Predictive Factors for Symptomatic Osteonecrosis in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To analyze predictive factors for the development of osteonecrosis (ON) in a large cohort of patients with systemic lupus erythematosus (SLE) followed in a single center.

Methods. A nested matched case control design was used. Patients with SLE who developed ON during followup were identified from the University of Toronto Lupus Clinic database. The diagnosis of ON was confirmed by either radiographs, bone scans, tomograms, or magnetic resonance imaging. A comparison group of patients with SLE without ON was selected from the same database, matched by year of birth, sex, and year of entry to the clinic to the patients with ON. Clinical, laboratory, and therapeutic factors thought to be relevant to the development of ON were compared between the 2 groups.

Results. Seventy patients with SLE developed ON in the course of followup at the clinic. In univariate analysis, arthritis was the only clinical feature predictive of the development of ON. Use of glucocorticosteroid therapy, dose and duration, as well as Cushingoid appearance and cytotoxic therapy were also predictive for the development of ON. Multivariate analysis revealed that glucocorticosteroid use, the presence of arthritis, and the use of cytotoxic medications remained significant.

Conclusion. Glucocorticosteroid therapy, the presence of arthritis, and use of cytotoxic medication are independent risk factors for development of ON in patients with SLE. (J Rheumatol 2001; 28:761–5)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS OSTEONECROSIS PROGNOSIS OUTCOMES

Osteonecrosis (ON) is a common complication in systemic lupus erythematosus (SLE). It was initially described by Dubois and Cozen in 11 of 400 patients with SLE[1]. They concluded that SLE led to the ON and that there was no association with steroid therapy. Subsequent reports describe an occurrence of ON in 5–40% of patients with SLE[2-11]. Symptomatic ON occurs in 10–12% of patients with SLE. Higher prevalences have been reported in series that used magnetic resonance imaging (MRI) for its detection[6].

Studies to date have included small numbers of patients, varying from 7 to 40 per study. Several factors, including steroid therapy, presence of Raynaud's phenomenon, vasculitis, myositis, and coagulation abnormalities have been reported to be associated with the development of ON in SLE. However, these factors have not been found consistently, possibly because of small sample size and low power.

We analyzed predictive factors for the development of ON in a large cohort of patients with SLE.

MATERIALS AND METHODS

University of Toronto Lupus Clinic cohort. A total of 744 patients with SLE had been registered and followed at the University of Toronto Lupus Clinic between 1970 and 1995. The demographics for this patient cohort have been described[12]. Patients are followed at the Clinic at 2–6 mo intervals. At each visit a complete history and physical and laboratory evaluations are carried out, including a history of ON and appropriate radiographs. All information collected on these patients is entered into a database.

Patients with ON. A search of the lupus clinic database identified 70 patients who developed ON during followup at the clinic. The diagnosis of ON was suspected clinically and confirmed by radiographic evaluation. A modification of the Marcus and Enneking staging system was used for the staging of ON by radiographs[13]. We previously demonstrated that this method was reliable for both reading the actual radiographs of ON of the hip in SLE and interpreting the radiologists' reports[13]. According to the modification, the following grades are recognized: Stage I — normal; Stage II — mixed necrosis and osteopenia; Stage III — a subchondral lucency, the crescent sign; Stage IV — collapse of the femoral head, no acetabular

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changes; Stage V — joint space narrowing and changes on either the femoral side or the acetabular side, with osteophytes, cysts, and sclerosis; Stage VI — advanced degenerative changes, defined as changes so severe that the original disease was unrecognizable. If radiographs were normal, but the clinical suspicion still present, other imaging techniques such as bone scans, tomograms, or MRI were utilized.

Control group. We used a nested, matched, case control study design. For each patient with ON, a control was chosen from the same database matched for year of birth, sex, and year of entry to the clinic. If more than one control was identified, the one with the closest year of entry and year of birth was selected. These controls had no evidence of symptomatic ON throughout their followup in the clinic.

Predictive factors. Clinical and laboratory variables as well as therapies previously reported to be associated with ON or considered to be causative of ON were considered as predictive factors. These included the following clinical variables: the degree of disease activity at first assessment as measured by the SLE Disease Activity Index (SLEDAI), a validated measure of disease activity[14], and the presence of arthritis, neuropsychiatric lupus, renal lupus, vasculitis, Raynaud's phenomenon, thrombophlebitis, thrombosis (venous or arterial), or livedo reticularis at any time prior to the diagnosis of ON. Therapeutic variables included the use, dosage, and duration of corticosteroids and cytotoxic drugs. Laboratory features included elevated partial thromboplastin time (PTT), anticardiolipin antibodies (aCL), positive Coombs' test, elevated cholesterol, and elevated triglycerides.

