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Mycoses and Connective Tissue Diseases

Speaker: Prof. F. Q. Zeng

The speaker first discussed the importance of infection in systemic lupus erythematosus (SLE) and then outlined the factors influencing susceptibility of patients to mycoses, the types of mycoses and the use of antifungal agents, with special reference to SLE.

Infection and SLE

Infection is a major cause of morbidity and mortality in SLE. The infections are still most commonly caused by pyogenic organisms like *Staphylococcus sp.* and *Escherichia coli*, but opportunistic pathogens like uncommon bacteria, fungi, viruses and protozoans are increasingly reported in the literature, including infection in multiple organs and multiple organisms at a single site. The increased infection rate is a result of the global dysregulation of the immune system in SLE, complicated by the use of corticosteroids and other immunosuppressive agents in its management.

Importance of infection in SLE

In a series of 223 SLE patients seen at the New York Downstate Medical Centre, 150 patients had 384 infections diagnosed over 655 patient-years, giving an overall infection rate of 59 per 100 patient-years. The

rates for bacterial and non-specific viral infections were respectively 25 per 100 patient-years and 28 per 100 patient-years. Twenty-eight opportunistic infections were found in 23 patients. Fifteen had oral candidiasis, three of which had evidence of systemic infection. Two of 11 patients with deep-seated mycoses had multiple organisms at a single site, two had also bacterial infection at the same site, and one had a single fungal organism at two sites.

In a Swedish epidemiologic study reported in 1985, an overall infection rate of 142 per 100 patient-years of SLE was found. Another study focused on hospitalised SLE patients. An overall cultured-confirmed infection rate of 1.22 per 100 hospital days was reported in 1974. The most common infection site was the urinary tract. About one-half of the patients with infections had multiple episodes, with recurrent sites frequently involving *Candida albicans*. The authors compared the infection rates in SLE to those in patients with rheumatoid arthritis and idiopathic nephrotic syndrome, controlling for corticosteroid dose. Infections were 10 times more common among SLE patients than in the other two categories.

With the availability of powerful broad-spectrum antibiotics to cover for the more common bacterial pathogens, opportunistic infections like systemic mycoses have assumed a more important cause of morbidity and mortality in SLE patients.

Risk factors for mycoses in SLE

Patients with SLE display numerous cellular and humoral defects which are expressed in a heterogeneous pattern and contribute in varying degree to susceptibility to infectious agents. The inherent defects of the immune effector cells may be supplemented by the possibility that their pre-existing activation render them refractory to any further stimulation. The plethora of circulating auto-antibodies may also interfere with various functions of the immune system. The use of corticosteroids and immunosuppressive agents is only

partially responsible for the high infection rate in lupus patients. The risk factors for mycoses in SLE patients are outlined below:

1. Decreased natural defence mechanisms

Mucocutaneous lupus lesions provide a portal of entry for microbes. The non-specific phagocytic ability of phagocytes is depressed.

2. T-lymphocyte defects

T-cell lymphopenia and especially CD-4 lymphopenia are most commonly observed. T-cell function is also deficient in many ways, like in vitro proliferative response to many soluble antigens and mitogens. Thymic architecture is abnormal in all murine model of spontaneous SLE. The function of thymic epithelial cells is abnormal with profound effects on positive and negative selection of T-cell repertoires in the thymus. Patients also frequently developed IgM and IgG auto-antibodies to molecules on the surface of lymphocytes and monocytes. The cold-reactive antilymphocyte autoantibodies may deplete circulating T cells, modulate target antigens, and have profound effects on cellular immune response in vitro.

3. Cytokine abnormalities

There are decreased production of interleukin 2 (IL-2) and interferon-gamma, consistent with impaired cellular immunity in SLE. The former may correlate with disease activity. The lymphocyte response to IL-2 following mitogenic stimulation is also depressed. IL-2 is produced by T cells and is an essential T cell growth factor. It is involved in the induction of T killer cells and regulatory cells. Interferon-gamma is produced by T cells and natural killer (NK) cells. It is involved in macrophage activation and induction of killer cell activity. It also enables B cells to produce complement fixing IgG antibodies. On the other hand, there is over-production of interleukin 6 (IL-6) which supports B-cell hyperactivity in SLE.

