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Editors:
Ade O Adebajo FRCP(Glasgow)
D John Dickson MBChB FRCP(Glasgow) FRCP(London) MRCGP

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CONNECTIVE TISSUE DISEASES AND THE ROLE OF THE GENERAL PRACTITIONER

Dr Yasmeen Ahmad
Consultant Rheumatologist

Dr Ian N Bruce
Senior Lecturer and Consultant Rheumatologist

University of Manchester Rheumatism Research Centre, Central Manchester and Manchester Children's University Hospitals NHS Trust, Manchester

- **Connective tissue diseases (CTDs) are more common than many general practitioners (GPs) realise**
- **Early symptoms often mimic other common conditions such as fibromyalgia**
- **Cases commonly present with a combination of non-specific and more suggestive clinical features**
- **Clinical features reflect the predilection for musculoskeletal, mucocutaneous and vascular involvement**
- **Thorough clinical notes review, and several simple investigations, often reveal additional diagnostic clues**
- **The GP has a pivotal role in filtering out possible cases from the many patients with non-specific symptoms, and long-term patient management through monitoring of blood pressure, other cardiovascular risk factors, and drug toxicity**
- **In both the short and long term these conditions can impact on many aspects of patients' health, so close liaison between primary and secondary care is essential**

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INTRODUCTION

Connective tissue diseases (CTDs) are a group of closely related multisystem conditions, with many overlapping clinical features. While uncommon, they cannot be considered rare. Sjögren's syndrome affects 6–10/1000 and systemic lupus erythematosus (SLE) 1/2000 of the UK population. Thus in a practice population of 2000 individuals there may be 12–20 patients with Sjögren's syndrome, 1 patient with SLE and 1–2 with other CTDs. Furthermore, based on an incidence of 4/100,000/year a general practitioner (GP) is likely to see a new SLE case once every 13 years (i.e. 2–3 in a career). Although CTDs are associated with much greater morbidity than mortality, an awareness of the potentially dangerous complications is obviously important if avoidable organ damage and death are to be prevented. Prompt referral to the relevant specialist is thus essential.

KEY CLINICAL FEATURES

Many of the features of CTDs involve the skin, joints, muscles or blood vessels. Serological examination reveals that CTDs are associated with a variety of antinuclear antigens (ANA) and other related antibodies (Figure 1). Internationally agreed criteria for many of the disorders have been devised, but early in their presentation many cases do not satisfy these criteria, making diagnostic confirmation difficult, even in the secondary care setting. The variable nature of clinical manifestations of the CTDs is related to the fact that several key pathogenic mechanisms underlie these conditions.

- **Tissue inflammation** This can cause many of the commonly recognised features such as arthritis, rashes, myositis, nephritis, alveolitis and serositis.
- **Tissue fibrosis** Certain CTDs, and particularly systemic sclerosis (SSc), have a strong tendency to produce a fibrotic reaction in many tissues, and untreated inflammation can also cause scarring. The resulting fibrosis can result in irreversible tissue damage, e.g. lung fibrosis, renal insufficiency.
- **Vascular thrombosis** This occurs either secondary to blood vessel damage or in association with circulating antibodies, e.g. anticardiolipin antibody. Venous and/or

arterial thrombosis can occur and cause deep vein thrombosis/pulmonary embolism (DVT/PE), myocardial infarction (MI), stroke and recurrent miscarriages.

CONSIDERING THE DIAGNOSIS

Many initial presenting features are quite non-specific – e.g. fatigue, arthralgias, myalgias – and these symptoms are frequently described by patients with conditions which are much more common than CTDs, including fibromyalgia syndrome (FMS), hypothyroidism and depression. In the early diagnosis of CTDs it is therefore important to distinguish between such *non-specific* features and those which are more *suggestive* of CTD (Table 1). Several such features are considered below.

