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Invasive fungal disease in systemic lupus erythematosus: A systematic review of disease characteristics, risk factors, and prognosis

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ABSTRACT

Objectives: Invasive fungal disease (IFD) is a life-threatening complication of systemic lupus erythematosus (SLE) and/or its treatment. We conducted a systematic review to characterize IFD in SLE and identify risk factors and outcomes.
Methods: MEDLINE, Embase, and Web of Science were searched up to June 2013 using MeSH terms and keywords pertaining to *SLE* and *IFD*. Two independent reviewers selected adult cohort studies and case series/reports on IFD in SLE based on the established classification criteria for both diseases.
Results: In total, 393 cases from 182 studies met the criteria for inclusion. *Cryptococcus* spp., *Aspergillus* spp., and *Candida* spp. were the most common fungal pathogens. Cohorts described IFD in 0.6–3.2% of SLE inpatients and 0.28% of SLE outpatients. IFD occurred at a median of 2 years of disease duration (IQR: 0.5–7.1), and 39% of cases occurred within the first year of SLE. Disease activity and corticosteroid dose >60 mg/day emerged as risk factors for IFD. IFD was associated with a mortality rate of 53% (161/316 cases), and worse in the absence of antifungal therapy ($n = 43$). Overall, 44 cases of IFD were only diagnosed on autopsy.
Conclusions: Our systematic review confirms the severe sequelae of IFD in SLE. Cases occurred in patients with active SLE, who were on high daily corticosteroids doses and at early stages of disease. This highlights the role of poor disease control and a high "net state of immunosuppression" in risk. IFD in SLE should be prospectively examined in the modern era.

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Introduction

Infections constitute a major cause of mortality and morbidity in patients with systemic lupus erythematosus (SLE). An estimated 20–40% of all SLE deaths are attributable to infection [1–4]. This greater susceptibility in SLE patients is hypothesized to be due to both the disease itself and the immunosuppressive agents used to treat it [5]. Although many infections in SLE are due to bacterial pathogens, there is emerging literature on invasive fungal diseases in SLE patients.

Typically occurring in hosts with human immunodeficiency virus (HIV) infection, or in patients immunosuppressed due to transplantation or chemotherapy [6], there is a substantial risk that invasive fungal infections in SLE are under-recognized by clinicians. In a case series, 3 of 10 cases of invasive fungal disease in SLE patients were only diagnosed post-mortem [7]. Furthermore, features of invasive fungal infection may overlap with findings of a SLE flare.

In contrast with superficial infections, such as oral thrush and vaginal candidiasis, which are far more common and readily treatable, invasive fungal diseases, such as Cryptococcal meningitis and Candidemia, are rare and life-threatening conditions. As invasive fungal infections are typically acquired from endogenous sources (such as from gastrointestinal flora or colonized skin through artificial lines) as well as environmental sources, a complex set of diagnostic criteria for invasive fungal disease must

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be used to distinguish these acute and devastating systemic infections from fungal colonization or superficial mucocutaneous infections. The recently revised consensus criteria for invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG 2008) provide case definitions for invasive fungal diseases to apply using rigorous mycological and clinical evidence [6].

In the absence of prospective population-based data describing the epidemiology of invasive fungal infections in SLE, we present a systematic review applying the EORTC/MSG 2008 criteria [6] to synthesize existing SLE literature, aiming to describe the epidemiologic patterns of infection frequency, risk factors for developing an invasive fungal infection, causative organisms for systemic infection, and clinical characteristics of the patients and their outcomes. This synthesis identifies characteristics of SLE patients who are most at risk of invasive fungal infections and highlights the possible clinical presentations of invasive fungal disease in SLE.

Methods

Search strategy

MEDLINE, Embase, and Web of Science were searched up to June 2013 using terms for the following 2 major themes: *Systemic lupus erythematosus* and *Invasive fungal disease* (search strategy shown in Appendix 1). These search terms were combined to create the initial list of abstracts for screening. Published English articles of adult cohorts, case series and reports, and autopsy studies documenting an invasive fungal infection in patients with SLE were included. Studies that met the American College of Rheumatology [8] and the retrospectively applied EORTC/MSG 2008 criteria [6] for SLE and invasive fungal disease were included.

