Gene 506 (2012) 184–187

Contents lists available at SciVerse ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Short Communication

Invasive fungal infection in patients with systemic lupus erythematosus: Experience from a single institute of Northern China

Yu-Chen Fan [a,*,1], Wen-Gang Li [b,1], Ming-Hua Zheng [c,1], Wei Gao [d], Yuan-Yuan Zhang [e], Li-Jun Song [f,**]

[a] Department of Hepatology, Qilu Hospital of Shandong University, Jinan, China
[b] Treatment & Research Center for Infectious Diseases, No. 302 Hospital of PLA, Beijing 100039, China
[c] Department of Infection and Liver Diseases, Liver Research Center, the First Affiliated Hospital of Wenzhou Medical College, Wenzhou, China
[d] Department of Clinical Laboratory, Hospital of Shandong University of TCM, Jinan 250012, China
[e] Department of Neurology, Jinan Central Hospital affiliated to Shandong University, Jinan, China
[f] Department of Rheumatology, Qilu Hospital of Shandong University, Jinan, China

ARTICLE INFO

Article history:
Accepted 19 June 2012
Available online 30 June 2012

Keywords:
Systemic lupus erythematosus
Invasive fungal infection
C reaction protein
Systemic lupus erythematosus disease activity
Risk factors

ABSTRACT

Invasive fungal infection (IFI) is a life-threatening infection occurring most often in patients with systemic lupus erythematosus (SLE) and few data has been reported in SLE patients particularly in China. This present study was aimed to determine IFI prevalence, associated risk factors and patterns of infection in Chinese SLE patients. A retrospective study was conducted in a single institute of Northern China from July 2004 and October 2010. Demographic characteristics, clinical and laboratory data, and mycological examinations were collected. Among 1534 patients included, 20 (1.6%) were diagnosed with IFI, of whom there were 18 females and 2 males with the average age of 35.4 ± 15.1 years old. Involved sites included nine lungs, six central nervous system and five disseminated cases. 6 of 20 IFIs cases (30%) were non-survivors including 2 lungs, 2 central nervous system and 2 disseminated cases. Compared with survivors, non-survivors had significantly higher equivalent prednisone doses, elevated level of serum C reactive protein (CRP), higher erythrocyte sedimentation rate (ESR), higher thrombocytopenia rate and higher systemic lupus erythematosus disease activity index (SLEDAI) score. These results strongly demonstrated that prednisone doses, CRP, ESR, thrombocytopenia and SLEDAI could be associated risk factors in the prognosis of SLE patients with IFI.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of multiple auto antibodies. The survival rate of SLE patients has been greatly improved due to the administration of glucocorticoid and other immunosuppressant agents. However, infection accompanied by long-term duration of glucocorticoid treatment remains a major risk factor to mortality of SLE patients (Gladman et al., 2002a; Juarez et al., 2003; Kim et al., 1999; Mok et al., 2000; Paton, 1997).

Invasive fungal infection (IFI) is a life-threatening infection occurring most often in SLE patients. IFI is mainly caused by opportunistic pathomycetes, including *candida*, *Aspergillus*, *Cryptococcus*, and so on. In the SLE patients, it is reported that the clinical use of glucocorticoid or other immunosuppressants, multiple antibiotics and steroid-induced diabetes always contributed to the dysfunction of immune response. And the dysfunction of immune cells including T cell, B cell and dendritic cell was demonstrated to promote SLE patients more susceptible for the occurrence of IFI (Nambiar et al., 2002; Nevzorova et al., 2006; Ramanujam et al., 2004; Reefman et al., 2007; Seta et al., 2002; Takeuchi, 2002; Traustadottir et al., 2002). Therefore, it is believed that the imbalancement of immune response of host be capable of increasing the risk for the incidence of IFI (Petri and Genovese, 1992).

Currently, SLE patients with IFI have seldom been documented over the past decades. In the regions of Taiwan and South Korea, high SLE disease activity has been reported to increase the incidence of IFI in SLE patients (Chen et al., 2007; Kim et al., 2009). These two retrospective reports also demonstrated that *Aspergillus* and *Cryptococcus* neoformans were the most common pathogenic microorganism (Chen et al., 2007; Kim et al., 2009). However, there are still limited data of IFI prevalence, associated risk factors and patterns of infection in SLE patients in Chinese mainland. In this retrospective study, demographic characteristics, clinical and laboratory data, and mycological examinations were collected.

Abbreviations: IFI, invasive fungal infection; SLE, systemic lupus erythematosus; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; SLEDAI, systemic lupus erythematosus disease activity index; EORTC/MSG, 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; ANA, antinuclear antibody; DM, diabetes mellitus.

* Correspondence to: Y. Fan, Department of Hepatology, Qilu Hospital of Shandong University, 107# Wenhua Xi Road, Jinan 250012, China.
** Correspondence to: L. Song, Department of Rheumatology, Qilu Hospital of Shandong University, Jinan 250012, China.
E-mail addresses: pyfanyuchen@yahoo.com.cn (Y.-C. Fan), slj_666@163.com (L.-J. Song).
[1] Yu-Chen Fan, Wen-Gang Li and Ming-Hua Zheng contributed equally to this work and should be co-first authors.

0378-1119/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.gene.2012.06.059

Furthermore, a comparison of survivors and non-survivors has also been performed to determine associated risk factors for mortality in SLE patients with IFI.

