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Abstract: Systemic lupus erythematosus (SLE) is a heterogenous autoimmune disease with a broad spectrum of clinical and immunological manifestations. The disease has a world-wide distribution and there are considerable inter-ethnic differences in the clinical presentation of the disease. A number of studies have been performed to examine the distinct clinical, immunological and genetic profile of the local SLE patients. In the first part of this article, data on the clinical manifestations and immunogenetics of southern Chinese SLE patients in Hong Kong are being reviewed.

Keywords: Clinical features, immunogenetics, immunological, lupus, prevalence

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune multisystemic disease of unknown etiology. The prevalence of SLE in mainland China was estimated to be around 0.1% (personal communication, HuaXia meeting Shanghai, 1999). Although there is no formal prevalence study in Hong Kong, it is the anecdotal experience of many physicians that SLE is fairly common among southern Chinese, especially if one is looking at the admission data in local hospitals (e.g. 1200 admissions to Tuen Mun Hospital between 1995 and 2000 from 260 SLE patients). A study of 52323 referrals to the medical outpatient clinics of Queen Mary Hospital and Nethersole Hospital from July 1983 to June 1985 revealed 133 cases of SLE, making an estimated prevalence rate of the disease to be 0.25%. However, this figure may be an overestimation because the sample included only those who presented with symptoms.

On the other hand, it was thought that southern Chinese SLE patients have more serious disease that those in the western countries. Asian SLE patients living in the United States and United Kingdom were reported to have more serious organ manifestations and higher mortality. As socioeconomic status is an important predictive factor for SLE mortality, whether the relatively low survival rate of the Asian-Americans is related to their lower socioeconomic background remains to be confirmed.

Data regarding survival of SLE in southern Chinese is limited. Koh et al studied the causes of death in 67 SLE patients who were followed for a mean of 48 months. Disease activity and infection were the main causes for mortality. However, the actuarial survival rate of their patients was not mentioned and the study population consisted of mixed ethnicity. A local prospective study of 163 SLE patients reported a 5-year survival rate to be 93%. Infection remained the main cause of death. High dose steroid and thrombocytopenia were independent predictors for poor survival.

Until a formal epidemiological survey is carried out in Hong Kong, the exact prevalence of SLE in our population remains unclear. Certainly with the judicious monitoring of disease activity and its treatment complications, survival rates of patients with SLE can be equivalent to those reported in most international series.

Clinical Manifestations

SLE is a heterogenous disorder with extremely diverse manifestations. The American College of Rheumatology (ACR) revised the classification criteria for SLE in 1997 with...
the addition of the antiphospholipid antibodies as one criterion to aid in diagnosis. The clinical manifestations of SLE in a large cohort of Hong Kong Chinese patients are shown in Table 1. At the time of disease diagnosis, the commonest presentation was with musculoskeletal and mucocutaneous features. Renal disease occurred in 27% of patients, while central nervous system (CNS) disease was rare at disease onset (4%). After a median follow-up period of 45 months, the prevalence of arthritis, hematological manifestations and renal disease increased significantly. Renal involvement is of particular importance in SLE because it is the commonest internal organ to be affected and is a major determinant for morbidity. The true prevalence of nephritis is likely to be under-estimated in this study because the cohort consisted only of patients being followed in the rheumatology clinics.

The long-term outcome of lupus nephritis in our local SLE patients has been reported. The overall 10-year survival and renal survival (survival without dialysis) of 183 patients with biopsy-proven lupus nephritis seen at a teaching hospital was 94% and 81%, respectively. Diffuse proliferative nephritis (WHO class IV), persistent hypertension and failure of achievement of complete remission in the first year of treatment were independent risk factors for the development of end-stage renal failure. This provides important clinical data for patient counseling because around one-fifth of patients with lupus nephritis are expected to develop renal failure after ten years. The actual dialysis rate, however, should be lower because patients without overt renal disease were not included in this study.

In accordance to previous published studies in Hong Kong, CNS manifestations appear to be uncommon in our local SLE population. Psychosis, in particular, was only reported in 6% of patients. The relatively low prevalence of CNS disease is probably related to the lack of formal neuropsychological testing in patients. Neurocognitive dysfunction is frequent among Caucasian SLE patients and its prevalence varies according to the subsets of patients being studied and the neurophysiological tools being used. In one study of 58 patients with inactive SLE, 43% demonstrated cognitive dysfunction. A more recent local study of a large cohort of 518 SLE patients with a mean disease duration of 7.3 years using the new 1999 ACR definitions for neuropsychiatric (NP) manifestations reported that the prevalence of primary NP events was 19%, after exclusion of subtle cognitive dysfunction. This figure will certainly be much higher if cognitive function is being assessed formally in every SLE patient.