Statistical analysis. Simple statistics were calculated for demographic information. Preliminary analysis included the screening of continuous variables for colinearity and categorical variables for extremely high agreement. Initially, univariate conditional logistic regression followed by multiple conditional logistic regression[15,16] for matched data was used to determine the predictors of ON. Backward elimination, stepwise selection, and best subset selection methods were used in choosing variables to determine the best fitting logistic regression model. The threshold for entry of variables into the model for the stepwise procedure was $p \leq 0.10$, and $p > 0.05$ for removal of variables from the model in the stepwise and backward procedures. The odds ratio estimates (based on the cross classification of members within pairs), their likelihood-ratio type p values, and 95% confidence intervals were reported. All clinically relevant variables and appropriate first order interaction terms were investigated. To determine the adequacy of the fitted model and leverage of individual observations, various residual and influence statistics were examined. All statistics were executed by SAS® software for Windows® version 7.0.

RESULTS

Of the 744 patients recorded in the lupus clinic database, 95 were documented with sustained ON. Of those, 25 presented to the clinic with known ON and were therefore excluded from this study because of missing data on applicable predictive factors. Seventy patients (59 women and 11 men) developed ON after entering the clinic and were included in the study. These study patients were mostly Caucasian with a mean age at diagnosis of 29.8 years and a mean disease duration of 7.9 years at the time of diagnosis of ON (Table 1). The control group was selected from the same cohort and was matched to the patient group in their sex and ethnicity as well as in the degree of disease activity at presentation (Table 1).

One hundred and fifty-three joints were affected by ON in the 70 study patients (Table 2). Forty-seven patients had ON of the hip, often in a bilateral distribution. Twenty-six patients had ON of the knee, 12 with bilateral involvement. Of the 70 patients, 22 had a single joint affected, 31 had 2 joints, 9 had 3 joints, 6 had 4 joints, and one each had 8 and 10 joints affected by ON.

Table 1. Demographics for patients with ON and controls.

Feature	Patients with ON	Controls
n	70	70
Female/male	59/11	59/11
Caucasian/Black/Other	56/7/7	58/4/8
Age at diagnosis of SLE*	29.8 (8.8–55.0)	30.9 (10.3–62.0)
Age at study*	37.7 (17.2–66.4)	38.5 (16.3–74.8)
Disease duration at study*	7.9 (0.3–33.2)	7.5 (0.3–23.5)
Duration of followup at study*	5.2 (0.0–19.4)	5.2 (0.0–19.6)
SLEDAI score at presentation**	13.7 (10.5; 0–51)	11.2 (10; 0–56)
SLEDAI score at study**	6.4 (4; 0–32)	6.5 (4; 0–24)

*Mean (range) in years; **mean (median; range).
SLEDAI: disease activity index.

Table 2. Type of ON documented in 70 patients with SLE.

Site	Patients, (n)*		Total Joints
	Unilateral	Bilateral	
Hip	11	36	83
Knee	14	12	38
Ankle	3	3	9
Shoulder	4	7	18
Elbow	1	1	3
Wrist	2	0	2

*Some patients had multiple sites involved.

The frequency of clinical features documented prior to the development of ON in comparison to the control group are shown in Table 3. In univariate conditional logistic regression analysis, arthritis was associated with the subsequent development of ON. Vasculitis and livedo reticularis were also more common among patients who went on to develop ON than in the controls, but the difference was not statistically significant. Raynaud's phenomenon was not more frequent among patients with ON. Laboratory features including aCL or elevated PTT, positive Coombs' test or elevated plasma lipids were not associated with the development of ON in our patients (Table 4). Since aCL testing has been routinely performed in our clinic only since 1991 (hence the low number of patients with aCL prior to development of ON), we looked for an association between aCL at any time and ON. Forty of the 70 patients with ON (54%) had at least one positive aCL test in comparison to 31/70 (44%) of controls ($p = 0.137$, OR 1.6, 95% CI 0.9,3.3).

All patients who went on to develop ON had been undergoing glucocorticosteroid therapy, although 2 patients were not taking glucocorticosteroids at the time ON was diagnosed (Table 5). In comparison, only 71% of the patients

Table 3. Clinical features in patients with ON and controls.

Feature	ON (%)	Controls (%)	p	OR Estimate (95% CI)
Arthritis	54 (77)	38 (54)	0.005	2.8 (1.3, 6.3)
Livedo reticularis	36 (48)	28 (40)	0.155	1.7 (0.8, 3.5)
NPSLE*	35 (47)	33 (47)	1.000	1.0 (0.5, 1.9)
Raynaud's	38 (51)	43 (60)	0.465	0.8 (0.4, 1.6)
Nephritis	51 (73)	52 (74)	0.853	0.9 (0.4, 1.9)
Thrombophlebitis	6 (9)	4 (6)	0.526	1.5 (0.4, 5.9)
Vasculitis	47 (67)	40 (57)	0.141	1.9 (0.8, 4.7)

*NPSLE: neuropsychiatric SLE.

