Clinical and Immunogenetic Factors Associated with Pneumonia in Patients with Systemic Lupus Erythematosus: A Case-Control Study

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ABSTRACT. ***Objective.*** To determine the incidence of pneumonia and associated factors in a single-center systemic lupus erythematosus (SLE) cohort.

Methods. We included all our SLE patients [1997 American College of Rheumatology (ACR) criteria] with ≥ 1 pneumonia event, and 196 age and sex-matched SLE controls with no pneumonia events. Cumulative clinical data, weighted Systemic Lupus International Collaborating Clinics/ACR damage index (wSLICC/ACR-DI), comorbidities, and risk factors for pneumonia were retrospectively collected. The standardized incidence ratio (SIR) of pneumonia was estimated. Polymorphisms at genes coding for mannose binding lectin (MBL), MBL-associated serine protease 2, Fc-gamma receptors, and surfactant proteins A1, A2, and D were determined, and their potential association with pneumonia was analyzed. Patients with and without pneumonia were compared using a multivariate logistic regression model for adjustment of pneumonia-associated factors.

Results. Thirty-six of 232 patients with SLE had experienced ≥ 1 pneumonia event. SIR for pneumonia was 5.1 (95% CI 3.5–7.4; $p < 0.0001$). Excluding patients receiving immunosuppressive therapy at the time of pneumonia (13%), associations were found for Katz Severity Index (KSI) ($p = 0.016$), wSLICC/ACR-DI ($p = 0.044$), number of SLE criteria ($p = 0.005$), hospital admissions ($p < 0.001$), FCGR2A HH genotype ($p = 0.03$), previous use of immunosuppressive therapy ($p = 0.049$), cutaneous ulcers ($p < 0.001$), and vasculitis ($p = 0.008$) in bivariate analyses. In the multivariate analysis adjusted to previous immunosuppressive treatment, only KSI and FCGR2A HH genotype remained statistically significant ($p = 0.05$ and $p = 0.03$, respectively).

Conclusion. The incidence of pneumonia in patients with SLE is higher than that in the general population, and particularly high in severe SLE, regardless of immunosuppressive therapy. The HH genetic variant of FCGR2A appears to predispose patients with SLE to pneumonia. (J Rheumatol First Release Aug 1 2014; doi:10.3899/jrheum131470)

Key Indexing Terms:
LUPUS PNEUMONIA IMMUNOGENETICS

Infection is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE), and up to half of all patients with SLE develop major infections during the course of their disease[1,2]. Retrospective studies have concluded that previous severe infectious events are associated to SLE-related mortality, even after adjustment for use of immunosuppressive therapy[3,4,5].

Pneumonia is not only the most common severe infection in SLE, but also the most common form of SLE pulmonary involvement and, together with bacteremia, is

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responsible for most hospitalizations due to infection[6,7]. Factors predisposing patients with SLE to pneumonia remain largely elusive, and only a few studies have addressed this topic[8,9]. Immunosuppression resulting from therapy, comorbidities, and the disease itself increases the susceptibility of patients to severe infections, but the relative contribution of each of these factors is not well known. Several lines of evidence suggest that the susceptibility to and the severity and outcome of respiratory infections in the general population are largely inherited[10,11], and particularly related to opsonization and phagocytosis disorders[12]. Consistently, some functional genetic polymorphisms of innate immune response-related proteins have been associated with susceptibility to infection, particularly pneumonia, in both patients with SLE[13,14,15] and the general population[16].

To analyze possible risk factors for pneumonia, clinical and demographic variables, and variability in opsonization-related genes, were evaluated in a case-control study in a well characterized single-center SLE cohort.

MATERIALS AND METHODS

All our adult patients with SLE (American College of Rheumatology 1997 modified criteria) with any pneumonia event (P-SLE) at any point in their lives, and 196 control patients with SLE (NP-SLE; followed in our rheumatology ward and with data available from at least 2 visits; 88.9% of all patients) joined our single-center cohort between 1988 and 2009, and were included in this case-control study. Cumulative clinical data, laboratory assessments, treatments, and traditional risk factors for pneumonia [tobacco use, alcohol abuse, chronic obstructive pulmonary disease (COPD), cancer, renal insufficiency, liver disease, diabetes, heart failure and other comorbidities] were retrospectively collected in a blinded manner, with regard to patients' genotypes (data updated at last available visit, including death or loss to followup).

