This new atlas provides an illustrated guide to the investigation, diagnosis and management of the systemic autoimmune diseases. The authors begin with an overview of the general principles of assessment. The main sections of the atlas focus in turn on specific inflammatory diseases affecting the connective tissues including the primary systemic vasculitides. Information is supported by high quality colour photographs, diagnostic algorithms and tables throughout. This up-to-date visual guide to the complex field of connective tissue disease provides an essential tool for differential diagnosis, thus enabling more rapid and effective management of the patient with these symptoms.

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An Atlas of Investigation and Management

CONNECTIVE TISSUE DISEASES

Caroline Gordon, MD FRCP
Professor and Consultant in Rheumatology
School of Immunity and Infection
College of Medical and Dental Sciences
The Medical School, University of Birmingham
Birmingham, UK

Wolfgang L Gross, MD PhD
Medical Director & Chairman
Department of Rheumatology
University of Luebeck & Clinic for Rheumatology, Bad Bramstedt
Luebeck, Germany

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Preface

Patients that present with a connective tissue disease are often a challenge to diagnose and treat. A connective tissue disease is a disorder in which the tissues of the body consisting of the cells and the matrix which holds them together are disrupted. This atlas will describe the multi-system conditions that result from inflammatory and immune-mediated disorders that can affect all the tissues of the body and their management, including presentation, investigation, differential diagnosis and treatment. Systemic lupus erythematosus, Sjögren’s syndrome, anti-phospholipid syndrome, idiopathic inflammatory myopathies, systemic sclerosis and the primary systemic vasculitides will be discussed in detail. These diseases are multifactorial conditions associated with a complex genetic predisposition and various, not well-understood, environmental triggers that induce inflammatory and immune-mediated responses directed against components of the person’s own body. As a result this group of diseases is known also as the systemic autoimmune diseases. This atlas will not discuss the inherited connective disorders due to genetic mutations that affect collagen (Ehlers–Danlos syndrome) and other connective tissue proteins, such as fibrillin-1 in Marfan’s syndrome.

Patients with a systemic autoimmune connective tissue disease can present with clinical symptoms and signs in one or more often, several, systems of the body. Some of these diseases affect people of certain ages and gender more often than others, including children, but this atlas will focus on the management of adult patients. These diseases are more common than is generally realized, cannot be cured, are associated with considerable morbidity and still cause significant mortality. Appropriate investigations are critical to making the correct diagnosis so that treatment can be tailored to the patient’s condition. It is important not only to recognize and treat the current disease activity, but also to prevent death and the development of chronic damage due to complications of the disease and the immunosuppressive drugs used to treat it. Treatment usually includes immunosuppressive therapy and other drugs depending on the effects of the disease on specific organs of the body. Principles of drug treatment will be discussed in this atlas, but the final choice of drug and exact dosages to be used will depend on the details of the patient’s condition and should be planned by a physician with relevant experience of these conditions and responsible for the management of the patient.

Due to the variable severity of these diseases and their multisystem nature that may deteriorate in pregnancy, patients with an autoimmune connective tissue disease may present to general practitioners, general physicians or internal medicine specialists, obstetricians, intensive care or any medical or surgical specialist. The majority of patients with these conditions are cared for long term by dermatologists, rheumatologists, and/or nephrologists, as it is the skin, joints and kidneys that are most often involved. However it should be noted that many patients develop cardio-respiratory or infectious complications, including accelerated atherosclerosis, due to the disease and/or its treatment. Multidisciplinary care is important and should involve the full range of allied health professionals, as well as the relevant clinical specialists depending on the organs and systems involved.

Caroline Gordon
Wolfgang L Gross
Editors and contributors

Editors

Caroline Gordon, MD FRCP
Professor and Consultant in Rheumatology
School of Immunity and Infection
College of Medical and Dental Services
The Medical School, University of Birmingham
Birmingham, UK

Wolfgang L Gross, MD PhD
Medical Director & Chairman
Department of Rheumatology
University of Luebeck & Clinic for Rheumatology,
Bad Bramstedt
Luebeck, Germany

Editors

Ariane L Herrick, MD FRCP
Professor of Rheumatology
The University of Manchester
Manchester Academic Health Science Centre
Salford Royal Hospital
Salford, UK

Julia U Holle, MD
Department of Rheumatology
University of Lübeck and Klinikum Bad Bramstedt
Bad Bramstedt, Germany

Iona Meryon, MBChB MRCP
Department of Rheumatology
Chelsea and Westminster Hospital NHS Foundation Trust
London, UK

Frank Moosig, MD PhD
University Hospital of Schleswig-Holstein and Klinikum
Bad Bramstedt
Bad Bramstedt, Germany

Contributors

Philip Clements, MD MPH
Professor of Medicine
Division of Rheumatology
David Geffen School of Medicine at UCLA
Los Angeles, CA, USA

Daniel E Furst, MD
Carl M Pearson Professor of Rheumatology
Director of Rheumatology Therapeutic Research
University of California in Los Angeles
Los Angeles, CA, USA
Abbreviations

