Invasive fungal infection in systemic lupus erythematosus: an analysis of 15 cases and a literature review

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Objective. To analyse 15 cases of invasive fungal infection and mortality parameters in the largest series in the last 35 yrs of patients with systemic lupus erythematosus (SLE) at a single medical centre.

Methods. Fifteen patients with SLE and invasive fungal infections were retrospectively enrolled. Clinical and laboratory data, fungal species and infected sites, corticosteroid and immunosuppressant doses and SLE disease activity index were assessed retrospectively. Comparison and correlation analyses utilized Fisher’s exact test, the chi-square test, Mann–Whitney U-test or the Wilcoxon signed-rank test where appropriate.

Results. In contrast to other review reports, Cryptococcus neoformans was the most commonly identified fungus in this Taiwanese series. Notably, the prevalence of autoimmune haemolytic anaemia and positive results for the anti-cardiolipin antibody in this study were significantly higher than those in SLE patients in general ($P < 0.0001$ and $P < 0.0001$, respectively). Fungal infection contributed to cause of death in 7 of 15 (46.7%) patients, of which Cryptococcus neoformans accounted for six of these infections. Low-dose prednisolone ($<1$ or $<0.5$ mg/kg/day based on arbitrary division) prior to fungal infection tended to correlate with 1 yr mortality after diagnosis of SLE ($P = 0.077$ or $P = 0.080$). However, following fungal infection, patients who died from infection itself had been prescribed with higher prednisolone dose or equivalent than surviving patients ($P = 0.016$). All SLE patients with fungal infections had active SLE (SLEDAI $>7$).

Conclusions. Cryptococcus neoformans infection accounted for most fatalities in SLE patients with fungal infections in this series. Active lupus disease is probably a risk factor for fungal infection in SLE patients. Notably, low prednisolone doses prior to fungal infection or high prednisolone doses following fungal infection tended to associate with or correlated to fatality, respectively. Therefore, we suggest that different prednisolone doses prescribed at various times impact the incidence of fungal infection and its associated mortality.

Key words: Systemic lupus erythematosus, Fungal infection, SLEDAI, Prednisolone.

Introduction

Infection is a principal cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE) [1–3]. Although opportunistic organisms account for a considerable number of infections, cases of SLE with fungaemia or invasive fungal infection have seldom been described [1–3]. Immunocompromised patients, such as those with malignancies treated with chemotherapy and in organ transplant patients, are the most frequently targeted by fungaemia or invasive fungal infection [4, 5]. Such infections can also occur in patients with renal failure, fulminant liver disease, alcoholism, diabetes mellitus, acquired immunodeficiency syndrome (AIDS), chronic granulomatous disease and otherwise healthy individuals. During the past 35 yrs, only case reports (the largest comprised three cases [6]) have described fungal infections in SLE patients. This study analyses invasive fungal infections in Taiwanese SLE patients and compares the characteristics of their infections with those reported in the literature. This retrospective study describes 15 patients with SLE who developed invasive fungal infection or fungaemia.

Patients and methods

Patients

Fifteen SLE patients with invasive fungal infections including fungaemia at Chang Gung Memorial Hospital (CGMH) between 1978 and 2004 were retrospectively enrolled in this study. The incidence of invasive fungal infection in the lupus population at CGMH was 0.640% (15 of 2344 lupus patients in 26 yrs). Diagnosis of SLE was based on American College Rheumatology (ACR) criteria [7]. Fungaemia confirmation was based on a blood culture positive for fungi. Invasive fungal infection was deemed a fungal infection at sites other than skin, urine or mucous membranes [8]. The following patient data were obtained: age; gender; clinical symptoms and signs; laboratory data such as serum complement, anti-dsDNA and anti-cardiolipin antibody levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haemogram, renal function, 24-h urine total protein and urinary analysis; fungi species; SLE activity when the fungal infection occurred or when a patient died; doses of prednisolone and other immunosuppressant agents administered prior to fungal infections; use of antibiotics prior to fungal infections;...
and lupus-involved organs when fungal infections occurred. Serum complement levels, anti-double-stranded (ds) DNA antibody titers, and SLE disease activity index (SLEDAI) were employed to determine SLE activity when fungal infections occurred. All data were acquired retrospectively.

