Infections in Patients with Systemic Lupus Erythematosus

Woon-Leung Ng

Abstract: Infection is a major contributor to morbidity and mortality in patients with systemic lupus erythematosus (SLE). In most clinical series, infection ranks first or second as the commonest cause of death in SLE patients worldwide including those in Hong Kong. In this article, the spectrum of infections and their protean manifestations in lupus patients will be reviewed with emphasis on clinical data from Hong Kong and other Asian countries. A high index of suspicion and dedicated work up to identify the causative pathogens is pivotal to the early diagnosis and effective management of infective complications in patients with SLE.

Keywords: Complication, infection, systemic lupus erythematosus

Introduction

Despite improvement in the long-term survival of patients with systemic lupus erythematosus (SLE), a significant degree of mortality and morbidity remains as a result of infective complications. Infection ranks first or second in most studies on mortality of SLE patients.1-3 There is an intricate interplay among the myriad of immunological perturbations due to lupus and its therapy. Factors related to the virulence and epidemiological profiles of the infective agents also play an important role.

Factors Predisposing SLE Patients to Infections (Table 1)

A myriad of intrinsic and acquired defects in both humoral and cellular immunity have been documented in patients with lupus (Table 1). Break down of cutaneous and mucosal surfaces due to vasculitis may serve as portal of entry for microbes. Leucopenia and lymphopenia were common in SLE patients with or without concomitant immunosuppressive therapies.4 Variable functional impairment had been reported in T and B lymphocytes, monocytes, macrophages, natural killer cells and granulocytes in SLE.5 Mannose-binding lectin (MBL) is a serum lectin important in the innate immune defense as an opsonin-enhancing clearer of various mannose-rich microorganisms by phagocytes. MBL helps the activation of the classical pathway of complement cascade. MBL deficiency is associated with increased risk of infection6 and low levels of MBL have been demonstrated in Chinese lupus patients.7 Functional hyposplenism was noted in 7% to 10% of screened SLE patients in one study and has been implicated in the susceptibility to pneumococcal and salmonella infections.8

Many studies have examined the risk factors that predispose to infection in SLE patients with variable results. Major clinical predictors identified include active lupus,9-12 lupus nephritis12 and renal insufficiency.13 Use of corticosteroids at daily doses greater than 20 mg to 60 mg has been reported to increase the risk of infection.9,10,12,13 However, other studies have also reported that the risk of infection was independent of the amount of steroids used.14 Use of pulse methylprednisolone11 and cyclophosphamide10-12 have also been implicated. Recently, lymphopenia at the time of presentation of lupus was found to be a predictor of subsequent development of tuberculosis15 and other major infections16 in a cohort of lupus patients in Hong Kong.
Spectrum of Infections in SLE

Lupus patients are susceptible to infection by a whole range of pathogens. These include the common, community-acquired infections as well as invasion of various body systems by exotic and opportunistic microbial agents.

Bacterial Infections

The most frequent sites of bacterial infections in patients with SLE are generally similar to those individuals without lupus. In a study of 91 SLE patients followed in a rheumatology clinic in Hong Kong over a six year period, a total of 48 episodes of major infections requiring hospital were recorded in 27 patients.16 The sites and number of episodes of infections in decreasing order of frequency were: pneumonia (16), urinary tract infection (13), skin (5), disseminated infection (5), lymphadenitis (4), meningitis (1), septic arthritis (1) and others (3). The organisms recovered included *E. coli* (10), *Staphylococcus aureus* (6), *Pseudomonas aeruginosa* (2), *Haemophilus influenzae* (1), *Haemophilus parainfluenzae* (1), *Klebsiella pneumoniae* (1), *Stenotrophomonas maltophilia* (1), *Listeria monocytogenes* (1) and *mycobacterium tuberculosis* (7). In 18 of the episodes, no pathogens could be identified although the clinical presentation, laboratory findings and response to antimicrobial therapy supported the presence of infection.