Hand-searched literature consisted of those gathered from reference lists of included articles. Patients with substantial confounding comorbidities, such as HIV, solid-organ or hematologic transplants, and concurrent chemotherapy for malignancy, were excluded. Studies providing negligible clinical information about the case and in which patient demographics and comorbidities could not be ascertained, such as pathologic cases describing only specimens, were excluded. Two independent reviewers (L.R.W. and C.E.B.) reviewed all citations for inclusion ($\kappa = 0.87$). Disagreements were resolved by consensus and, where needed, an infectious diseases specialist (A.S.J.) was consulted. Authors were contacted to obtain individual patient data for case series reporting only summary data for measures of interest and/or to clarify ambiguous data.

Outcome classification

All cases were retrospectively classified according to the EORTC/MSG 2008 Guidelines [6] into proven, probable, or possible invasive fungal infections. A proven invasive fungal infection required culture or microscopic evidence of the organism from a normally sterile site, with the exception of disseminated cryptococcosis, which could be diagnosed by the detection of a cryptococcal antigen. A probable infection required the presence of a host factor, mycological evidence, and clinical findings (including imaging) specific to the disease entity. A possible infection was a case in which a host factor and a clinical criterion were present, but no mycological criteria were met [6]. In the interest of capturing cases most likely to be truly invasive infections, only cases retrospectively classified as proven or probable invasive fungal infections were included in the present study.

The diagnosis of endemic mycoses (dimorphic fungi) was divided into either proven or probable categories, as clinical and host factors are insufficiently specific to define possible infection [6]. A proven endemic mycosis required culture or microscopic evidence of the organism from the affected site or blood in a host with an illness consistent with endemic mycosis, although certain serological tests were also accepted in place of isolation of the organism. Probable endemic mycosis required the presence of a host factor, clinical picture consistent with endemic mycosis, and mycological evidence (including tests that may be less specific than those required for a diagnosis of proven endemic mycoses) [6].

Characteristics of invasive fungal disease

Clinical and microbiologic characteristics and outcomes were abstracted from each included case, such as symptoms and signs, recent or concurrent antibiotic use at infection presentation, laboratory results (for example, Hemoglobin (Hgb) count, leukocyte count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, alanine transaminase (ALT) levels), imaging results, method of diagnosis of invasive fungal infection (e.g., histology, culture, serological, or imaging), and the organisms and the sites from which they were isolated. Antifungal and other therapies used were also recorded. Outcomes, including mortality, post-mortem diagnosis, and other complications during the course of hospitalization were recorded.

SLE history

Demographic and SLE history recorded included age, sex, duration of SLE at infection presentation, other comorbidities, and SLE manifestations [renal, pulmonary, central nervous system (CNS), hematologic, immunologic, and other]. Where reported, the SLE disease activity index (SLEDAI) [9] or its modification, the SELENA-SLEDAI [10], and the SLE International Collaborating Clinics (SLICC) [11] damage index was captured. SLE treatment at the time of infection including corticosteroids, hydroxychloroquine, cytotoxic, and monoclonal antibody therapies were captured. Laboratory markers for SLE disease activity at the time of infection were also recorded including complement (C3 and C4), anti-double-stranded DNA antibody, and creatinine.

Statistical analysis

Extracted data was recorded and analyzed in Microsoft Office Excel® 2007. Measures of central tenancy were reported. Prevalence and incidence estimates were captured from cohorts that systematically captured all cases of invasive fungal infection in a defined SLE patient population. Due to the significant heterogeneity of the studies, no formal meta-analysis was attempted.

Results

Study characteristics

Of 3348 records returned from the search strategy, 182 studies from 35 countries were ultimately included (Fig.), detailing 393 total cases (252 females, 48 males, and 98 unreported sex), which met the SLE and the invasive fungal disease criteria for inclusion. Cases from historical and prospective cohorts, case reports, and case series were captured (Table 1). Of the 32 historical cohorts and 8 prospective cohorts, only 10 performed comparative analyses with a control group.

