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Original Article

Osteonecrosis in Systemic Lupus Erythematosus☆

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ABSTRACT

Objectives: To define the proportion of osteonecrosis (ON) in our patient population with lupus and to identify factors associated with the development of ON in systemic lupus erythematosus, as well as to carry out a descriptive analysis of ON cases.
Materials and methods: Observational retrospective study of 158 patients with SLE (ACR 1982 criteria). Demographic and laboratory data, clinical manifestations, SLICC, SLEDAI, cytotoxic and steroid treatments were compared. In patients with ON, we analyzed time of disease progression and age at ON diagnosis, form of presentation, joints involved, diagnostic methods, Ficat–Arlet classification, and treatment. To compare the means, *t*-test or Mann–Whitney's test was employed and the cHi-2 test or Fisher's exact test, as appropriate, was used to measure the equality of proportions.
Results: ON was present in 15 out 158 patients (9.5%), 13 women and 2 men, with a mean age of 30 (r: 16–66) at diagnosis and 35 months of evolution until diagnosis (r: 1–195). Among the 15 patients, 34 joints presented ON, 23 were symptomatic and 22 were diagnosed by magnetic resonance images. Twenty-six occurred in hips (24 bilateral), 4 in knees and 4 in shoulders. In 13 patients, ON involved 2 or more joints. At onset, 28 joints were in stage I–II, one in stage III and 5 had no data and; in the end, 14 were in stage III–IV, 5 in stage I–II and 15 had no data. Twenty-nine underwent conservative treatment with rest and 8 hips required joint replacement. ON progression was associated with Cushing's syndrome (P=0.014) OR 4.16 (95% CI 1.4–12.6) and 2nd year SLICC (P=0.042). No relation with clinical manifestations, lab results, cytotoxic treatment, steroid treatment (total accumulated dose, mean daily dose and duration) metilprednisolone pulses, or activity was found. All patients with ON received antimalarials, in contrast to 77% of those without ON.
Conclusions: The proportion of ON was 9.5%, mainly in women, 76% in hips (26) and 92% bilaterally. They were associated significantly with Cushing's syndrome and accumulated damage at second year.

Osteonecrosis en lupus eritematoso sistémico

Palabras clave:
Osteonecrosis
Lupus eritematoso sistémico
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RESUMEN

Objetivos: Definir la proporción de osteonecrosis (ON) en nuestra población lúpica, identificar factores asociados a su desarrollo y realizar un análisis descriptivo de las ON.
Materiales y métodos: Estudio retrospectivo observacional. Se incluyó a 158 pacientes con lupus eritematoso sistémico (criterios ACR 1982), comparando datos demográficos, de laboratorio, manifestaciones clínicas, SLICC, SLEDAI, tratamiento citotóxico y esteroideo. En pacientes con ON se analizaron el tiempo de evolución y la edad al diagnóstico de ON, la forma de presentación, la articulación comprometida, el método diagnóstico, la clasificación Ficat y Arlet y el tratamiento realizado. Se utilizó la prueba de la t o la prueba de Mann–Whitney para la comparación de medias y para igualdad de proporciones o independencia, la prueba de la chi al cuadrado o exacta de Fisher, según correspondiera.
Resultados: La ON ocurrió en 15/158 pacientes (9,5%), 13 mujeres y 2 hombres. Edad al diagnóstico de ON (mediana): 30 años (r: 16–66) y el tiempo de evolución hasta el diagnóstico de ON: 35 meses (r: 1-195). En los 15 pacientes hubo 34 articulaciones con ON, 23 sintomáticas y 22 diagnosticadas por RM. Veintiséis ON fueron en caderas (24 bilaterales), 4 en rodillas y 4 en hombros. En 13 pacientes la ON

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afectó a 2 o más articulaciones. Al inicio, 28 articulaciones estaban en estadio I-II, uno en estadio III y 5 sin datos y al final, 14 en estadio III-IV, 5 en estadio I-II y 15 sin datos. Veintinueve se trataron con reposo y 8 caderas requirieron reemplazo articular. La ON se asoció a aspecto Cushing (p = 0,014), OR 4,16 (IC 95% 1,4-12,6) y SLICC 2.° año (p = 0,042). No hubo relación con manifestaciones clínicas, datos de laboratorio, tratamiento citotóxico o dosis de esteroides ni actividad. Todos los pacientes con ON recibieron antipalúdicos, a diferencia de un 77% de aquellos sin ON.

Conclusiones: La proporción de ON fue del 9,5%, la mayoría fue en mujeres, el 76% en caderas (26) y el 92% bilateral. Se asociaron significativamente a aspecto Cushing y daño acumulado al segundo año. No se halló relación con el resto de las variables evaluadas.