Raynaud's phenomenon

Raynaud's phenomenon (RP) is due to variable spasm of the digital arteries. When spasm is severe, and blood flow absent, the digits appear white. When spasm is partial and blood flow present but impaired, tissue over-extraction of capillary oxygen renders the draining blood cyanotic, so the digits appear blue. During recovery from spasm, reactive hyperaemia makes the digits appear red, thus explaining the classic triphasic colour changes originally described. RP affects approximately 5% of the general population, and it is important to differentiate primary from secondary causes. Primary RP usually begins during the teens and early 20s, and represents an exaggerated physiological response to cold stimuli. It is usually not associated with any other disease entity. The development of RP at an older age (>30 years old), and especially in males, suggests the possibility that it is secondary to some underlying CTD, and this should prompt investigation for an underlying cause. Thus RP occurs in >90% of patients with SSc and in up to 50% of cases with SLE and idiopathic inflammatory myositis (IIM). In a patient with RP any one of several additional features makes a secondary cause of RP more likely:

- year-round symptoms, or digital ulceration
- abnormal nailfold capillaries (viewed with an ophthalmoscope with the +20 lens)
- asymmetric upper limb pulses or bruits
- tightness/puffiness of the finger skin
- elevated erythrocyte sedimentation rate (ESR)
- positive ANA or other antibodies (e.g. Ro/La/Scl-70).

TABLE 1. Common non-specific and suggestive features which occur early in the connective tissue diseases – i.e. as would present in general practice.

Non-specific features	Suggestive features*
Fatigue Arthralgia Myalgia Depression Malaise Weight loss Fever Lymphadenopathy	Raynaud's phenomenon Dryness of mucosal surfaces Inflammatory arthritis Skin rashes: • Photosensitivity • Mucosal ulceration • Discoid lupus • Skin tightness/puffiness of digits Muscle weakness Recurrent unexplained foetal loss (≥3, usually mid-trimester) Pleurisy (in the absence of infection) Vascular events (myocardial infarction, stroke) at an early age

* The presence of one or more of these, particularly in combination with non-specific features, increases the likelihood of a connective tissue disease. Additional investigation and/or specialist referral is then appropriate.

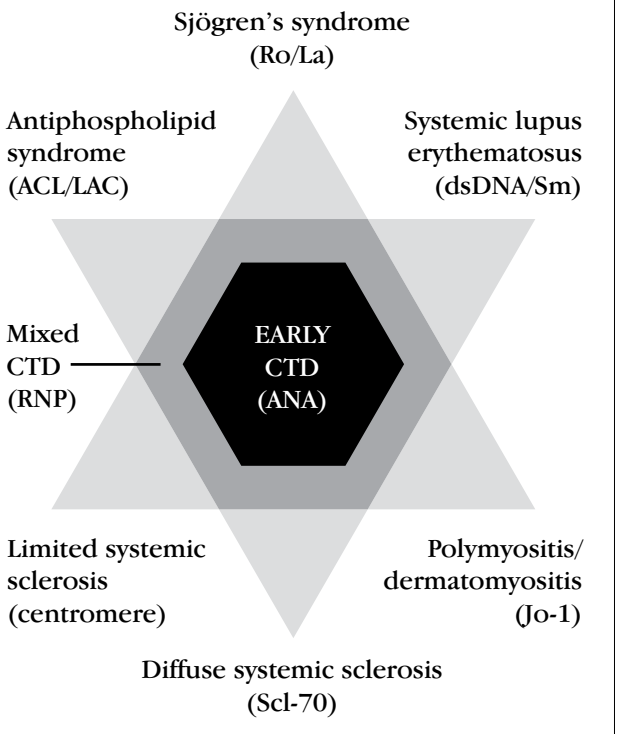

FIGURE 1. The overlapping spectrum of connective tissue diseases, and associated antibodies in serum (shown in parentheses)

ACL anticardiolipin antibody; ANA antinuclear antigen; CTD connective tissue disease; dsDNA double-stranded DNA antibody; Jo-1 anti-Jo-1 antibody; LAC lupus anticoagulant; RNP anti-ribonucleoprotein antibody; Ro/La anti-Ro/La antibodies; Scl-70 anti-Scl-70 antibody; Sm anti-Sm antibody

Dryness of mucosal surfaces

Dryness of the eyes or mouth are common subjective symptoms in the general population. The menopause, diabetes mellitus and drugs such as antidepressants are all associated with such symptoms. Having excluded these, several additional features suggest Sjögren's syndrome, which may occur alone or in association with other CTDs:

- persistence of *daily* ocular or oral dryness >3 months
- recurrent sensation of sand/gravel in the eyes

- using tear substitutes >3 times a day
- frequently drinking liquids to aid food swallowing
- recurrent or persistent salivary gland swelling or infections in an adult
- abnormal Schirmer's test
- elevated ESR or positive antibodies (ANA/Ro/La).