The Katz Severity Index (KSI)[17] and Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (weighted version; wSLICC/ACR-DI) were calculated.

We defined pneumonia as a consistent clinical picture, with alveolar opacities on chest radiograph, with no alternative explanation and resolution with antimicrobial therapy. Microbiological confirmation was required in all cases of poor outcome. Recording of immunosuppressant drug use included the following: azathioprine, methotrexate, cyclosporine, cyclophosphamide, biological agents, and mycophenolate.

Genotyping. Genotyping was carried out for Spanish patients only, as follows. Variants at exon 1 of the gene coding for mannose binding lectin (MBL), and alleles B (rs1800450), C (rs1800451), and D (rs5030737) (termed O alleles — A being the wild-type allele), and the X variant (rs7096206) of promoter allele were determined by polymerase chain reaction with restriction fragment-length polymorphism (PCR-RFLP), single-sequence polymorphism (PCR-SSP), or site-directed mutagenesis (PCR-SDM) as described[18,19,20]. The presence of the promoter allele X has an important downregulating effect, and O/O or XA/O genotypes are considered low-producer MBL genotypes[18]. MBL-associated serine protease (MASP-2) deficiency due to the D105G (rs72550870) mutation was assessed by PCR-RFLP as described[20]. Functional genotypes affecting immunoglobulin (Ig) G subclasses binding Fc receptors *FCGR2A*-H131R [rs1801274; detected using allele-specific restriction enzyme digestion (ASRED)], *FCGR3A*-V158F (rs396991; by real-time PCR), and *FCGR3B*-NA1/NA2 were analyzed as described (by PCR-SSP)[21,22]. The gene deletion responsible for C2 deficiency of type I human complement (28-bp deletion) was also analyzed with minor modifications to described procedures[23].

Functional missense polymorphism at surfactant protein genes *SFTPA1* (rs1059047; rs1136450; rs4253527), *SFTPA2* (rs105904, rs17886395, rs4253527), and *SFTPD* (rs721917) (determined by PCR-RFLP and PCR-SSP) and haplotype analysis were performed as described[24,25].

All these genetic studies were not originally designed for evaluation of pneumonia in SLE, but based on previous evidence of association with infection in SLE and on our own data in the general population, we included these data in the study.

Statistical analysis. The following descriptive statistics were used: means, medians or proportions, and lower and upper quartiles. Differences were analyzed using Pearson 2 or Fisher exact tests, as appropriate, and Student t-tests or Wilcoxon tests were used for qualitative variables. Odds ratios and corresponding 95% confidence intervals and p values were obtained. Significance was defined as $p < 0.05$. The standardized annual incidence ratio (SIR) of pneumonia was calculated by comparison with the Spanish population. A multivariate logistic regression model was used for adjustment of possible pneumonia-associated factors. All variables with p values < 0.20 in the bivariate analyses were entered into multivariate analysis using stepwise methods.

SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all analyses.

All procedures were in compliance with the Declaration of Helsinki and principles of good clinical practice. The institutional review board of Doctor Negrín Hospital approved the study protocol. Informed consent was obtained for genetic analyses.