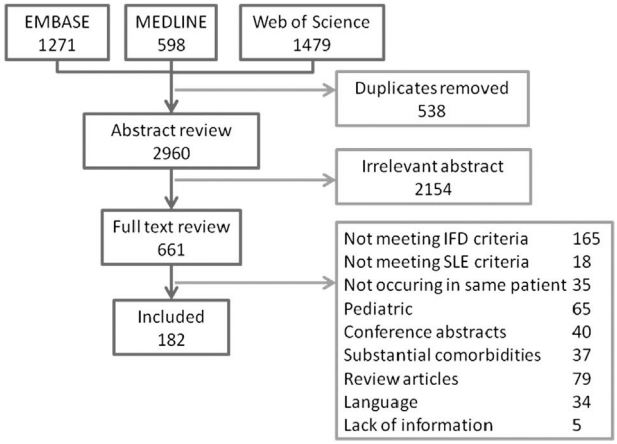

Fig. Selection process of included articles in the systematic review.

Prevalence of invasive fungal infections in cohort studies

Seven cohorts systematically captured invasive fungal infections in SLE inpatients. Of these, 6 reported an estimated prevalence of invasive fungal infections in 0.64–1.33% of SLE patients hospitalized for any cause (Table 2), while a single study from Mexico [7] reported a prevalence that was 3 fold higher (3.24%). A Canadian case–control study of SLE outpatients by Gladman et al. [12] reported invasive fungal disease meeting the inclusion criteria in 0.28% of the participants.

Clinical characteristics of SLE at invasive fungal infection diagnosis

Of 156 cases reporting SLE duration, invasive fungal infections occurred at a median of 2 years after SLE diagnosis (IQR: 0.5–7.1 years); 67 cases occurred within the first year (Table 3). In 15 cases, new-onset SLE was diagnosed concurrently with the infection. Most patients had active SLE at onset of infection with a median SELENA-SLEDAI of 11 (IQR: 7–18, $n = 103$), and 89% were on corticosteroids at presentation (232 of 261 where data was available). The median dose of prednisone equivalent was 30 mg daily (IQR: 10–60), with 71 (34%) patients on ≥ 60 mg/day. Overall, 29 patients had recently or concurrently received pulse IV corticosteroid. Over half were using immunosuppressant medications (117/222 patients), the most common being azathioprine (41 cases), recent or concurrent cyclophosphamide (37 cases), and mycophenolate mofetil (20 cases) (Table 3). Overall, 19 patients were on hydroxychloroquine, only 1 of whom was on hydroxychloroquine alone.

Although infrequently reported, hematologic and biochemical abnormalities at invasive fungal disease presentation were documented. Of 139 cases reporting leukocyte count at presentation, 40% ($n = 56$) of patients had leukopenia, 17% ($n = 24$) had leukocytosis, and 42% ($n = 59$) had a normal leukocyte count. Of 48 cases reporting creatinine, 67% ($n = 32$) had elevated creatinine levels with a median of 2.6 mg/dl (IQR: 1.25–5.12).

Characteristics of invasive fungal disease

Cryptococcal meningitis was the most common clinical syndrome reported, followed by candidemia, pulmonary aspergillosis, and disseminated fungal infections (Table 4). The most common endemic mycoses reported were coccidioidomycosis, followed by histoplasmosis, penicillosis, and blastomycosis, consistent with the known geographic distributions of each organism. A total of 56 patients with documented invasive fungal infections were found to have a co-infection with a bacterial or viral pathogen.

Antifungal treatment was specified in 217 cases. Prior to 1990, Amphotericin was used almost exclusively as the initial antifungal agent (27 of 30 treated patients), sometimes in combination with 5-flucytosine (11 cases). Fluconazole has also become increasingly used, mainly as combination or maintenance therapy for cryptococcal meningitis, since its introduction to market in 1990. Since the year 2000, a variety of newer antifungals has been successfully used as a first-line therapy, particularly voriconazole (used in 14 cases, 11 survived).

Treatments other than antifungal therapy were detailed in 135 cases: 71 of these were treated with antibacterial agents—20 for a documented bacterial co-infection and the remainder for empiric coverage for bacterial pathogens. Only 7 patients received empiric antifungal as well as antibacterial therapy.

