

Cytomegalovirus infection in patients with systemic lupus erythematosus

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ABSTRACT

Cytomegalovirus (CMV) infection is known to induce several autoimmune abnormalities in mice that resemble those found in systemic lupus erythematosus (SLE). In addition, a potential role for CMV in the development and/or progression of SLE has been suggested. In order to further clarify this issue, we reviewed the relationship between SLE and CMV infection on the basis of the clinical and immunological features of cases reported in the literature and our own patients.

Introduction

An etiologic role of several viruses in the onset of SLE has been proposed over the last few decades. SLE patients show an increased risk of viral infection and this is a leading cause of morbidity and mortality (1-3). Recent evidence has suggested an important role of retroviruses, especially human endogenous retroviruses (HERV), as a causative agent of SLE and HERV appear to be involved in a genetic predisposition to the development of SLE (3, 4). On the other hand, viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19 seem to play a role as environmental factors that may trigger the development of SLE (2, 5-7).

There have been reports of CMV infection in SLE patients causing various conditions, including interstitial pneumonia, thrombocytopenia, hepatitis, and vasculitis (8-16). In these patients, it is sometimes difficult to decide whether the clinical manifestations are due to CMV infection or the exacerbation of SLE because similar features are shared by both diseases (10). Furthermore, CMV infection may be a factor triggering the onset of SLE in certain patients (15, 16). This article discusses the potential role of CMV infec-

tion in the onset and progression of SLE, based on the relevant literature and our own cases.

Profile and classification of SLE patients with CMV infection

Representative cases from the literature and our own SLE patients with CMV infection are summarized in Table I. Fever (temperature > 38°C) was observed in all of our patients, but was not described in some of the other patients (cases 1 and 4). Case 1 developed alveolar hemorrhage related to CMV-induced pneumonia during treatment of proteinuria with prednisolone (PSL) and azathioprine (AZP). Case 2 was being treated with PSL, cyclophosphamide (CPA), and AZP for malar rash, sudden blindness (retinal vasculitis), and an acute confusional state (lupus cerebritis). Skin ulceration and subcutaneous nodules mimicking the cutaneous manifestations of SLE developed, but a skin biopsy revealed a diagnosis of CMV-mediated vasculitis. Case 3 had been treated with various doses of steroids for 20 years. After a high anti-CMV IgM antibody titer and atypical peripheral lymphocytes were detected, CMV-induced severe pancytopenia was diagnosed. Case 4 was being treated with prednisone and CPA for idiopathic thrombocytopenic purpura (ITP) and/or SLE-related symptoms including proteinuria when CMV-related interstitial pneumonia developed. Cases 5 and 6 respectively developed fatal interstitial pneumonia and acute hepatitis due to CMV infection during treatment of SLE with hydroxychloroquine in case 5 and with PSL and AZP in case 6.

In case 7 (our patient), thrombocytopenia was induced by CMV infection during maintenance therapy (PSL at 5 mg/day) for symptoms of SLE (a malar rash and proteinuria). Cases 8, 9, and

Table I. Cases of SLE associated with CMV infection.