RESULTS

The mean age of the total population was 45 years (range 13–84 yrs) and 92% were women. The mean age at diagnosis of SLE was 31 years (range 24–40) and mean age at SLE onset was 29 years (range 21–36). The mean duration of disease (± SD) was 12.7 ± 8.4 years (range 0–42, median 11.7 yrs, 25th–75th percentiles 6.1–18.9), and there were no differences between P-SLE (12.8 ± 8.9) and NP-SLE (12.7 ± 8.3) ($p = 0.926$). Mean length of followup was 7.3 ± 5.7 years (range 0–21.2, median 6.7 yrs, 25th–75th percentiles 2.2–11.5), with no differences between P-SLE (8.1 ± 6.0) and NP-SLE (7.2 ± 5.7) ($p = 0.397$). A total of 52 patients (23.1%) had class III or IV (World Health Organization) lupus nephritis; 5 patients had ever undergone dialysis, and only 1 needed a kidney transplant. Eighty-two percent of patients had low C3 or C4, and 48% had had leukopenia at some point. A total of 36 (15%) patients had had 1 or more episodes of pneumonia, with a total of 41 pneumonia events throughout life; 9 patients had had pneumonia before onset of SLE. Pneumonia was severe (intensive care admission or death) in 5 patients, after SLE onset in all cases. The causal agent had been identified in 8 (19.5%) of the 41 pneumonia cases. Regarding SLE-related treatment, 58% of patients had received steroids, 16% of them at high doses, and 44% had received immunosuppressant drugs at any time. Remarkably, only 6 patients (13%, 22% considering only pneumonia events after SLE diagnosis) were receiving immunosuppressive therapy at the time of pneumonia. Only 3 of the 36 P-SLE patients had received antipneumococcal vaccine before their first

pneumonia event. According to Spanish general population data[26], the estimated annual SIR for pneumonia in our SLE patients was 5.1 (95% CI 3.5–7.4; p < 0.0001). Twenty-three pneumonia events occurred in women within the age range 15–39 years (SIR 8.2; 95% CI 5.1–12.6). Interestingly, when only patients with pneumonia before SLE onset were considered, numerically, we also found more pneumonia episodes than expected, but this difference did not achieve statistical significance (SIR 1.7; 95% CI 0.6-3.6).

In bivariate analyses, in an attempt to separate immunosuppressive therapy use from SLE severity, we excluded patients receiving immunosuppressant drugs at the time of pneumonia or up to 2 months before (n = 6). No differences were found between P-SLE and NP-SLE in age (45 ± 13 vs 46 ± 15 yrs; p = 0.65), sex, or age at SLE onset (30.4 ± 12 vs 31.6 ± 17 yrs; p = 0.77). No differences were observed in SLE duration, median duration of followup, or classical pneumonia risk factors, except for the incidence of COPD (2 patients among P-SLE vs none in NP-SLE; p = 0.017). Pneumonia-associated variables with p values < 0.2 the bivariate analysis are shown in Table 1. Regarding KSI values, the association with pneumonia remained significant when patients with pneumonia events before SLE onset (n = 9) were excluded (OR 1.2, 95% CI 1.03–1.38; p = 0.016). Using KSI ≥ 3 as a cutoff point, the best KSI cutoff for mortality in our cohort (unpublished data), the OR of the association between previous pneumonia and KSI was 3.8 (95% CI 1.5–9.8; p = 0.003). A history of pneumonia was also associated with other severity markers: wSLICC/ACR-DI (p = 0.044), number of SLE criteria (p = 0.005), and number of SLE-related hospital admissions (p < 0.001) in the bivariate analyses. We also found associations with the use of immunosuppressant drugs at any time (OR 2.2, 95% CI 1.0–4.9; p = 0.049), cutaneous ulcers (OR 6.7, 95% CI 2.1–21; p < 0.001), and vasculitis (OR 3, 95% CI 1.3–7.2; p = 0.008) (Table 1).

Immunogenetic results. None of the analyzed single-nucleotide polymorphisms showed a significant deviation from Hardy-Weinberg equilibrium in SLE patients or controls. The *FCGR2A* R/R genotype was overrepresented in SLE patients analyzed for these variants compared with our previously reported group of healthy controls[27] (35.6% vs 25.3%; p = 0.0053), but this association did not remain significant after correction for multiple comparisons. The frequencies of other genetic variants were similar in SLE patients and in controls (data not shown). We compared genetic variants at *MBL2*, *MASP2*, *FCGR2A*, *FCGR3A*, *FCGR3B*, *SFTPA1*, *SFTPA2*, *SFTPD*, and *C2* between P-SLE and NP-SLE patients. Only the *FCGR2A* HH genotype was increased in P-SLE patients compared with NP-SLE patients (OR 2.9, 95% CI 1.09–7.68; p = 0.03). No association between *FCGR3A* 158VF or *FCGR3B* NA1/NA2 and susceptibility to pneumonia was found, and no linkage disequilibrium (LD) of *FCGR2A* 131H/R with *FCGR3A* 158 VF or *FCGR3B* NA1/NA2 was observed (data not shown). Similarly, no LD at these variants had been observed previously in healthy controls from our population[27]. We observed no association with the other genetic variants analyzed in our study.