Mortality

Fatal outcomes from invasive fungal diseases were reported in 161 of 316 cases. A trend of decreasing mortality rates over time was observed, from 85% in the 1960s to 34% in the 2010s. All 43 patients who did not receive antifungal therapy died, and in 44 cases, diagnosis of the infection was made only at autopsy. In the 8 cohort studies of invasive fungal infections in SLE, the mortality rates ranged from 25% to 70%, and the pooled mortality rate was 43% (32 of 74 patients), 19% of which were diagnosed post-mortem (6 of 32 deaths). The most common complications were sepsis, acute renal failure, respiratory failure, seizures, and coma.

Discussion

Our systematic review of the reported epidemiology, risk factors, clinical characteristics, and outcomes of invasive fungal infections in SLE reported in the medical literature, although not population-based

Table 1
Characteristics of studies included

Study characteristic	Number of studies	Total number of cases
Study type		
Case reports	127	131
Case series	12	63
Case control	1	1
Prospective cohorts	8	19
Retrospective cohorts	32	175
Other	2	4
Decade of publication		
1960–1969	8	13
1970–1979	13	16
1980–1989	22	38
1990–1999	42	63
2000–2009	68	165
2010–Present	29	98
Geographic region		
North America	72	107
South America	6	22
East Asia	47	183
Southeast Asia	11	26
South Asia	9	11
West Asia (Middle East)	5	5
Western Europe	16	23
Eastern Europe	1	1
Northern Europe	1	1
Southern Europe	9	9
Australia and New Zealand	4	4
North Africa	1	1
IFD diagnosis		
Proven cases		354
Probable cases		39

Table 2
Prevalence estimates of IFD in SLE and characteristics of studies systematically capturing IFD in SLE population

References	Study type	Country (city)	Total SLE cases	Cases of SLE + IFD	Study period (y)	Prevalence (%)	Incidence (%/y)
Chen et al. [18]	Retrospective cohort of IFD in SLE inpatients	Taiwan (Taoyuan)	2344	15	26	0.64	0.02
Fan et al. [19]	Retrospective cohort of IFD in SLE inpatients	China (Jinan)	1534	18	6	1.17	0.20
Gladman et al. [12]	Prospective nested case–control of infections in SLE outpatients	Canada (Toronto)	363	1[a]	5	0.28	0.06
Khalifa et al. [20]	Retrospective cohort of infections in SLE inpatients	Tunisia (Sousse)	75	1[a]	14	1.33	0.10
Kim et al. [21]	Retrospective cohort of IFD in SLE inpatients	South Korea (Seoul)	1155	12	15	1.04	0.07
Martinez-Martinez et al. [7]	Retrospective cohort of IFD in SLE inpatients	Mexico (San Luis Potosí)	309	10	7	3.24	0.46
Nishimaki et al. [22]	Retrospective cohort of infections in SLE inpatients, including autopsies	Japan (Fukushima)	132	1[a]	20	0.76	0.04
Weng et al. [23]	Retrospective cohort of IFD in SLE inpatients	Taiwan (Tainan)	2397	20[a]	21	0.83	0.04

[a] Gladman et al. identified 5 other cases of candida had unspecified sites, including mucocutaneous; Khalifa et al. identified 11 total candida infections including any site, for example mucocutaneous and 1 candida septicemia; Nishimaki et al. identified 3 other cases of esophageal candidiasis only, which does not meet the proven/probable IFD criteria; Weng et al. did not state the number of pediatric SLE patients. Prevalence estimate includes pediatric in both numerator (4 pediatric SLE-IFD cases) and denominator, but only adult cases were included in further analyses.

and incorporating historical data, suggests that invasive fungal disease contributes between 0.64% and 3.24% of hospital admissions for SLE. Most commonly, invasive fungal infections presented early in the disease course of SLE, associated with high disease activity and corticosteroid use. These infections resulted in significant mortality, and many were only diagnosed post-mortem.

Prevalence estimates of invasive fungal infections in SLE varied widely (between 0.64% and 3.24%), although most studies estimated invasive fungal infections in 0.64–1.33% of SLE inpatients. The study reporting the highest prevalence of invasive fungal infections also reported the highest proportion of post-mortem diagnoses (30%) [7], raising the possibility of underestimation due to undiagnosed fatal cases. Clinical differences in the underlying population, reporting bias, and variation in reporting standards of different countries likely also contributed to variation in prevalence estimates. The application of modern criteria to historical cases also limited the inclusion of cases, as necessary information under the current criteria may have been inaccessible to authors at the time. Prospective population-based studies examining invasive fungal infections in SLE inpatients and outpatients would greatly improve prevalence estimates.