| Case no. sex (age) | Underlying disease (yrs. since onset) | Main symptoms | Prior therapies | | Treatment for CMV | Diagnosis of CMV | | | SLE | | Outcome | Ref. |
|--------------------------|---|---|--------------------|------------|----------------------|---------------------|----|----------------|-------------------|------------|-------------|---------------|
| | | | STR | IMS | | Ab | Ag | Path | Exacer- bation | On- set | | |
| 1. M (37) | SLE (?) | pneumonia alveolar hemorrhage | + | AZP | - | + | / | + | + | - | improvement | 8 |
| 2. F (45) | SLE (4) | skin ulcers/nodules | + | CPA AZP | - | + | - | + | + | - | death | 9 |
| 3. F (45) | SLE (20) | pancytopenia | + | - | I | + | / | ND (IgM) | + | - | improvement | 10 |
| 4. M (72) | ITP SLE (1) | intestinal pneumonia proteinuria thrombocytopenia | + | CPA | G | + | + | + | - | - | death | 11 |
| 5. F (25) | SLE (3) | pneumonia thrombocytopenia | - | - | G, I | + | + | + | + | - | death | 12 |
| 6. F (35) | SLE (8) | hepatitis pancytopenia | + | AZP | G | + | - | + | - | - | improvement | 13 |
| 7. F (33) | SLE (4) | thrombocytopenia | + | - | I | + | + | ND (IgG,M) | - | - | improvement | 14 our pt. |
| 8. M (21) | - | meningitis proteinuria | - | - | G, I | + | + | ND (IgG, M) | - | + | improvement | 15 our pt. |
| 9. F (16) | - | thrombocytopenia proteinuria | - | - | - | + | + | ND (IgG, M) | - | + | improvement | 16 our pt. |
| 10. M (12) | - | malar rash, alopecia proteinuria | - | - | - | + | - | - (IgG, M) | - | + | improvement | our pt. |

STR:steroid; IMS:immunosuppressant; AZP:azathioprine; CPA: cyclophosphamide; Ab: detection of antibody; Ag:detection of antigen in serum or urine; Path:pathological findings (inclusion bodies); ITP:idiopathic thrombocytopenic purpura; G: ganciclovir; I:immunoglobulin; ND:not done; /:not described.

10 were also our patients and their clinical courses are outlined in Figure 1. Case 8 had some underlying autoimmune abnormalities, such as antinuclear antibody (ANA) positivity, when examined three months before the onset of CMV infection, but these abnormalities did not fit the criteria for a diagnosis of SLE. After meningitis developed due to CMV infection, anti-DNA antibodies and proteinuria were detected and then the patient fulfilled the criteria for SLE. Cases 9 and 10 showed high titers of IgM antibodies for CMV and similar symptoms to CMV infection including fever, lymphadenopathy, and thrombocytopenia at the onset of SLE, which presented with proteinuria in the former and malar rash/alopecia in the latter. CMV antigen was also detected in the serum of case 9, but not case 10.

Based on the findings in these previously reported cases and our patients,

the relationship between SLE and CMV infection seems to fit one of three patterns. CMV infection can occur during the treatment of SLE with steroid therapy and/or immunosuppressants and there are two types in these patients. In type 1 patients, CMV infection induces the exacerbation of underlying SLE. In type 2 patients, exacerbation of SLE is not induced by CMV infection and symptoms (such as fever, lymphadenopathy, and thrombocytopenia) appear to be due to the virus itself. In the former type, the exacerbation of several SLE-related immunologic parameters (e.g., an increase of ANA and anti-DNA antibodies or a decrease of complement) as well as SLE-related symptoms occur with the onset of CMV infection. In the latter type, changes of SLE-related immunological parameters do not occur with the onset of CMV infection. In certain patients (type 3), CMV infection may actually

trigger the onset of SLE. In this type of patient, the diagnosis of SLE has not been established and treatment has not been instituted before the onset of CMV infection. This mode of onset of SLE may be especially important in young patients such as our cases. A predisposition to certain autoimmune abnormalities may be required before CMV infection can induce the SLE, as indicated by cases 8. Interestingly, the father of case 10 showed ANA positivity although he did not have any autoimmune disease.

Among the patients listed in Table I, cases 1, 2, 3 and 5 represent type 1, cases 4, 6 and 7 correspond to type 2, and cases 8, 9 and 10 represent type 3.