Multiple regression analysis. A stepwise multivariate analysis including variables with p ≤ 0.2 the bivariate analyses showed that the *FCGR2A* HH genotype was an independent factor for susceptibility to pneumonia in our

Table 1. Variables associated with pneumonia with p < 0.2 in bivariate analysis.

	No Pneumonia, n = 196 (%)	≥ 1 Pneumonia[a], n = 30 (%)	OR (95% CI)	p
Cutaneous ulcers, n (%)	7 (4)	6 (20)	6.7 (2.1–21)	< 0.001
Hospitalization for non-pneumonia infections, n (%)	43 (22)	11 (37)	2 (0.9–4.6)	0.087
Major organ involvement, n (%)	101 (52)	18 (60)	1.4 (0.6–3)	0.18
Vasculitis, n (%)	27 (14)	10 (33)	3 (1.3–7.2)	0.008
SLE pneumonitis	9 (5)	4 (13.3)	3.2 (0.9–11)	0.077
No. SLE criteria, mean ± SD	5.8 ± 1.5	6.7 ± 1.5	1.1–1.8	0.005
Weighted SDI, mean ± SD	3.1 ± 5	4.2 ± 4.3	1.04 (0.1–1.1)	0.044
Katz Severity Index, mean ± SD	3.4 ± 2.2	4.3 ± 1.2	1.2 (1–1.4)	0.016
Katz Severity Index ≥ 3, n (%)	100 (51)	24 (80)	3.8 (1.5–9.8)	0.003
Hospitalization for SLE, n (%)	123 (63)	29 (97)	17 (2.4–130)	< 0.001
Alcohol, n (%)	8 (4)	3 (10)	2.6 (0.6–10.3)	0.17
Chronic obstructive pulmonary disease, n (%)	0	2 (6)	—	0.017
Death from SLE, n (%)	9 (5)	4 (13)	3.2 (0.9–11.1)	0.077
Immunosuppressants use at any time, n (%)	79 (40)	23 (60)	2.2 (1–4.9)	0.049
Cyclophosphamide use at any time, n (%)	57 (29)	13 (43)	1.9 (0.85–4)	0.116
Corticosteroids (high doses), n (%)	47 (24)	11 (39)	2 (0.9–4.6)	0.087
FCGR2A HH genotype (n = 158), n (%)	24 (16)	10 (33.3)	2.9 (1.09–7.68)	0.03

[a]Pneumonia without immunosuppressant use at the time of the event. SLE: systemic lupus erythematosus; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

patients (OR 3.0, 95% CI 1.1–8.1; p = 0.03; Table 2). The OR for *FCGR2A* HH did not change appreciably when patients receiving immunosuppressant drugs at the time of the pneumonia event were added to the model. Only in this last model did KSI ≥ 3 remain significantly associated with pneumonia (Table 2). Further, these results did not change when patients treated with doses of corticosteroids ≥ 30 mg at the time of pneumonia (n = 2) were also excluded (data not shown).

DISCUSSION

Our study confirms a substantially elevated SIR of pneumonia in patients with SLE, consistent with previous studies[8,28], and even higher in female patients in the age range 15–39 years. Our data also suggest that the increased risk of pneumonia might precede the diagnosis of SLE, this suggesting the presence of genetic factors that might predispose to both infection and SLE. In addition, we identified several clinical features that appeared to be associated with the occurrence of one or more pneumonia events in our SLE population-based cohort. It is well known that the use of immunosuppressive therapy in SLE carries a significant risk for infection[29], but certain data suggest that patients with SLE may also have intrinsic defects in innate and adaptive immune responses predisposing patients to infection. The influence of these potential defects on clinical infection is less clear. Deficiencies of the complement system might be a possible cause. An impaired C3b/iC3b deposition in *Streptococcus pneumoniae* has been observed in serum samples from patients with SLE[30]. No C2 deficiency in the classical complement pathway, the most common genetic complement defect in the European population, was observed among our patients. In addition, no primary C3 or C4 homozygous deficiencies were suspected based on C3 and C4 level, and no differences in the prevalence of hypocomplementemia were observed between patients with and those without pneumonia. Of interest, most patients in our study were not receiving immunosuppressive treatment at the time of the pneumonia event. This contrasts with data from Kinder, *et al*, who reported that 50% of cases were on immunosuppressive therapy at the time of the pneumonia event, but comparison between these 2 studies is difficult because, among other reasons, the authors used a slightly different case definition of pneumonia[8]. Our data reinforce the role of immune disturbances of lupus itself (probably inherited), and/or genetic variation in components of the immune system in the predisposition to infection.

