

SYSTEMIC LUPUS ERYTHEMATOSUS

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Pathogenesis

1. Davies KA, Peters AM, Beyon HL, et al. Immune complex processing in patients with systemic lupus erythematosus. *In vivo* imaging and clearance studies. J Clin Invest 90:2075-2083, 1992.

Study documenting defective clearance of immune complexes in lupus.

2. Rubin RL, Bell SA, Burlingame RW. Autoantibodies associated with lupus induced by diverse drugs target a similar epitope in the (H2A-H2B)-DNA complex. J Clin Invest 90:165-173, 1992.

Identical histone DNA complex epitope shown for several different drugs associated with drug-induced autoimmunity.

3. Hartung K, Bauer MP, Coldewey R, et al. Major histocompatibility complex haplotypes and complement C4 alleles in systemic lupus erythematosus. Results of a multicenter study. J Clin Invest 90:1346-1351, 1992.

MHC-linked susceptibility factors were found in Caucasian lupus patients; C4Q0 alleles were not considered to be major importance.

4. Koren E, Reichlin MW, Kosec M, et al. Autoantibodies to the ribosomal P proteins react with a plasma membrane-related target on human cells. J Clin Invest 89:1236-1241, 1992.

Epitope antigenically related to ribosomal P protein is expressed on cell membranes, including human neuroblastoma cells. This finding may be relevant to the reported clinical association of autoantibodies to ribosomal P protein and lupus neurologic disease.

5. Cacciola-Rosen LA, Anholt G, Rosen A. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. J Exp Med 179:1371-1430, 1994.

Study showing that the autoantigens associated with autoimmunity cluster within surface blebs of apoptotic cells. Induction of apoptosis of keratinocytes by exposure to ultraviolet light produced blebs containing nucleosomal DNA, Ro, La, snRNP, and fragments of the endoplasmic reticulum.

6. Drake CG, Rozzo SJ, Hirschfield HF, Smarnworawong NP, Palmer E, Kotzin BL. Analysis of the New Zealand black contribution to lupus-like renal disease. J Immunol 154:2441-2447, 1995.

Study emphasizing that multiple combinations of genes operating in a threshold manner contribute to the development of lupus nephritis.

7. Desai-Mehta A, Lu L, Ramsey-Goldman R, Datta SK. Hyperexpression of CD40 ligand by B and T cells in human lupus and its role in pathogenic autoantibody production. *J Clin Invest* 97:2063-2073, 1996.

Study demonstrating abnormalities in expression, regulation and function of CD40 ligand on T and B lymphocytes of patients with lupus.

8. Liszewski MD, Farries TC, Lublin DM, Rooney IA, Atkinson JP. Control of the complement system. *Adv Immunol* 61:201-283, 1996.

State of the art discussion of the regulation of complement activation.

9. Scofield RH, Henry WE, Kurien BT, James JA, Harley JB. Immunization with short peptides from the sequence of the systemic lupus erythematosus-associated 60kDa Ro autoantigen results in anti-Ro ribonuclear autoimmunity. *J Immunol* 156:4059-4066, 1996.

Study in rabbits provides evidence of 'spreading' of the autoantibody response. Immunization with Ro-60kD derived peptide resulted in antibodies to the entire 60kD protein as well as the La antigen. (See also editorial in Arthritis Rheum 40:1374-1382, 1997.)

10. Tsoa PH, Cantor RM, Kalunian KC, et al. Evidence for linkage of a candidate chromosome 1 region to human systemic lupus erythematosus. *J Clin Invest* 99:725-731, 1997.

The distal end of chromosome 1 has been linked to autoimmunity in murine models of lupus. This study used a microsatellite marker technique to scan the homologous human region of chromosome 1 in 52 lupus affected sibling pairs. A strong linkage was identified for the distal region of 1q41-q42 suggesting that it contains a susceptibility gene(s) that confers risk for SLE.

11. Wakeland EK, Morel L, Mohan C, Yui M. Genetic dissection of lupus nephritis in murine models of SLE. *J Clin Immunol* 17:272-281, 1997.

Series of studies suggest that multiple susceptibility genes located on different chromosomes are necessary for the development of glomerulonephritis in murine models of lupus.

12. Daikh DI, Finck BK, Linsley PS, Hollenbaugh D, Wofsy D. Long-term inhibition of murine lupus by brief simultaneous blockade of the B7/CD28 and CD40/gp39 costimulation pathways. *J Immunology* 159:3104-3108, 1997.