Table 4. Laboratory features in patients with ON and controls.

Feature	ON (%)	Controls (%)	p	OR Estimate (95% CI)
aCL	4 (6)	3 (4)	0.654	1.5 (0.2, 11.4)
PTT	38 (54)	44 (63)	0.176	0.5 (0.2, 1.3)
Coombs' test	11 (16)	12 (17)	0.819	0.9 (0.4, 2.2)
Cholesterol	53 (76)	49 (70)	0.432	1.4 (0.6, 3.0)
Triglycerides	38 (54)	43 (61)	1.000	1.0 (0.5, 2.0)

without ON were on glucocorticosteroid therapy. Moreover, the maximum and cumulative dose of glucocorticosteroids was higher in patients who went on to develop ON than in controls. Eight patients who developed ON and 6 patients who did not had received pulse methylprednisolone. There was no significant difference in the maximum ($p = 0.306$) or cumulative ($p = 0.105$) doses of methylprednisolone between the 2 groups. Antimalarial therapy was used more commonly among patients who went on to develop ON. The use of cytotoxic medication was also statistically higher among patients who developed ON than controls.

Using multivariate analysis (Table 6), glucocorticosteroid therapy, arthritis, and antimalarial and cytotoxic therapy maintained their significant association with subsequent development of ON.

Table 6. Results of multivariate analysis.

Variable	OR Estimate (95% CI)	p
Glucocorticosteroid use	18.5 (3.2, 359.6)	0.0002
Arthritis	4.2 (1.6, 13.7)	0.002
Cytotoxics	2.7 (1.02, 8.8)	0.046
Antimalarials	2.2 (0.998, 8.1)	0.051

DISCUSSION

ON is a frequent complication in patients with SLE and has been recognized as a feature of the accumulated damage in SLE[17]. The prevalence of symptomatic ON varies from 5 to 12%[1-6].

Factors associated with ON have varied. Previous cohort studies compared patients who developed ON to patients who did not, so comparison groups were not necessarily followed for the same period of time (Table 7).

It has long been thought that ON in patients with SLE is related to glucocorticosteroid therapy[1-5,7,9,11,18-23]. Nonetheless, ON has not been reported with the same frequency in other patient groups treated with glucocorticosteroids[19] and it has been reported in a few patients with SLE who have not received glucocorticosteroid therapy1[19]. Moreover, the dose of glucocorticosteroids has been considered a predisposing factor[2,4,9,11]. Indeed, glucocorticosteroid therapy is the only factor associated with ON in all studies (Table 7). The presence of Raynaud's phenomenon was found to be associated with ON in the early Baltimore studies[2], but has not been confirmed by others[4,5,11,23]. The most recent study from the Baltimore cohort found that vasculitis was associated with ON[9]. Mont[9] suggested that the presence of aCL predisposes to the development of ON, and Sheikh[21] suggested that a defect in fibrinolysis is operative in the development of ON. However, this has not been supported by others[7,22]. We did not collect these data prospectively, so are unable to comment on this latter. Similarly, it has been suggested that certain autoantibody profiles may predispose to the development of ON, but this observation was based on a very small number of patients[8].

Table 5. Therapies in patients with ON and controls

Feature	ON (%)	Controls (%)	p	OR Estimate (95% CI)*
Glucocorticosteroid use	68 (97)	50 (71)	< 0.0001	19.0 (3.9, 341.2)
Glucocorticosteroid duration, yrs	4.3	3.3	0.035	1.15 (1.01, 1.36)
Cumulative dose, g	23.1	15.0	0.002	1.04 (1.01, 1.07)**
Maximum dose, mg	44.4	28.1	0.001	1.02 (1.01, 1.04)
Cushingoid	59 (84)	42 (60)	0.001	3.8 (1.7, 10.4)
Antimalarials	50 (71)	38 (54)	0.032	2.2 (1.07, 4.9)
Cytotoxics	33 (47)	18 (26)	0.006	2.9 (1.3, 6.9)

*The odds ratios are computed based on a matched-pairs analysis.**Per 10 g of cumulative dose.

Table 7. Factors associated with ON in patients with SLE.