4. Genetic defects

There are increased frequencies of certain human leucocyte antigens (HLA) encoded from the major histocompatibility complex (MHC) in patients with SLE. Also hereditary deficiencies of early components of the complement system, some of which mapped to the MHC, are found to increase susceptibility to SLE. These include homozygous deficiencies of C4 and C2 as well as partial deficiency of C4, especially C4A. A

null allele for C4A is the HLA-linked (class III) gene most consistently associated with predisposition to SLE in different ethnic groups. However it is not absolutely essential for the disease. The absence of early components of complement can alter the way an individual controls infections and the activation of complement by immune complex. These may impair the body defence against infection.

5. Deranged neuro-endocrine-immune interaction

Neurologic manifestations of SLE are frequent, varying from mild to severe. As cytokines released by cells in inflammatory and immune sites can regulate cytokines released in the neural system, the two systems are closely linked. On the other hand, the preponderance of SLE in women of child-bearing age has led to numerous investigations into the disease's hormonal effects and interactions. Complex interactions occur among neurotransmitters, sex hormones and immune functions. Estrogens can depress cell-mediated immunity, natural killer cell function and cancer cell immune surveillance. It was also shown to inhibit T-suppressor cells, which might enhance T-helper activity. B-cell maturation is therefore enhanced, resulting in an increase in immunoglobulin production. The effects of estrogens have been demonstrated in murine models. While occupying a role in SLE pathogenesis, estrogens may also have an adverse effect on cellular immunity against infection.

6. Drug therapy

The use of corticosteroids and immunosuppressive agents in SLE can increase the susceptibility to infection, especially those due to opportunistic organisms. Corticosteroids predispose to infection by affecting host's responses to micro-organisms, including a decrease in inflammatory response, decreased effector cell response in cell-mediated immunity, lysis of lymphoid follicles, and decreased immunoglobulin synthesis etc. Regarding predisposition to mycoses, the inhibition of cellular host responses, particularly impaired proliferation of epithelioid and giant cells as well as decreased digestive capability of these cells and macrophages were responsible.

SLE patients treated with immunosuppressive agents have been showed to be more susceptible to infection than patients with other rheumatic diseases treated comparably. These findings suggest that immunosuppressive drugs are only partially responsible

for the high infection rate. They have a dual effect on the immune system in SLE patients. Suppression of abnormally functioning cells may normalise other aspects of the immune system. The increased infection rate in some studies of patients receiving immunosuppressive therapy may be attributed to active or advanced disease.

The empirical early use of broad-spectrum antibiotics effective against gram-negative bacteria has changed the pattern of infection in immunocompromised patients. Gram-positive infections are now more common than gram-negative ones, and fungal infections are the leading factor in the morbidity and mortality in immunocompromised host.

Spectrum and characteristics of mycoses in SLE

The spectrum of mycoses seen in SLE is showed in table 1.

Candida albicans is the most common opportunistic pathogen in lupus patients. It can manifest clinically as oral, vaginal, invasive or disseminated infection. *Aspergillus fumigatus* is acquired through the respiratory tract. It can cause pulmonary and central nervous system (CNS) infection. *Cryptococcus neoformans* can cause meningitis in immunocompromised patients. In 1975, Sieving et al reported three SLE patients with deep fungal infections and reviewed 30 patients in the literature. Fourteen patients had *Candida* and 11 *cryptococcus* infection. Of the 33, 28 were receiving corticosteroids, and 27 died.

The clinical features of these infections may be atypical and may be masked by high dose corticosteroids. There may be multi-system involvement, multiple organisms at a single site or concomitant bacterial infection. As the symptoms of SLE and of infection often are similar, a high index of suspicion is important. The most helpful clues to

infection are the presence of shaking chills, leucocytosis (unless steroids are being given), and the absence of active SLE in multiple systems. In the absence of serositis, C-reactive protein levels exceeding 60 mg/mL were always associated with infection according to a study.

Systemic mycoses should be considered in SLE patients with unexplained fever, especially those on high dose corticosteroids and broad-spectrum antibiotics, as well as patients with pulmonary infiltrates or unexplained CNS symptoms. Investigations for fungal organisms should be undertaken. One should advise the laboratory to hold specimens for fungal cultures, and store acute serum to match with convalescent serum. In difficult cases, a tissue diagnosis may be essential. Percutaneous, endoscopic or open surgical biopsy procedures may be necessary. These may be guided by radiographic techniques (e.g. computed tomography, magnetic resonance imaging) or by nuclear imaging (e.g. bone scan). Polymerase chain reaction (PCR) provides a new means for the diagnosis of infection. Amplification of a few copies of pathogens existing in body fluid or tissue specimens provides rapid and reliable diagnosis of infection in the immunocompromised host.

