EDUCATION

How to monitor SLE in routine clinical practice

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A century ago syphilis was regarded as the great masquerader. Its modern equivalent is lupus. It may present to a wide range of specialists and its outcome, while much improved, remains uncertain in a significant number of patients.

Systemic lupus erythematosus (SLE) is a multisystem autoimmune rheumatic disease. The aetiology of the disease is unknown, but genetic, hormonal, and environmental influences have a major role. The clinical manifestations of the disease are diverse, often complex, and result from inflammation in a variety of organs. Patients may present to a variety of specialists owing to the variable clinical and serological expression of disease. SLE is 10–15 times more common in women than in men. The American College of Rheumatology published its further revised criteria for the classification of SLE in 1997 (table 1). The manifestations of SLE are protean. Although arthritis and photosensitive skin rash are common presenting features as table 2 indicates, pleuropericarditis, renal disease, and involvement of the central nervous system are often seen. In some patients the disease may run a relatively benign course. Other patients may manifest serious and life threatening complications of the disease with relapses and remissions.

As SLE can manifest in many different guises (table 2), a thorough history and physical examination, including all major systems, must be undertaken at each clinic visit. Any new symptoms/signs or changes in symptoms/signs since the patient's previous visit require further evaluation. The patient's blood pressure and urine analysis must be checked at every clinic visit.

It may be difficult to distinguish active current inflammation from symptoms due to damage which implies permanent change. Thus a pain in the hip might be the consequence of synovitis or aseptic necrosis. In the former case anti-inflammatory drugs including steroids may be required. In the latter case steroids need to be reduced or stopped and surgical intervention sought. Thus one needs to be able to distinguish symptoms due to lupus activity from those due to irreversible damage, and much effort has been expended to develop validated and reliable "tools" to do this.

ASSESSING DISEASE ACTIVITY

An assessment of disease activity in a patient with SLE is crucial to the physician as it forms the basis of most treatment decisions. There have been over 60 attempts at developing disease activity indices in SLE since the 1950s. However, few are reliable or reproducible. Over the past 20 years, a number of validated activity indices have been widely used that either assess global disease activity or provide an organ based index. These include the BILAG (British Isles Lupus Assessment Group), SLAM (Systemic Lupus Activity Measure), ECLAM (European Community Lupus Activity Measure), and the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index). The SLAM, SLEDAI, and ECLAM are global indices, whereas the BILAG, established on the principle of the physician's intention to treat, provides a more comprehensive "at a glance" overview of activity in eight organs/systems.[1] In practice when a patient is seen a form recording 86 pieces of information (mostly clinical) is completed. The recorded clinical data are only entered if the physician is sure that the feature is due to SLE. Thus if the physician feels that shortness of breath is due to concomitant asthma a "0" will be recorded. If, however, based on an assessment over the previous month a given symptom is improving, the same, worse, or new a "1", "2", "3", or "4", respectively, is recorded.

> "Initial assessment of disease activity is crucial, forming the basis of treatment decisions"

The conversion from features recorded as 0, 1, 2, 3, 4 to the A, B, C, D, E scores depends upon different combinations of these features (and in the renal and haematology systems some urine/blood test results) in each of the organs/systems. For example, in the musculoskeletal system newly diagnosed definite myositis or severe polyarthritis (non-responsive to up to 10 mg prednisolone) was thought to constitute an "A" score. In the haematology system an "A" score would be recorded if the white cell count was $<1.0\times10^9$/l, the platelet count $<25\times10^9$/l, or the haemoglobin <80 g/l. Lesser degrees of activity constitute the "B" and "C" scores. A score of "D" implies previous activity but no present activity, while an "E" score implies that this organ/system has never been active.