Study demonstrating that the interruption of interactions of accessory molecules CD28-B7 or CTLA4-B7 inhibits autoantibody formation and prolongs life in NZB/NZW F1 mice.

Reviews

13. Ropes MW. Observations on the natural course of disseminated lupus erythematosus. *Medicine* 43:387-391, 1964.

Clinical description of disease, including large number of patients not treated with corticosteroids.

14. Wallace DJ, Podell TE, Weiner JM, et al. Systemic lupus erythematosus - survival patterns. Experience with 609 patients. *JAMA* 245:934-938, 1981.

*Description of the changing mortality over a thirty year period (see *Am J Med* 1982; 72:209-220 for companion article lupus nephritis).*

15. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25:1271-1277, 1982.

Description of classification criteria for SLE.

16. Calvo-Alen J, Bastian HM, Straaton KV, Burgard SL, Mikhail IS, Alarcon GS. Identification of patient subsets among those preemptively diagnosed with referred and/or followed up for systemic lupus erythematosus at a large tertiary care center. *Arthritis Rheum* 38:1475-1484, 1995.

Study from tertiary referral center documenting the limitations of ACR classification criteria for diagnosis of SLE with patients with unequivocal SLE who fail to satisfy criteria and ANA positive patients with a fibromyalgia-like syndrome who meet criteria, but are not considered to be part of the lupus spectrum.

17. Autoimmune-associated congenital heart block: demographics, mortality, morbidity, and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol* 31:1658-1666, 1998.

18. Kaplanski G, Cacoub P, Farnarier C, et al. Increased soluble vascular cell adhesion molecule 1 concentrations in patients with primary or systemic lupus erythematosus-related antiphospholipid syndrome: correlations with the severity of thrombosis. *Arthritis Rheum* 43:55-64, 2000.

Manifestations

Renal:

19. Nossent HC, Swaak TJ, Berden JH. Systemic lupus erythematosus after renal transplantation: patient and graft survival and disease activity. The Dutch Working Party on Systemic Lupus Erythematosus. *Ann Intern Med* 114:183-188, 1991.

One and five year graft survival of 68% and 54% were found following renal transplantation. Disease activity was unrelated to post-transplant course; one case of recurrence of lupus nephritis in the graft was documented.

20. Boumpas DT, Austin HA, Vaughan EM, et al. Severe lupus nephritis: controlled trial of pulse methylprednisolone versus two different regimens of pulse cyclophosphamide. *Lancet* 340:741-744, 1992.

Randomized trial comparing intravenous regimens of methylprednisolone and cyclophosphamide. Results indicate superiority of cyclophosphamide in prevention of loss of renal function and need for long-term therapy to prevent relapse.

21. Packham DK, Lam SS, Nichols K, et al. Lupus nephritis and pregnancy. *Quart J Med* 83:315-324, 1992.

Large and well documented clinical experience with pregnant lupus patients.

22. Ginzler EM, Felson DT, Anthony JM, et al. Hypertension increases the risk of renal deterioration in systemic lupus erythematosus. *J Rheum* 20:1694-1700, 1993.

Underscores the critical importance of blood pressure control in patients with lupus nephritis.

23. Esdaile JM, Abrahamowicz M, MacKenzie T, et al. The time- dependence of long-term prediction in lupus nephritis. *Arthritis Rheum* 37:359-368, 1994.

Study of clinical, laboratory, and renal predictors of long- term outcome in lupus nephritis.

24. Austin HA, Boumpas DT, Vaughan EM, Balow JE. Predicating renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. *Kidney Int* 54:544-550, 1994

25. Herbert LA, Dillon JJ, Middendorf DF, Lewis EJ, Peter JB. Relationship between appearance of urinary red blood cell/white blood cell casts and the onset of renal relapse in systemic lupus erythematosus. *Am J Kid Dis* 26:432-438, 1995.

Study shows that the appearance of RBC or WBC casts is the single most reliable predictor of relapse of lupus nephritis.

26. Baqi N, Moazami S, Singh A, Ahmad H, Balachandra S, Tejani A. Lupus nephritis in children: a longitudinal study of prognostic factors and therapy. *J Am Soc Nephrol* 7:924-929, 1996.

Large series of children with lupus nephritis. Prognostic factors association with poor outcome similar to those found in adults include WHO Class IV histology, hypertension, low C3, and elevated serum creatinine.

27. Lochhead KM, Pirsch JD, D'Alessandro AM, Knechtle SJ, Kalayoglu M, Sollinger HW, Belzer FO. Risk factors for renal allograft loss in patients with systemic lupus erythematosus. *Kidney Int* 49:512-517, 1996.