Non-typhoidal salmonellosis is another important infection reported in patients with SLE. A study of fifty cases in Singapore showed that the majority of patients presented with bacteremia without a localizing focus.17 Localized infections caused by Salmonella included spinal osteomyelitis, septic arthritis, acute cholecystitis, septic pericarditis, infective endocarditis and mediastinal abscess. Chan et al reviewed the records of 427 SLE patients followed up in Hong Kong over a twelve year period and observed 14 cases of salmonella bacteremia and 7 patients with localized salmonella infection, including 5 with gastroenteritis.18 Widal test was performed in 8 patients and all showed insignificant findings, suggesting that the test was not helpful to the diagnosis. Defective function of the reticuloendothelial system in SLE patients may result in susceptibility to Salmonella infection.19

Fulminant pneumococcal sepsis is a widely recognized life-threatening infection in patients with absent or defective splenic function. Impaired splenic function and splenic atrophy have been described in SLE patients.20,21 The presence of Howell-Jolly bodies, target cells and spherocytosis in a lupus patient may suggest splenic hypofunction. Pneumococcal septicemia and invasive soft tissue infection of the head and neck regions or the upper chest have been described.22,23 Likewise, increased risk of neisserial infections have been reported in SLE patients.24

Listeriosis is a rare but aggressive infection in patients with connective tissue diseases. SLE was overrepresented as the predisposing condition in a case series of culture proven listeriosis.25 Bacteremia and meningitis are the two serious modes of presentation. Listeria has predilection for pregnant women and may give rise to severe intrauterine infection26 and hence vigilance is needed for this infection in lupus patients, especially in those who are pregnant.

**Table 1.** Factors predisposing SLE patients to infections

<table>
<thead>
<tr>
<th>Breakdown of integument and mucosal barriers</th>
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<tr>
<td>Lymphocyte defects</td>
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<tr>
<td>• Lymphopenia</td>
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<tr>
<td>• Defective CD4 positive T cell proliferation and IL-2 production to antigenic and mitogenic stimulation</td>
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<tr>
<td>• Reduce cytotoxicity of CD8 positive T cells</td>
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<tr>
<td>Impaired effector cell response: Macrophage, Monocytes, Granulocyte</td>
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<tr>
<td>• Hypocomplementemia</td>
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<tr>
<td>• Impaired antigen-presenting function of monocytes and macrophages</td>
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<tr>
<td>• Defective opsonization</td>
</tr>
<tr>
<td>• Impaired neutrophil chemotaxis and phagocytosis</td>
</tr>
<tr>
<td>• Defective natural killer cells</td>
</tr>
<tr>
<td>• Low serum level of mannose-binding lectin (MBL)</td>
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<tr>
<td>Autosplenectomy and functional hyposplenia / asplenia</td>
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</table>
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Nocardia is a group of gram-positive and weakly acid-fast bacteria with branching filaments. Nocardioses is an important opportunistic infection in patients with impaired cell-mediated immunity. Mok et al reported six cases of nocardioses among a cohort of 215 SLE patients over an eighteen-year period, yielding a prevalence of 2.8%. An extensive literature review by the author showed that the lung was the commonest site of involvement (81%). Patients may present with fever, cough and dyspnea, with lung infiltrates, pleural effusion, empyema or lung abscess with cavitation. The central nervous system was the next commonest affected site (13%), presenting as brain abscesses or lymphocytic meningitis. Aggressive diagnostic procedures such as bronchoalveolar lavage, percutaneous lung biopsy and aspiration of abscesses are often needed and justified in view of the high mortality rate of nocardioses in SLE patients (35%), especially in patients with CNS involvement. A case of nocardioses is presented in Figure 1.

Mycobacterial Infections

Tuberculosis (TB) is endemic in Hong Kong. A review by Tam et al of 526 SLE patients from 1984 to 2001 recorded 61 episodes of TB in 57 patients, giving an incidence of 17 per 1000 patient-year of follow up. Two-thirds of the episodes were due to extra-pulmonary infection. Multivariate analysis revealed the presence of nephritis and higher cumulative dose of steroid to be risk factors associated with development of TB. In another local database of 91 lupus patients, Chu and Ng reported lymphopenia as the sole factor associated with occurrence of TB.

Mycobacterium other than tuberculosis can cause infection in SLE patients. Important organisms include M. fortuitum, M. kansasii, M. marinum and M. avium complex (MAC). Most cases presented with soft tissue infections with or without abscess formation.

