

Infections in Systemic Lupus Erythematosus Patients

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Abstract

Infection is a frequent problem in patients with systemic lupus erythematosus (SLE), especially in those hospitalised with complications of disease. Infections contribute greatly to the morbidity of patients and are one of the commonest causes of death. The high frequency and unusual spectrum of infections can be attributed to the multiple disturbances of immune function in SLE in combination with the effects of immunosuppressive therapy. High doses of corticosteroids are particularly implicated as a risk factor for infection, although cyclophosphamide may also play a role. The majority of infections where a pathogen can be identified are due to typical gram-positive and negative bacteria. However, there is increasing evidence to indicate that opportunistic infections make a large contribution to the infectious mortality in SLE. Opportunistic infections are considerably under-reported due to difficulties in diagnosis pre-mortem and the fact that they can mimic or be superimposed upon active lupus. The presenting features of tuberculosis, listeriosis, nocardiosis, candidiasis, cryptococcal meningitis, Pneumocystis carinii pneumonia and invasive aspergillosis in patients with SLE are discussed in this review, with particular attention to presentation in SLE patients in Asia. Heightened awareness of the potential for opportunistic pathogens to infect SLE patients, together with earlier investigation and appropriate therapy for such infections, are likely to make a significant contribution to decreasing the mortality in patients with SLE.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with heterogeneous clinical features and complications. It presents enormous challenges to the physician, not the least of which is the diagnosis and management of the frequent episodes of infection which punctuate the disease course. Patients with lupus are vulnerable to infection with an ever-expanding range of pathogens which often affect unusual sites in the body and present in subtle and misleading ways. The separation of an infectious from an immunological cause for symptoms is often difficult.

This review will initially describe the contribution of infections to morbidity and mortality of patients with SLE and examine the reasons for the high infection rate in these patients. The common bacterial and viral infections which occur in SLE will be covered briefly, but the main focus of this review will be on opportunistic infections in SLE. Infections with these unusual pathogens are emerging as an important and under-recognised problem in the lupus patient and undoubtedly make a significant contribution to overall disease mortality. As

the spectrum of infections in patients with SLE largely reflects exposure to potential pathogens in the environment, emphasis will also be given to infections which are likely to represent particular problems in Asia.

The Importance of Infections in SLE

A number of cohort studies have been conducted in Europe, America and Canada to determine the frequency of infections in patients with SLE. The rate of major infections (usually defined as infections requiring parenteral antimicrobial therapy or a confirmed pneumonia) was 6.9 infections per 100 patient-years of follow-up in Canadian¹ and Swedish cohorts.² This rate was doubled in a more socially-disadvantaged population in Brooklyn, New York.³ Few studies of frequency of infection have been conducted in Asia, but one recent study from Malaysia⁴ found an incidence of 13.7 major infections per 100 patient-years, almost identical to that seen in Brooklyn.

Infections frequently precipitate admission to hospital and prolonged hospitalisation leads to a further increase in risk of nosocomial infection. Studies of in-patients

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with SLE have, not surprisingly, shown higher rates of infections than cohorts of out-patients; rates of 0.84 and 1.2 major infections per 100 hospital days have been reported in American and Canadian studies, respectively.^{5,6} In Singapore, 17% of SLE admissions to hospital were complicated by infection.⁷ Not only are in-patients at greater risk of contracting infection, but nosocomial pathogens are often more difficult to identify and treat, partly due to associated problems with antibiotic resistance.

In addition to the problem with major infections, SLE patients are often plagued by recurrent minor infections such as cutaneous bacterial infections, oral and vaginal candidiasis, urinary tract infections and frequent attacks of herpes zoster. Although not directly life-threatening, such infections contribute greatly to the morbidity of the disease. Relatively minor infections, which might be treated as an out-patient in otherwise healthy individuals, often necessitate precautionary hospital admission in immunosuppressed patients. It has also been suggested that infection may trigger flares of disease activity although the true temporal relationship is hard to discern.³

As well as their contribution to disease morbidity, infections are a major cause of mortality in SLE, accounting for 27% and 49% of deaths in Canadian and American SLE patients respectively.^{8,9} Infection may be a particularly common cause of death in Asia, being directly implicated in 30% of lupus deaths in Thailand,¹⁰ 37% in Hong Kong,¹¹ and 40% in Singapore.¹² In Malaysia infection directly caused 52% of SLE deaths and was a contributing cause in a further 19%.¹³