Many patients with Sjögren's syndrome also have long-standing dental problems or periodontitis due to decreased saliva production.

Inflammatory arthritis

Joint inflammation is associated with joint pain and stiffness (>1 hour) as well as objective evidence of soft tissue joint swelling. This needs to be distinguished from arthralgia, which often occurs in common conditions mimicking CTDs (e.g. FMS, hypothyroidism). All patients with true inflammatory arthritis signs should be referred for specialist assessment since, in addition to rheumatoid arthritis, this may also be a presenting feature of the CTDs.

Skin rashes

The classic skin rashes associated with CTDs include:

- **Photosensitivity** Abnormal sensitivity to sunshine resulting in a diffuse erythematous eruption with or without blistering. This rash frequently involves the bridge of the nose and malar area, and classically spares the nasolabial folds.
- **Recurrent mucosal ulceration** Clinically these ulcers resemble idiopathic aphthous mouth ulcers, and may involve the nasal mucosa.
- **Discoid lupus** A discrete, raised rash associated with hyperkeratosis. It frequently results in cutaneous scarring and pigmentary changes. It is often photosensitive, and when it involves the scalp patchy hair loss is usually permanent.
- **Skin tightening** In SSc there is initial puffiness and oedema of the skin, particularly affecting the fingers, dorsum of hand and forearm. There is loss of definition of the skin creases on the fingers. The skin is difficult to pinch as it feels thickened and tightly bound to the deeper layers.

Muscle symptoms

Chronic fatigue syndromes are often associated with musculoskeletal pain. Similarly, polymyalgia rheumatica (PMR) in the elderly frequently presents with stiffness and pain in limb girdle muscles. Inflammatory muscle disease such as polymyositis and dermatomyositis (PM/DM) is clinically characterised by subjective and objective proximal muscle weakness, which may be accompanied by tenderness and wasting. These clinical findings warrant further investigation, and an elevated creatinine kinase (CK) strongly supports the diagnosis.

A thorough clinical assessment therefore provides valuable clues that may increase the suspicion of a CTD. In the presence of one of the *suggestive* features, the other non-specific and suggestive symptoms should also be enquired about (Table 1). A CTD becomes increasingly more likely as more such features are noted.

INVESTIGATIONS

Laboratory tests must always be interpreted in the light of the clinical context. Approximately 5% of the general population have a clinically irrelevant, positive ANA in the serum, especially females, so a positive ANA in isolation may have no diagnostic significance. In contrast, someone with photosensitivity, inflammatory arthritis and recent pleurisy may have a 50% pre-test probability of SLE. In this context, a positive ANA significantly increases the post-test likelihood that the diagnosis is SLE. Several simple investigations help support the initial clinical suspicion.

- **Clinical notes review** The value of this cannot be understated, since this may uncover relevant facts which were not previously thought of as important, e.g. a history of DVT, recurrent miscarriages, mouth ulcers.
- **Full blood count and differential white cell count** This may demonstrate leucopenia ($<4.0 \times 10^9$/l), lymphopenia ($<1.5 \times 10^9$/l), thrombocytopenia ($<100 \times 10^9$/l), or evidence for haemolysis.
- **Urine dipstick and renal function** These should always be performed when a CTD is suspected. By the time the serum creatinine is elevated the patient will have already (potentially permanently) lost 50% of functioning renal tissue, so, in the context of renal abnormalities, a normal serum creatinine is not necessarily reassuring and further investigation is warranted.
- **Creatinine kinase** While this is often normal in cases of PM/DM, an elevated result in the context of muscle symptoms and signs clearly requires further investigation.
- **Acute phase response** The ESR is frequently raised in the CTDs, while in contrast the C-reactive protein may be normal, particularly in SLE.
- **Serology** The best screening test is the ANA. It is positive in up to 90% of patients with CTD. Other antibodies may also suggest a particular type of CTD or pattern of organ involvement (Figure 1).