5-FDG 5-fluorodeoxyglucose
AAV ANCA-associated vasculitides
ACEI angiotensin-converting enzyme inhibitor
ACR American College of Rheumatology
ALT alanine transferase
AMA anti-mitochondrial antibody
ANA anti-nuclear antibody
ANCA anti-neutrophil cytoplasmic antibody
APS anti-phospholipid syndrome
ARB angiotensin-receptor blocker
ARDS acute respiratory distress syndrome
AST aspartate transaminase
AZA azathioprine
BMD bone mineral density
BVAS Birmingham Vasculitis Activity Score
cANCA cytoplasmic ANCA
CAP community acquired pneumonia
CCB calcium-channel blocker
CHCC Chapel Hill Consensus Conference
CK creatine kinase
CK-MB creatine kinase MB isoenzyme
CLA cutaneous (isolated) leukocytoclastic angiitis
CMV cytomegalovirus
CNS central nervous system
CRP C-reactive protein
CSS Churg–Strauss syndrome
CT computed tomography
CV cryoglobulinaemic vasculitis
CYC cyclophosphamide
DEXA dual energy X-ray absorptiometry
DILS diffuse infiltrative lymphocytosis syndrome
DM dermatomyositis
(ds)DNA (double-stranded) deoxyribonucleic acid
DVT deep vein thrombosis
EBV Epstein–Barr virus
ECG electrocardiogram
EGD oesophago-gastroduodenostomy
EMG electromyography
ENA extractable nuclear antigen
ENT ear, nose, and throat
ERA endothelin receptor antagonist
ESR erythrocyte sedimentation rate
FVC forced vital capacity
GC glucocorticoids
GCA giant cell arteritis
GERD gastro-oesophageal reflux disease
GI gastrointestinal
HCQ hydroxychloroquine
HCV hepatitis C-associated cryoglobulinaemic vasculitis
HDU high dependency unit
HIV human immunodeficiency virus
HRCT high resolution computed tomography
HSP Henoch–Schönlein purpura
HTLV human T-lymphotrophic virus
IBM inclusion body myositis
IFN interferon
Ig immunoglobulin
IIM idiopathic inflammatory myopathy
IL interleukin
ILD interstitial lung disease
INR international normalized ratio
ITP immune thrombocytopaenic purpura
IVIG intravenous immunoglobulin
KD Kawasaki’s disease
LDH lactate dehydrogenase
MAA myositis-associated autoantibody
MALT mucosa-associated lymphoid tissue
MI myocardial infarction
MMF mycophenolate mofetil
MPA microscopic polyangiitis
Abbreviations

MPO myeloperoxidase
MR magnetic resonance
MRC Medical Research Council
MS multiple sclerosis
MSA myositis-specific autoantibody
MTX methotrexate
NHL non-Hodgkin’s lymphoma
NIH National Institutes of Health
NISP nonspecific interstitial pneumonitis
NSAID nonsteroidal anti-inflammatory drug
NTG nitroglycerin
PAH pulmonary arterial hypertension
PAN polyarteritis nodosa
PBC primary biliary cirrhosis
PCR polymerase chain reaction
PDE-5 phosphodiesterase-5
PET positron emission tomography
PM polymyositis
PMR polymyalgia rheumatica
PPI proton-pump inhibitor
PR3 proteinase 3
PSV primary systemic vasculitides

PVD pulmonary vascular disease
RCT randomized controlled trial
RF rheumatoid factor
RV rheumatoid vasculitis
RVSP right ventricular systolic pressure
SGOT serum glutamic oxaloacetic transaminase
SGPT serum glutamic pyruvic transaminase
SIBO small intestinal bacterial overgrowth
SLAM systemic lupus activity measure
SLE systemic lupus erythematosus
SPARC secreted protein, acidic and rich in cysteine
SRC scleroderma renal crisis
SS Sjögren’s syndrome
SSc systemic sclerosis
STIR short tau inversion recovery
TA Takayasu’s arteritis
TGF tumour growth factor
TIA transient ischaemic attack
TNF tumour necrosis factor
ULN upper limit of normal
UV ultraviolet
WG Wegener’s granulomatosis
Chapter 1

General approach to the assessment of patients with a suspected connective tissue disease

Ariane L Herrick

Introduction

Connective tissue diseases including the vasculitides can be difficult to diagnose, yet early diagnosis is essential in order to initiate effective treatment as soon as possible, and thereby prevent/minimize tissue injury. Therefore, the key point is to be able to recognize the clinical features which prompt the question ‘Could this patient have a connective tissue disease or vasculitis?’ Early treatment can be lifesaving, as exemplified by Scenarios 1 and 2.

Scenario 1

A 55-year-old male was admitted with profound lethargy and swollen wrists, knees, and ankles, and recent haemoptysis (he was a heavy smoker). On examination he was pale, with synovitis of his wrists and knees (with small knee effusions) and pitting oedema of both ankles. He was anaemic with a haemoglobin of 99 g/l (normocytic), erythrocyte sedimentation rate (ESR) was very high at 113 mm/h. Plasma biochemistry showed impaired renal function (urea 14.8 mmol/l, creatinine 190 μmol/l) with a low albumin at 30 g/l. Plasma biochemistry showed impaired renal function (urea 14.8 mmol/l, creatinine 190 μmol/l) with a low albumin at 30 g/l. Chest X-ray showed a cavitating lesion of the left upper zone. The following day his creatinine had risen to 250 μmol/l. No dipstick testing of urine had been performed on admission – 1 day later this showed blood and protein.