Treatment of mycoses in SLE patients

A classification of antifungal drugs is given in table 2. Echinocandins is a new antifungal class with a novel mode of action. They are non-competitive inhibitors of (1,3)- β -D-glucan synthase, an enzyme complex which forms glucan polymers in the fungal cell wall. Cilofungin is the first clinically applied compound of this class. Their unique mode of action specific to fungal cell wall, bodes well for minimal toxicity. It is active against *Pneumocystis carinii* and *Candida* sp. It is active in vitro against the common *Candida* species with the exception of *Candida parapsilosis*, but it was less active against *Candida glabrata* and *Candida krusei*. Another compound LY303,366 of the group is active against all

Table 1. Spectrum of mycoses in SLE patients

Types of mycoses	Examples
Superficial mycoses	Dermatophytoses, candidiasis
Subcutaneous / Systemic mycoses	Candidiasis, cryptococcosis, aspergillosis, histoplasmosis, actinomycosis, sporotrichosis, mucormycosis, coccidioidomycosis, hyalohyphomycosis (e.g. <i>Fusarium</i> infection), phaeohyphomycosis, <i>Penicillium marneffei</i> infection

Table 2. A simple classification of antifungal drugs

Type	Action
Polyenes e.g. amphotericin B	Bind to ergosterol of cell membrane and disrupt membrane barrier function
Azoles e.g. ketoconazole, itraconazole, fluconazole	Inhibit cytochrome P450-dependent 14 alpha-demethylase in the formation of ergosterol of cell membrane
Allylamines e.g. terbinafine	Inhibit squalene epoxidase in the formation of ergosterol of cell membrane
5-flucytosine	Active uptake by cytosine permease and then block DNA and RNA synthesis
Griseofulvin	Bind to intracellular micro-tubules and inhibit fungal cell mitosis

these species and has marked activity against *Candida albicans*, including azole-resistant isolates.

Parenteral amphotericin is the drug of choice for many forms of systemic fungal infection, including candidiasis, aspergillosis, cryptococcosis, blastomycosis, coccidioidomycosis, histoplasmosis, mucormycosis, paracoccidioidomycosis. It is often used in combination with flucytosine in serious infections. Liposomal amphotericin is better tolerated and much higher doses can be given with fewer toxic reactions. Apart from its action on superficial fungi, itraconazole is a promising drug for oral treatment of aspergillosis, cryptococcosis and deep forms of candidiasis. Fluconazole is used for treatment of mucosal and cutaneous candidiasis. It is also useful in cryptococcal meningitis.

Combination therapy using immuno-modifying agents and antifungal drugs may offer a new strategy for treatment of systemic mycoses in immunocompromised host. Interleukin 1, gamma-interferon and tumor necrosis factor have been tried in murine models.

Prevention and prophylactic treatment

Precautions like keeping the environment clean, strict infection control, appropriate use of broad-spectrum antibiotics and corticosteroids etc are useful. The prophylactic use of antifungal drugs like itraconazole and fluconazole may be considered in patients receiving high dose corticosteroid and immunosuppressive therapy.

Conclusion

Infections especially mycoses are important causes of morbidity and mortality in SLE patients. Presentations of SLE and infection are often difficult to differentiate. Early diagnosis would rest on a high index of suspicion and an efficient laboratory service.

Learning points:

Systemic mycoses should be considered in SLE patients with unexplained fever, especially those on high dose corticosteroids and broad-spectrum antibiotics, as well as patients with pulmonary infiltrates or unexplained CNS symptoms.

Analysis of 13-years' Culture Findings of Superficial Mycoses in Eastern Guangdong

Speaker: Dr. Y. Q. Zhang

The speaker presented the culture findings from cases of superficial mycoses in eastern Guangdong isolated during the period from 1985 to 1998. A total of 1823 positive cultures were included in the analysis. These were mainly from patients with clinical diagnoses of tinea corporis, tinea cruris, tinea manuum, tinea pedis, onychomycosis and pityriasis vesicolor.

Dermatophytes were cultured in modified Sabouraud's medium while *Malassezia* species were cultured in medium containing 5% sesame oil. Identification of the fungi was proceeded in the usual manner. The findings are presented in figure 1.

Dermatophytes were the main cause of superficial mycoses through the years and *Trichophyton rubrum* was the major species. There was a change in the causative organism for tinea capitis: *Trichophyton ferrugineum* which was the predominant fungus isolated

in 1980's has been gradually replaced by *Microsporum canis* in 1990's. *Trichophyton violaceum* was also decreasing with time. On the other hand, *Candida* species were increasingly isolated as a cause for superficial mycoses.

