The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

EASi™
European Autoimmunity
Standardisation Initiative


ThermoFisher
SCIENTIFIC

The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

Pabst Science Publishers
Lengerich, Berlin, Bremen, Miami,
Riga, Viernheim, Wien, Zagreb

Bibliographic information published by Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

http://www.pabst-publishers.de

Printing: MercedesDruck, Berlin
Typesetting: Hilmar Schlegel, Berlin
Cover: Agentur für zeitgemäße Kommunikation Kaner Thompson
www.kanerthompson.de

ISBN 978-3-89967-770-6

Systemic lupus erythematosus

Jaime Solís, Torsten Witte, Falk Hiepe, Gerald Messer, Georges Chyderiotis, Lucile Musset, Bach-Nga Pham, Nicole Fabien, Nils-Olivier Olsson, Ricard Cervera

1 Introduction

Systemic lupus erythematosus (SLE) is a chronic, multi-system autoimmune disease of unknown aetiology characterised by the production of non-organ specific autoantibodies and tissue immune-complex deposition which can potentially involve any organ and, therefore, has a wide range of clinical manifestations (Table 1). Renal involvement is frequently seen (30–50 %), and it is considered the most important predictor of the outcome of the disease.

SLE mostly affects young women (female : male ratio is 9 : 1), with an age at onset ranging from 15 to 55 years, and with some ethnic variability, being most frequent in Afro-Caribbean and Asian females.

In order to classify a patient as having SLE, 4 out of 11 criteria defined by the American College of Rheumatology (ACR) should be present at any time of the evolution of the disease (Table 2).

Table 1. Most common signs and symptoms in the "Euro-Lupus" cohort ($n = 1000$) during the 10-year prospective study (1990–2000).

Arthritis	84 %	Sicca syndrome	16 %
Malar rash	58 %	Livedo reticularis	14 %
Fever	52 %	Thrombosis	14 %
Photosensitivity	45 %	Lymphadenopathy	12 %
Nephropathy	39 %	Discoid lesions	10 %
Serositis	36 %	Myositis	9 %
Raynaud's phenomenon	34 %	Haemolytic anaemia	8 %
Neurologic involvement	27 %	Lung involvement	7 %
Oral ulcers	24 %	Subacute cutaneous lesions	6 %
Thrombocytopenia	22 %	Chorea	2 %

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

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
   - Pleurisy
   - Pericarditis
7. Renal disorder
   - Persistent proteinuria
   - Cellular casts
8. Neurologic disorder
   - Psychosis
   - Seizures
9. Haematologic disorder
   - Haemolytic anaemia
   - Leukopenia
   - Lymphopenia
   - Thrombocytopenia
10. Immunologic disorder
    - Anti-dsDNA
    - Anti-Sm
    - Antiphospholipid antibodies
11. Antinuclear antibody

2 Diagnostic measurements for experts

In a patient with suspected SLE, laboratory measurements should be performed to detect the presence of non-organ specific autoantibodies, which are the hallmark of the disease. Antinuclear antibodies (ANA) are detected in more than 95 % of SLE patients, although their presence is not specific for the disease, and

they may also appear either in other autoimmune disorders or even in healthy population. Anti-double stranded DNA (anti-dsDNA) antibodies are useful for diagnosis, follow-up and prognosis of the disorder. They are present in 60–80 % of SLE patients, and there is a correlation between anti-dsDNA levels and disease activity, particularly predicting renal involvement. Anti-C1q antibodies are also useful for predicting renal involvement. Anti-Sm antibodies are the most specific antibodies, but are less frequently detected (10 %), and have no relation to disease course. The presence of anti-Ro (SS-A) and anti-La (SS-B) antibodies is related to some clinical features such as neonatal lupus, congenital heart block, subacute cutaneous lupus and leucopenia. Antiphospholipid antibodies, such as lupus anticoagulant (LA), IgG and IgM anticardiolipin antibodies (aCL) and IgG and IgM anti-β_2-glycoprotein I antibodies, are seen in nearly one third of patients with SLE, and they are associated with an increased risk of arterial and venous thrombosis as well as with pregnancy morbidity. Complement levels (C3, C4 and CH50) should be measured during follow-up because low levels have a strong correlation with SLE activity.

