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Kidney Manifestation of Systemic Lupus Erythematosus

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1. Introduction

Kidney disease secondary to SLE can affects up to 50% of patients with SLE and largely mediated by deposition of immune complex in the kidneys (1) (2).
The clinical diagnosis of lupus nephritis is usually made following a diagnostic kidney biopsy in the presence of proteinuria and/or hematouria,positive serology,and extrarenal manifestation of SLE. The presence of kidney disease is the most important predictor of morbidity and mortality in the patients with SLE.
Several demographic,serologic,and genetic risk factors are associated with an increased risk for developing kidney disease. Patient with lupus nephritis are more likely than SLE patients without kidney involvement to have a family history of SLE,anemia,high anti-dsDNA antibody titer,and hypocomplementemia. Children with SLE develop nephritis more frequently than adults and so do males.

2. Pathogenesis

Autoimmunity plays a major role in the pathogenesis of lupus nephritis. The immunologic mechanisms include production of autoantibodies directed against nuclear elements. These autoantibodies form pathogenic immune complexes. Deposition of these immune deposits in the kidneys initiates an inflammatory response by activating the complement cascade and recruiting inflammatory cells that can subsequently be observed on biopsy specimens.
Glomerular thrombosis is another mechanism that may play a role in pathogenesis of lupus nephritis, mainly in patients with antiphospholipid antibody syndrome, and is believed to be the result of antibodies directed against negatively charged phospholipid-protein complexes.

3. Symptoms and signs of lupus nephritis

Clinically lupus nephritis varies in its expression mild ,asymptomatic proteinuria to an overt nephrotic syndrome or acute nephritis associated with rapidly progressive azotemia. Glomerulonephritis is uncommonly the sentinel manifestation of SLE.
The key challenge for the clinician is to detect clinically significant lupus nephritis befor the appearance of the overt disease.

Patients can present with proteinuria during regular follow up. Hypertention is more common in patient with diffuse prolifrative lupus nephritis compared with focal prolifrative lupus nephritis or membranous lupus nephritis. Edema is an other presentation of lupus nephritis.

4. Prognostic factors

Different factors have been identified to predict the prognosis of lupus nephritis (3).
Histological factors:

- Histological class IV(diffuse proliferative LN)
- High activity and chronicity on Biopsy
- Crescents and interstitial fibrosis
- Segmental necrotizing lesion

Clinical Predictors:

- Hypertension
- Anemia
- high baseline creatinine
- high base line proteinuria
- Delay in therapy

Epidemiological Predictors

- Low socioeconomic status
- African American Race

5. Classification of Lupus Nephritis (LN)

Types of lupus nephritis

Renal biopsy is essential for the staging the type and the severity of lupus nephritis and planning the treatment.

Indication of renal biopsy

Renal biopsy is indicated in patients who have one or both of the following clinical manifestations:

- Protein excretion greater than 500 mg/day.
- An active urinary sediment with hematuria (five or more red blood cells per high power field, most of which are dysmorphic) and often pyuria and cellular casts. The urine may be contaminated with vaginal blood in menstruating women. Red cells from this source are not dysmorphic.

Lupus patients who have an inactive sediment and less than 500 mg/day of proteinuria are unlikely to have focal or diffuse proliferative or membranous lupus nephritis (LN). They may have minimal mesangial or mesangial proliferative disease, neither of which requires immunosuppressive treatment.
Such patients should be followed for evidence of progressive disease such as increasing proteinuria, emergence of an active sediment, and/or an increase in serum creatinine. These manifestations suggest transformation to a more severe lesion and warrant renal biopsy.
In patients with an inactive sediment and less than 500 mg/day of proteinuria, it is advisable to do a urinalysis every three to six months for three years; every three months is preferred in patients with anti-double-stranded DNA antibodies and/or hypocomplementemia.