Factors Predisposing to Infection

Defects of Immune Defense in SLE

Patients with SLE have a higher rate of infections in comparison to equivalent groups of patients with rheumatoid arthritis, even after adjustment is made for corticosteroid dose.^{6,14} Further evidence that lupus itself results in a predisposition to infection is the finding that disease activity (as measured by the SLE Disease Activity Index) is significantly associated with the rate of infection in hospitalised patients, independent of steroid dose.⁵

Numerous defects in the immune system have been identified in SLE. These have been described in detail in several reviews and are mentioned only briefly here.¹⁵ Vasculitic skin and mucosal lesions result in disruption of the integrity of the mechanical barrier to infection, thereby allowing entry of microorganisms into the blood. Neutropenia is a common feature of SLE¹⁶ and defective neutrophil chemotaxis and phagocytosis are also well documented.¹⁷ Multiple disturbances in the monocyte macrophage system including defective phagocytosis

are also likely to have functional importance in the defence against infection.¹⁸

There is polyclonal activation of B cells in lupus patients, although the cells appear to be able to produce antibody appropriately in response to infection or immunisation. Some patients have low IgG2 levels, which may present difficulties in overcoming infections with encapsulated bacteria.¹⁹ Many disorders of T cells have been observed in SLE. T-cell lymphopenia is a common finding during disease flares and CD4 cells may be predominantly affected.²⁰ Decreased numbers and activity of natural killer (NK) cells have also been described.²¹

Deficiency of complement components in SLE may result from congenital deficiency (especially C2 which may be present in up to 6% of patients)²² or consumption during active disease. Functional asplenia has also been reported²³ which, in conjunction with deficiencies of complement, may be responsible for the susceptibility to salmonella infection (see below).

The Effects of Immunosuppressive Agents

Many investigators have attempted to quantify the risk of infection associated with particular immunosuppressive agents in SLE. It is clear that corticosteroids increase the risk of infection in SLE.^{3,6} In one study, the rate of bacterial infections was approximately 8 times higher in patients taking 40 to 100 mg of prednisolone compared with those taking no prednisolone.³ The risk appears to rise with increasing dose of steroids.^{3,6} High-dose pulse methylprednisolone may further increase infection risk. In Malaysia, the use of pulse methylprednisolone was associated with a dramatic increase in the infection rate, more so than would be expected simply from high-dose oral corticosteroids.⁴ *In vitro* studies suggest that high-dose methylprednisolone has effects on phagocyte function which differ from those seen with conventional low-dose steroid therapy.²⁴

The effects of other immunosuppressive agents on infection rate are more controversial. Azathioprine has been shown not to increase the risk of major infections,^{3,4} but it does appear to result in an increase in the rate of localised herpes zoster in lupus patients.³ Cyclophosphamide has also been associated with localised zoster infection²⁵ and increased risk of more serious bacterial infections^{4,26} although this is difficult to separate from the risk attributable to the concomitant high-dose steroid treatment.

Common Bacterial and Viral Infections

The wide variety of immune disturbances resulting from the disease and its therapy lead to an equally diverse spectrum of infections in patients with SLE. Conventional bacterial and viral pathogens are still the most common causes of infection, although they may

produce disease in unusual sites or follow a severe or protracted course.

Pneumonia is the commonest major infection in SLE patients^{4,10} with conventional gram-positive organisms, *Pseudomonas* spp and *Klebsiella* being the commonest identified pathogens in most series. Staphylococcal and streptococcal infections are common, especially those involving soft tissues, and may frequently progress to septicaemia. There appears to be a particular predisposition for SLE patients to develop salmonella infection which may reflect the defective complement activity and reticuloendothelial system dysfunction. Several studies have found that salmonella was the most frequent cause of septicaemia in SLE.^{10,27} A number of cases of salmonella arthritis and osteomyelitis have also been reported.^{28,29} Furthermore, it has been suggested that salmonella may have a higher recurrence rate in patients with SLE, necessitating a longer treatment course for cure.²⁹ Pneumococcal vaccination is recommended as a preventive measure in SLE patients and consideration should be given to the use of prophylactic antibiotics during discrete episodes of intensive immunosuppressive therapy (particularly high-dose steroids).