The medical registrar initially queried a paraneoplastic syndrome with some dehydration. However, when the dipstick and repeat renal function results were seen the following day, the working diagnosis was revised to a connective tissue disease, possibly vasculitis. The renal team performed an urgent renal biopsy and intravenous methylprednisolone was commenced. Renal biopsy showed necrotizing glomerulonephritis, and intravenous cyclophosphamide was added to the drug regime. Initially the renal function deteriorated further but 2 weeks later began to improve. Immunology testing was positive for anti-neutrophil cytoplasmic antibody (cytoplasmic pattern, cANCA), consistent with the clinical impression of Wegener’s granulomatosis, which had been made on the basis of a cavitating lung lesion, renal vasculitis, inflammatory arthritis, and systemic inflammation.

Scenario 2

A 43-year-old female was admitted with a 3-day history of breathlessness and general malaise. On examination, her temperature was 38°C, she had basal crackles, and poor air entry. Haemoglobin was 109 g/l, white blood cell count 4.9 × 10⁹/l, platelets 120 × 10⁹/l. ESR was 45 mm/h. Chest X-ray showed widespread interstitial shadowing.

The working diagnosis was of community acquired pneumonia (CAP). However, despite antibiotic therapy her condition deteriorated rapidly with falling PO₂ and she was transferred to the high dependency unit (HDU). The medical registrar who assessed the patient in the HDU noted that she had felt tired for around 2 months, had been suffering from mouth ulcers, and had recently begun experiencing Raynaud’s phenomenon. An autoimmune screen showed that she was strongly anti-nuclear antibody (ANA) positive (1/10,000) with a high titre of anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies (155 U/ml, reference range 0–7).

The diagnosis was revised to pneumonitis secondary to systemic lupus erythematosus (SLE), and she was treated with intravenous methylprednisolone, followed later by oral prednisolone. After commencing steroids her clinical condition improved and the shadowing on chest X-ray resolved.
Discussion of Scenarios 1 and 2
Although Scenarios 1 and 2 describe patients with recent onset, fulminating illness, most patients with connective tissue disease (including vasculitis) do not present with immediately life-threatening illnesses, but have been unwell for some time before a diagnosis is made. Clinical features are often nonspecific, especially early in the disease. Connective tissue disease should always be suspected in a patient who presents with multisystem inflammatory disease.

The first step is to establish the diagnosis, recognizing that many patients have overlapping features between different connective tissue diseases/vasculitides. Once a diagnosis is made, the emphasis of assessment changes. It then concentrates on assessment of activity and severity, and identification of new internal organ involvement. Assessment of activity and severity of the different connective tissue diseases is discussed mainly in the disease-based chapters. Patients with connective tissue disease usually need to be under long-term specialist review, the main purpose of this being to recognize changes in disease activity and severity necessitating changes in management.

History-taking and the assessment of symptoms
The key point is to take a full history as most tissues/organs can be affected in patients with connective tissue disease.

Presenting complaint
This may be virtually anything, examples being lethargy, breathlessness, heartburn, abdominal pain, paraesthesia, and rash.

Systemic enquiry
General
Common symptoms are tiredness and weight loss. Patients may also report fever, but it must be remembered that fever in patients with suspected or established connective tissue disease may be due to infection, to which they may be predisposed as a result of either the underlying disease or its treatment. For example, infection is a major contributor to mortality in patients with SLE, who are often complement deficient and who are frequently treated with steroids and/or immunosuppressant drugs. These symptoms – tiredness, weight loss, and fever – are all nonspecific and occur in malignancy and infection as well as in connective tissue disease (Table 1.1). To complicate matters further, there are associations between certain autoimmune diseases and malignancy; therefore, even in the patient with established connective tissue disease, the clinician always needs to be alert to the development of concomitant disease.

Skin and mucous membranes
Rashes occur in several of the connective tissue diseases, as described more fully under ‘Examination’. If a patient complains of a rash, always ask if it is photosensitive: classically the ‘butterfly’ rash of SLE is photosensitive. Cutaneous ulcers occur especially in systemic sclerosis (SSc), when usually the fingers or toes are affected (see below), and in the vasculitides. Hair loss (patchy or diffuse) occurs commonly in SLE (1.1). Mouth ulcers (1.2) occur commonly in SLE and Behçet’s syndrome (in which genital ulcers also occur). Oral dryness is one of the main symptoms of Sjögren’s syndrome. Other features are described in Table 1.2 and below under ‘Examination’.