In addition to KSI, a number of variables associated with history of pneumonia in the bivariate analysis are, in fact, SLE severity-related factors, e.g., hospitalization due to SLE, wSLICC/ACR-DI, and SLE-related death. Accordingly, another case-control study also found an association between pneumonia and SLICC/ACR-DI, known to be strongly related to mortality in SLE[9]. However, the relationship of SLE to severity and infection has not been fully investigated, and no studies have used a specific severity index for this purpose. We found an association between the history of pneumonia and the KSI-estimated severity of SLE. In an attempt to separate SLE severity from use of immunosuppressive therapy, we included in the analysis only those patients with pneumonia who were not taking immunosuppressant drugs at the time of the event; with this method, KSI data showed a strong trend toward association with pneumonia. In this respect, it is notable that previous studies showed that serious but nonfatal infections predicted a decreased overall survival of patients with SLE[31,32]. Interestingly, pulmonary infiltrates and/or recurrent pneumonias were associated with increased risk of developing lymphoma in patients with SLE in at least 1 study[33], perhaps indicating a more severe immunoregulation defect in this type of patient.

Thus, more severe disease could mean a more significant defect in immune regulation, resulting in both severe infectious events and an increased risk of lymphoma.

We do not have a good explanation for the association between pneumonia, cutaneous ulcers, and vasculitis; the possibility of chance associations in relation to the multiple comparisons in our analysis cannot be ruled out. Alternatively, cutaneous ulceration might be a separate marker of more severe disease. Supporting this hypothesis, we have found an association between cutaneous ulcers, vasculitis, and SLE mortality in our own cohort[34].

Only a few studies have evaluated the role of genetic variability at genes involved in immune response in relation to susceptibility to pneumonia in patients with SLE[8,15].

Table 2. FCGR2A HH genotype was an independent factor for susceptibility to pneumonia in patients with systemic lupus erythematosus (SLE) on multivariable analysis.

	SLE Patients with Pneumonia without Immunosuppressant Therapy vs Non-pneumonia SLE Patients (N = 158)		SLE Patients with Pneumonia vs Non-pneumonia SLE Patients (N = 163)	
	p	OR (95% CI)	p	OR (95% CI)
HH	0.03	3.01 (1.11–8.15)	0.017	3.08 (1.25–7.76)
KSI	0.058	2.64 (0.97–7.24)	0.034	2.76 (1.08–7.03)

HH: *FCGR2A* HH genotype; KSI: Katz Severity Index ≥ 3.

MBL deficiency due to the presence of low or nonproductive alleles was reported to be associated with development of pneumonia in patients with SLE[15], but the role of MBL deficiency in susceptibility to infection remains controversial. Indeed, no association of MBL-deficient alleles or genotypes with pneumonia was observed in our study, or in a previous study[8]. Our results are also in agreement with our previous studies showing no association between MBL or MASP-2 deficiency and susceptibility to community-acquired pneumonia, particularly *Pneumococcus*, in the general population[19,20,35]. Our study was underpowered to detect an association between MBL deficiency and pneumonia, with 80% power to detect a minimum OR of 3.37 for XO + OO genotypes in this comparison.

We found an association between homozygosity for the *FCGR2A*-H131 variant and the development of pneumonia in our patients. This association remained significant in multivariate analysis.