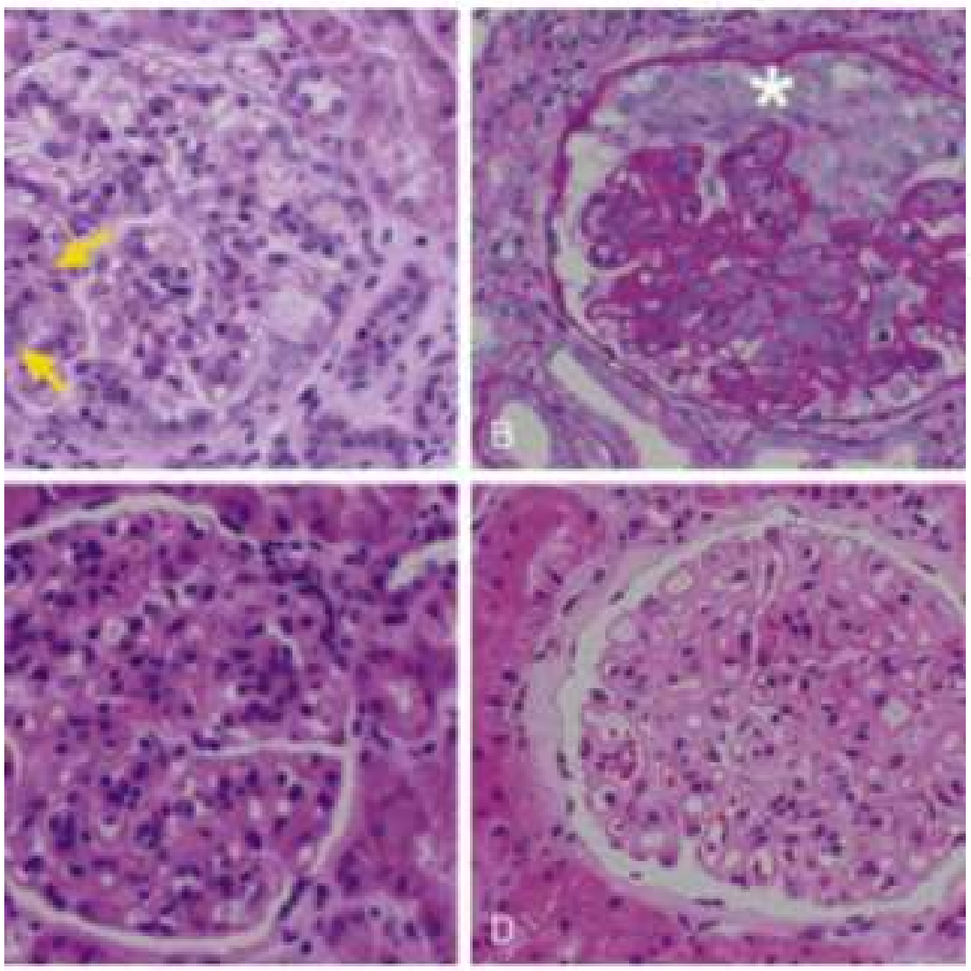
The initial classification is WHO that have been modified in 1982 and 1995(4).The most recent classification is ISN/RPS 2004(international society of nephrology and renal pathology society) (5).

DESIGNATION	DESCRIPTION
Class I: Minimal mesangial LGN	Near-normal glomeruli by LM; mesangial deposits are present by IF and/or EM
Class II: Mesangial proliferative LGN	Mesangial hypercellularity and matrix expansion, with mesangial deposits by IF and EM
Class III: Focal LGN	<50% of glomeruli display active or inactive segmental (<50% of the tuft) or global (>50% of the tuft) endocapillary proliferation or sclerosis; predominantly mesangial and subendothelial deposits are present on IF and EM
Class IV: Diffuse LGN	>50% of glomeruli have endocapillary or extracapillary glomerulonephritis;predominantly mesangial and subendothelial deposits are present on IF and EM; two subsets are defined
Class IV-S: Segmental diffuse LGN	>50% of affected glomeruli have segmental lesions
Class IV-G: Global diffuse LGN	>50% of affected glomeruli have global lesions
Class V: Membranous LGN	Capillary loop thickening in association with predominantly subepithelial deposits by IF and EM
Class VI: Advanced sclerosis	>90% of glomeruli are obsolescent, with substantial activity in remaining glomeruli

Table 1. International Society of Nephrology—Renal Pathology Society, 2004 Classification of Lupus Glomerulonephritis

Characteristic clinical features of patients with the various classes of pathology can be summarized as follows:

- Class I, Minimal mesangial lupus glomerulonephritis (LGN)—normal urine or microscopic hematuria
- Class II, Mesangial proliferative LGN—microscopic hematuria and/or low-grade proteinuria
- Class III, Focal proliferative LGN—nephritic urine sediment and subnephrotic proteinuria
- Class IV, Diffuse proliferative LGN—nephritic and nephrotic syndromes, hypertension, azotemia
- Class V, Membranous LGN—nephrotic syndrome
- Class VI, Sclerosing disease—hypertension and reduced kidney function



EM, electron microscopy; IF, immunofluorescence; LGN, lupus glomerulonephritis; LM, light microscopy

Fig. 1. Light microscopic changes in lupus glomerulonephritis (LGN). A, Segmental proliferative LGN. The glomerulus shows a discrete segmental lesion with karyorrhexis and necrosis *(gold arrows)*; the remaining capillary loops are patent with only mild mesangial expansion (hematoxylin and eosin stain). B, Global proliferative LGN with an extracapillary cellular crescent *(asterisk)*; the integrity of the glomerular tuft is compromised by proliferation and thickening of the capillary loops (hematoxylin and eosin stain). C, Pure global proliferative LGN (hematoxylin and eosin stain). D, Membranous LGN; capillary loops are uniformly thickened (hematoxylin and eosin stain).

6. Treatment of lupus nephritis

Treatment depends mainly on the clinical presentation and the pathological classification of LN. The treatment usually consists of two phases, the induction phase and the maintenance phase. The total duration of treatment around two years but it can varies based on the clinical response. But all patients need to be on non-immunosuppressive therapy.

Non-immunosuprressive therapy

Angiotensin inhibition – Administration of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) is recommended in virtually all patients with proteinuric chronic kidney disease, since such therapy may significantly reduce the rate of disease progression, acting at least in part by lowering the intraglomerular pressure. The recommended goal for protein excretion is at least a 60 percent reduction from the baseline value and optimally less than 500 to 1000 mg/day. Patients with baseline protein excretion below 500 mg/day do not appear to benefit from angiotensin inhibition.(21).