To validate the hypothesis the outcome of over 350 patients was studied to determine if the

Abbreviations: BILAG, British Isles Lupus Assessment Group; CRP, C reactive protein; DXA, dual energy x ray absorptiometry; ESR, erythrocyte sedimentation rate; FBC, full blood count; GFR, glomerular filtration rate; SF-36, Short Form-36; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

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Table 1 Revised criteria of the American College of Rheumatology for the classification of SLE (modified from Hochberg, *Arthritis Rheum* 1997;**40**:1725–34)

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
   (a) Pleuritis
   (b) Pericarditis
7. Renal disorder
   (a) Proteinuria >0.5 g/24 h or 3+, persistently
   (b) Cellular casts
8. Neurological disorder
   (a) Seizures
   (b) Psychosis (having excluded other causes—for example, drugs)
9. Haemolytic disorder
   (a) Haemolytic anaemia
   (b) Leucopenia or $<4.0\times10^9$/l on two or more occasions
   (c) Lymphopenia or $<1.5\times10^9$/l on two or more occasions
   (d) Thrombocytopenia $<100\times10^9$/l
10. Immunological disorders
   (a) Raised anti-native DNA antibody binding
   (b) Anti-Sm antibody
   (c) Positive finding of antiphospholipid antibodies based on:
      (i) IgG/M anticardiolipin antibodies
      (ii) Lupus anticoagulant
      (iii) False positive serological test for syphilis, present for at least 6 months
11. Antinuclear antibody in raised titre

"...a person shall be said to have SLE if four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation."

Table 2 Clinical features of SLE cohort (n = 300) attending UCH/The Middlesex SLE clinic 1978–2002 (n = 300)

Organ involvement	No	% Of total
Alopecia	51	17
Oral ulcers	84	28
Joints	290	97
Jaccoud's	7	2
Erosive	15	5
Serositis	153	51
Kidney	100	33
CNS	70	23
Lung	7	2
Haemolytic anaemia	16	5
Thrombocytopenia	52	17
Sjögren's syndrome	36	12
Antiphospholipid antibody syndrome	25	8

CNS, central nervous system.

patients who were rated as having an "A" score really did get treated with high dose steroids and/or immunosuppressant drugs.

All of the published activity scales (most of which are global scores) have been validated by positive correlation with each other in real and paper patient exercises and with disease activity markers.[2]

ASSESSING DAMAGE

Permanent organ damage in SLE may be due to disease, treatment of disease, or unrelated factors. As the presumption for a damage index is that the changes recorded are permanent, or have a permanent effect, damage can only remain the same or increase over time. The SLICC/ACR (Systemic Lupus International Cooperating Clinics/American College of Rheumatology) damage index assesses the cumulative effect of the disease since onset. It has shown good inter- and intraobserver reliability.[3] The index records damage in 12 organs or systems. The change must have been present for at least 6 months and is ascertained clinically or by simple investigations. The SLICC/ACR score has been independently validated.[4] It has been shown by several groups that the early acquisition of damage is a sign of a poor prognosis.[4 5]

ASSESSING PATIENT HEALTH STATUS

The above mentioned disease activity and damage scores do not take into account the patient's health related quality of life (HRQoL), degree of disability, or impact of disease. The HRQoL incorporates mental, social, and physical health and is assessed by questionnaire. Many scales are available, but most have not been validated in SLE and therefore are not recommended.

The Health Assessment Questionnaire (HAQ) is simple to use and is widely used in rheumatoid arthritis. It has been validated in patients with SLE who have arthritis. However, no correlation with the SLEDAI activity index was seen and, clearly, the index focuses on joint disease, which is only part of the problem in patients with SLE. Currently, the Short Form-36 (SF-36) index is preferred for use in clinical practice. It is easy to complete and assesses health status over the preceding month. The SF-36 has been validated by Stoll and colleagues.[6]

The methods of assessment mentioned above are most useful in clinical trials and in the longitudinal follow up of patients with SLE.[7]

DRUG TREATMENT

Owing to the multisystem and complex nature of SLE, patients are often required to take a number of drugs and may be receiving care from several specialists. It is therefore extremely important that an accurate drug history is taken at each visit to ensure that both patient and physician are aware of a particular person's drug regimen. Problems in lupus all too often arise owing to patient non-compliance with drug treatment, with potentially serious consequences. Patients receiving disease modifying antirheumatic drugs such as azathioprine and methotrexate should be monitored in the usual way with regular full blood counts and liver function tests.