WHEN TO REFER

It is difficult to give definitive guidelines on referral. In those patients with a number of suggestive clinical features and laboratory results the decision to refer is straightforward. Features confined to a particular organ

system may also prompt referral for further evaluation. In many such cases laboratory abnormalities or past medical history will increase the clinical suspicion. It is the specialist's role to coordinate detailed investigations. After this, therapy can be planned according to the distribution and severity of organ involvement.

THE CONTINUING ROLE OF THE GENERAL PRACTITIONER

CTDs are chronic, often relapsing/remitting conditions, so close liaison between primary and secondary care is necessary in managing these patients. Since the diagnosis is often only made over a prolonged period of time, i.e. when the variable and suggestive early features have been superseded by more compelling evidence, patients frequently feel aggrieved with doctors whom they have consulted in the early period. In addition, patients often feel quite isolated when they have such an uncommon disorder. GPs and specialists therefore need to co-manage patients as part of a team, which may include other healthcare professionals, e.g. rheumatology nurse specialists and physiotherapists. Local patient support groups can also help patients and carers. In long-term management of affected patients the GP has a vital role in several key areas:

- **Blood pressure** Measuring and maintaining normal blood pressure is of central importance in long-term management, especially in those patients with renal organ damage and those whose treatment requires higher dose steroids.
- **Monitoring** The GP and specialist must work closely together in monitoring the toxicity and efficacy of immunosuppressive drugs, and GPs should reasonably expect support in the form of clear monitoring and prescribing information from the specialist involved, as well as direct access to telephone advice from the hospital-based team.
- **Referrals** The GP needs to alert other practice and hospital colleagues to the diagnosis, especially when a patient is being referred between departments or hospitals. This is particularly important if a patient requires surgery or anaesthesia for any reason.
- **Women's health** These diseases commonly affect women of reproductive age, and oestrogen therapies can contribute to the inflammatory and pro-thrombotic tendencies. Contraception, pregnancy and hormone replacement therapy (HRT) should all be considered in the context of the diagnosis.
- **Infection and vaccination** Infection should be treated promptly as it may trigger a flare of inflammatory disease. A poor response to initial antibiotic therapy, especially in the immunosuppressed, may suggest an atypical or opportunistic infection. These patients should also have pneumococcal and annual influenza vaccinations.
- **Prescribing points** Ibuprofen has been associated with aseptic meningitis in patients with CTDs, while lipid-lowering agents (such as statins) may produce myositis and should thus be used cautiously in patients with known myositis.
- **Atherosclerosis risk** There is a recognised risk of premature atherosclerosis in SLE, especially in those on long-term higher dose steroids and those with renal impairment. Regular screening for atherosclerosis risk factors and a low threshold for interventions to modify risk are recommended. CTD patients should be encouraged and supported to stop smoking, maintain a regular exercise programme and control their weight.
- **Carcinoma** Patients with Sjögren's syndrome are at higher than normal risk of non-Hodgkin's lymphoma, and there is an increased risk of various malignancies in association with PM/DM. Women with CTDs who are on immunosuppressive therapy may have an increased risk of cervical disease and it is particularly important that they should have regular cervical smears.

CONCLUSION

CTDs are a group of closely related multi-system disorders associated with positive ANAs. While uncommon they are not rare. A GP should be aware of the clinical and laboratory features that suggest a CTD, and refer to a specialist for prompt evaluation. The GP also has a central role in long-term management, e.g. by sharing in the monitoring of drug therapy, blood pressure and other cardiovascular risk factors. These conditions also impact on healthcare needs in many ways. The GP is well positioned to work with the specialist to optimise the life-long management of these patients.

FURTHER READING

Hochberg MC, Silman AJ, Smolen JS, Weinblatt MC, Weisman MH (ed). Primary care rheumatology. 3rd edn. London: Mosby; 2004.

American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Guidelines for referral and management of systemic lupus erythematosus in adults. Arthritis Rheum 1999; 42(9):1785-96.

USEFUL ORGANISATIONS

British Sjögren's Syndrome Association (BSSA)
www.bssa.uk.net

Lupus UK
www.lupusuk.com

Raynaud's & Scleroderma Association
www.raynauds.org.uk