Author	Type of Study	ON/ Comparison	Steroid	Raynaud's	Vasculitis	aCL/ LAC*
Zizic, 1980[17]	Cohort	16/124	+	+	NA	NA
Zizic, 1985[2]	Prospective Cohort	28/26	+	–	NA	NA
Weiner, 1989[4]	Cohort	12/15	+	–	–	NA
Massadro, 1992[5]	Cohort	17/176	+	–	–	NA
Migliaresi, 1994[23]	Cohort	7/69	+	NA	NA	+/–
Rascu, 1996[22]	Cohort	9/271	+	–		–/NA
Mont, 1997[9]	Cohort	31/72	+	NA	+	+/–
Mok, 1998[11]	Cohort	38/143	+	–	NA	–/+
Gladman, current	Matched case-control	70/70	+	–	–	–/–

*aCL: anticardiolipin antibody; LAC: lupus anticoagulant; NA: not assessed.

In our cohort of 744 patients, the largest collection of patients with ON reported to date, followed prospectively since 1970, the prevalence of symptomatic ON is 12.8%. While we do not perform radiographs routinely on all patients, we do review all patients at regular intervals with complete assessments for any indication of lupus activity (measured as an increase in SLEDAI score) or its complications. The availability of clinical, laboratory, and therapeutic information collected prospectively on our patient cohort provides an opportunity to investigate the relationship of ON with a number of possible factors. For the purpose of looking at predictive factors associated with development of ON, only patients who were diagnosed with ON after entering our prospective study were included, to ensure that we had baseline information recorded prior to the onset of ON. Seventy such patients were identified and matched by age, year of entry to clinic, and sex with patients with SLE followed at the same clinic but who did not develop ON in the course of their followup.

Our study confirms that glucocorticosteroids play a major role in the development of ON in patients with SLE. Significantly higher numbers of patients who went on to develop ON had been treated with glucocorticosteroids than patients without ON. Indeed, all patients with ON had taken glucocorticosteroids, while only 71% of controls used these drugs. While it is possible that patients with more severe and active disease would have required more glucocorticosteroid therapy, the fact that SLEDAI scores at presentation to the Lupus Clinic were not significantly different between the 2 groups and that the frequency of major organ manifestations was similar in both groups suggests that their disease activity and severity were similar. Moreover, the use of glucocorticosteroids may reflect not only disease severity but also physician and patient preferences. There are patients who refuse to take glucocorticosteroids, and there are physicians who use higher doses for constitutional complaints. It had been suggested that pulse therapy may reduce the risk of ON[23]. Massadro[5] reports on the development of ON among patients treated with pulse therapy. We found that usage and dosage were similar among patients who developed ON and patients who did not. The exact mechanism through which glucocorticosteroids exert their effect to develop ON is unclear.

Antimalarial and cytotoxic therapy were also higher among patients who went on to develop ON. This may suggest that these patients had more active and severe disease. However, looking specifically at clinical and laboratory features of SLE, only arthritis was significantly associated with the development of ON in our patients. It should be noted that this is lupus arthritis, involving an inflammation in at least 2 joints. It is possible that there is some predilection for the development of ON in patients who develop arthritis. Arthritis remains an important factor in the multivariate analysis. The presence of Raynaud's and vasculitis was not found to be a risk for the development of ON in our study. Importantly, the presence of features of the antiphospholipid syndrome was not associated with the development of ON nor were any of the laboratory features associated with the development of ON in our patient cohort.

While one may document observations from previous studies, it is not possible to compare the studies. Previous cohort studies included small numbers of patients with ON, varying from 7 to 38, with variable comparison groups representing the remainder of the patients in the cohort (Table 7). However, the duration of disease, patient age, sex, and followup time were not usually included in their analyses. Thus in the previous studies, patients with variable opportunities to develop ON and the predictive factors were compared. As a result, only associations could be documented and not predictive factors. The only previous case control study included patients who had taken steroids, but patients were not matched on any other factor[23]. The nested case control study from a prospective cohort used in the current study has an advantage over cohort studies because data are collected prospectively and in a similar format for

all cohort members, both cases and controls. We selected the controls who had been followed for a similar period of time and would have the same opportunity to develop both ON and the predictive features. Moreover, our study included twice as many patients in the ON group as the previous largest group.

One potential weakness of our study is that we only analyzed symptomatic patients with ON. Although it is possible that with use of MRI imaging we may have detected additional cases of ON, it is not yet clear of what clinical importance this is. It is possible that some of these cases may go on to repair spontaneously and never present clinically. We felt it prudent to analyze only patients with symptomatic ON.

Patients with SLE who have been treated with large doses of steroids or cytotoxic medications or who have had arthritis are at risk of developing ON of bone. Judicious use of corticosteroid and cytotoxic agents is necessary to minimize the risk of developing ON in patients with SLE.

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