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<td>Fever</td>
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<td>Weight loss</td>
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<td>Enlarged lymph nodes</td>
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Raynaud’s phenomenon
This occurs commonly in connective tissue disease, especially in SSc, in which it is rare not to have Raynaud’s. The classic episodic colour changes of the fingers (white, then blue/purple, then red) occur typically in response to cold exposure or to stress (1.3). In Scenario 2, the point of interest about the Raynaud’s phenomenon was that it had commenced only recently: patients with primary (idiopathic) Raynaud’s phenomenon typically develop this in their teens or early 20s. When Raynaud’s phenomenon occurs in patients with underlying connective tissue disease it can progress to irreversible tissue injury with ulceration, scarring, or gangrene. Worrying features in the history are a persistent fingertip discoloration and the development of digital ulceration.

Musculoskeletal
Involvement of the musculoskeletal system is common (Table 1.3). Patients with connective tissue disease often have arthralgia. They may also develop an inflammatory arthritis with joint pain, swelling, and stiffness. Proximal
muscle pain and weakness occur in inflammatory muscle disease: the patient has difficulty getting out of bed or out of a chair, especially first thing in the morning. Proximal muscle weakness may also be a side-effect of chronic use of corticosteroids.

**Cardiorespiratory**
A number of different forms of heart or lung involvement may occur including pulmonary fibrosis, pneumonia, pulmonary embolism (especially in those with anti-phospholipid syndrome [APS]), pericardial effusion, valvular heart disease or (especially in SSc) arrhythmia (*Table 1.4*). Therefore, all cardiorespiratory symptoms should be asked about if not volunteered, including breathlessness, chest pain, and oedema. Patients with connective tissue disease, especially SLE, are at increased

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<td>Early morning stiffness</td>
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<td>Joint line tenderness</td>
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<td>Joint swelling (synovial hypertrophy +/- effusion)</td>
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<td>Reduced range of movement</td>
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<td><strong>Muscles</strong></td>
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<tr>
<td>Pain (myalgia)</td>
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<tr>
<td>Early morning stiffness</td>
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<tr>
<td>Proximal muscle tenderness</td>
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<td>Proximal muscle weakness</td>
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<td>Pericardial effusion</td>
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<td>Pulmonary embolism</td>
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<td>Pneumonitis</td>
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<td>Lung fibrosis</td>
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<td>Haemoptysis</td>
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<td><strong>Upper gastrointestinal tract</strong></td>
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<td>Mucosal ulceration</td>
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<td>Acid reflux</td>
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<td>Dysphagia</td>
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<tr>
<td><strong>Lower gastrointestinal tract</strong></td>
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<td>Abdominal pain</td>
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<td>Change in bowel habit</td>
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<td>Blood loss in stools</td>
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risk of coronary artery disease and should therefore be specifically asked about symptoms.

**Gastrointestinal**
Gastrointestinal (GI) features are often not recognized as being due to connective tissue disease or vasculitis (Table 1.5). Swallowing difficulty, often with reflux symptoms, is very common in patients with SSc who may experience a wide range of GI symptoms including alteration in bowel habit: diarrhoea may reflect bacterial overgrowth, and constipation, colonic dysmotility. Abdominal pain can (rarely) be caused by mesenteric ischaemia, which can occur in patients with vasculitis.

**Renal**
Ankle swelling has a long differential diagnosis but includes nephrotic syndrome, which can occur for example in SLE.

**Neuropsychiatric**
As with the other organ systems, almost any symptom can occur in patients with connective tissue disease. SLE can be associated with involvement of peripheral, central, and autonomic nervous systems as well as with cognitive impairment and psychiatric disturbance (Table 1.6). An important point is that neuropsychiatric features can occur not only as a primary manifestation of connective tissue disease but also indirectly: for example, as a result of hypertension, uraemia, infection, coagulation problems (as in APS), or as a result of drug treatment, especially with corticosteroids. Paraesthesia is a common feature in patients with connective tissue disease and can have many causes, for example, peripheral neuropathy or (in the upper limb) carpal tunnel syndrome. Many patients with connective tissue diseases, as with other chronic diseases, become depressed.

**Eyes**
The commonest symptom is of dry, gritty eyes, occurring in patients with Sjögren’s syndrome. Eye dryness can be confirmed using Schirmer’s tear test (1.4).

![Schirmer’s test](1.4 Schirmer’s test. In this case showing satisfactory wetting of the filter paper.)

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<th>Table 1.6 Some examples of neuropsychiatric manifestations of connective tissue disease or vasculitis by region</th>
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<td><strong>Region</strong></td>
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<td>Central nervous system</td>
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<tr>
<td>Autonomic nervous system</td>
</tr>
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6 General approach to the assessment of patients

**Drug history**
A detailed drug history is important because:

- Connective tissue disease (especially SLE and small vessel vasculitis) can be a side-effect of certain drugs. For example, minocycline can cause SLE or vasculitis.
- Drugs used in the treatment of connective tissue disease may cause side-effects which are difficult to distinguish from active disease. For example, methotrexate may cause pneumonitis and several immunosuppressants may cause pancytopenia.

Two common clinical dilemmas are:

1. A patient with dermatomyositis complains of increasing muscle weakness. Is this active disease despite steroids (necessitating an increase in dosage) or is it steroid-related myopathy (necessitating a reduction in dosage)?
2. A patient with SLE on azathioprine (or another immunosuppressant) develops pancytopenia. Is this active SLE (necessitating an increase in dosage) or is it azathioprine-related bone marrow toxicity (necessitating a reduction in dosage)?