Diagnosis of CMV infection

The diagnosis of CMV infection in these patients was made by widely accepted methods, such as the detection of anti-CMV IgM antibodies (which

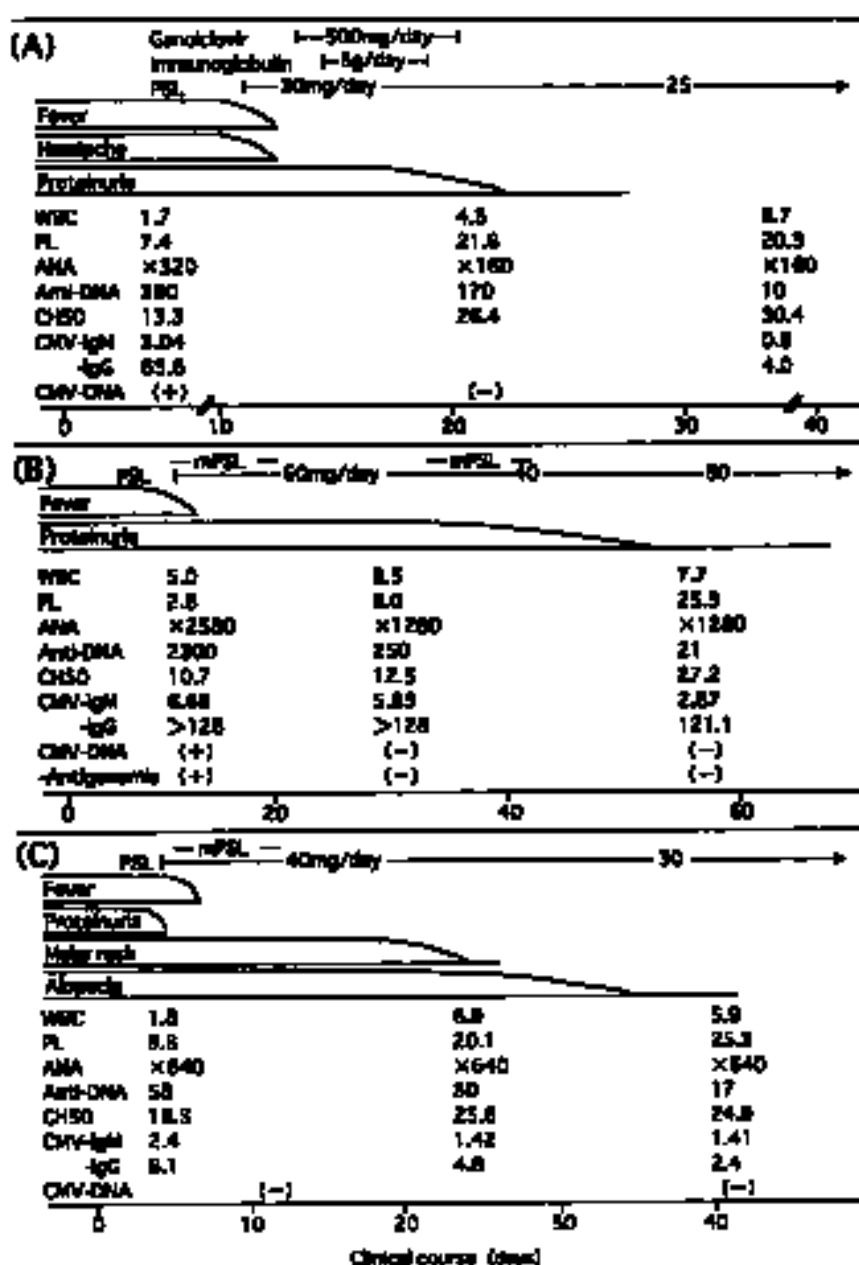


Fig. 1. Clinical course of cases 8 (A), 9 (B), and 10 (C). CMV-DNA and CMV-antigenemia were detected by the PCR and enzyme immunoassay, respectively. WBC; white blood cell count ($\times 10^4/\text{mm}^3$), PL; platelet count ($\times 10^3/\text{mm}^3$), ANA; antinuclear antibody (normal range; $n, < \times 40$), Anti-DNA; anti-DNA antibody ($n < 6.0$ IU/ml), CH50; hemolytic complement activity ($n = 30-40$ U/ml), CMV-IgM; anti-CMV IgM antibody ($n < 1.0$), CMV-IgG; anti-CMV IgG antibody ($n < 1.0$), PSL; prednisolone, mPSL; methyl-prednisolone pulse therapy (500 mg/day \times 3 days).