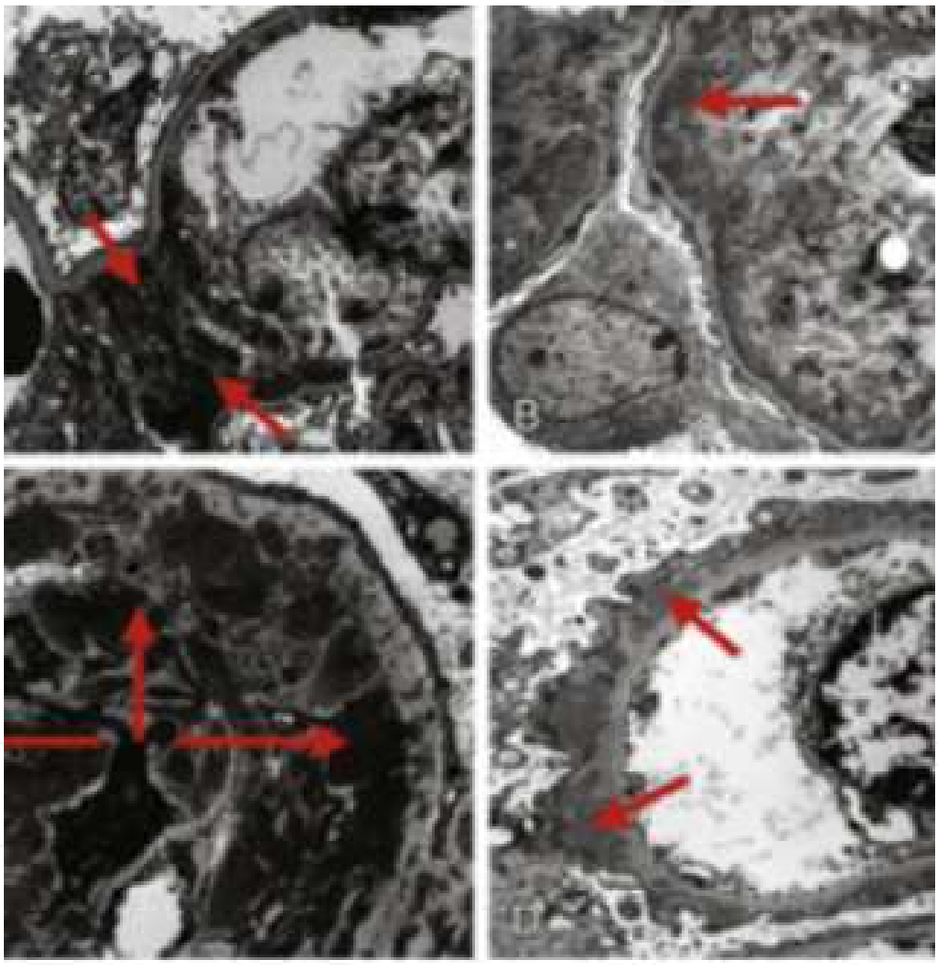


Fig. 2. Ultrastructural changes in lupus glomerulonephritis (LGN). A, Mesangial proliferative LGN; electron-dense deposits corresponding to immune complexes are concentrated in mesangial region *(red arrows)*. B and C, Continuum of subendothelial and intraluminal electron-dense deposits characteristic of proliferative forms of LGN *(red arrows)*. D, Subepithelial electron-dense deposits characteristic of membranous LGN *(red arrows)*.

Blood pressure control – The goal blood pressure in patients with any form of proteinuric chronic kidney disease is less than 130/80 mmHg, if the proteinuria is more than 3.5g/day the target is less than 125/70. Reaching this goal can slow the progression of proteinuric chronic kidney disease. It may also provide cardiovascular protection, since chronic kidney disease is associated with a marked increase in cardiovascular risk. BP control through rennin angiotensin aldosterone(RAAS) blockade is a cornerstone of conservative therapy in lupus nephritis. The RAAS, and its pharmacologic blockade, may play a role in the pathogenesis and prognosis of SLE independent of its effects on systemic BP and glomerular hemodynamics. A number of animal studies have highlighted the inflammatory components of the RAAS and the potential benefits of RAAS blockade in reducing or eliminating this inflammation in lupus nephritis (22).

Lipid lowering – Hyperlipidemia, with often dramatic elevations in the serum cholesterol concentration, is commonly present in patients with nephrotic syndrome. Although control of serum LDL cholesterol is the main indication for statin therapy, there is some evidence in patients with chronic kidney disease that it may also slow the progression of the underlying renal disease (22).

7. Immunosuppressive therapy

Different immunosuppressive medication can be used as induction and/or maintenance therapy as follows:

induction	maintaince
cyclophosphamide	**cyclophosphamide**
Mycophenolate mofetil	Mycophenolate mofetil
Rituximab	**Rituximab**
Steroids	**Steroids**
	Cyclosporine
	Azathioprine

1. Steroids

During the induction phase Methylprednisolone in doses of 7mg/kg/day as intravenous pulse therapy for three days followed by 1 mg/kg/day for 4-6 weeks to be tapered during the maintenance phase slowly according to the clinical response (6).it is usually used in combination with other drugs.

2. Cyclophosphamide

The most studied in lupus nephritis. The data for using Cyclophosphamide is coming mainly from two major randomized control trial. The first one is the National Institutes of Health (NIH) study(6), which used cyclophsphamide as intravenous monthly doses for 6 consecutive months, starting at a dose of 0.5g/m2 body surface not to exceed 1g/m^2. After the first 6 months .pulse cyclophosphamide is given every 3 months for a total of 24 months. The second trial is EURO Lupus trial (7) (8).intravenous cyclophosphamide is given every 2 weeks in a fixed dose of 500 mg for 6 doses, followed by Azathioprine (2mg/kg/day) to finish 30 months of treatment.

The downside of treatment with cyclophosphamide is the side effect profile associated with it including leucopenia, increase risk of infection, hemorrhagic cystitis ,hair loss and increase risk of malignancy.
Both regimen were equally effective in various renal and extra-renal outcomes. The low dose regimen(Euro-lupus) had less toxicity with significantly less sever and total infections as a complication of treatment(8).
During the treatment with cyclophsphamide physician need to monitor the patient with biweekly WBC count during the first six months them monthly and adjust the dose if the WBC count drop below 3000 mm2.