In both these examples, a careful history and examination, backed up by appropriate investigations, should indicate whether the drug treatment should be increased or reduced.

**Family history**
There is likely to be a genetic component to most of the connective tissue diseases, although the absolute risk to family members is small. For example, although the single most important risk factor for SSc is a positive family history, the risk for each family member is less than 1%. Perhaps more important to the clinician is the anxiety generated by the family history: the patient with tiredness is concerned because his/her mother had SLE, or the patient with Raynaud’s phenomenon is concerned because his/her mother had SSc. These fears/anxieties should not be underestimated.

**Social history**
Smoking causes vascular injury, and therefore should be strongly discouraged in patients with connective tissue diseases who often already have a compromised vasculature. Details about occupation, housing, and social support are important to establish (as in other chronic diseases) whether or not a patient is able to work, and the level of home support, as these parameters are often major contributors to quality of life.

**Examination for signs of connective tissue disease**
A full examination is required for the same reason as a full history: these are multisystem diseases and (in patients with established connective tissue disease or a vasculitis) drugs used in their treatment may cause a wide range of adverse effects.

**Systemic enquiry**

**General**
Examine the temperature chart. As stated above, fever can be a manifestation of connective tissue disease. Many patients are anaemic and therefore pale. Lymphadenopathy is described in connective tissue disease but is uncommon, therefore other causes should also be considered (Table 1.1). In the patient with parotid gland enlargement, consider Sjögren’s syndrome (1.5).

**Skin and mucous membranes**
The skin and mucous membranes should always be examined carefully because these can often give clues to an underlying connective tissue disease. Typical skin manifestations of the different connective tissue diseases are summarized in Table 1.2. While these have been listed by disease, it should be recognized that the skin and mucous membrane abnormalities overlap between diseases and so these are often false distinctions. For example, digital ischaemic ulcers can occur in SLE, SSc, and in the vasculitides.

- **SLE.** While the typical rash is facial (“butterfly”) (2.2A, B) and photosensitive, more chronic lesions occur in discoid (2.6, 2.7A) and subacute cutaneous lupus erythematosus (1.6). Alopecia, which may be scarring especially in discoid lupus (2.9), and mouth ulcers are also common. Mouth ulcers are a common side-effect of immunosuppressant drugs and so this possibility should be considered where relevant.
- **APS.** This diagnosis should be considered in patients with livedo reticularis (1.7).
- **SSc.** This is associated with many different cutaneous manifestations:
  - Skin thickening (scleroderma). Scleroderma proximal to the metacarpophalangeal joints is the major classification criterion for SSc and its development often leads to the diagnosis. Skin thickening usually begins in the fingers (sclerodactyly [1.8]), feet, and face and then may progress proximally especially in those with the diffuse cutaneous subtype. It must be remembered, however, that scleroderma occurs in conditions other than SSc and it is important to differentiate SSc from, for example, generalized morphoea (1.9) or eosinophilic fasciitis.
1.5 Right-sided parotid gland enlargement in a patient with Sjögren's syndrome secondary to SSc.

1.6 Subacute cutaneous lupus erythematosus.

1.7 Livedo reticularis. The rash is more obvious over the left knee than the right.

1.8 Sclerodactyly. The skin is thickened, giving rise to flexion contractures of the fingers.

1.9 Generalized morphea, most marked over the thorax posteriorly where the skin is thickened, tight, and shiny. This is not SSc: the patient did not have Raynaud’s phenomenon and the skin thickening did not commence distally.

General approach to the assessment of patients
Digital ulceration/ischaemia. An underlying connective tissue disease should always be suspected when a patient with good peripheral pulses presents with digital ulcers or ischaemia, because the pathology is likely to involve the digital arteries and/or the microvessels. Digital ulcers tend to occur at the fingertips in patients with limited cutaneous SSc (1.10) and over the proximal and distal interphalangeal joints in patients with diffuse cutaneous disease (1.11). Digital ulcers can become infected and severe digital ischaemia can progress to gangrene (1.12). Digital pitting (1.13) is one of the three minor classification criteria of SSc and reflects chronic digital ischaemia.

Telangiectases (1.14). If accompanied by other characteristic symptoms and signs, for example, Raynaud's phenomenon, these should make one suspect SSc.

Calcification. Subcutaneous calcinosis (1.15) should also always make one query an underlying diagnosis of SSc (1.16).

Dermatomyositis. This diagnosis may be suspected from the typical rash, which commonly affects the face (sometimes with heliotrope discoloration and periorbital oedema, 5.5A, B), neck and upper back, the extensor aspects of the hands (Gottron's papules, 5.6A, B), elbows, and knees, and the periungual areas. Dermatomyositis is associated with marked abnormalities of the nailfold capillaries, which can sometimes be seen with the naked eye (1.17A, B).