usually indicate current CMV infection) and IgG antibodies in the serum, and/or the detection of CMV antigen by the polymerase chain reaction (PCR) or an enzyme immunoassay using monoclonal anti-CMV antibodies (17). In certain patients (cases 1, 2, 4, 5, 6), pathological findings characteristic for CMV infection such as inclusion bodies were observed in lesions of the

lung, skin, and liver. Case 3 and 10 had similar features to those of CMV infection, including fever, lymphadenopathy, atypical lymphocytosis, and thrombocytopenia. However, both patients showed high titers only of anti-CMV IgM antibodies, and no CMV antigen or CMV-related pathological findings. CMV antigen generally becomes negative in the serum after the early stage of

infection, while anti-CMV IgM antibodies show prolonged positivity, as observed in case 9 (Fig. 1B). Therefore, these patients were thought to have CMV infection. In cases 2 and 6, the pathological findings of the lesions in the skin and liver were consistent with CMV infection, although serum and/or urine CMV antigens were negative. On the other hand, cases 4 and 5 had detectable serum CMV antigens and compatible pathological findings in the lungs despite being negative for serum anti-IgM (but not IgG) CMV antibodies.

Thus, the relationship among CMV antibodies, antigens, and pathological findings is probably more complex than is generally appreciated, especially in patients with autoimmune abnormalities including those due to SLE. In order to investigate the association between SLE and CMV infection, cross-sectional and longitudinal studies of SLE patients have been performed by the measurement of viral antibodies and antigens using the enzyme-linked immunosorbent assay (ELISA) and the PCR, respectively (7, 18-20). Some investigations have suggested the possibility that virus-related antibodies are produced in SLE as a consequence of polyclonal B cell activation (21, 22). Another study found no evidence of active CMV infection, as judged by anti-CMV IgG and IgM antibodies, and no correlation between SLE disease activity and CMV serology/viremia during observation of their patients (20). In contrast, it has been reported that a very high proportion of SLE patients or conditions with related symptoms (Raynaud's phenomenon) show positivity for anti-CMV antibodies (18, 19) and it has been suggested that this represents genuine CMV infection because there is no correlation between the antibodies and serum immunoglobulin levels and no similar selective increase in seropositivity for other viral antibodies such as herpes simplex virus in SLE patients when compared with controls (18). Thus, the results of these studies have been inconsistent and this may depend on the complexities of the relationship between CMV antibodies and antigens, as described above.

Treatment of CMV infection in SLE patients

Antiviral agents such as ganciclovir are generally used to treat SLE patients with severe CMV-mediated organ damage such as pneumonia or meningitis (cases 4-6 and 8). In cases 3 and 7, who had pancytopenia or thrombocytopenia, immunoglobulin therapy (without ganciclovir) was given in addition to steroid. Steroid therapy was given for SLE-related clinical and laboratory findings (proteinuria, malar rash, thrombocytopenia, and autoimmune abnormalities such as high anti-DNA antibody titers and low serum complement levels) were performed in the type 3 patients shown in Table I (cases 8-10). Case 8 received ganciclovir and immunoglobulin in addition to steroid therapy because these agents were thought to be necessary for CMV meningitis (Fig. 1A).

Cases 9 and 10 did not show any severe CMV-mediated visceral damage (such as pneumonia or meningitis) despite having positive of viral tests for CMV infection, and steroids alone without antiviral therapy were effective in controlling their symptoms and laboratory changes. With treatment, a decrease of anti-CMV IgM and IgG levels and disappearance of CMV antigens were observed in the early stage of the disease, probably due to host defenses against viral infection (Fig. 1B and C). Both patients are now being followed as outpatients and have not shown further exacerbation of their SLE. However, we cannot rule out the possibility that more aggressive treatment (including ganciclovir) should be used for such patients because of a strong tendency for CMV infection to show chronic latency, as described later.