LABORATORY ASSESSMENT

Laboratory measures can be used to assess disease activity and damage.

We recommend that the following procedures should be performed at each clinic visit:

- Full blood count (FBC) and white cell differential to assess anaemia (which may be due to iron deficiency, haemolysis with a positive Coombs's test, or the anaemia of chronic disease), neutropenia, leucopenia, lymphopenia, and thrombocytopenia. It is important to remember that haematological abnormalities may be due to concomitant drug treatment—in particular, with cyclophosphamide, which lowers the white blood cell count, and azathioprine, which often increases the mean corpuscular volume but rarely causes a pancytopenia.
- Erythrocyte sedimentation rate (ESR) paired with C reactive protein (CRP) may help to distinguish lupus flare from infection, in which one would expect a raised ESR with a normal CRP in the former, and a raised ESR and CRP in the latter. Clinically such a distinction may be more complicated as CRP maybe raised in patients with intercurrent infections, serositis, or erosive arthritis.

- Urea and serum creatinine, although these tests are often normal. A rapidly rising urea and/or creatinine implies that renal activity is ''turning into'' damage.
- Liver function tests are mandatory in patients receiving particular disease modifying antirheumatic drugs. They may be deranged secondary to non-steroidal anti-inflammatory drugs or autoimmune liver disease. As with the FBC, abnormal liver function tests may be due to concomitant drugs.
- Urine analysis for red and white cells, protein, and cellular casts are useful tests of renal activity and may reveal clinically silent renal disease. If any of these analyses are abnormal and especially if serial tests are increasingly abnormal further investigations including a 24 hour urinary protein estimation or the often preferred protein/creatinine ratio estimation, and creatinine clearance, should be undertaken together with a renal ultrasound (renal size, structural abnormalities). In patients with renal disease an annual assessment of glomerular filtration rate (GFR), preferably using the EDTA clearance method, is advisable. If the method is not available it may be calculated according to the following formula:

$$\text{Estimated GFR (ml/min)} = 1.2 \times \frac{(140 - \text{age (years)}) \times \text{weight (kg)}}{\text{plasma creatinine concentration } (\mu\text{mol/l})}$$

(In women use a factor of 0.85 instead of 1.2.)

Renal biopsies are recommended in those with persistently abnormal urine analyses or reduced GFR.

SEROLOGY

Antinuclear antibodies (ANA) are positive in more than 95% of patients with lupus. Anti-double stranded DNA (dsDNA) antibodies are positive in about 60% of these patients and can be detected by immunofluorescent *Crithidia* testing, ELISA, or radioimmunoassay. Antibodies to dsDNA may fluctuate with disease activity in many patients, but not in all.[8] At the very minimum, rising antibodies to dsDNA should alert the physician that a flare maybe imminent and should encourage increased surveillance, particularly when associated with falling C3 levels.

Other routinely available autoantibodies have not been demonstrated to be helpful as markers of lupus activity. They may, however, be associated with lupus subsets. Anti-Ro antibodies, for example, are linked to photosensitivity, subacute cutaneous lupus, and the neonatal lupus syndrome. Anti-La antibodies are associated with concomitant Sjögren's syndrome. Antiphospholipid antibodies often correlate with an increased risk of thrombosis, spontaneous miscarriage, or livedo reticularis. These antibodies are identified in the form of anticardiolipin antibodies, a positive ''so-called'' lupus anticoagulant test, or anti-β_2-glycoprotein I antibodies.

Table 3 A suggested plan for the assessment and monitoring of patients with SLE in routine practice

Method of assessment	Each visit	Annually
BILAG	+	−
FBC	+	−
ESR and CRP	+	−
Urea, creatinine, electrolytes	+	−
Liver function	+	−
dsDNA titre	+	−
C3/C4	+	−
Urine analysis	+	−
Blood pressure	+	−
SF-36	−	+
SLICC/ACR	−	+
Cr-EDTA GFR	−	+*
DXA	−	+†

*In patients with suspected/proven renal disease; †to monitor treatment in established osteoporosis; the interval between scans will vary depending on severity of disease—for example, biannually.