The culture results were basically similar to those from other major cities of China like Beijing. These data were also comparable to those obtained from a national survey of 28 provinces in China. The speaker concluded by suggesting that the shift of causative species might be related to changes in global environment, changes in life style, increasing use of immunosuppressives and corticosteroids, abuse of antibiotics, alternations in biological characteristics of fungi, etc.

Learning points:

The pattern of causative organisms of superficial mycoses in Guangdong is largely in line with what we have observed in Hong Kong with the exception of *Malassezia* sp. that we seldom perform culture.

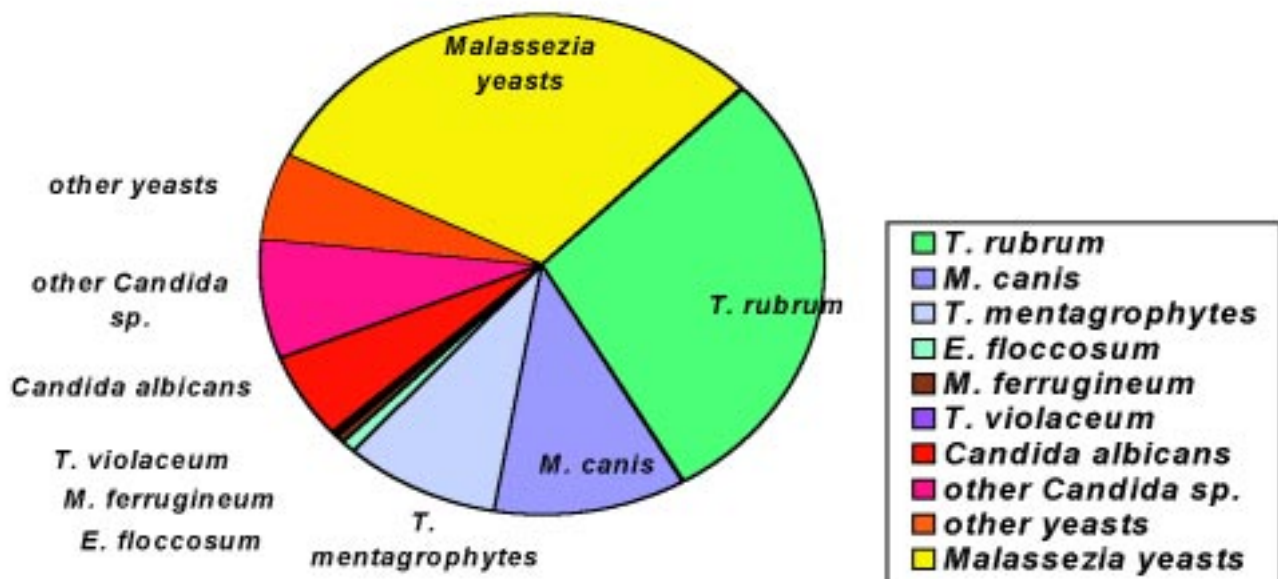


Figure 1: Culture findings of superficial mycoses in eastern Guangdong (1985 - 1998)

Etiology of Contact Dermatitis due to Cosmetics/Skin Care Products in Hong Kong

Speaker: Dr. T. Y. Lee

44 female patients (mean age 33.9, range: 22-39) with a clinical diagnosis of contact dermatitis to cosmetics/skin care products at the head and neck region underwent a patch test. The subjects were patch tested with (a) cosmetic series (Chemotechniques), (b) their own cosmetics and (c) other suspected allergens, using I.Q. chambers and reading taken at 48 and 96 hours.

Kathon CG and thimerosal were the commonest allergens showing positive reactions in the cosmetic series. 289 items of cosmetics/skin care products brought by 38 patients were tested and 23 patients (60.5%) showed positive reactions. Common causative agents were foundation/moisturizing creams, eye cosmetics, bleaching/anti-aging creams, face-mask materials and anti-acne preparations.

It was recommended that Kathon CG and thimerosal be included in the standard battery of allergens for Hong Kong.

Determination of the Levels of Plasma DNA, DNase and Anti-DNA Antibodies and Their Relationship in SLE Patients

Speaker: Dr. Y. F. Chen

The levels of plasma DNA, DNase and anti-DNA antibodies were determined in 63 SLE patients and 38 control subjects. The level of DNA was significantly higher ($p < 0.01$) in SLE patients (76.7 ± 26.8 vs. 39.5 ± 5.8 mg/ml), whereas DNase was significantly lower (28.5 ± 8.3 vs. 51.2 ± 3.7 ng/ml). 38.1% of SLE patients were tested positive for anti-DNA antibodies, which was absent in all control subjects.