Regarding immunoglobulins (especially with a high anti-CMV titer), it must be kept in mind that such immunoglobulins can have antiplatelet activity due to cross-antigenicity between the CMV envelope and platelet surface-glycoprotein, leading to the exacerbation of CMV-mediated thrombocytopenia, as indicated previously (15, 23). Thus, it seems that the use of antiviral therapy is still controversial in SLE patients with CMV infection, especially type 3

patients, and investigation of more such cases is required to establish suitable treatments.

Onset of CMV infection in SLE patients

The importance of steroids and/or immunosuppressants has been noted with regard to the onset of opportunistic infections in SLE, including CMV infection (1). In fact, six patients in Table I were treated with steroids and four of them also received immunosuppressants such as AZP and CPA, although the doses and treatment period were variable. Case 5 had inactive SLE (nephropathy) and was only receiving hydroxychloroquine as maintenance therapy (no steroids or immunosuppressants), but showed several CMV-related symptoms including pneumonia and thrombocytopenia. Similarly, the onset of CMV infection was observed in case 7 when SLE was stable and the steroid dose was low (5 mg/day). This indicates the possibility that opportunistic infection in SLE may be attributable to the derangement of T cells in certain patients. Recent evidence about the relationship between opportunistic infections and human immunodeficiency virus (HIV) infection is of interest with respect to this issue.

Several reports have indicated that an increase of CD4⁺ T cells following active antiretroviral therapy (HAART) can induce the development of symptoms related to opportunistic infections such as CMV-related retinitis in certain HIV-infected patients (immune restoration disease: IRD) and that steroids are effective for suppressing such symptoms (24, 25). This is thought to result from normalization of the immune response by a recovery of memory CD4⁺ T cell numbers and activity against opportunistic pathogens. A similar mechanism to IRD may apply to the onset of opportunistic infection in SLE. The CD4⁺/CD8⁺ T cell ratio (CD4/CD8 ratio) is generally lower in SLE patients as compared to normal individuals (the average ratio for 30 SLE patients was 0.587 ± 0.3 and that for 33 normal controls was 1.608 ± 0.5 in our laboratory, $P < 0.001$) and the ratio increases with improvement of the

disease (26). Normalization of immunity in patients who have inactive SLE and are receiving relatively low doses of immunosuppressive therapy may contribute to the manifestation of opportunistic infections, since the immune system of SLE patients may originally show hyper-responsiveness to non-self as well as self-antigens (27). This mechanism may be significant for the development of opportunistic infections in SLE patients, in addition to the important role of immunosuppressive agents.

Possible mechanisms of CMV-induced autoimmunity

There have been a number of investigations into the mechanisms of CMV-related autoimmunity using murine models of CMV infection. In these models, multiple autoantibodies are found in the serum, probably due to molecular mimicry of self determinants by viral antigens, as well as polyclonal B cell activation and the resultant hypergammaglobulinemia (28-31).

Healthy individuals with CMV infection are known to have an increased frequency and quantity of autoantibodies to ribonucleoprotein (U1 snRNP), and a significant association between the presence of antibodies to CMV and antibodies to Sm/RNP autoantigens has been reported in patients with SLE, probably as a result of cross reactivities (32). Furthermore, epitopes of La (SS-B) antigens in humans with autoimmune disease show sequence similarities to proteins from the herpes group of viruses, including CMV (33). Also, the expression of La antigens together with human leukocyte antigen (HLA) class II molecules is induced on the surface of CMV-infected cells in the presence of interferon-gamma and this may be the basis for a T cell-dependent mechanism of anti-La autoantibody production (34).