Herpes viruses are a common cause of infectious morbidity in SLE. Herpes simplex virus (HSV)-associated oral ulcers and cold sores are often seen. Herpes zoster is a frequent problem,^{4,30} the disease may be disseminated and recovery protracted.^{30,31} In countries such as Singapore where adults lack immunity, primary varicella with visceral dissemination represents a real threat to SLE patients. Varicella zoster immunoglobulin should be given as a prophylactic measure following varicella exposure in an immunosuppressed SLE patient who lacks antibodies. Active cytomegalovirus (CMV) infection is relatively uncommon in SLE, but viraemia does occur in heavily immunosuppressed patients and cases of CMV-related organ damage such as pneumonitis and retinitis have been documented.³² Other specific viral infections are rarely diagnosed and are often impossible to separate clinically from a flare of disease.

There are no particular associations between tropical infections and SLE. Although renal disease and steroid therapy have been identified as risk factors for *Burkholderia pseudomallei* infection,³³ melioidosis is not especially common in SLE. The predisposition to salmonella infection (described above) results in an excess of mainly non-typhoid salmonella infections rather than cases of typhoid fever. There is no evidence that malaria is either more common or more severe in patients with SLE.

Opportunistic Infections

A number of opportunistic bacterial and fungal organisms have been described in SLE. Although these organ-

isms can cause disease in immunocompetent people, they are much more commonly associated with immunosuppressed states. Relatively few cases of each of these opportunistic infections have been described in patients with SLE, a situation which largely reflects the difficulties in making the diagnosis. With improving diagnostic techniques and increasing use of intensive immunosuppressive regimens they are emerging as important causes of infectious mortality in SLE. In a recent study of SLE patients receiving cyclophosphamide and high-dose corticosteroids, opportunistic organisms accounted for 24% of all infections and half the infections resulted in deaths.²⁶ The remainder of this review will therefore focus on these important emerging infections.

Tuberculosis (TB)

After many years of decline, the incidence of tuberculosis has recently started to increase again. This is partly attributable to the spread of HIV infection, deterioration in living conditions in inner city areas and also to relaxation of public health control measures. Thus environmental exposure to mycobacterium tuberculosis is increasing in Western nations and remains high in many Asian countries. When an immunocompetent adult encounters mycobacterium tuberculosis, the infection is usually controlled and rarely leads to progressive disease. However, should the immune defences weaken, the infection can reactivate at a later stage to cause disease. Immunosuppressed patients with SLE are at risk both from developing progressive primary infection after first encounter with the mycobacterium or reactivating previous infection resulting in post-primary disease. Due to higher environmental exposure to tuberculosis, this risk may be particularly great in Asia.

Tuberculosis was responsible for 40% of pneumonia cases in which a pathogen was identified in Malaysia⁴ and 48% of pneumonia cases in Thailand.¹⁰ Feng and Tan³⁴ described 16 cases of active TB, mainly pulmonary, in a cohort of 311 SLE patients in Singapore, 5 of whom died of the infection. In a report from the Philippines, 26% of all documented infections in lupus patients were caused by mycobacterium tuberculosis. This was predominantly pulmonary disease and all 8 patients who had diffuse or miliary shadowing on chest X-ray died.^{35,36}

Extrapulmonary tuberculosis is also more common in the immunocompromised patient and infections of unusual sites can be challenging to diagnose. In a report of neurological disease in SLE patients in Hong Kong, tuberculous meningitis accounted for 5 out of 36 (14%) neurological episodes, presenting as headaches, mental confusion or seizures.³⁷ Cases of primary tuberculous muscle abscess³⁸ and other soft tissue abscesses,³⁵ gastrointestinal disease,³⁹ lymphadenitis,^{34,35} osteomy-

elitis³⁵ and arthritis³⁴ have all been reported in SLE patients.

The majority of cases of pulmonary tuberculosis, at least, will be readily identified providing the clinician maintains a high index of suspicion for the disease. It is particularly important to remain alert for tuberculosis, not only because it is curable (longer courses of chemotherapy may be required in the immunosuppressed), but also because of the potential for nosocomial transmission in a population of immunosuppressed SLE patients.

Patients should be screened for tuberculosis at the time of SLE diagnosis and regularly thereafter. A full course of combination therapy (if there is any suggestion of active tuberculosis) or isoniazid prophylaxis (where there is evidence of past exposure but no active disease) should be instituted when immunosuppressive therapy is required for management of SLE disease activity.