Compared with SLE patients in remission, those with active disease were found to have significantly higher levels of DNA, lower levels of DNase, and a higher positive rate for anti-DNA antibodies. There was a positive correlation between the level of DNA with ESR and ANA, and a negative correlation with C3 and C4. As for DNase, there was a negative correlation with ESR and ANA, and a positive correlation with C3 and C4. The levels of DNA and anti-DNA showed positive

correlation with disease score, whereas DNase showed a negative correlation. The strength of association for the three markers with disease score in decreasing order are as follows: DNase > DNA > anti-DNA.

SLE with renal involvement had a significantly lower level of DNase (15.5 ± 5.8) and higher positive rate for anti-DNA antibodies (71.4%) when compared to those without renal involvement (35.0 ± 4.8 and 21.4%). However, the difference in the DNA levels between the two groups did not reach statistical significance (54 ± 18.5 in patients with renal involvement vs. 52 ± 11.6 in patients without renal involvement).

It remained to be determined the cause of the decreased level of DNase and its role in pathogenesis in SLE patients.

A Study of the Effects of Chronic Cigarette Smoking on the Response of Male Patients with Genital Warts to 25% Topical Podophyllin Therapy

Speaker: Dr. M. K. T. Chan

A prospective study was carried out in Yaumatei and South Kwai Chung Social Hygiene Clinics to determine the effect of chronic cigarette smoking on the treatment of male genital warts using topical podophyllin. 178 patients were recruited. Each patient with genital warts received 25% podophyllin therapy on every fifth day. The number of treatment sessions required for the clearance of genital warts in chronic smokers was compared with non-smokers at 2 months' interval.

Of the 155 patients completed the study, 83 (53.6%) were smokers and 72 (46.4%) non-smokers. After 2 months of treatment, among the non-smokers, genital warts in 57 (79.1%) had disappeared, whereas among the smokers, only 30 (36.1%) experienced clearance of genital warts. In addition, it was observed that male genital warts were significantly associated with smoking with an odds ratio of 1.7 and $p < 0.02$. Moreover, the positive association was still present after controlling for confounding variables such as recent sexual partners and past history of sexually transmitted diseases. Possible explanation is that there are many well-proven carcinogens in cigarette smoke like nicotine

and cotinine. These substances act as immuno-suppressors possibly via the Langerhans cells, which are the main sentinel site in the epidermis in the defense against HPV infection.

The Use of Q-switched Laser in the Treatment of Naevus of Ota

Speaker: Dr. S. Y. Ying

Previous treatment options for naevus of Ota including cryotherapy and surgical excision were ineffective and were associated with significant scarring. The introduction of Q-switched laser system has revolutionised the treatment of this condition. A previous study comparing patients' tolerability had shown that Q-switched Alexandrite (QS Alex) to be more superior than Q-switched Nd:YAG (QS Nd:YAG).

To study the long term complication rate and clinical efficacy of the two systems, 139 patients with naevus of Ota who had been treated with QS Alex or QS Nd:YAG had been recruited. The subjects were assessed using a questionnaire and examined for complications by a dermatologist and a plastic surgeon.

36.7% of the patients felt that their lesion had significantly lightened (50% or more improvement). Three sessions or more were necessary to achieve any significant degree of clinical improvement and the alternative use of QS systems (QS Alex for one session then QS Nd:YAG for the next) seemed to be more rewarding. Complication rate was 21.6% with hypopigmentation being the commonest (12.6%) suggesting that better epidermal protection such as barrier cooling may be necessary.



Web sites of Dermatology & Venereology in Hong Kong

The homepage of the Hong Kong Society of Dermatology & Venereology
<http://www.medicine.org.hk/hksdv/>

Hong Kong Dermatology & Venereology Bulletin

(Official Publication of the Hong Kong Society of Dermatology & Venereology)
<http://www.medicine.org.hk/hksdv/bulletin.htm>

Hong Kong Dermatology & Venereology Bulletin

(Subscription site of Blackwell Science Ltd.)
<http://www.blacksci.co.uk/~cgilib/jnlpage.bin?Journal=hdv&File=hdv&Page=ed>

Handbook of Dermatology & Venereology

(Published by Social Hygiene Service, Department of Health)
<http://www.hkmj.org.hk/skin/>

CME Online (Dermatology)

(CME Programme accredited by the Hong Kong College of Family Physicians)
<http://www.medicine.org.hk/cme/>

