rash. The most common symptoms consist of proximal muscle weakness, muscular stiffness and aching, tenderness and wasting (symmetrical distribution in shoulder or pelvic girdle), skin eruptions, oedema and fever. In DM, the cutaneous manifestations may precede the muscle inflammation (DM sine myositis). Patients with new onset of DM should be assessed for malignancy as 10% of DM patients develop a malignancy within 1 year of disease onset especially in older patients. However, it is not necessary to run exhaustive tests for malignancies as these are usually fairly obvious on careful clinical assessment.

Laboratory findings include: raised CK (often grossly elevated) and aldolase often with apparent elevations of liver enzyme. The ESR is often elevated but may be normal even in severe myositis. Anti-Jo-1 antibody may be

Figure 6. a. Mechanics hands and (b) interstial lung disease in a patient with anti-Jo1 anti-synthetase syndrome.



positive especially with lung involvement – the so-called antisynthetase syndrome (*Figures 6a* and *b*). Electromyography usually shows the characteristic picture of inflammatory myopathies and muscle biopsy shows necrosis and inflammatory cell infiltrate.

PM and DM respond to treatment with corticosteroids and in refractory cases immunosuppressives, e.g. azathioprine or methotrexate, may be considered. The prognosis depends on whether an underlying neoplasm is present and whether there is severe involvement of the lungs or heart.

Sjögren's syndrome

Sjögren's syndrome (SS) is a chronic disorder defined by immune-mediated destruction of exocrine glands (*Table 5*). It is considered to be a disorder at the turning point of autoimmune diseases and lymphoproliferative disorders and occurs in primary and secondary forms.

Primary SS represents an idiopathic inflammatory exocrinopathy characterized by both organ-specific autoimmunity of the salivary and/or lacrimal glands, and systemic manifestations. The characteristic hallmarks of primary SS are focal lymphocytic infiltrates and subsequent destruction of the lacrimal and salivary glands, resulting in keratoconjunctivitis sicca and xerostomia. Primary SS is mainly diagnosed in women, with a female:male ratio of 9:1 and an age range of 30–50 years. Secondary SS represents the sicca complex associated with any of the CTDs, but most commonly RA and SLE.

Characteristic laboratory parameters include hypergammaglobulinaemia, positive serology for RFs, ANA in 70% cases, anti-Ro in 40–65% cases, anti-La in 70–80%, positive Schirmer's test (≤5 mm in 5 minutes), and positive labial salivary gland biopsy (Vitali et al, 2002).

The American-European Consensus group classification criteria consist of six items (subjective dry eyes, subjective dry mouth, objective ocular involvement, abnormal focus score in lower lip biopsy, objective tests of oral involvement, and presence of anti-Ro or anti-La). At least four must be positive to diagnose primary SS, including the demonstration of anti-Ro or anti-La or a characteristic minor salivary gland biopsy (Vitali et al, 2002).

Table 5. Classification criteria for Sjögren's syndrome (≥ 4 criteria)

Dry eyes ≥3 months, sensation of sand or irritation in eyes, or use of tear substitutes ≥ three times a day
Dry mouth ≥3 months, recurrent or persistent swollen salivary glands, or frequent drinking of liquids to aid in swallowing dry foods
Schirmer test ≤5 mm in 5 minutes or Rose Bengal score ≥4
≥50 mononuclear cells/4 mm² glandular tissue
Abnormal salivary scintigraphy or parotid sialography or unstimulated salivary flow ≤1.5 ml in 15 minutes
Presence of anti-Ro/SS-A, anti-La/SS-B, antinuclear antibodies or rheumatoid factor
Exclusion criteria: preexisting lymphoma, AIDS, sarcoidosis or GVHD

AIDS = acquired immunodeficiency syndrome; GVHD = graft-versus-host disease. From Vitali et al (2002)

Mixed connective-tissue disease (overlap syndrome)

Mixed connective-tissue disease (MCTD) describes a distinct entity that may include features of SLE, SSc and inflammatory myopathy. The term was coined in 1972 and is an overlap syndrome, which involves two or more of SLE, PM/DM or SSc. The incidence of MCTD is unknown but occurs more frequently than SSc or PM, mainly in women, with a ratio of 15:1 and mean age of onset 40 years. The term MCTD remains controversial, with some authors preferring 'overlap syndrome'.

The diagnosis is based on the presence of overlapping symptoms of SLE, SSc, and PM (at least three out of five clinical symptoms: swollen hands, synovitis, biologically or histologically proven myositis, Raynaud's phenomenon, acrosclerosis with or without proximal SSc, and detection of increased titres of anti-RNP antibody (Bodolay, 2005)). The most common clinical features are arthritis, sclerodactyly, Raynaud's phenomenon, oesophageal dysmotility and myositis. Pulmonary involvement occurs in 20–85% of patients with MCTD and cardiac and renal involvement occurs in 25%.