Statistical analysis
Statistical analyses—Fisher’s exact test, the chi-square test, Mann-Whitney U-test or Wilcoxon signed-ranks test—utilized SPSS 10 for Windows (SPSS Inc., Illinois, USA). Data are presented as means ± s.d. A value of $P < 0.05$ was considered statistically significant. However, as invasive fungal infections in SLE patients are uncommon, a value of $P < 0.1$ was considered 'tend to correlate' or 'a noticeable trend' as described previously [9].

Results
Clinical characteristics
The female-to-male ratio for the 15 patients was 2.75:1 (Table 1). Notably, a comparison of 1-yr mortality for patients on prednisolone ≥ 1 and < 1 mg/kg/day (including no prednisolone) or taking prednisolone ≥ 0.5 and < 0.5 mg/kg/day (including no prednisolone) indicated that < 1 or < 0.5 mg/kg/day prior to fungal infections tended to correlate with the 1-yr mortality rate (Table 2). No statistical significance existed for 5-yr mortality rate with prednisolone cut-off values of 1 and 0.5 mg/kg/day. Moreover, no significant difference was observed between C3 ($P = 0.4497$), C4 ($P = 0.9362$), anti-dsDNA levels ($P = 0.767$) and SLEDAI ($P = 0.2716$ by Mann-Whitney U-test) when fungal infection occurred in high and low-dose groups that used prednisolone (≥ 1 and < 1 mg/kg/day) prior to fungal infection. Patients were also divided into three groups based on prednisolone doses (< 11 mg/day, 11–30 mg/day and > 30 mg/day) before fungal infections. No statistically significant difference existed for 1-yr mortality rate among these three groups (chi-square test).

All patients with SLEDAI scores > 7 at fungal infection onset were deemed to have active, instead of severe, disease [10] (Table 1). No significant difference was noted for both 1- and 5-yr mortality rates between those with SLEDAI scores > 11 and those with SLEDAI scores < 11 (by arbitrary division). One- and 5-yr mortality rates did not differ between those who were administered broad-spectrum antibiotics prior to infection onset and those who were not (Table 1).

Half of patients had haemolytic anaemia during the course of SLE (Table 3). The prevalence of haemolytic anaemia in a lupus population identified by L.B.L between 1 August 1994 and 31 July 2004 was 1.55% (10 of 644 lupus patients over 10 years). The percentage of patients with haemolytic anaemia in this series was significantly different (Table 3) than that in L.B.L’s lupus population ($P < 0.0001$; odds ratio = 63.40; confidence interval, 17.41–230.91 by chi-square test). Conversely, various complications accompanied in SLE patients at fungal infection onset (Table 3).

Laboratory data for inflammatory and lupus activity
One- and 5-yr mortality rates were not significantly different between patients with and without leucopenia (Table 4). Table 4 presents several abnormal laboratory parameters. Notably, no statistical difference existed for C3 ($P = 0.093$), C4 ($P = 0.114$) and anti-dsDNA ($P = 0.310$, by Wilcoxon signed-rank test) levels
between at time of SLE diagnosis and when fungal infection occurred.

No patient had leucopenia at fungal infection onset (Table 4). Of the 11 patients with fungal infections, the percentage with low C3 and C4 levels was much less than those for SLE patients at diagnosis (Table 4). Of the eight patients examined, three (37.5%) were abnormally positive for anti-dsDNA antibody (vs. 10/14 = 71.4% at SLE diagnosis).

**Fungal infection in SLE patients**

Fungal infection diagnosis was based on blood, cerebrospinal fluid (CSF), and sputum cultures and cultures of soft tissue harvested from the thigh and lung (Table 5). Two (13.3%) patients had both Aspergillus niger and Cryptococcus neoformans. One (6.7%) patient had both nocardia and candida infections. In total, three (20.0%) patients had infections with two fungal species. Notably, one (6.7%) patient had recurrent symptomatic cryptococcal meningitis with an interval of 2.67 years (see Discussion).

Ten patients died, of which eight died within 1 yr of fungal infection onset (Table 6). Of these, mortality in seven patients (six had Cryptococcus and one had Nocardia and Candida albicans) was directly related to fungal infection. The prednisolone dose administered before fungal infection was assessed in these eight patients. In the high-dose group (four patients administered ≥1 mg/kg/day prednisolone), three patients (75%) died directly from fungal infection. In the low-dose group (four patients administered <1 mg/kg/day prednisolone), four patient (100%) deaths were directly due to fungal infections.