Study reveals higher rates of acute and chronic renal allograft rejection in SLE patients compared to non-diabetic transplant control group.

28. Moroni G, Quaglini S, Maccario M, Banfi G, Ponticelli C. "Nephritic flares" are predictors of bad long-term outcome in lupus nephritis. *Kidney Int* 50:2047-2053, 1996.

The probability of doubling the serum creatinine in lupus nephritis associated with male sex, anemia, renal flares (increases in serum creatinine or proteinuria), and failure of serum creatinine to return to basal levels within 2 months of treatment.

29. Stone JH, Asmed WJC, Criswell LA. Outcome of renal transplantation in systemic lupus erythematosus. *Sem Arthritis Rheum* 27:17-26, 1997.

30. Abramson SB, Dobro J, Eberle MA, et al. Acute reversible hypoxemia in systemic lupus erythematosus. *Ann Intern Med* 114:941-947, 1991.

Description of acute hypoxemia with normal chest radiographs; pathology postulated to involve pulmonary leukoaggregation.

Neuro/Psych:

31. Johnson RT, Richardson EP. The neurological manifestations of systemic lupus erythematosus. A clinical-pathological study of 24 cases and review of the literature. *Medicine* 47:337-369, 1968.

Classic description of diversity of clinical neurologic and psychiatric manifestations possible in lupus, often with absence of pathologic findings.

32. Ginsburg KS, Wright EA, Larson MG, Fossel AH, Albert M, Schur PH, et al. A controlled study of the prevalence of cognitive dysfunction in randomly selected patients with systemic lupus erythematosus. *Arthritis Rheum* 35:776-782, 1992.

33. Hanly JG, Fisk JD, Sherwood G, Eastwood B. Clinical course of cognitive dysfunction in systemic lupus erythematosus. *J Rheum* 21:1825-1831, 1994.

High prevalence of cognitive dysfunction documented in course of SLE which was evanescent and not clearly associated with lupus disease activity, other signs of neuropsychiatric manifestations, or corticosteroids.

34. West SG, Emlen W, Wener MH, Kotzin BL. Neuropsychiatric lupus erythematosus: a 10-year prospective study on the value of diagnostic tests. *Am J Med* 99:153-163, 1995.

Prospective study separating patients with neurologic/psychiatric manifestations into diffuse and focal presentations. Serologic abnormalities (serum antiribosomal P antibodies, CSF IgG index or oligoclonal bands) were detectable in the majority of patients with diffuse disorders whereas antiphospholipid antibodies, cutaneous vasculitis, livedo reticularis and abnormalities of MRI scans were characteristic in patients with focal presentations.

35. Chinn RJS, Wilkinson ID, Hall-Craggs MA, et al. Magnetic resonance imaging of the brain and cerebral proton spectroscopy in patients with system lupus erythematosus. *Arthritis Rheum* 40:36-46, 1997.

*Study indicating the value of MRI and MRS in the evaluation of patients with cerebral complications of SLE. (Also see editorial *Arthritis Rheum* 36:1193-1195, 1993 regarding recent advances in 'functional' CNS imaging).*

36. Hellman DB, Petri M, Whiting-O'Keefe Q. Fatal infections in systemic lupus erythematosus: the role of opportunistic organisms. *Medicine* 66:341-348, 1987.

Infections were present at time of death in 55% of lupus patients and were the direct cause of death in 30%. Infections, particularly from opportunistic organisms, were significantly associated with immunosuppressive therapy with prednisone and cytotoxic drugs.

Cardiovascular:

37. Sturfelt G, Eskilsson J, Nived O, et al. Cardiovascular disease in systemic lupus erythematosus. A study of 75 patients from a defined population. *Medicine* 71:216-223, 1992.

Clinical description of cardiovascular features of lupus with particular emphasis on the role of anticardiolipin antibodies in valvular heart lesions and corticosteroid therapy in coronary artery disease.

38. Petri M, Spence D, Bone LR, et al. Coronary artery disease risk factors in the Hopkins lupus cohort: prevalence, patient recognition, and preventive practices. *Medicine* 71:291-302, 1992.

High prevalence of coronary artery disease was found in lupus patients with typical atherosclerotic risk factors.

39. Waltuck J, Buyon JP. Autoantibody-associated congenital heart block: outcome in mothers and children. *Ann Intern Med* 120:544-551, 1994.