Introduction

Osteonecrosis (ON) is the joint manifestation of systemic lupus erythematosus (SLE) that leads to higher morbidity. Incidence of ON in SLE varies from 2.1% to 52%.[1–19]

Multiple factors have been associated with ON in SLE, including: Cushing's phenotype,[1–7] Raynaud's phenomenon,[4,5,8] vasculitis,[4,6] neurological involvement,[1,8] disease activity,[9,10] arthritis[3] cytotoxic treatment,[1,3] superficial thrombophlebitis[6] hematuria and proteinuria[2] and antiphospholipid antibodies,[1,6] among others. There is consensus among most authors regarding the relationship of ON with steroid treatment, but there is controversy whether this relationship depends on the cumulative dose, duration of treatment or the use of large monthly or bimonthly doses. The objectives of this study were to determine the proportion and distribution of bone necrosis in this population and to identify factors associated with its development.

Materials and Methods

158 files of patients diagnosed with SLE who were treated at the JM Cullen Hospital in Santa Fe between 1989 and 2012 were retrospectively reviewed. They all met at least 4 classification criteria for SLE (ACR 1982).

Patients considered for inclusion into the study were those in whom the diagnosis of ON was clinically suspected and confirmed through X-rays (Rx), computed tomography (CT), magnetic resonance imaging (MRI) and/or scintigraphy. ON was staged using the Ficat and Arlet[11] classification at baseline and at the last valuation of the joint: stage I: normal radiograph with positive MRI, CT scan or pathology; stage II: cystic or sclerotic changes in the X-ray with no signs of collapse; stage III: collapse of the affected bone, and stage IV: both sides of the joint showing degenerative changes.

Both groups of patients with SLE (with and without ON), were compared for: demographic data, clinical manifestations, comorbidities, antibody profile, accumulated damage by Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index at first, second, fifth and tenth year of SLE progression, excluding the score for ON; activity of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and exposure to immunosuppressive and antimalarial drugs prior to diagnosis of ON. Total cumulative dose of steroids was also reviewed and expressed as prednisone equivalents up until the diagnosis of ON or until the last control in patients who did present this complication, the duration of steroid therapy and the average daily dose that each patient received since the onset until treatment with corticosteroids ended. Methylprednisolone pulses were defined as the administration of 1000 mg or more of prednisone equivalents.

The antibody profile included: antinuclear antibody (Hep 2 epithelial cells), anti-native DNA antibodies by indirect immunofluorescence on Crithidia luciliae, anti-extractable core antigen (anti-Ro, anti-La, anti-Sm and anti-RNP), anticardiolipin (IgG, IgM) and lupus anticoagulant.

Table 1
Method Used for the Diagnosis of Osteonecrosis (n = 34).

Diagnostic method	No. joints with ON
MRI	22
Rx	7
CT	2
MRI + Rx	2
MRI + bone scan	1

The study was approved by the Ethics Committee of the Hospital. It did not require informed consent because of the anonymous nature of the study.

Statistical Analysis

The Mann–Whitney test was used for comparison of means and proportions and for equal or independent proportions. The chi-square or Fisher's exact test was employed, as appropriate. Data were processed using SPSS 17.0, available from the Department of Mathematics FBCB-UNL. Statistical significance was set at 0.05.

Results

The total population of 158 patients with SLE was composed of 92% women, with an average age of onset of SLE of 28 years (*R*=9–62). Time on follow-up (median) was 87 months (*R*=0–497).

Among the 158 patients with SLE, 15 were identified as presenting ON (9.5%), 13 women and 2 men. The median time between the onset of SLE and diagnosis of ON was 35 months (*R*=1–195), the mean age at ON diagnosis was 30 years (*R*=16–66). Only 6/15 of ON patients had SLEDAI data in the year prior to an episode of ON and 3 of them showed activity of SLE, while four were active at the time of developing ON.

These 15 patients had a total of 34 affected joints: 23 were symptomatic, 9 were asymptomatic and in 2 cases the form of presentation was unknown. Twenty-two were diagnosed by MRI, 7 by X-ray and 2 using CT, with the rest diagnosed by a combination of methods (Table 1). The most commonly affected site was the femoral head (14 patients), being bilateral in 12 cases. These were followed in frequency by the knees and shoulders in 2 patients in each case, and all of them bilaterally (Table 2). Thirteen patients had

Table 2
Patterns of Osteonecrosis in 15 Patients.

Affected sites	No. of patients		No. of joints
	Unilateral	Bilateral	
Hips	2	12	26 (76%)
Knees	0	2	4 (12%)
Shoulders	0	2	4 (12%)
Total			34