Viral Infections

Herpes zoster is the most common specific viral infection in SLE patients. A large case control study comprising 348 SLE patients identified herpes zoster in 13.5% of patients. Dissemination occurred in 11% and was more frequent during immunosuppressive therapies. However, 65% of zoster episodes occurred during mild or inactive SLE with daily prednisolone dosage less than 20 mg and in the absence of concurrent cytotoxic agents. Lupus patients, especially those taking corticosteroid or immunosuppressive agents should be cautioned for this common complication as early medical attention and anti-viral treatment may reduce the incidence and duration of post-herpetic neuralgia.

In lupus patients on heavy immunosuppressive therapy, cytomegalovirus (CMV) infection may present in a myriad of ways including pneumonitis, enteritis, retinitis and cutaneous ulcerations. Prompt diagnosis ascertained by targeted imaging and biopsies may prove life-saving. Two illustrative cases are presented in Figures 2 and 3.

Fungal Infections

Pneumocystis carinii pneumonia (PCP, now officially renamed Pneumocystis jiroveci pneumonia) is a life threatening opportunistic infection in SLE patients. Case fatality was up to 55.6% in one case series from Malaysia. Most of the patients were having active disease and taking corticosteroid with or without other immunosuppressants. A low peripheral lymphocyte count and background interstitial fibrosis were found to be risk factors for PCP infection in a Japanese study. Patients may present with fever, dry cough,
A 31-year-old lady had relapse of class IV lupus nephritis treated with high dose corticosteroid and mycophenolate mofetil. She presented with fever, skin ulcers and progressive SOB. (a) Skin ulceration due to cytomegalovirus (CMV) infection over the left gluteal region with serous exudate. (b) Chest X-ray showing haziness over both lower lung fields. The right pleural effusion was transudative and sterile. (c) Transbronchial biopsy showed a few alveolar epithelial cells exhibiting nuclear enlargement with cytoplasmic and nuclear inclusion (arrow) typical of CMV pneumonitis. (d) Transbronchial lung biopsy showing pneumocystis carinii (Grocott stain).

A 32-year-old lady with refractory arthritis due to SLE was given prednisolone at a dose of 0.75 mg/kg/day. She developed low abdominal pain and per rectal bleeding. (a) Colonoscopy detected ulceration at the terminal ileum. (b) Biopsy of the terminal ileum revealed perivascular lymphohistiocytic inflammatory infiltrate around capillaries. A few viral inclusions were seen in the endothelial cells. Immunostaining was positive for cytomegalovirus (CMV).

Cryptococcus neoformans is an important opportunistic infectious agent in immunocompromised hosts including lupus. Sato et al reported a case of pulmonary cryptococcosis and reviewed 44 other reported cases of cryptococcosis in SLE patients in Japan over a 35-year-period. There were 34 cases of meningitis; 22 with pulmonary cryptococcosis; 6 presented as sepsis; and there were 6 cases of cutaneous cryptococcosis. Twenty (44 percent) of the patients died. Locally, Mok et al reported a unique case of cryptococcal meningitis presenting concurrently with SLE in the absence of immunosuppressive therapy. Intrinsic immunological defects including low complement levels, low natural killer cell count and probable defective CD4 positive T cell and macrophage functions were postulated to have contributed to the patient's susceptibility to cryptococcal infection.

Mucormycosis caused by species from the family Mucoraceae is a rare but fatal fungal infection in SLE. Rhinocerebral invasion involving the paranasal sinuses, orbits and brain were the most frequent presentations followed by pulmonary and disseminated infection. Delay in recognition is common and case fatality is high. Patients with active lupus on immunosuppressive therapies presenting with headache, unexplained facial pain, nasal discharge or bleeding should raise the clinical suspicion. Mucosal thickening in paranasal sinuses and cerebral invasion may be demonstrated on imaging. Aggressive investigations including tissue biopsy and culture were pivotal to early diagnosis.

Systemic fungal infections, such as candidiasis and aspergillosus, which commonly occur in immunocompromised hosts, are fortunately uncommon in lupus.
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patients. Nonetheless, early diagnosis and prompt treatment is paramount to prevent potentially fatal outcome.