Further evaluation, including renal biopsy, should be performed if significant proteinuria or haematuria is present. The classification of lupus nephritis according to the International Society of Nephrology and Renal Pathology Society (Table 3) provides prognostic and therapeutic information. Diffuse proliferative glomerulonephritis (class IV) is both the most frequent and the most severe lesion, resulting in nearly 10 % of patients having end stage renal disease at 5 years.

Table 3. International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis.

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis
Class IV	Diffuse lupus nephritis
Class V	Membranous lupus nephritis
Class VI	Advanced sclerosis lupus nephritis

3 Requirements for family practitioners

Because of the wide spectrum of clinical features, many symptoms and signs could be the initial manifestations of the disease. SLE should be suspected mainly in young patients (especially women) with polyarthritis/polyarthralgias, cutaneous lesions (especially in photo-exposed areas) (Fig. 1), recurrent oral ulcers, unexplained anaemia, lymphopenia or thrombocytopenia. The presence of persistent proteinuria or haematuria can be the first manifestation of lupus nephritis.

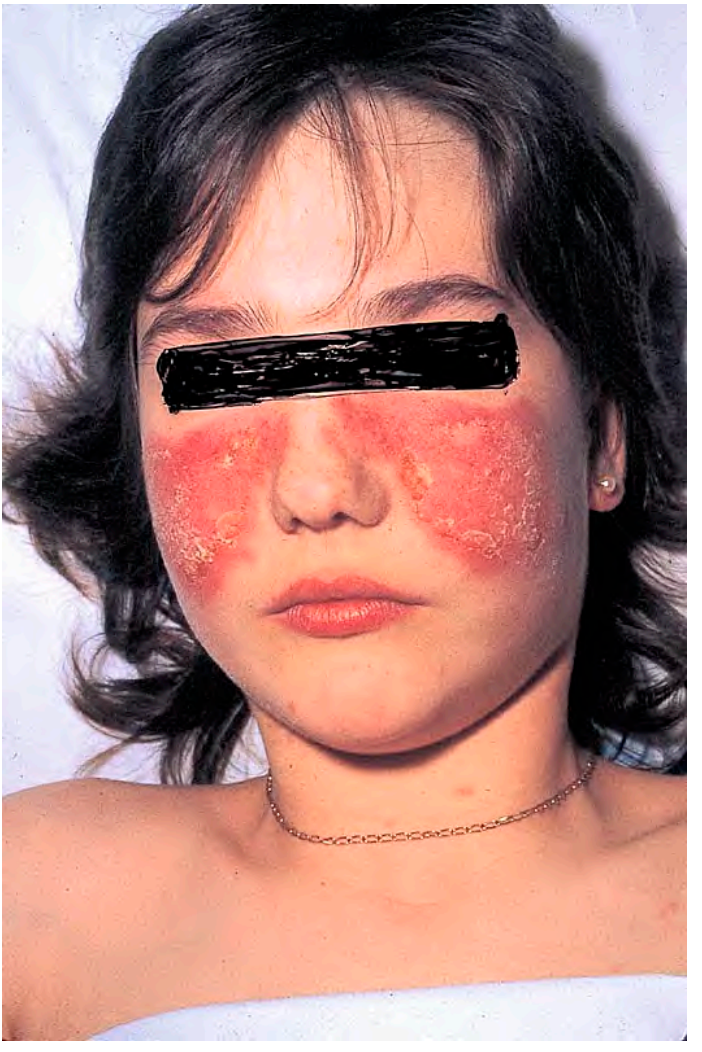

Figure 1. Malar rash in a patient with systemic lupus erythematosus.

When SLE is suspected, the patient should be referred to a specialist department for further evaluation in order to confirm the diagnosis, check organ involvement and start therapy.