Acute transverse myelopathy is a rare but well recognized manifestation of SLE. The pathogenesis is unclear but vasculitis, vasculopathy related to the antiphospholipid antibodies, and direct antibody-mediated neurotoxicity have

| Table 1. Clinical features of a cohort of Hong Kong Chinese SLE patients (N=182) |
|-------------------------------------------------|-----------------|-----------------|
| At presentation | Prevalence of various clinical features after 45 months, N (%) | *p |
| N (%) | N (%) |
| Alopecia | 73 (40) | 85 (47) | NS |
| Raynaud’s phenomenon | 41 (23) | 46 (25) | NS |
| Arthritis | 149 (82) | 173 (95) | 0.01 |
| Malar rash | 101 (55) | 118 (65) | NS |
| Discoid lesions | 16 (9) | 22 (12) | NS |
| Oral ulcers | 16 (9) | 24 (13) | NS |
| Photosensitivity | 41 (23) | 62 (34) | 0.02 |
| Leucopenia (<4 x 10^9/L) | 42 (23) | 64 (35) | 0.02 |
| Thrombocytopenia (<100 x 10^9/L) | 31 (17) | 48 (26) | 0.02 |
| Hemolytic anemia | 29 (16) | 46 (25) | 0.01 |
| Lymphadenopathy | 25 (14) | 41 (23) | 0.02 |
| CNS disease | 7 (4) | 16 (9) | NS |
| Renal disease | 50 (27) | 82 (45) | 0.01 |
| Serositis | 29 (16) | 40 (22) | NS |
| Cutaneous vasculitis | 32 (18) | 41 (23) | NS |
| Low C3 (<60 mg/dl) | 94 (52) | 130 (71) | 0.01 |
| Positive anti-dsDNA (≥154 IU/ml) | 100 (55) | 125 (69) | 0.01 |

*p values were corrected by the Bonferroni method and were considered significant when they were <0.05, NS=non-significant.
been implicated. There are still no specific diagnostic tests. Hypocomplementemia and disease activity in other organs may be absent. Cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings may not be informative. The treatment and outcome of ten Chinese patients with lupus-related myelitis has been reviewed. The response to immunosuppressive treatment was variable and complete recovery occurred in only 40% of the patients. Delay in the institution of treatment may contribute to an unsatisfactory neurological outcome.

Hematological manifestations are common in patients with SLE and often correlates with disease activity. Lymphopenia, defined as a lymphocyte count of less than 1.5 x 10^9/L, is one of the criteria for the classification of SLE. Thrombocytopenia in SLE can be mild or serious. Several studies have revealed that thrombocytopenia is a predictor for poor outcome. Danazol and intravenous immunoglobulin have been used with success in the treatment of lupus-related thrombocytopenia.

Cardiopulmonary involvement is uncommon but important in SLE. Pneumonitis, pulmonary hemorrhage, shrunken lung syndrome, pericarditis, myocarditis and serositis (pleuro-pericardial effusion) are well documented features. One study from mainland China revealed an occurrence of pulmonary arterial hypertension (defined as a systolic PAP >30 mmHg or mean PAP >20 mmHg) in 11% of a cohort of 84 SLE patients. Pulmonary arterial hypertension was associated with disease activity, Raynaud’s phenomenon and serum endothelin level.

SLE patients with severe pulmonary hypertension, similar to those with primary pulmonary hypertension, suffer from significant morbidity and mortality. Immunosuppressive treatment and the use of intermittent iloprost infusion may be beneficial.

Echocardiographic evaluation of Chinese SLE patients has been performed and revealed a significantly higher incidence of pericardial abnormalities, left ventricular hypertrophy, left atrial enlargement, left ventricular dysfunction, valvular thickening and regurgitation when compared with age and sex matched controls. Subtle myocardial dysfunction is also frequently detected by Doppler’s study in SLE patients.

The gastrointestinal (GI) manifestations of SLE have been reviewed. Intestinal pseudo-obstruction, though uncommon, should not be overlooked in patients presenting with abdominal pain.