It has been reported that viral infection is associated with the development of neuroendocrine autoimmune diseases such as type 1 (insulin-dependent) diabetes and stiff-man syndrome though the mechanism is unknown, and that both diseases share glutamic acid decarboxylase (GAD65) as a major

autoantigen recognized by the patient's CD4+ T cells (35). CMV-derived peptides can also be recognized by GAD65-reactive T cells, so CMV may be involved in the loss of T cell tolerance to autoantigens by a mechanism of molecular mimicry that leads to autoimmunity (36).

Chronic graft versus host disease (GVHD) is known to have many features in common with SLE. Interestingly, CMV infection can provoke chronic GVHD in recipients of bone marrow transplantation and patients with GVHD develop antibodies to the CD13 (aminopeptidase N) molecule on peripheral blood mononuclear cells. This molecule is present on all CMV-susceptible cells and is incorporated into the surface envelope of newly synthesized CMV virion, thereby perhaps forming an autoantigenic target (37). Taken together, it seems that CMV-induced autoimmunity may arise from complex cross-reactivities between the virus and the host or autoreactive T cells, as well from a relationship between EBV and autoantigens (6,7), and polyclonal B cell activation.

Finally, virus-infected cells are eliminated by CD8+ cytotoxic T lymphocytes (CTL) and/or natural killer (NK) cells. The binding of killer cell inhibitory receptor (KIR) on CD8+ cells with E antigens of HLA class I molecules on virus-infected cells can inhibit the cytolytic activity of CD8+ cells against the infected cells (38). A glycoprotein homologous with HLA class I antigens is encoded by CMV and is known to be a ligand of KIR (39, 40). This mechanism may be related to inhibition of the killing of CMV by CTL and/or NK cells, resulting in latency and recurrence of CMV infection and the subsequent CMV-related provocation of autoimmune abnormalities in infected patients.

Conclusion

Based on the findings in reported cases and our patients, we think that CMV infection shows three patterns of association with SLE: 1) infection occurs during treatment and exacerbates pre-existing SLE (type 1); 2) symptoms arise due to CMV infection itself rather

than an exacerbation of underlying SLE (type 2); and 3) CMV infection directly provokes the onset of SLE (type 3). In addition, mixed types may exist among SLE patients with CMV infection. We think that type 3 patients are more common than was formerly supposed, especially among young patients with SLE. This type of classification may also be applied to the relationship between SLE and other viruses such as EBV or parvovirus and may be useful in the planning of more effective therapy.

Further clinical and laboratory studies on CMV infection in patients with SLE are needed to clarify the mechanism of CMV-induced autoimmune abnormalities and to establish suitable treatments for CMV-associated SLE, because there still seems to be a considerable amount of work required on the association between SLE and opportunistic infections including CMV, despite their widely recognized clinical importance.