COMPLEMENT

As with rising antibodies to dsDNA, falling levels of C3 and C4 may herald a lupus flare in patients with previously documented concordance. Some laboratories prefer to use complement breakdown products such as C3d or C4d, which increase when the disease is active.[9] Rarely, patients may have persistent hypocomplementaemia due to inherited complement deficiencies, such as the C4A/C4B null allele that is associated with lupus.

CARDIOVASCULAR RISK

Cardiovascular risk is an underappreciated complication of SLE. Coronary artery disease is more common in patients with lupus, and the incidence of myocardial infarction in women with lupus between the ages of 35 and 45 is thought to be 50 times greater than in healthy controls matched for age.[10] The cause of this increased risk is uncertain. Clearly, careful assessment of any patient with SLE who complains of chest pain is mandatory at any age. This assessment is likely, as a minimum, to require an ECG but the full panoply of cardiac tests, including a thallium scan and cardiac angiogram, may be required. The ''classic'' risk factors such as hypertension, hyperlipidaemia, and diabetes mellitus are similar to those of controls matched for age. The authors' recommend that hypertension and hyperlipidaemia are treated aggressively, the cholesterol level for example should be <5.2 mmol/l and other modifiable risk factors, such as smoking, lack of exercise, and obesity, should be addressed. Corticosteroid doses should be kept to a minimum.

OSTEOPOROSIS

Several studies have shown that lupus patients have low bone mineral density in comparison with healthy controls matched for age. It is therefore important to assess patients for risk factors for osteoporosis. These include age, menopausal status, history of low trauma fracture, duration and current dose of corticosteroid treatment, family history, diet, smoking, alcohol, weightbearing exercise, malabsorption syndromes, and lack of sun exposure.[11] Modifiable risk factors should be dealt with. Patients receiving prolonged courses of corticosteroids or those with a number of risk factors for osteoporosis should have their bone mineral density measured by dual energy *x* ray absorptiometry (DXA). Additional treatment with calcium and vitamin D and bisphosphonates may be necessary. Follow up DXA scans are invariably required.

PREGNANCY AND SLE

Patients with lupus who become pregnant require input from an obstetrician with an interest in such potentially complicated pregnancies. Patients with lupus are, in general, no less fertile than healthy controls. However, antiphospholipid antibodies threaten the longevity of the pregnancy and maternal anti-Ro antibodies are linked to the neonatal lupus syndrome. Whether patients with SLE who become pregnant are more likely to flare than those who are not pregnant is controversial. Pre-eclampsia is a major complication and can be difficult to differentiate from worsening pre-existing renal disease.

ROLE OF OTHER HEALTHCARE PROFESSIONALS

Optimal management requires assiduous monitoring and close collaboration with other medical specialists and healthcare professionals. The primary care physician/general practitioner provides a crucial link between the patient and the hospital specialist and it is important that there is good communication between the two. Clinic letters after each outpatient visit should indicate the current level of disease activity, management plan (table 3), and contact details should any problems arise.

Clinical nurse specialists are invaluable in counselling patients about starting and monitoring drug treatment, data collection, providing a constant familiar face in hospital, and providing a first port of call in emergencies.

Physiotherapists are helpful in the management of fatigue and pain as well as other musculoskeletal problems, including improving mobility. Occupational therapists can advise about home adaptations and manufacture splints for patients with arthritis. Clinical psychologists can help patients who have difficulty in accepting their disease and patients with neuropsychiatric lupus.[12]

CONCLUSION

A century ago syphilis was regarded as the great masquerader. Its modern equivalent is lupus. It may present to a wide range of specialists and its outcome, while much improved, remains uncertain in a significant number of patients.

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