Vasculitis. Typical features pointing to an underlying vasculitis include splinter haemorrhages, nailfold infarcts, a purpuric rash (1.18, 1.19A, B) and vasculitic ulcers (1.20A, B, 1.21). If any of these are observed, then this should prompt a search for evidence of vasculitis elsewhere, for example renal vasculitis. As already mentioned, digital ischaemia and mouth ulcers (1.2) can also occur in the vasculitides. Because vasculitis can occur as part of other multisystem inflammatory diseases, for example in patients with rheumatoid arthritis and SLE, it is important always to be on the alert for signs of vasculitis because these might influence management (1.21).
1.13 Digital pitting (demonstrated in the finger on the left side of the image) in a patient with SSc.

1.14 Telangiectases in a patient with SSc.

1.15 Calcinosis of the thumb.

1.16 Several clinical features of SSc: cyanosis of the middle and ring finger, digital pitting of the middle finger, a calcinotic nodule of the pulp of the ring finger, telangiectases, and amputation of the index finger (this was due to severe digital ischaemia).

1.17A: Periungual erythema in a patient with probable early dermatomyositis. Dilated capillaries can be seen with the naked eye, as well as being well demonstrated with capillary microscopy (B).
10 General approach to the assessment of patients

1.18 Purpuric rash of the lower limbs. Histology showed leucocytoclastic vasculitis.

1.19A: Purpuric rash in a patient with Henoch–Schönlein purpura; B: histology of a skin biopsy from the patient shown in (A) shows superficial vessels surrounded and infiltrated by neutrophil polymorphs along with karyorrhectic debris. There is vascular damage with red blood cell extravasation. Magnification ×10. (Courtesy of Dr. L. Jamieson.)

1.20A: Vasculitic ulcers, the most obvious one being over the lateral aspect of the midfoot. There is also a vasculitic rash of the left leg and ischaemic change of the right 5th toe; B: histology of one of the ulcers of the patient shown in (A) shows a dense leucocytoclastic neutrophilic infiltrate involving both large and small vessels leading to fibrinoid necrosis of the vessels as well as necrosis of the epidermis and striking papillary dermal oedema. Magnification ×4. (Courtesy of Dr. L. Jamieson.)
Musculoskeletal

There are a large number of possible findings on musculoskeletal examination (Table 1.3), underscoring the need for a careful assessment in all patients in whom connective tissue disease is either confirmed or suspected. In inflammatory arthritis there is usually warmth, tenderness, and swelling (1.22). As with the skin, the characteristic musculoskeletal findings are considered under disease subheadings but again, this is a false distinction as there is considerable overlap in the possible manifestations between diseases.

• SLE. This is in the differential diagnosis in patients, especially young women, presenting with an inflammatory arthritis. There may be reversible deformities of the fingers.

• SSc. Contractures occur especially in patients with diffuse cutaneous disease (1.8). Patients with early diffuse disease may have friction rubs, for example at the knees and ankles.

• Inflammatory muscle disease. Pointers to the diagnosis are proximal muscle weakness and tenderness.

As a final point, fibromyalgia can occur in patients with connective tissue disease so if a patient has multiple tender points then this diagnosis should be considered.

Cardiorespiratory

Key points to look for in patients with suspected or proven connective tissue disease are shown in Table 1.4 and include:

• Raised blood pressure. This may reflect renal involvement or concomitant ‘essential’ hypertension. Either way, it is imperative that the blood pressure be well controlled. Hypertension in a patient with SSc may occur in ‘scleroderma renal crisis’, which is a medical emergency; therefore, the blood pressure must be checked in any patient with SSc who develops new symptoms such as headache or new breathlessness.

• A loud pulmonary component to the second heart sound, suggesting pulmonary hypertension.

• Basal crackles, suggesting pulmonary fibrosis.

Gastrointestinal

Key points to look for include signs of weight loss, abdominal tenderness (which can occur in SLE-related serositis or in patients with mesenteric ischaemia), and abdominal distension (which can occur in patients with SSc and episodes of pseudo-obstruction secondary to small bowel involvement).

Nervous system

Connective tissue diseases can give rise to a wide spectrum of neurological signs reflecting how peripheral, central, and autonomic nervous systems can all be involved (Table 1.6). Points to highlight are as follows:

• If a patient has signs of mononeuritis multiplex, consider whether he/she might have vasculitis.

• Peripheral neuropathy (which may be asymptomatic) may be a feature of several of the connective tissue diseases.
Trigeminal neuropathy, clinical features of which include impaired sensation in the distribution of one or more branches of the trigeminal nerve, may be the presenting feature of connective tissue disease.

Meningitis should always be suspected in the unwell patient with SLE, for example with drowsiness and pyrexia. The immediate concern is bacterial meningitis, although aseptic meningitis can also occur in SLE.

**Eyes**
Abnormalities include redness in the patient with conjunctivitis or uveitis (for example in Behçet’s disease), abnormalities of the sclera in vasculitis, and proptosis in Wegener’s granulomatosis. The fundi should be examined if there is any possibility of retinal vasculitis, for example in the patient with SLE, in whom cotton wool exudates may be found.