Our study highlights the importance of disease control, as 86% of cases appeared to have clinically active SLE at presentation of invasive fungal disease as defined by the SLEDAI and a substantial proportion were on >60 mg prednisone equivalent daily. Although a comparative risk analysis could not be performed due to clinical heterogeneity, such a high proportion of patients with active SLE suggests that disease activity and corticosteroid use may be important risk factors predisposing to invasive fungal infections, as both impair cellular immunity [5]. The relatively early presentation of invasive fungal infections in SLE is also consistent with the known bimodal temporal pattern in SLE mortality [13] and is likely due to high disease activity and immunosuppression. This is a population with a high burden of disease and a precarious balance between immunosuppression and disease activity, both of which may have fatal consequences.

It was also noted that only a small proportion of patients in this study were on hydroxychloroquine, which is now considered a standard therapy in all SLE patients. Hydroxychloroquine use may improve disease control and/or prevent flares; thus, more potent immunosuppressants that increase the risk of invasive fungal disease were not required.

The diagnosis of invasive fungal infections may be complicated by the overlap of clinical characteristics with active SLE. Patients were

Table 3
Characteristics of systemic lupus (SLE) patients with invasive fungal disease (IFD)

Patient characteristic	Statistic	*n* (Total reported)
Demographics		
Males:females	47:248	295
Age at IFD onset (y)	35.8 (SD = 13.5)	264
Duration of SLE (y)	2, (IQR: 0.5–7)	156
No. within first year of diagnosis	67 (39%)	170
No. of concurrent IFD with first SLE flare	15 (9%)	163
Comorbidities		
Diabetes mellitus	23 (27%)	85
Tuberculosis	6 (13%)	48
Other infections	8 (13%)	64
SLE organ manifestations		
Renal	162 (87%)	186
CNS	20 (19%)	106
Pulmonary	28 (34%)	82
Hematologic	83 (67%)	124
Immunologic	86 (90%)	96
SLE characteristics		
SLEDAI at presentation	11 (IQR: 7–18)	103
No. of active SLE (SLEDAI $\geq$ 4)	135 (86%)	157
No. of corticosteroid use at IFD presentation	248 (90%)	277
Median corticosteroid dose (mg/day prednisone equivalent)	20 (IQR 10–50)	211
No. of high-dose corticosteroid ($\geq$60 mg/d)	72 (33%)	216
No. of concurrent/recent pulse corticosteroid	29 (21%)	137
Use of immunosuppressants and other agents		
Total no. of other immunosuppressants	117 (53%)	222
Azathioprine		
Cyclophosphamide (recent or concurrent)	41	
Mycophenolate mofetil	37	
Cyclosporine	20	
Mizoribine	8	
Rituximab	5	
Methotrexate	4	
6-Mercaptopurine	3	
Etanercept	2	
Interferon	1	
Methoxsalen	1	
Other agents	1	
Hyroxychloroquine	14	
Plasma exchange	2	

Statistics are reported as percentage, mean, and standard deviation (SD), or median and Interquartile range (IQR), depending on distribution of data.
Central nervous system (CNS), invasive fungal disease (IFD), systemic lupus erythematosus (SLE), and systemic lupus erythematosus disease activity index (SLEDAI)

Table 4
Organisms and documented sites implicated in invasive fungal infections in lupus patients