Corticosteroids and immunosuppression are the mainstays of treatment with a positive response in about two thirds of patients.

Systemic necrotizing vasculitis

The systemic vasculitides are a cluster of life-threatening multisystem autoimmune CTDs defined by vascular inflammation and necrosis (D'Cruz, 2005). They are relatively uncommon, but are an important cause of mortality and morbidity. The diagnosis is clinical, supported where possible by laboratory and tissue assessments. Autoantibodies to neutrophil cytoplasmic antigens (ANCA) have a high sensitivity and specificity, although a negative ANCA does not exclude the diagnosis of vasculitis. Their classification is not yet perfect but include the ACR criteria and the Chapel Hill Consensus nomenclature (Jennette et al, 1994).

Pulmonary-renal vasculitic syndromes are associated with a high risk of mortality even in specialized centres. Patients with Wegener's granulomatosis and microscopic polyangiitis are most at risk from rapidly progressive glomerulonephritis and pulmonary haemorrhage (*Figure 7*). Renal vasculitis is the most common severe manifestation of ANCA associated systemic vasculitides, occuring in 70–85% of cases during the course of the disease (Watts and Scott, 2003). The incidence of renal vasculitis in Europe is 10–20/million/year (Watts and Scott, 2003) and increases with age. Rises in ANCA titres are associated with an increased risk of disease relapse. Other risk factors for relapse include the presence of Wegener's granulomatosis or PR3-ANCA at diagnosis, upper airway infections, reappearance of ANCA levels during clinical remission and reduction or withdrawal of immunosuppressive therapy. Clinical evaluation of patients with systemic vasculitis is the cornerstone of clinical management of these patients.

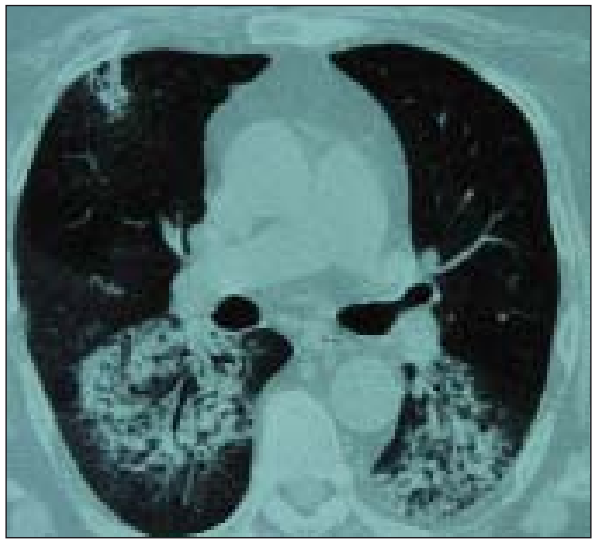


Figure 7. Computed tomography scan showing pulmonary haemorrhage in Wegener's granulomatosis.

Flares of systemic vasculitides require the gold standard therapies including corticosteroids and cyclophosphamide as induction therapy and other agents such as azathioprine and methotrexate to maintain remission. MMF is increasingly being used in autoimmune disorders and its introduction in the management of systemic vasculitides promises significant improvements in mortality and the morbidity of these disorders (D'Cruz, 2005).

Conclusions

Many patients presenting acutely with connective tissue disorders have characteristic clinical features. However, it may be difficult to differentiate these disorders from other conditions such as malignancy or infection. Indeed, these patients may well have complex combinations of immune mediated and other pathologies. A team approach with specialist involvement at an early stage will improve the recognition of these patients and will improve prognosis.

Conflict of interest: none.

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KEY POINTS

- The multisystem autoimmune diseases are interrelated but are distinct clinical entities characterized by formation of autoantibodies, B cell hyperactivity, predisposing genetic factors, increased frequency in women of child-bearing age, overlap syndromes, and immune-mediated tissue injury.
- Acute manifestations of connective tissue disorders are common in clinical practice.
- Systemic lupus erythematosus is a prototype multisystem autoimmune disease in which tissue injury is often caused by immune complex deposits.
- The significant degree of overlap in symptoms and signs among the systemic autoimmune diseases can make diagnosis a challenge.
- Autoantibodies are helpful tests to screen for multisystem autoimmune diseases.
- Precise diagnosis is important because treatments and prognoses differ.
- Infections, thrombosis and major organ involvement are early causes of death.
- Accelerated atherosclerosis appears later in the disease course and increases morbidity and mortality.