2. Patients and methods

2.1. Patients

A retrospective medical records review was performed in 1534 lupus patients who visited Department of Rheumatology, Qilu Hospital of Shandong University from July 2004 to October 2010. Twenty SLE hospitalized patients were definitely diagnosed with IFI and included in this present study. Included criteria of IFI were based on the updated revised definitions of 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) Consensus Group (De Pauw et al., 2008). The revised definitions retained the original classifications of "proven," "probable," and "possible" invasive fungal disease. The category of proven invasive fungal disease could apply to any patient, regardless of whether the patient was immunocompromised, whereas the probable and possible categories were proposed for immunocompromised patients only (De Pauw et al., 2008). The research protocol of the study was approved by the Ethics Committee of Qilu Hospital of Shandong University.

2.2. Clinical and laboratory data

The following patients data were collected: age; gender; clinical symptoms and signs; doses of glucocorticoid and accumulative quantities of other immunosuppressant agents administered prior to fungal infection; use of antibiotics prior to fungal infection; laboratory data such as blood routine test, serum complement, antinuclear antibody (ANA) and anti-dsDNA, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood sugar, Galactomannan antigen detection, β-D-glucan detection in serum; species and sites of fungal infection; imaging findings such as brain MRI or CT, chest CT and abdominal ultrasound. Individual disease activity assessment was quantified using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). The patients with SLEDAI-2K score > 5 were defined as active, while those patients with SLEDAI-2K <= 5 were classed as inactive (Gladman et al., 2002b).

2.3. Statistical analysis

The demographic features of patients were presented as mean and range. Descriptive data were expressed as the mean ± standard deviations and compared using independent Student's *t* –test. Categorical variables were compared by Chi-square test or the Fisher's exact test. *P* value of less than 0.05 was considered statistically significant. All the statistical analyses were performed using SPSS 13.0 software for Windows (SPSS Inc, Chicago, IL, USA).

3. Results

In this retrospective analysis, twenty cases with definitely diagnosis of IFI were identified according to included flowchart in Fig. 1. Totally, IFI patients accounted for a 1.6% incidence in all lupus patients. All the demographic characteristics of the SLE patients with IFI were shown in Table 1. Among the 20 IFI patients, 14 patients were diagnosed as "proven," 4 for "probable" and 2 for "possible." In total, 55% (11/20) of the patients had diabetes mellitus (DM), including 9 patients with steroid-induced diabetes mellitus. All the patients were ANA positive, and only 25% (5/20) were with positive anti-dsDNA antibody. There were 12 patients for leucopenia, 14 for anemia, and 12 for thrombocytopenia. 12 patients appeared as reduction of both C3 and C4, 2 patients simply showed the reduction of C3. The means of CRP, ESR and SLEDAI were all above the normal levels.

As shown in Table 2, the most common species were *Aspergillus* (33.33%) and *Cryptococcus neoformans* (33.33%), followed by *Candida albicans* (22.22%). Involved sites included nine lungs, six central nervous system and five disseminated cases. *Cryptococcus neoformans* were found only in CSF and *Candida glabrata* and *Candida krusei* were only in blood. 2 patients were considered as possible IFI based on prolonged use of corticosteroids and the presence of cavity and air-crescent signs on chest CT without mycological evidence. Due to

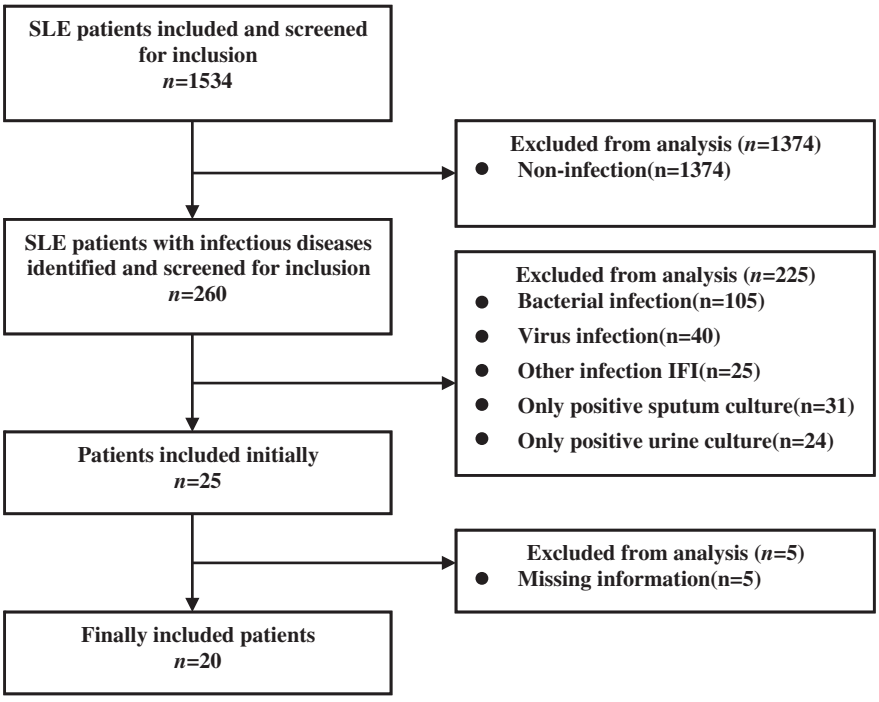

Fig. 1. Flowchart of the included and excluded patients.