Genus	Total	Lung	CNS	Hematologic	ENT	Cardiovascular	Abdominal	Eye	Skin and soft tissues	Bone and joint	Lymphatic	Renal/urinary	Other solid organs	disseminated	Unreported
Candida spp.[a]	53	16		26		4	6		2	5		2	6	11	3
Cryptococcus spp.[b]	163	18	119	43		2	3	2	4	1	5	9	9	32	13
Rhodotorula glutinis	1		1	1										1	
Blastomyces dermititidis	1		1	1					1						
Coccidioides spp.[c]	12	8			1				1		1	1	4	3	
Histoplasma capsulatum	12	5	3	5	1				1		1	3	6	7	
Penicillium marneffei	16	3		4					1	1	3		1	3	
Aspergillus spp.[d]	57	39	12		2	8	3	1			2	6	6	12	5
Mucormycosis[e]	20	9	3	2	3	7	1			1		2	2	5	
Zygomycosis	3	1			1	2						1	1	2	
Xylohypha bantiana	1		2												
Ramichloridium mackenziei	1		1												
Pseudoallescheria boydii	3	2	1						2	1		1	2	2	
Organism unreported	118	4	6	2								1	1		33
Total infections	461	105	149	84	8	23	13	3	12	9	12	26	38	78	54

Each infection is enumerated separately when co-occurring in the same case. Shading represents relative frequency of the site and organism.

[a] *Candida*: mainly *albicans*, also includes *glabrata* [1], *krusei* [1], *parapsilos* [1], and *sake* [1].

[b] *Cryptococcus*: mainly *neoformans*, also includes *albidus* [1], *gattii* [1], and *laurentii* [1].

[c] *Coccidioides*: mainly *immitis* [9], also includes *posadasii* [1].

[d] *Aspergillus*: mainly *fumigatus*, also includes *terreus* [2] and *flavus* [1].

[e] Mucormycosis: includes *Mucor*, *Rhizopus*, and *Cunninghamella*.

far more likely to be leukopenic (40%) or have a normal leukocyte count (42%) than to have leukocytosis (17%), likely due to the immunological deficiencies of active SLE. Numerous studies reported attributing symptoms such as headache, hemoptysis, or seizures to active SLE, and a substantial proportion of patients received increased corticosteroid doses or pulse steroids prior to diagnosis of the infection, often with the result of brief improvement followed by dramatic worsening of symptoms [14–17]. Such overlap may also have contributed to a higher SLEDAI score and more apparently active disease. Clinical vigilance is crucial to detect this fatal complication, as invasive fungal infections may be superimposed on active SLE or difficult to distinguish from active SLE itself.

Although empiric antibacterial therapy tended to be started early, investigation and treatment of fungal disease was often significantly delayed despite clinical worsening. Increased index of suspicion for invasive fungal infections may shorten time to diagnosis and appropriate antifungal therapy and reduce mortality.

This systematic review confirms the high mortality and morbidity associated with invasive fungal infections in the reported literature. Overall, over half of patients with these infections died despite antifungal therapy during hospitalization, and a significant proportion were diagnosed post-mortem. Aside from the severity of such infections and already complicated condition of the patients, delays and limited availability in diagnosis and therapy were likely major contributing factors to the high mortality. However, the reported rates of mortality and post-mortem diagnoses appear to have decreased over the past 5 decades. A variety of factors may explain these trends, and factors such as reporting bias, publication bias, and secular trends in post-mortem examinations in general cannot be excluded as potential explanations. Nevertheless, mortality rates have decreased even when excluding invasive fungal diseases diagnosed on autopsy. Although a meta-regression could not be performed, this trend may be due to the broader variety of agents available for the management of SLE, the expanded armamentarium of antifungals that have become available, and, most importantly, less delay in diagnosing an potential invasive fungal infection. We are hopeful that with the improved clinician awareness, diagnostic and therapeutic options, and access to infectious disease consultation, the mortality and morbidity of invasive fungal disease in SLE will continue to decrease. Prospective controlled trials are needed to further elucidate the characteristics and risk factors of this complication, in light of the extensive advances in the management of both SLE and invasive fungal disease in the modern era.

Conclusion

Clinicians should maintain a high index of suspicion for invasive fungal infections in SLE, especially in a patient with high disease activity at early stages of disease or with significant corticosteroid use (high “net state of immunosuppression”). It is often difficult to distinguish the presentation of invasive fungal infections from active SLE, resulting in increased immunosuppression rather than appropriate antifungal treatment. Our study was limited by the uncontrolled retrospective design with bias towards more severe cases. In the modern era, with a broader armamentarium of immunosuppressive agents and biologics for the treatment of SLE and improved fungal diagnostics and antifungal agents, invasive fungal infections in SLE should be prospectively examined.

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Appendix A. Supporting Information

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.semarthrit.2014.06.001.

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