**Investigations in a patient with suspected connective tissue disease**

As a generalization, investigations are indicated to:

- **Inform diagnosis.** Some investigations are highly specific for different connective tissue diseases. For example, a diffuse cANCA staining is very suggestive of Wegener’s granulomatosis. The finding of histological vasculitis will confirm a suspected diagnosis and may give confidence to the clinician that immunosuppressant therapy is justified.
- **Monitor disease activity.** Monitoring of the acute phase response (ESR and/or C-reactive protein [CRP]) is standard practice in assessing disease activity/treatment response in most of the connective tissue diseases. In certain connective tissue diseases, monitoring levels of certain specific autoantibodies can also be useful (for example cANCA in Wegener’s granulomatosis or anti-double-stranded DNA [dsDNA] antibodies in patients with SLE).

Because connective tissue diseases, including the vasculitides, are often complex and multisystem, a large number of investigations may be required in any one individual, firstly at the time of diagnosis, and secondly in the monitoring of disease activity/severity and in the documentation of the degree of involvement (if any) of the different internal organs. Therefore, it is not possible to give a comprehensive list of all the investigations which might be required, nor of all the possible abnormalities. This section will give a summary of some of the tests which are most frequently requested/helpful. Most patients with a proven or suspected diagnosis of connective tissue disease will, on presentation, require the following investigative ‘work-up’:

- A full blood count.
- A biochemical profile.
- Assay of an acute phase reactant, usually the ESR or CRP.
- Dipstick testing of urine, and microscopy of urine.
- Immunology testing, including ANA.
- A chest X-ray.
- Other tests as clinically indicated.

The broad principles will be discussed here.

**Tests**

**Haematology**
Patients with active connective tissue disease typically have a normochromic normocytic anaemia, a slightly raised platelet count, and a raised ESR. However, this is not true of patients with ‘primary’ APS (i.e. not associated with a connective tissue disease such as SLE) and SSc, which are not usually associated with a major inflammatory component. A high ESR in the patient with SSc should make one query whether there is an overlap with another connective tissue disease, or whether there is an additional pathology such as infection or malignancy.

Active SLE may be associated with a fall in the haemoglobin, white cell count, and/or platelet count. A proportion of patients with SLE develop autoimmune haemolytic anaemia. Thrombocytopenia occurs in APS. Eosinophilia occurs in Churg–Strauss syndrome.

It is essential to monitor the full blood count in patients on immunosuppressive therapy. A fall in any of the components of the blood count should alert the clinician to the possibility of drug toxicity. As already discussed above, a common clinical dilemma is the patient with SLE and pancytopenia. Bone marrow examination may be helpful.

**Blood biochemistry**

- Blood biochemical profile. This should always be checked. Many patients with connective tissue disease have renal or (less frequently) hepatic involvement which may be asymptomatic.
- CRP. This is typically raised in active inflammation, although not usually elevated in SLE unless there is serositis. Therefore, a raised CRP in the patient with SLE should always prompt the clinician to look for underlying infection.
- Muscle enzymes. These should always be checked if an inflammatory muscle disease is suspected. Creatine phosphokinase is most commonly used in diagnosis and
monitoring: blood levels may be very high on presentation with polymyositis. Circulating levels of aldolase, transaminases, and lactate dehydrogenase may all be high in patients with muscle inflammation.

Globulins. Hypergammaglobulinaemia (polyclonal) may be seen especially in patients with Sjögren’s syndrome.

Urine
All patients with a suspected or proven diagnosis of connective tissue disease should have dipstick testing of urine. So often this simple test is omitted or delayed (Scenario 1) yet an abnormal dipstick may be the first clue to renal involvement. Glomerulonephritis can occur in SLE or the vasculitides. Dipstick testing may then show protein and/or blood, and microscopy of urine an active sediment with white and red blood cells and casts. If renal involvement is suspected, then a urine sample should be sent for estimation of protein/creatinine ratio and for creatinine clearance.

Immunology
The connective tissue diseases are associated with circulating autoantibodies and as already stated these can be useful in diagnosis. Also, in individual connective tissue diseases, particular autoantibodies are associated with certain phenotypes. For example, in patients with SSc, anti-centromere antibody is highly specific (but not sensitive) for the limited cutaneous disease subtype whereas antitopoiseromerase (anti-Scl-70) is specific (but not sensitive) for the diffuse cutaneous subtype. Some of the autoantibody associations with the different connective tissue diseases are listed in Table 1.7.
If a patient presents with what could be a connective tissue disease (e.g. fever, rash, splinter haemorrhages, anaemia, and a raised ESR), one or more of the following immunological tests are indicated, depending on the clinical context:

- **ANA.** This is a nonspecific test but useful in screening. Over 95% of patients with SLE are ANA positive. The higher the titre, the more likely the patient is to have an autoimmune disease: an ANA titre of 1/1,600 is much more likely to be clinically relevant than a titre of 1/100.
- **Antibodies to dsDNA.** These should be assayed if the ANA is positive and the patient is suspected of having SLE. The level of anti-dsDNA antibodies can be a useful measure of disease activity.
- **Antibodies to specific antigens.** These are more disease-specific than the ANA. Some useful disease-autoantibody associations are listed in Table 1.7. As a generalization, most of the disease-specific autoantibodies are not sensitive, i.e. many patients with the disease do not have the autoantibody.
- **Cryoglobulins.** These are proteins that precipitate when cold, and can occur in connective tissue disease and vasculitis, infections (particularly hepatitis C), or malignancy. Cryoglobulins may be monoclonal (in which case myeloma or another haematological malignancy should be suspected), polyclonal, or ‘mixed’.
- **Testing for APS.** Testing for both lupus anticoagulant (a functional assay which measures the ability of a patient’s serum to prolong in vitro measures of clotting) and anticardiolipin antibodies should be requested if a patient is suspected of having an APS. This is because one test may be negative but the other positive.