**Effect of Age and Gender on Clinical Manifestations**

SLE predominantly affects women of the childbearing age. Occurrence of SLE in men and first onset of SLE in women before puberty or after menopause is very uncommon. Moreover, disease activity of SLE tends to quench out after menopause in women. While this may be related to effect of endogenous estrogen level on disease activity, the contribution of age may also be important. Late onset SLE, defined arbitrarily as onset of the disease after the age of 50, has been shown to run a more benign disease course with less major organ involvement and fewer flare-up. However, a local retrospective study conducted in a renal unit did not reveal a lower incidence of major organ disease in late onset SLE patients, which was probably due to a referral bias with only patients with more serious disease being included.

The effect of gender on the manifestations of SLE is a still a matter of controversy. Earlier reports have demonstrated a poorer prognosis in men with SLE. However, studies of large cohorts of SLE patients did not reveal a significant difference in major organ involvement between women and men. A local study of a cohort of 630 patients, with a female to male ratio of 11.4 to 1, reported no significant difference in major organ involvement between the two sexes. However, males appeared to have more renal impairment and cardiovascular damage than their female counterparts. Moreover, male SLE patients tend to have more discoid skin lesions but less diffuse alopecia and Raynaud’s phenomenon.

**Anti-ENA (Extractable Nuclear Antigen) and Antiphospholipid Antibodies**

Table 2 shows the prevalence of several commonly available autoantibodies in a local cohort of SLE patients. Among the anti-ENA antibodies, the prevalence of anti-Ro is 59%, which is much higher than that quoted in the Caucasian series (29-36%). The high prevalence of anti-Ro among southern Chinese SLE patients in this study is consistent with previous local reports. As a similar methodology (counter-immunoelectrophoresis [CIEP]) is being employed for the routine detection of anti-Ro in the Caucasian studies, the high prevalence of the anti-Ro is likely to be a genuine inter-ethnic difference in the immunological manifestation of the disease. However, whether anti-Ro has a different clinical association in southern Chinese SLE patients warrants further studies.
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The anticardiolipin antibodies (aCL) and the lupus anticoagulant are the two antiphospholipid antibodies that are available for assay in our local laboratories. IgG-or IgM-aCL occurs in up to 50% of SLE patients during activity while lupus anticoagulant occurs in around one-sixth of all patients. Weakly positive aCL are often insignificant but high titre of aCL has been associated with cerebrovascular disease in southern Chinese SLE patients.\(^\text{15}\) In addition to vascular thrombosis, lupus anticoagulant in SLE is also associated with avascular bone necrosis,\(^\text{36}\) valvular abnormalities and left ventricular dysfunction.\(^\text{25}\) However, the association of thrombocytopenia and the antiphospholipid antibodies could not be established in an earlier study.\(^\text{37}\)

### Immunogenetics

The genetics of SLE is complex. The concordance rates in identical twins (24-69%), the increase in frequency of SLE among first-degree relatives and the increase in risk of siblings of SLE patients to develop the disease emphasize the importance of genetic or shared environmental influence on disease predisposition. The association between certain major histocompatibility complex (MHC) class II alleles and complement gene deficiencies (homozygous deficiency of C2, C4 and C1q), and the susceptibility to SLE is well established. However, no single gene defect has been discovered as the cause of SLE. Recent studies have shown that SLE is likely to be a polygenic disease with the susceptibility genes located at the long arm of chromosome 1.\(^\text{38}\) It has been estimated that as many as 100 genes may be involved.

Studies in southern Chinese patients confirmed that HLA-DR2 and the C4A null genes are associated with SLE development.\(^\text{39,40}\) Anti-Ro antibody was associated with HLA-DR2 in our SLE population.\(^\text{40}\) A number of non-MHC genes such as the interleukin-10 promoter, mannose binding lectin (MBL) gene mutation, and plasminogen activator inhibitor-1 gene polymorphisms have also been studied in our local SLE patients.\(^\text{41-44}\) Except for the MBL gene, these polymorphisms did not seem to confer susceptibility to SLE, although they might be associated with certain disease manifestations and their severity. However, it is beyond the scope of this review to describe them in detail.

### Conclusions

SLE is such an intriguing disease that multiple clinical and genetic studies have been performed in our locality. SLE among southern Chinese patients is likely to have a distinct clinical profile in comparison to the western countries. Further multi-centered prospective studies are needed to clarify the disease course, morbidity and prognosis of SLE patients in Hong Kong.

### References

8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic
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