Protozoal Infections

Protozoal infections in SLE patients are fortunately rare. The most important one is infection by toxoplasma gondii. Cerebral toxoplasmosis may mimic lupus cerebritis. Basal ganglia calcification is a suggestive but non-specific finding that should alert the clinical suspicion in a SLE patient presenting with features of encephalopathy.

Parasitic Infections

Hyperinfection with Strongyloides stercoralis may occur in immunocompromised patients including lupus. The syndrome can mimic a lupus flare and eosinophilia may be absent as a result of steroid administration. Recurrent or polymicrobial gram-negative bacteremia may occur as a result of migration of larvae through the bowel walls.

Difficulties in Diagnosis of Infections in SLE

Diagnostic difficulties for infections may occur in lupus patients. Commonly encountered pathogens may cause infections in atypical sites. Examples included pneumococcal soft tissue infections and salmonella pericarditis. Alternatively, lupus patients may develop uncommon opportunistic infections like pneumocystis carinii pneumonia and mucormycosis. Infection may masquerade as lupus activity or treatment-related complications. Signs and symptoms of sepsis may be masked or modified by medication taken for lupus such as corticosteroids and non-steroid anti-inflammatory drugs. Co-infections are not uncommon (Figures 1 & 2), especially in the presence of profound immunosuppression.

Diagnostic Approach to Infections in SLE

For all SLE patients whose clinical conditions warrant hospital admission, infections should be considered as a potential underlying or contributing cause. Other causes that must be distinguished including active lupus, disease or treatment related complications and other unrelated disorders. Infections can mimic, co-exist or precipitate active disease. Infections can develop or supervene during the course of lupus.

It is of paramount importance to evaluate the background and baseline conditions of the patient. Particular attention should be paid to previous disease manifestations and recent lupus disease activity. Patients with active disease given augmented immunosuppressive therapies such as corticosteroid and immunosuppressive therapies will have the highest risk for infective complications. Likewise, organ damage such as significant renal impairment, nephrotic syndrome, pulmonary damage and poor nutritional status may pose additional risks. Note the presence of other comorbidities such as diabetes mellitus or chronic hepatitis. Epidemiological factors that should be considered included any history of recent travel, animal or avian contact, venereal exposure, recent hospital admission or invasive procedures. Past infections such as tuberculosis should be noted.

Table 2 described some hints to help distinguishing infections and active disease in lupus. However, it should be emphasized that none of the parameters are sufficiently sensitive and specific to differentiate between the two conditions. Significant overlapping and coexistence of both infection and active disease are not uncommon. Individual clinical judgment is necessary.

One point of note is that patients with active systemic lupus erythematosus (SLE) are often reported to have normal C-reactive protein (CRP) levels whereas bacterial infections often produce significant elevation of CRP. Therefore it has been proposed that measuring the CRP levels in pyrexial patients with SLE can help to differentiate between active disease and infection. In a case-control study of Korean lupus patients, CRP levels trend to be higher in patients with proven infections than control and CRP levels greater than 50 mg/l were only seen in infective episodes. However, lupus patients with serositis can have very high CRP levels. Conversely, persistently normal CRP levels have been reported in proven bacteraemic episodes in lupus patients.

One study showed that in SLE patients receiving prednisone at maintenance doses or greater, lupus fever is rare. When fever does develop, it is usually due to infection. In conclusion, infections should be presumed in all fevers associated with SLE patients until proven otherwise.
Table 2. Helpful features to differentiate between lupus disease activity and infective complications