References

- PETRI M: Infection in systemic lupus erythematosus. *Rheum Dis Clin North Am* 1998; 24: 423-56.
- DENMANAM: Systemic lupus erythematosus – is a viral aetiology a credible hypothesis? *J Infect* 2000; 40: 229-33.
- SEKIGAWA I, OGASAWARA H, KANEKO H, HISHIKAWA T, HASHIMOTO H: Retroviruses and autoimmunity. *Intern Med* 2001; 40: 80-6.
- OGASAWARA H, NAITO T, KANEKO H *et al.*: Quantitative analyses of messenger RNA of human endogenous retrovirus in SLE patients. *J Rheumatol* 2001; 28: 533-8.
- TANAKA A, SUGAWARA A, SAWAI K, KUWAHARA T: Human parvovirus B19 infection resembling systemic lupus erythematosus. *Intern Med* 1998; 37: 708-10.
- INCARPERA M, RINDI L, BAZZICHI A, GARZELLI C: Potential role of the Epstein-Barr virus in systemic lupus erythematosus autoimmunity. *Clin Exp Rheumatol* 1998; 16: 289-94.
- JAMES JA, NEAS BR, MOSER KL *et al.*: Systemic lupus erythematosus in adults is associated with previous Epstein-Barr virus exposure. *Arthritis Rheum* 2001; 44: 1122-6.
- KWONG YL, WONG KL, KUNG ITM, CHAN PCK, LAM WK: Concomitant alveolar haemorrhage and cytomegalovirus infection in a patient with systemic lupus erythematosus. *Postgrad Med J* 1988; 64: 56-9.
- BURPITT KJ, BRAHN E: Systemic lupus erythematosus and concurrent cytomegalovirus vasculitis: diagnosis by antemortem skin biopsy. *J Rheumatol* 1989; 16: 677-80.
- VASQUEZ V, BARZAGA RA, CUNHA BA: Cytomegalovirus-induced flare of systemic lupus erythematosus. *Heart Lung* 1992; 21: 407-8.
- GARCIA-PORRUA C, GONZÁLEZ-GAY MA, PÉREZ DE LLANO LA, ALVAREZ-FERREIRA J: Fatal intestinal pneumonia due to cytomegalovirus following cyclophosphamide treatment in a patient with systemic lupus erythematosus. *Scand J Rheumatol* 1998; 27: 465-6.
- KU SC, YU CJ, CHANG YL, YANG PC: Disseminated cytomegalovirus disease in a patient with systemic lupus erythematosus not undergoing immunosuppressive therapy. *J Formos Med Assoc* 1999; 98: 855-8.
- MCCURDY L, JIRJIS JN: Acute cytomegalovirus hepatitis with systemic lupus erythematosus. *Tennessee Med* 1998; 91: 187-9.
- LEE S, SUGIYAMA M, HISHIKAWA T *et al.*: Thrombocytopenia in systemic lupus erythematosus associated with cytomegalovirus infection. *Scand J Rheumatol* 1997; 26: 69.
- HAYASHI T, LEE S, OGASAWARA H *et al.*: Exacerbation of systemic lupus erythematosus related to cytomegalovirus infection. *Lupus* 1998; 7: 561-4.
- NAWATA M, SETA N, YAMADA M, SEKIGAWA I, IIDA N, HASHIMOTO H: Possible triggering effect of cytomegalovirus infection on systemic lupus erythematosus. *Scand J Rheumatol* 2001; 30: 360-2.
- VAN DER BIJ W, SCHIRM J, TORENSMA R, VAN SON WJ, TEGZESS AM, THE TH: Comparison between viremia and antigenemia for detection of cytomegalovirus in blood. *J Clin Microbiol* 1988; 26: 2531-5.
- RIDER JR, OLLIER WER, LOCK RJ, BROOKES ST, PAMPHILON DH: Human cytomegalovirus infection and systemic lupus erythematosus. *Clin Exp Rheumatol* 1997; 15: 405-9.
- STRATTA P, CANAVESE C, CICCONE G *et al.*: Correlation between cytomegalovirus infection and Raynaud's phenomenon in lupus nephritis. *Nephron* 1999; 82: 145-54.
- BENDIKSEN S, VAN GHELE M, REKVIG OP, GUTTEBERG T, HAGA HJ, MOENS U: A longitudinal study of human cytomegalovirus serology and viremia fails to detect active viral infection in 20 systemic lupus erythematosus patients. *Lupus* 2000; 9: 120-6.
- BORG EJT, HOARST G, HUMMEL E, LIMBURG PC, KALLENBERG CGM: Rises in anti-double stranded DNA antibody levels prior to exacerbations of systemic lupus erythematosus are not merely due to polyclonal B cell activation. *Clin Immunol Immunopathol* 1991; 59: 117-28.
- KRUEGER GRF, ARGOTE VF: A unifying concept of viral immunopathogenesis of proliferative and a proliferative diseases (working hypothesis). *In Vitro* 1994; 8: 493-3.
- SNYDER JR HW, SEAWELL BW, COCHRAN SK, BALINT JR JP, JONES FR: Specificity of antibody responses affected by extracorporeal immunoadsorption of plasma over columns of protein A silica. *J Clin Apheresis* 1992; 7: 110-8.
- SEPKOWITZ KA: Effect of HAART on natural history of AIDS-related opportunistic disorders. *Lancet* 351; 351: 228-30.
- FRENCH MA, PRICE P: Immune restoration disease in HIV-infected patients after antiretroviral therapy. *Clin Infect Dis* 2001; 32:

- 325-6.
26. SEKIGAWA I, MATSUSHITA M, LEE S *et al.*: A possible pathogenic role of CD8+ T cells and their derived cytokine, IL-16, in SLE. *Autoimmunity* 2001; 33: 37-44.
 27. MIZUKAWA Y, SHIOHARA T: Virus-induced immune dysregulation as a triggering factor for the development of drug rashes and autoimmune diseases: With emphasis on EB virus, human herpesvirus 6 and hepatitis C virus. *J Dermatol Sci* 2000; 22: 169-80.
 28. OLDING LB, KINGSBURY DT, OLDSTONE MB: Pathogenesis of cytomegalovirus infection. Distribution of viral products, immune complexes and autoimmunity during latent murine infection. *J Gen Virol* 1976; 33: 267-80.
 29. VON HERRATH MG, OLDSTONE MB: Virus-induced autoimmune disease. *Curr Opin Immunol* 1996; 8: 878-5.
 30. FAIRWEATHER D, KAYA Z, SHELLAM GR, LAWSON CM, ROSE NR: From infection to autoimmunity. *J Autoimmunity* 2001; 16: 175-86.
 31. PRICE P, OLVER SD, GIBBONS AE, SHELLAM GR: B-cell activation following murine cytomegalovirus infection: Implications for autoimmunity. *Immunology* 1993; 78: 14-21.
 32. NEWKIRK NM, VAN VENROOIJ WJ, MARSHALL GS: Autoimmune response U1 small nuclear ribonucleoprotein (U1 snRNP) associated with cytomegalovirus infection. *Arthritis Res* 2001; 3: 253-8.
 33. HAAHEIM LR, HALSE AK, KVAKESTAD R, STERN B, NORMANN O, JONSSON R: Serum antibodies from patients with primary Sjögren's syndrome and systemic lupus erythematosus recognize multiple epitopes on the La (SS-B) autoantigen resembling viral protein sequences. *Scand J Immunol* 1996; 43: 115-21.
 34. BABOONIAN C, VENABLES PJ, BOOTH J, WILLIAMS DG, ROFFE LM, MAINI RN: Virus infection induces redistribution and membrane localization of the nuclear antigen La (SS-B): A possible mechanism for autoimmunity. *Clin Exp Immunol* 1989; 78: 454-9.
 35. BAEKKESKOV S, AANSTOOT HJ, CHRISTGAU S *et al.*: Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. *Nature* 1990; 347: 151-6.
 36. HIEMSTRA HS, SCHLOOT NC, VAN VEELEN PA *et al.*: Cytomegalovirus in autoimmunity: T cell crossreactivity to viral antigen and autoantigen glutamic acid decarboxylase. *Proc Natl Acad Sci USA* 2001; 98: 3988-91.
 37. NAUCLER CS, LASSON S, MOLLER E: A novel mechanism for virus-induced autoimmunity in humans. *Immunol Rev* 1996; 152: 175-92.
 38. MINGARI MC, MORRETTA A, MORRETTA L: Regulation of KIR expression in human T cells: A safety mechanism that may impair protective T-cell responses. *Immunol Today* 1998; 19: 153-7.
 39. FARRELL HE, VALLY H, LYNCH DM *et al.*: Inhibition of natural killer cells by a cytomegalovirus MHC class I homologue *in vivo*. *Nature* 1977; 386: 510-4.
 40. REYBURN HT, MANDELBOIM O, VALEGOMEZ M, DAVIS DM, PAZMANY L, STROMINGER JL: The class I MHC homology of human cytomegalovirus inhibits attack by natural killer cells. *Nature* 1997; 386: 514-7.