Of all 15 patients, sequelae following fungal infection were as follows: death, seven patients (Table 6); increasing proteinuria, one patient; hepatitis, one patient; disseminated intravascular coagulation, one patient; CNS lupus, one patient; thrombocytopenia, one patient; acute myocardial infarction (AMI), one patient; chronic renal failure with hemodialysis and cerebral infarcts, one patient; and, hypoxic encephalopathy, one patient. No difference in prednisolone doses before infection was noted (P = 1.00 by Mann–Whitney U-test) between mortality cases due to fungal infection and surviving patients (Table 6). Conversely, prednisolone doses prescribed after fungal infection differed significantly (P = 0.016, by Mann–Whitney U-test) between mortality cases due to fungal infection and surviving patients (Table 6). Moreover, no difference existed for disease parameters [leucocyte (WBC) count, SLEDAI, C3, C4, anti-dsDNA, 24 h urine protein, serositis and skin rash] at fungal infection onset was found between deceased and surviving patients (P = 0.940 for SLEDAI scores on fungal infection). For example, P = 1.000 for serum C3 levels between deceased and surviving patients at fungal infection onset, and P = 0.107 for serum C4 levels and P = 0.346 (by Mann–Whitney U-test) for SLEDAI between deceased and surviving patients.
Infection is a serious complication for SLE patients. Although the incidence of infectious complications for SLE patients remains unknown, Staples et al. [11] identified that infection rates for SLE patients were significantly higher than that for rheumatoid arthritis patients. However, most documented infections were bacterial rather than fungal. Sieving et al. [6] reported three SLE cases with deep fungal infections and reviewed 30 cases in the literature. In their literature review [6], most patients were young females, a typical SLE population. Among these 30 patients, the most common infection was candida species (n = 13), C. neoformans in 10 and followed by aspergillus species infected four, etc. Candida infection was identified as the most common fungal infection. In contrast, cryptococcal infection was the most common pathogen in this study (Table 5). Notably, a clinical study [12] of 59 patients with C. neoformans infection at National Taiwan University Hospital from 1982 to 1997 generated an estimate of 0.010%, which likely represents the incidence of cryptococcal infection in Taiwan.

Nocardial infections are common fungal infections in steroid-treated SLE patients, particularly for lung lesions [13, 14] as for one patient in this study (Table 6). Disseminated and invasive infections with Allescheria boydii are primarily seen in immuno-compromised hosts, including those with pneumonitis, osteomyelitis, endophthalmitis and prosthetic valve endocarditis [15]. Clinical evidence indicates that amphotericin B and an azole in vitro attain synergistic effects against Pseudallescheria boydii [16] as for patient 5 (Table 6).

Although inhalation of aspergillus spores is extremely common, the clinical disease is rare. Lung tissue invasion is almost entirely confined to immuno-suppressed patients as for patient 10 (Table 6). Treatment with intravenous amphotericin B typically cures invasive aspergillosis when immuno-suppression is less than severe [17].

Severe candida infection is the most frequently identified opportunistic fungal infection in numerous SLE series [6, 18]. Predisposing factors are recent steroid and cytotoxic drug therapy, heroin addiction, thermal injury, surgery, cardiac prostheses and antibiotic use [6]. However, no patients had a heroin addiction, thermal injury, surgery or cardiac prostheses in this study.

Gonzalez-Crespo et al. [19] underscored the importance of broad-spectrum antibiotic use prior to fungal infection. However, no number difference in patients receiving antibiotics or not in this study (Table 1). In this series, therefore, whether patients received antibiotics had no affect on the incidence of fungal infection.

Autoimmune haemolytic anaemia occurs in roughly 5–10% of SLE patients [20–23]. In this study, 50% of patients had haemolytic anaemia during the course of SLE (Table 3). However, whether this high prevalence of previous haemolytic anaemia in this study resulted in susceptibility to fungal infection in SLE patients warrants further study. Notably, the patient percentage with abnormal IgG anti-cardiolipin levels (Table 4) was significantly higher than that reported for Taiwanese SLE patients (34.76%, P < 0.0001; odds ratio = 2.88; confidence interval 2.33–3.55 by chi-square test) [24]. Moreover, all patients with fungal infections had active SLE (SLEDAI ≥7) (Table 6), indicating that SLEDAI ≥7 may be a predisposing factor for fungal infection. However, as this study was not prospective, a large prospective study is required to confirm this proposition.