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Active disease</th>
<th>Infection</th>
</tr>
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<tbody>
<tr>
<td>Level of immunosuppression</td>
<td>• Occurs more commonly while using low level of immunosuppression</td>
<td>• Occurs more likely in the context of profound or prolonged immunosuppression</td>
</tr>
<tr>
<td>Fever</td>
<td>• Variable, usually mild to moderate fever (≤38.0°C)</td>
<td>• Variable. High swinging fever ≥39.0°C and presence of rigors more suggestive of infections</td>
</tr>
<tr>
<td></td>
<td>• Rigors are unusual</td>
<td></td>
</tr>
<tr>
<td>Time course</td>
<td>• Variable, depending on the specific manifestations. Active disease generally evolve over a period of days to a few weeks</td>
<td>• Variable. Abrupt onset of symptoms favors infection but subacute presentation may occur with more indolent infections</td>
</tr>
<tr>
<td>General condition</td>
<td>• Variable but patients generally remain in satisfactory condition</td>
<td>• Variable. Patients with pyogenic and opportunistic infections tend to be more septic-looking with rigors and prostration</td>
</tr>
<tr>
<td>White blood cell</td>
<td>• Low or normal</td>
<td>• Elevated with neutrophilia ± toxic granulation in pyogenic infections</td>
</tr>
<tr>
<td></td>
<td>• Lymphopenia often present but profound lymphopenia (&lt;0.5 x 10^9/L) due to lupus per se is uncommon</td>
<td>• Profound lymphopenia (&lt;0.5 x 10^9/L) associated with immunosuppressive therapy is a predisposing factor for severe infections</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>• Usually normal. May be elevated for lupus serositis</td>
<td>• Usually raised</td>
</tr>
<tr>
<td>Complement (especially C3)</td>
<td>• Usually depressed especially in cases of class IV lupus nephritis</td>
<td>• Can be normal or elevated as part of an acute phase response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May be depressed if infection occurred in the presence of active disease</td>
</tr>
<tr>
<td>Anti-ds DNA level</td>
<td>• Usually elevated in lupus nephritis or vasculitis; may be normal for some other manifestations</td>
<td>• Infections per se should not increase the anti-ds DNA level but infections may co-exist with active disease associated with high anti-ds DNA</td>
</tr>
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</table>

Patients with Localizing Features

Patients with obvious localizing signs and symptoms of infection should be worked up accordingly with targeted investigations. Particular attention should be given to cutaneous lesions, lymphadenopathy, arthritis, heart murmurs, signs and symptoms of the ear, throat and nose; visual disturbances as well as fundal and neurological examination. Negative findings on plain radiographs should be reevaluated by more sensitive imaging modalities such as the computerized tomography (CT), magnetic resonance imaging (MRI), bone scan or echocardiogram where appropriate. Obtain relevant body fluids (e.g. blood, sputum, urine, stool, cerebrospinal fluid) for microbiological examination. Pleural effusion, ascitic fluid, joint effusion, lymphadenopathy and soft tissue collections should be aspirated if present. More invasive diagnostic procedures such as bone marrow aspiration, bronchoalveolar lavage, synovial biopsy, pericardiocentesis and other surgical or endoscopic procedures may be necessary if infection is suspected in the respective anatomical sites. Separate specimens should be obtained for cytohistological examination and microbiological studies for bacterial, mycobacterial, fungal and viral cultures where appropriate.

Patients without Localizing Features

Patients presenting with fever, prostration or haemodynamic instability but without localizing clues should have full septic workup comprising at least two blood cultures, urine culture, chest radiograph plus ultrasonogram of the abdomen.
Empirical broad spectrum antibiotics that can cover more than 90% of pyogenic infections should be commenced while awaiting microbiological results. If the patient's condition does not improve after 72 hours, more aggressive work up targeting at occult septic foci and opportunistic infections should be performed. Consider repeating the cultures in 1 to 2 week if clinical condition shows no improvement and initial studies were negative.

The search for more exotic infections may include blood and urine cultures for mycobacterial and fungal organisms. Specialized culture medium such as the BACTEC system can increase the yield for mycobacterial culture by suppressing other bacterial growth. Blood for cytomegalovirus pp65 antigen, cryptococcal antigen and Penicillium marneffei antibodies may be sent if indicated.

Gallium scan or Positron Emission Tomography (PET scan) may be considered if basic investigations failed to localize the site and source of infection. Alternatively, computerized tomography of the thorax, abdomen and pelvis may reveal unsuspected lesions. Magnetic resonance imaging is usually reserved for targeted pathologies. For patients with severe infections, aggressive and invasive investigations should be considered to allow early identification of the culprit pathogen.

**Conclusion**

Patients with systemic lupus erythematosus are at risk of infections caused by a wide range of pathogens as a result of intrinsic defects and iatrogenic insult of the immune system. Physicians taking care of lupus patients should be alerted to the multitudinous presentations of infections. A heightened level of vigilance and dedicated work up is pivotal for the prompt recognition and effective management of potentially fatal infective complications.

**Acknowledgements**

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