An association between *FCGR2A*-H131 homozygosity and susceptibility to bacteremic pneumococcal pneumonia in the general population was previously observed by our group[27]. In addition, when data from Kinder, *et al*[8] are analyzed, a significantly higher frequency of *FCGR2A* H131 homozygosity emerges in SLE patients with pneumonia, compared to patients without pneumonia.

This finding might make sense from a biologic point of view, because presence of the H131 allele causes a decrease in the ability of the receptor IIa for the Fc portion of immunoglobulin G (FcγRIIa) to bind C-reactive protein (CRP), which preferentially binds to the isoform encoded by the R131 allele[36,37,38]. Recent studies indicated that CRP plays a key role in the innate immune system by opsonizing capsulated bacteria, particularly *S. pneumoniae*[39,40]. CRP binds to polysaccharides present on the cell wall of *S. pneumoniae* and other bacteria, and is recognized by Fcγ-receptors (FcγR) with affinity levels similar to those observed among isoforms of IgG[41]. Indeed, the major receptor for CRP on leukocytes is FcγRIIa[42]. CRP binding to FcγR on leukocytes promotes phagocytosis and cytokine synthesis[43]. Thus, our results are in accord with recent experimental data from pulmonary infection models that suggest that the innate recognition of *S. pneumoniae* by CRP protects against infection and improves survival through FcγR-dependent uptake of CRP-opsonized bacteria[44]. Homozygosity for the *FCGR2A-R* allele has been found to predispose to SLE[45]. The rationale for such an association was suggested to be a different ability to bind IgG2 of the FCγRIIa H and R variants. FCγRIIa expressed in phagocytic cells is the only FCγR capable of efficiently interacting with IgG2, a poor activator of the classical complement pathway; hence, FCγRIIa would be essential for handling IgG2 immune complexes. However, only the FCγRIIa-H variant is able to efficiently recognize IgG2. Our data suggest that, probably due to the different affinity levels for IgG2 and CRP of the FCγRIIa R and H variants, the *FCGR2A* H/R polymorphism may play a dual and opposing role in susceptibility to SLE and in the risk of development of pneumonia in patients with SLE.

Our data are in apparent contrast with those from Yee, *et al*[14]. In their small case-series study, 4 of 5 SLE patients with severe invasive pneumococcal infections were determined to be homozygous for the *FCGR2A* R131 allele. In our cohort, only a few patients (n = 5) had had severe pneumonia, as defined by intensive care unit admission or death, precluding further analyses on this topic.

Our study has some potential limitations. The retrospective design limited the number of covariates we could examine. Some data had not been collected at the time of the pneumonia event, precluding a cause-effect analysis. Although patients had a wide range of duration of followup, potentially leading to misclassification of patients who will develop pneumonia at a later date, the median disease duration was 12 years, allowing a substantial period of time for development of pneumonia. Further, the length of followup did not differ between patients and controls. Sample size is a further limitation of our study, and larger studies are necessary to confirm these results.

The low prevalence of classic risk factors for pneumonia in our study did not allow firm conclusions on the relative importance of comorbidities, such as COPD or renal insufficiency, as risk factors for pneumonia in SLE. However, their low prevalence suggests that comorbidities have little clinical relevance as risk factors for pneumonia in SLE.

Microbiological confirmation of diagnosis was documented in only 8 cases (19.5%). This low rate of etiologic diagnoses could be explained by a tendency to treat patients with antibiotics early and aggressively when a severe infection is suspected, which would entail a low performance of cultures. Nevertheless, this result does not differ significantly from data in other reports, which range from 10% to 71.5% for etiological diagnosis of pneumonia cases in SLE[8,46]. On the other hand, the cumulative incidence of acute lupus pneumonitis in our cohort was 4% (unpublished data), a rate very close to those reported in recent literature[47], suggesting a low probability of misclassification of pneumonia events in this study.

The incidence of pneumonia in patients with SLE is substantially higher compared with that of the general population. Certain genetic variants of *FCGR2A* appear to predispose SLE patients to pneumonia. Pneumonia is more frequent in patients with severe SLE, and this predisposition appears to be to some extent independent of the use of immunosuppressive therapy. As suggested by current literature, infections, pneumonia in our study, might be a severity marker of SLE.

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