Death of SLE patients is most commonly caused by infection and severe nephritis, particularly early in the lupus disease course. Reported survival of SLE patients is 95–97% at 1 yr, 90–95% at 2 months after fungal infection.

When invasive fungal infections occurred.

M = male, F = female, NA = not available, B/C = blood culture, pul. = pulmonary, AMI = acute myocardial infarction, C. neoformans = Cryptococcus neoformans, C. albicans = Candida albicans and CNS = central nervous system.

Discussion

Table 6. Clinical and laboratory findings for SLE patients with fungal infections

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Prednisolone dosea before fungal infection (mg/kg/day)</th>
<th>SLEDAI fungi</th>
<th>Prednisolone dosea after fungal infection (mg/kg/day)</th>
<th>Species of fungi and involved organs</th>
<th>Cause of mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>1.6</td>
<td>16</td>
<td>0.5</td>
<td>Cryptococcus and aspergillus in the lungs</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>1.1</td>
<td>16</td>
<td>0.0</td>
<td>Cryptococcal meningitis</td>
<td>AMI with cardiogenic shock</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>1.0</td>
<td>11</td>
<td>0.4</td>
<td>Fungaemia with C. albicans pneumonia</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>1.0</td>
<td>10</td>
<td>0.8</td>
<td>B/C with C. neoformans and cryptococcal meningitis</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>1.2</td>
<td>9</td>
<td>1.0</td>
<td>Allescheria boydii of the thigh</td>
<td>CNS lupus</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>0.0</td>
<td>17</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>0.6</td>
<td>12</td>
<td>0.0</td>
<td>Candida pneumonia</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>0.3</td>
<td>20</td>
<td>1.2</td>
<td>B/C with C. neoformans and cryptococcal meningitis</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>5.0</td>
<td>28</td>
<td>NA</td>
<td>B/C with C. neoformans and cryptococcal meningitis</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>0.0</td>
<td>11</td>
<td>37.5</td>
<td>Fungaemia with meningitis, and pulmonary with Aspergillus niger</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>1.2</td>
<td>8</td>
<td>1.5</td>
<td>Pneumonia with Norcardia and C. albicans</td>
<td>AMI with respiratory failure</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>0.8</td>
<td>26</td>
<td>0.6</td>
<td>B/C with C. neoformans and cryptococcal meningitis</td>
<td>AMI with septic shock</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>1.2</td>
<td>13</td>
<td>NA</td>
<td>B/C with C. neoformans and cryptococcal meningitis</td>
<td>AMI with respiratory failure</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>0.5</td>
<td>9</td>
<td>2.0</td>
<td>B/C with C. neoformans and cryptococcal meningitis</td>
<td>AMI with septic shock</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>0.4</td>
<td>28</td>
<td>0.4</td>
<td>Cryptococcal meningitis</td>
<td>SL with pul. haemorrhage and ventricular tachycardia</td>
</tr>
</tbody>
</table>

*Average dose (or equivalent) 3 months before or after fungal infection occurred; 3, 5, 15 died beyond 4 months after fungal infection; others died within 2 months after fungal infection.

When invasive fungal infections occurred.

M = male, F = female, NA = not available, B/C = blood culture, pul. = pulmonary, AMI = acute myocardial infarction, C. neoformans = Cryptococcus neoformans, C. albicans = Candida albicans and CNS = central nervous system.
2 yrs, 82–90% at 5 yrs, and 71–80% at 10 yrs [25, 26]. Poor prognosis (approximately 50% mortality at 10 yrs) is related to high serum creatinine levels, hypertension, nephrotic syndrome, anaemia, hypoalbuminaemia, hypocomplementaemia and anti-phospholipid antibody at diagnosis. In this study, survival was 80% at 1 yr (SLE diagnosis to death) for SLE patients suffering fungal infections, 73.3% at 2 yrs, 66.7% at 5 yrs and 60% at 10 yrs. Therefore, SLE patients with fungal infections in this study had poorer prognosis than the general SLE population. In the later stages of the disease, deaths were commonly attributed to coronary artery disease [27]. Women with lupus in the 35-44 yr age group were >50 times more likely to have a myocardial infarction than were women of similar age in the control group [28].