Mycophenolate mofetil l(MMF)

The active component of MMF, mycophenolic acid, is an inhibitor of inosine 5'-monophosphate dehydrogenase, the rate-controlling enzyme in *de novo* biosynthesis of guanosine triphosphate, used by antigen-activated B cells and T cells. Mycophenolic acid exhibits a selective antiproliferative effect on lymphocytes with anti-inflammatory effects and a profound effect on autoantibody production by B cells.
Because of its favorable safety profile, there has been great interest in the use of Mycophenolate mofet(MMF) as both induction and maintenance therapy(9)(10)(16). Since 2000 two controlled trials comparing induction therapy with MMF versus cyclophosphamide have indicated comparable rates of renal remission and short term renal survival but fewer side effects in patients treated with MMF. The best data are from international trial (ALMS) that compared MMF in a dose of 3g/day as induction therapy for six months with monthly intravenous Cyclophosphamide(IVC) for six doses (11). Overall response rates similar with MMF and IVC in all renal and non-renal parameters. In this trial MMF in a dose of 1g twice daily for 36 months was superior to Azathioprine in 2mg/kg/day as maintenance therapy.
MMF can be used in a dose of 3g/day in divided dose for 6 months as induction therapy followed by 1g twice daily for 36 months as maintenance therapy.

Cyclosporine (CSA)

The available data suggest that CSA may be a useful drug in patients with lupus nephritis showing persistent sever proteinuria after induction therapy or intolerance to other immunosuppressive drugs (12).

Azathioprine(AZA)

The role of AZA is much less established as induction therapy. The available data support the use of AZA as maintenance therapy for 24-30 months (7) (12).
preferred in women who are in complete remission and want to become pregnant. Cyclosporine is an alternative if azathioprine is not tolerated. MMF has a boxed warning because of an increased risk of congenital malformations and spontaneous abortion.

Rituximab

An anti-CD20 monoclonal antibody that depletes B cells, is useful in inducucing remissions in some patients. Currently rituximab is used for refractory or non-responder cases, alone or in combination with other immunosuppressive agents (13)(17)

Plasmapheresis

Randomized trials showed no add benefit value of plasmapheresis to immunosuppressive therapy in patient with lupus nephritis (14) (15). However, plasmapheresis may have a role in selected patients, such as those with severe crescentic LN who require dialysis (especially those with concomitant ANCA, extrapolating from the MEPEX trial of patients with Wegener's granulomatosis) or those with proliferative LN and thrombotic thrombocytopenic purpura with antiphospholipid antibodies.

The above mentioned lines of treatment usually indicated for class three and four.

Treatment of membranous lupus nephritis still controversial. Most of the clinical trial included patients with focal or diffuse proliferative lupus nephritis.

In general patients with membranous lupus nephritis who have normal renal function and subnephrotic proteinuria may not require intensive immunosuppressant while patient with high grade nephrotic syndrome or abnormal renal function or mixed membranous and proliferative lesions on biopsy which may be present at diagnosis or develop later need to be treated with immunosuppressant.

The only randomized trial limited to patients with pure lupus MN, the National Institutes of Health (NIH) trial, showed equivalent efficacy with cyclophosphamide plus glucocorticoids and cyclosporine plus glucocorticoids [18]. There were trends with cyclosporine toward higher rates of both remission (83 versus 60 percent at one year) and of relapse after the cessation of therapy (60 percent within 36 months versus 20 percent within 50 months.

A randomized trial (ALMS) compared MMF with cyclophosphamide in 370 patients with LN, including 60 with pure membranous LN [11]. The primary outcome was a prespecified reduction in the urine protein-to-creatinine ratio to less than 3 or by at least 50 percent. Secondary outcomes included stabilization or improvement of the serum creatinine, reduction of protein excretion to less than 0.5 g/day, and attainment of inactive urinary sediment. At 24 weeks, there was no difference in the two groups in the percentage of patients with pure membranous LN who achieved either the primary or secondary outcome.