The role of the general practitioner in SLE has paramount importance because close follow-up allows early diagnosis, recognition of reactivation and manage-

ment of side effects of medications, such as infections, cytopenias, and renal or hepatic toxicity.

Close control of cardiovascular risk factors, such as hypertension, diabetes, hyperlipidaemia, smoking or obesity, is essential for better disease prognosis because accelerated atherosclerosis currently constitutes one of the main causes of morbidity and mortality in SLE.

4 Follow up

Clinical observations

SLE is a chronic disease whose course is characterised by periods of flares and remissions. Some patients have chronic manifestations and other stay asymptomatic for long periods.

Expectations

The long term prognosis for patients with SLE has improved to nearly 90 % survival 10 years after diagnosis due to the better recognition and management of the disease.

Blood tests

Routine blood and urine analysis should be performed every 3–6 months, together with the measurement of anti-dsDNA antibodies and C3, C4 and CH50 levels in order to monitor disease activity.

5 Management

Because of the multiplicity of clinical presentations, SLE treatment must be individualised according to each patient's features, with special attention given to the presence and severity of renal involvement.

In general, mild manifestations, such as fatigue, cutaneous lesions or oral ulcers should be treated with antimalarial drugs as the first choice. Hydroxychloroquine is preferred over chloroquine because of its lower retinal toxicity, although periodic ophthalmologic controls are still recommended to minimise it.

Non steroidal anti-inflammatory drugs (NSAID) are indicated for arthralgias or arthritis, but it is necessary to monitor renal function to avoid nephrotoxicity.

Corticosteroids have probably been the most useful treatment for control of the disease, but should be prescribed at the lowest possible dose and for the shortest period of time in order to minimise their adverse effects. Nevertheless, many patients require low dose corticosteroids as maintenance treatment for long periods in order to avoid flares.

When high doses are needed, or internal organ involvement (especially renal) is present, other immunosuppressive agents, such as azathioprine, cyclophosphamide or mycophenolate mofetil should be introduced.

In cases of refractory disease in which at least two immunosuppressive drugs have failed, rituximab, a monoclonal antibody directed against B cells, appears to be effective, although no randomised, controlled trials have confirmed this formal indication yet.

In patients with aCL or LA, special care should be taken to prevent thrombosis, usually by the prescription of platelet aggregation inhibiting drugs, such as aspirin. In cases in which thrombosis has already occurred, anticoagulant therapy should be maintained to prevent new recurrences.

Recently, belimumab, a monoclonal antibody directed against soluble B lymphocyte stimulator (BLyS), has been licensed for the use in serologically active patients that do not respond to the standard therapy.

6 Diagnostic tests

Indirect immunofluorescence tests are the preferred methods for the detection of ANA. They have been performed on many rodent tissues, but currently are performed on HEp-2 cells, where several patterns have been recognised depending on the predominant autoantibody in serum. The most frequent pattern is the diffuse or homogeneous nuclear staining.

ANA are present in more than 95 % of SLE patients but they can also appear in other autoimmune diseases and in healthy people. Negative ANA test extensively excludes the diagnosis. By contrast, anti-dsDNA and anti-Sm antibodies are rarely seen in conditions other than SLE, and are therefore highly specific.

References

[1] Bertolaccini ML, Hughes GRV, Khamashta MA. Systemic lupus erythematosus. In: Shoenfeld Y, Cervera R, Gershwin ME, eds. Diagnostic criteria in autoimmune diseases. Totowa (NJ), USA: Humana Press, 2008: 3–7.

[2] D'Cruz D, Khamashta MA, Hughes GRV. Systemic lupus erythematosus. Lancet 2007; 369: 587–96.

[3] Scofield RH. Autoantibodies as predictors of disease. Lancet 2004; 363: 1544–6.

[4] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40: 1725.

[5] Cervera R. Systemic lupus erythematosus in Europe at the change of the millennium: lessons from the "Euro-Lupus" Project. Autoimmun Rev 2006; 5: 180–6.