**Other investigations**

These will be indicated according to the clinical picture. However, some general points can be made.

**Investigation of suspected muscle inflammation**

The muscle enzymes should be checked as above. Other tests are: electromyography (EMG), muscle biopsy, and magnetic resonance (MR) scanning (1.23A, B). An important clinical point is that a normal muscle biopsy does not exclude the diagnosis of inflammatory muscle disease because the myositis process is patchy and may be missed on biopsy.

**Investigation of suspected vasculitis**

The ‘gold standard’ investigation is biopsy, as appearances may be diagnostic. Sometimes the histological appearances will point to a specific type of vasculitis. For example, a necrotizing granulomatous vasculitis affecting small and medium vessels would be highly suggestive of Wegener’s granulomatosis. The site of the biopsy will depend upon the clinical scenario. For example, renal biopsy was indicated in Scenario 1 because of the renal impairment and the haematuria and proteinuria. Other common biopsy sites are skin, sural nerve, temporal artery (if temporal arteritis is suspected), and muscle. Angiography may also play a key role in the diagnosis and assessment of vasculitis. For example, if a diagnosis of vasculitis is suspected in a patient with abdominal pain, then the finding of aneurysms and/or vascular occlusions on mesenteric angiography may point to a diagnosis of polyarteritis nodosa. Newer techniques, including MR and computed tomographic (CT) angiography, which are less invasive than conventional (X-ray) angiography, are now used in the monitoring of large-vessel vasculitis such as Takayasu’s arteritis.

**Investigation of the patient with Raynaud’s phenomenon**

In the patient with primary (idiopathic) Raynaud’s phenomenon, there should be no symptoms or signs suggestive of an underlying connective tissue disease. In addition, the ANA should be negative or present in low titre only (<1/100), the ESR should be normal, and the nailfold capillaries should be normal. Nailfold capillaroscopy is believed to be the investigation best predictive of underlying connective tissue disease, abnormal capillaries (1.24A, B) conferring a relative risk of an underlying SSc (or ‘scleroderma’)-spectrum disorder in the order of 13.

**Other investigations to identify presence and degree of internal organ involvement**

It is not possible to provide a comprehensive list, as the multisystem and heterogeneous nature of the connective tissue diseases means that almost any investigation might be required. Some challenging and relatively common clinical scenarios are as follows:

- **Investigation of breathlessness in a patient with SLE or other connective tissue disease.** The differential diagnosis is extensive, but investigations will include a chest X-ray (1.25, 1.26), pulmonary function tests with transfer factor, an electrocardiogram (ECG) (1.27), an echocardiogram (to include estimation of the pulmonary artery pressure), and most likely a high-resolution CT scan of the thorax.
- **Investigation of weight loss in a patient with SSc or other connective tissue disease.** Weight loss is often multifactorial and has several possible causes. Investigation in the patient with SSc should include checking for bacterial overgrowth with hydrogen and [14C] labelled breath test.
General approach to the assessment of patients

1.23 MR images showing myositis. **A**: T1-weighted image shows the replacement of the posterior muscle groups with fat, fat atrophy; **B**: STIR image shows the muscle as patchy high signal, indicating an increase in the muscle water content (oedema). (Courtesy of Dr. C. Hutchinson.)

1.24 Normal (A) and abnormal (B) capillaroscopy in a patient with SSc, showing dilated loops and (left side of image) giant capillaries and areas of haemorrhage.

1.25 Chest X-ray showing basal shadowing (pulmonary fibrosis) in a patient with SLE.

1.26 Chest X-ray showing pericardial effusion in a patient with SSc. The patient was breathless and the pericardial effusion was drained.
General approach to the assessment of patients

Investigation of lethargy in a patient with connective tissue disease. A common clinical dilemma is to decide how far to pursue the symptom of fatigue, which is one of the main symptoms of connective tissue disease and yet which can have other causes. It is not possible to generalize, but it is important to remember that patients with autoimmune connective tissue disease have an increased prevalence of thyroid disease over the general population, and are often anaemic via a variety of possible mechanisms. The key is a careful clinical assessment.

Conclusions

Assessment of patients with connective tissue diseases including the vasculitides is complex. Even once a diagnosis is made, the disease course is often unpredictable and for that reason most patients will require long-term follow-up, often involving more than one specialist. A detailed history and examination, backed up by relevant investigations, are key factors in defining the problem at any one point in time so that an appropriate management strategy may be followed. Any new symptom or sign must be pursued. Even if not directly attributable to the underlying connective tissue disease, any comorbidity and its treatment may impact on the patient, underscoring the need for a holistic approach to investigation and management.

Further reading