8. In summary

1. lupus nephritis stage III and IV with active disease(high creatinine and/or proteinuria > 500 mg/day and/or active sediment: should be treated with cyclophosphamide intravenous as monthly dose for six months as induction therapy followed by cyclophosphamide intravenous every 3 months to finish 24 months.
2. The other approach to treat stage 3 and 4 lupus nephritis is to use cyclophosphamide intravenous in a fixed dose 500 mg every 2 weeks for six doses as induction therapy followed by MMF in a dose of 1 mg orally twice daily for 36 months which has been superior to Azathioprine as maintenance therapy. This approach is preferable to the former approach because the risk of side effect is much less.
3. If the patient can not take cyclophosphamide or prefer not to, MMF can be used in a dose of 3g/day in divided dose for six months as induction therapy followed by MMF in a dose of 1-2 g/day for 36 months as maintenance dose.
4. For stage 5 lupus nephritis with active disease(nephritic range proteinuria,active sediment and/or abnormal renal function, can be treated with oral cyclosporine in a

dose of 5mg/kg /day in divided doses but the dose need to be adjusted if the creatinine is rising. this treatment need to be continued for one year.

Intra venous Cyclophosphamide can be used (0.5-1.0g/m2) given every other month for one year.

If patient can not tolerate cyclosporine or cyclophosphamide,MMF can be used as it was beneficial in ALMS trial. It can be used in dose of 3g/day for 6 months then to be reduced to 1-2g/day.

9. Criteria for clinical reemission

Most of the clinical trials defined complete remission can be defined by the following criteria,

1. Inactive urinary sediment defined as ≤5 red blood cells per high power field, ≤5 white blood cells per high power field, a reading of 0 to 1+ on the urine dipstick for heme, and no red cell casts.
2. Normalization of the serum creatinine and protein excretion below 500 mg/day.

Partial remission can be defined by reduction of proteinuria by 50% or more.

10. Kidney transplantation in patient with lupus nephritis

If patient with lupus nephritis progress to ESRD and require dialysis, data suggest that renal transplant has better outcome than dialysis in such patients. (19)

Long-term patient and graft survivals were similar in SLE and non-SLE renal transplant recipients. The risk for thrombotic complications was greater among SLE patients (19).

Patients need to be clinically and serologically inactive at the time of transplant.

The rate of clinically recurrent disease in the renal transplant of 2.0 to 9.0 percent in patients with lupus nephritis, which is thought to reflect, diminished immunologic activity (20). The incidence of recurrent symptoms of systemic lupus was also low at 5.7 percent.

11. Experimental therapy

Several studies involving novel therapeutic agents for lupus nephritis are underway. The agents being evaluated in these studies are summarized in Table 24-3. The Web site www.clinicaltrials.gov is a potentially useful resource in searching for studies that may be recruiting patients, along with information about eligibility and exclusion criteria.

12. Prognosis

The prognosis of class III and IV proliferative lupus nephritis has improved, from a 5-year renal survival rate of less than 20% during the period 1960-1980 to a rate of more than 80% during 1980-2000. This improvement in prognosis has been ascribed mostly to increasing use of cyclophosphamide. Although preliminary data based on achievement of renal remission suggest that mycophenolate mofetil may have comparable benefits, it remains to be established whether mycophenolate mofetil will achieve comparable long-term renal survival.

Monoclonal Antibodies (Targets)
Rituximab (CD20, B cells)[* † ‡]
Epratuzumab (CD22, B cells)[*]
MEDI-545 (interferon-α)[‡]
Belimumab (BLyS cytokine)[‡]
Tocilizumab (interleukin-6 receptor)[‡]
Infliximab (tumor necrosis factor)[* ‡]
Costimulation Inhibitors
CTLA4-Ig, abatacept, belatacept (CD80/86)[‡]
Tolerogens
Abetimus, LJP-394 (anti-DNA)[‡]
Hematopoietic stem cell transplants

* Case reports.
† Case series.
‡ Ongoing clinical trials.

Table 2. Experimental Therapies for Systemic Lupus Erythematosus and Lupus Nephritis

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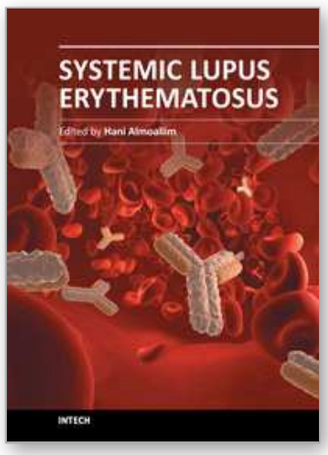

Systemic Lupus Erythematosus

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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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