Listeriosis

Listeria monocytogenes is a gram-positive rod which is ubiquitous in animals and the environment. Humans can acquire the infection by ingestion of uncooked foods, especially unpasteurised milk and soft cheeses. Person to person spread may also occur.⁴⁰ Listeriosis is best known as an infection of pregnant women and neonates, but a large proportion of the cases actually occur in older children and adults. In the latter age group, it affects mainly immunosuppressed patients, particularly those with haematological malignancies and after organ transplantation. Treatment with corticosteroids is also a recognised risk factor. In the immunosuppressed, listeria usually causes meningitis (but not the brainstem encephalitis which is a feature of listeria infection in the immunocompetent), bacteraemia or peritonitis.

In addition to numerous isolated case reports, there are two series reporting listeria infection in patients with SLE.^{41,42} Bacteraemia, meningitis and peritonitis were all observed and the mortality was high. Although not a common infection in SLE, it is important to consider listeriosis in the differential diagnosis as it responds poorly to cephalosporins which may be given as standard broad-spectrum empirical treatment for meningitis and septicaemia. The treatment of choice is high-dose ampicillin together with gentamicin, but even with optimal therapy the response may be poor and the risk of relapse substantial.

Nocardiosis

Nocardia asteroides is a gram-positive bacterium which is related to mycobacteria but which produces branching filaments and thereby resembles a fungus. It has a worldwide distribution and is being increasingly recognised as an important opportunistic pathogen, particularly in patients with neoplastic disease, and those on

steroid therapy.⁴³ The lung is the usual primary site of infection, presenting with pneumonia which is often cavitating. Haematogenous dissemination, especially to the central nervous system and soft tissues, occurs in approximately one third of cases. Cerebral abscesses are usually multiple and all areas of the brain can be affected. As well as haematogenous spread from the lung, cutaneous infection can also result from direct skin inoculation with nocardia producing a classical mycetoma, lymphangitic picture, pustular cellulitis or localised cutaneous infection.⁴⁴ Nocardia is slow to grow, sometimes requiring several weeks for successful culture and thus needs special laboratory preparation to prevent overgrowth of other organisms and permit identification. The treatment is high-dose co-trimoxazole; prolonged treatment courses are needed (up to 1 year) as relapse is common.

Many cases of nocardia infection have been described in patients with SLE usually presenting as pneumonia or cerebral abscess.³¹ Nocardiosis has been reported in SLE patients in Asia presenting with lung and cerebral abscesses in Thailand,¹⁰ meningitis without abscess in Hong Kong⁴⁵ and lung abscess and cutaneous infections in Malaysia.^{4,46} It therefore appears that nocardiosis presents a real threat to patients with SLE on immunosuppressive therapy and a high index of suspicion is essential. The diagnosis should be suspected in an immunosuppressed patient with cavitating pulmonary infiltrates, especially if there is evidence of associated skin or cerebral disease and a lack of response to conventional antibiotic therapy. Diagnosis can be made by appropriate staining and culture of sputum specimens or biopsy of affected tissue and is worthwhile as appropriate therapy can be life-saving in an infection which otherwise carries a high mortality.

Candidiasis

Candida is a common skin commensal which can cause disease when the immune defences are compromised. In patients with SLE, especially those treated with corticosteroids and antibiotics, oral and vaginal candidiasis are common minor infections. Oesophageal candidiasis has also been reported.⁴ In one of the few studies of infection in SLE based on substantial autopsy data, *Candida* was the commonest opportunistic infection at the time of death, although it may not have been the direct cause of death.³¹ Thus disseminated candidiasis is likely to represent a significant but under-reported problem in SLE patients.

Cryptococcal meningitis

Cryptococcus neoformans is a yeast with a worldwide distribution. It can cause disease in many sites including skin and lungs, but is usually associated with meningitis. Two varieties of *Cryptococcus neoformans* are recog-

nised, *var gattii* and *var neoformans*. The former is known to be a cause of meningitis in immunocompetent adults in Southeast Asia and Australia whereas the latter is associated principally with meningitis in immunosuppressed individuals.⁴⁷