SLE was present in 15/52 mothers with children with autoantibody-associated (anti-SSA/Ro or anti SSA/SSB) congenital heart block. High infant mortality was noted(one-third) and the majority of surviving infants required pacemakers.

40. Manzi S, Seilahn EN, Rairie Joe, et al. Age-specific incidence rates of myocardial infarction and angina in women with system lupus erythematosus. *Am J Epi* 145:408-415, 1997.

High prevalence of coronary artery disease in lupus compared to Framingham data (i.e., women 35-44 years 50 times more likely to develop myocardial infarction). Risk factors associated with cardiovascular event included older age of onset, disease duration, duration of corticosteroid use, hypercholesterolemia, and menopause.

41. Naiker IP, Chrystal V, Randeree IGH, et al. The significance of arterial hypertension at the onset of clinical lupus nephritis. *Postgrad Med J* 73:230-233, 1997.

Misc:

42. Zmaroa MR, Warner ML, Tuder R et al. Diffuse alveolar hemorrhage and systemic lupus erythematosus: Clinical presentation, history survival, and outcome. *Medicine* 76:192-202, 1997.

43. van Vugt RM, Derksen RHW, Kater L, et al. Deforming arthropathy or lupus and rhus hands in systemic lupus erythematosus. *Ann Rheum Dis* 57:540-544, 1998.

Skin:

44. Callen JP, Klein J. Subacute cutaneous lupus erythematosus. Clinical, serologic, immunogenetic and therapeutic considerations in seventy-two patients. *Arthritis Rheum* 31:1007-1013, 1988.

Clinical description of unique cutaneous subset of lupus.

45. Laman SD, Provost TT. Cutaneous manifestations of lupus erythematosus. *Rheum Dis Cline N Am* 20:195-212, 1994.

Excellent review of cutaneous features of lupus.

Treatments:

46. Austin HA, Klippel JH, Balow JE, leRiche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *Lupus*. N Engl J Med 314:614-619, 1986
47. Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. N Engl J Med 324:150-154, 1991.
Study demonstrates 2.5 relative risk of flaring SLE in the 6-month period following discontinuation of hydroxychloroquine in patients with quiescent clinical lupus; relative risk for severe exacerbation was 6.1.
48. Van Vollenhoven RF, Engleman EG, Mc Guire JL. Dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 38:1826-1831, 1995
49. Dooley MA, Hogan S, Jennette C, Falk R, et al. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. *Kidney Int* 51:1188-1195, 1997.
Study shows that African-American patients are more prone to develop severe, progressive diffuse proliferative nephritis (WHO IV) that is less responsive to treatment with intravenous cyclophosphamide.
50. Bansal VK, Beto JA. Treatment of lupus nephritis: A meta analysis of clinical trials. *Am J Kidney Dis* 29:193-199, 1997
51. Corna D, Morigi M, Facchinetti D, et al. Mycophenylate Mofetil limits renal damage and prolongs life in murine lupus autoimmune disease. *Kidney Int* 51: 1583-1589, 1997.
52. Edwards MH, Pierangeli S, Liu XW, et al. Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. *Circulation* 96:4380-4384, 1997.
53. Brigs WA, Chor MJ, Scheal PJ Jr. Successful mycophenolate mofetil treatment of glomerular disease. *Am J Kidney Dis* 31:213-218, 1998
54. Rahman P, Humphrey-Murto S, Gladman DD, et al. Efficacy and tolerability of methotrexate in antimalarial resistant lupus arthritis. *J Rheumatol* 25: 243-246, 1998.
55. Mok CC, Lau CS, Wong RWS. Risk factors of ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy. *Arthritis Rheum* 41:831-837, 1998.

56. Grundmann-Kollmann M, Korting HC, Behrens S, et al. Mycophenolate mofetil: a new therapeutic option in the treatment of blistering autoimmune diseases. *J Am Acad Dermatol* 40:957-960, 1999.
57. Traynor AE, Schroeder J, Rosa RM, Cheng D, et al. Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and haemopoietic stem cell transplantation: A phase one study. *Lancet* 356:701-707, 2000.
58. Robbins IM, Gaine SP, Schilz R, et al. Epoprostenol for treatment of pulmonary hypertension in patients with systemic lupus erythematosus. *Chest* 117:14-18, 2000.
59. Elkayam O, Paran D, Milo R, et al. Acute myocardial infarction associated with high dose intravenous immunoglobulin infusion for autoimmune disorders: a study of four cases. *Ann Rheum Dis* 59:77-80, 2000.