The role of cell-mediated immunity in resistance to fungal infections has been described in many experimental animal models [29, 30]. A high percentage of patients in this study had taken corticosteroids prior to fungal infection onset (Table 1). Clinical and experimental evidence indicates that corticosteroids suppress cell-mediated immunity in humans [31, 32]. Additionally, corticosteroids inhibit recruitment of neutrophils and monocyte-macrophages to the inflammatory site and depress monocyte and neutrophil bacterial activity [33–35]. Notably, the differences in 1-yr and 5-yr mortality for patients with steroid usage vs those without steroid usage within 3 months before fungal infection were not statistically significant (Table 2). Study results obtained previously [29–35], therefore, are not in total agreement with those obtained by this study (see the Section ‘Results’). However, in this series, a noticeable trend existed, implying that low-dose prednisolone (>1 or <0.5 mg/kg/day) prior to infection tended to correlate with 1-yr mortality (Table 2). Hence, the mechanism underlying these phenomena remain unclear as no differences existed in serum C3, C4, and anti- dsDNA levels, and SLEDAI scores between low- and high-dose prednisolone groups (see Clinical characteristics). Nevertheless, high-dose prednisolone used after infection in the mortality cases likely predisposes these patients to death, in contrast to surviving patients receiving low-dose prednisolone (Table 6); these propositions require validation. Moreover, whether different corticosteroid doses predispose patients to fungal infection regardless of earlier lupus involvement (such as haemolytic anaemia or positive anti-cardiolipin antibody; see Clinical characteristics) in SLE patients requires further prospective study.

Typically, patients with AIDS and cryptococcosis are treated initially with intravenous amphotericin B for at least 2 weeks until patient clinical condition stabilizes. Fluconazole 400 mg is then administered once daily for 8 weeks. Once patients are asymptomatic and have negative CSF cultures, fluconazole 200 mg daily is continued indefinitely [36]. In patients without AIDS, amphotericin B is usually given for a minimum 10 weeks when CSF culture is negative, typically resulting in decreased antigen titre levels and glucose normalization. Bennett [36] recommended treating some immuno-suppressed patients as AIDS patients with indefinite fluconazole maintenance therapy. Notably, one male patient in this study (patient 6 in Table 6) contracted cryptococcal meningitis at age 37, 1 yr after SLE diagnosis and was not treated for lupus. This patient was initially prescribed intravenous amphotericin B 0.8 mg/kg/day for 2 weeks and then intravenous fluconazole 400 mg/day for 2 weeks. Subsequently, oral fluconazole 400 mg/day was administered for 6 weeks. Following 10 weeks of treatment, oral fluconazole 200 mg/day was continued for an additional 14 weeks. The patient, however, experienced recurrent cryptococcal meningitis 26 months after halting antifungal therapy. At this time, the patient’s serum cryptococcal antigen level was positive at 1:512 (May 2004). Again, the patient was treated with intravenous amphotericin B (same dosage administered 31.5 months earlier) for 4 weeks, then oral fluconazole 400 mg/day for over 20 months (to date). His serum cryptococcal antigen levels declined over time (positive at 1:64, March 2005; positive at 1:32, October 2005); to date, the patient has had no symptoms or signs associated with cryptococcal meningitis (serum cryptococcal antigen level positive at 1:4, February 2006; positive at 1:2, May 2006). Therefore, we suggest that 10 weeks of anti-fungal therapy [36] is insufficient for SLE patients. Therapy exceeding 6 months is likely required for cryptococcal meningitis in SLE patients; however, a large series is needed to confirm this proposition.

In summary, C. neoformans was the fungus most commonly identified in this Taiwanese series. Fungal infection contributed to the death of seven patients, in which six had cryptococcal infection. Low-dose prednisolone prior to infection (<1 or <0.5 mg/kg/day by arbitrary division) tended to correlate with 1-yr mortality. Furthermore, we suggest that high-dose corticosteroid use following fungal infection probably predisposes SLE patients toward death. In excess of 6 months of anti-fungal therapy may be needed to treat cryptococcal meningitis in SLE patients as suggested for immuno-compromised patients [36]; however, additional case experience is required to confirm this point.

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