Cryptococcal meningitis was usually absent in early reviews of disease complications in SLE⁴⁸ but is being increasingly recognised as an important infection in this patient group. Many cases have been described in patients with SLE⁴⁹ including some in Asia.^{10,37,50} Pulmonary and cutaneous cryptococcal diseases have also been reported in SLE.⁵¹ Cryptococcal meningitis typically presents with a subacute onset of headache and fever; cranial nerve palsies and psychiatric manifestations may occur.⁴⁹ Thus it can closely mimic cerebral lupus and the distinction between the two is rarely possible on clinical grounds alone. In fact, in a study of neurological manifestations in SLE from Hong Kong, only the minority neurological episodes were due to primary central nervous system involvement by SLE, the rest being due to infection.³⁷ Therefore, all lupus patients presenting with neurological features should have investigations for an infectious cause, including a lumbar puncture in appropriate cases. If cryptococcal meningitis is identified, therapy with amphotericin B or fluconazole is very effective, but the mortality in SLE is high, largely due to delays in diagnosis.

Pneumocystis carinii Pneumonia

Pneumocystis carinii pneumonia (PCP) came to prominence as a result of its major association with HIV infection, but had been recognised as a cause of interstitial pneumonia in immunocompromised patients for several decades prior to the HIV epidemic. Whereas PCP in AIDS typically produces an indolent onset of cough, dyspnoea and fever, the course may be more rapid in patients on immunosuppressive treatment.⁵²

An accumulating body of evidence suggests that *P. carinii* is becoming a common cause of pneumonia in patients with SLE, perhaps due to the use of increasingly aggressive immunosuppressive regimens. In 6 cases of PCP in SLE patients reported in the USA, all the affected patients were lymphocytopenic and were being treated with cytotoxic chemotherapy and steroids.⁵³ PCP has also been reported in SLE patients in Malaysia⁵⁴ where 9 cases were diagnosed in a two-year period at one centre. Eight of these patients were receiving prednisolone and four were also being treated with cyclophosphamide. Five of the patients died from PCP. It is important to remain alert for PCP as induced sputum or bronchoscopy is needed for diagnosis and therapy with high-dose co-trimoxazole can prove life-saving. There is also an argument for giving prophylactic doses of co-trimoxazole to patients treated with aggressive immunosuppressive

regimens.⁵³

Invasive Aspergillosis

Aspergillus species are widespread in the environment and inhabit dark spaces such as the ventilation ducts. Although they can produce disease in previously healthy individuals,⁵⁵ invasive aspergillosis is mainly a problem of immunosuppressed patients. The respiratory tract is the usual portal of entry and the lung is almost always affected, but aspergillosis can involve every organ in the body. The common presentation is with cough, dyspnoea and patchy infiltrates on chest X-ray. Bronchoscopy with biopsy, or open lung biopsy is required in order to demonstrate tissue invasion required for definitive diagnosis. In practicality, however, a positive sputum culture in a patient with suggestive clinical features is probably sufficient grounds to start treatment. Amphotericin B is the standard therapy with itraconazole as second line, but the disease carries a high mortality.

Less than 30 cases of invasive aspergillosis in SLE patients have been described in the English language literature.⁵⁶ This is probably a reflection of the difficulty in diagnosing the disease (all but 2 of these reported cases were detected at post-mortem) and the true frequency of infection is undoubtedly much higher. Overly intensive immunosuppressive treatment may be a risk factor.⁵⁷ *Aspergillus* species have a worldwide distribution and are almost certainly responsible for disease in SLE patients in Asia although, due to the infrequency of autopsies, it largely goes undetected in this population. Nevertheless, two cases of fatal pulmonary aspergillosis in SLE have been reported from Thailand.¹⁰ Increased awareness of this pathogen, combined with appropriate investigation and possibly empirical antifungal therapy in suggestive cases may be warranted.

Conclusion

Over the last few decades, considerable advances have been made in the treatment of SLE and its complications, thereby resulting in steady improvements in mortality from active disease. However, the mortality from infections remains high. With increasing use of immunosuppressive drugs, unusual opportunistic infections are emerging as an important problem in SLE. These infections are considerably under-reported due to difficulties in pre-mortem diagnosis. They may present in subtle ways, often mimicking manifestations of active SLE, and usually respond poorly to conventional empirical antibacterial therapy such as third-generation cephalosporins. Although still relatively uncommon, opportunistic infections make a disproportionately large contribution to overall disease mortality. The most important step is to suspect the diagnosis so that appropriate investigations and cultures can be undertaken and definitive treatment started. Aggressive immunosup-

pression must always be accompanied by an aggressive approach to the detection of infection when complications arise, otherwise the additional mortality caused from infection may exceed that prevented by the immunosuppressive treatment.

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