

Clinical profile of osteonecrosis in systemic lupus erythematosus – Experience from a tertiary care centre in South India

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ABSTRACT

Introduction: Osteonecrosis or Avascular necrosis of bone (AVN) is a well recognized complication of systemic lupus erythematosus (SLE) leading to significant morbidity. **Methods:** We did a cross sectional descriptive study in cohort of SLE patients, on regular follow-up at our Rheumatology OPD over a period of 5 years from 2012 to 2017. Results: Of the total 415 SLE, 5.1% (n = 21) patients were diagnosed to have osteonecrosis. The mean age was 32.8 ± 7.6 years. Male: female were 1:4.2. Mean time interval between the onset of SLE and diagnosis of osteonecrosis was 4.1 ± 2.7 years. Pain (100%) was the most common presenting symptom followed by limping gait (42.8%). Most common site affected by osteonecrosis was femoral head (80.9%) (n = 17). 14.3% (n = 3) had multifocal involvement. The most common systemic involvement was musculoskeletal system (80.9%). In total 28.5% had secondary antiphospholipid syndrome. Mean SLEDAI-2K at the time of diagnosis of osteonecrosis was 5.3 ± 2.9 . Hypertension 19%, hypothyroidism 9.5%, osteoporosis 24%, and chronic HCV infection 4.7% were the associated comorbidities. The most common stage by imaging at diagnosis was stage IV (38%), followed by 24% stage V, 19% stage III and 9.5% stage II and 9.5% stage VI. Medical management include bisphosphonates (100%), statins (90.4%) and anticoagulant therapy (28.5%), while 9.5% received core decompression surgery and 14.3% underwent total hip replacement. The mean daily dose of prednisolone at diagnosis of osteonecrosis was 8.5mg (range 5–20mg). **Conclusion:** This study described the prevalence and epidemiology of osteonecrosis in our cohort of SLE patients.

Keywords: Antiphospholipid antibodies, avascular necrosis of bone, prednisolone, steinberg staging

Introduction

Osteonecrosis or Avascular necrosis of bone (AVN) is characterized by death of the cellular elements of bone due to compromise in the blood supply. The etiology of osteonecrosis is multifactorial. Any bony fractures or dislocation following trauma,

can compromise the arterial supply to the involved bone leading to traumatic osteonecrosis. Nontraumatic osteonecrosis may occur secondary to various systemic illness, drugs, etc., Systemic diseases that predispose to osteonecrosis were hyperlipidemia, hyperparathyroidism, diabetes, chronic liver diseases, gaucher's disease, hemoglobinopathies, coagulopathies, and rheumatological disorders. Rheumatological diseases associated with osteonecrosis include systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), mixed connective disease disorder, rheumatoid arthritis, polymyositis, necrotising arteritis, and

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sarcoidosis. Other risk factors for osteonecrosis include chronic alcohol consumption, cigarette smoking, radiation exposure, pregnancy, and corticosteroid therapy.^[1,2]

Osteonecrosis in SLE is a well recognized complication that leads to significant morbidity. The risk factors for the development of osteonecrosis in patients with SLE include corticosteroid use, vasculitis, Raynaud phenomenon, inflammatory mediators, cytotoxic drugs, defects in fibrinolysis, genetic polymorphisms, and antiphospholipid antibody syndrome. Factors like maximum dosage, cumulative dosage, duration of therapy, and route of administration determines the risk of developing osteonecrosis in SLE patients on steroids.^[3]

The prevalence of symptomatic osteonecrosis in SLE varies from 0.8% to 33%. Asymptomatic osteonecrosis was reported in about 29% of SLE patients.^[4] There is paucity of data regarding the prevalence of osteonecrosis associated with SLE in our population. The objective of our study is to determine the prevalence of osteonecrosis among adult SLE patients in our population and to study the clinical profile of osteonecrosis in these patients.

Materials and Methods

This was a cross sectional descriptive study done in the department of Rheumatology at tertiary care centre from South India. Consecutive medical records of patients diagnosed as SLE who were on regular follow-up in our lupus clinic over a period of 5 years from 2012 to 2017 were taken up for the study. SLE patients who had strong clinical suspicion of osteonecrosis underwent detailed imaging studies (Computed tomography (CT) or Magnetic resonance imaging (MRI)) as per the department protocol. SLE patients above the age of 18 years with documented osteonecrosis were included in the study. Patients with SLE overlap syndrome were excluded from the study.

Baseline demographic data of SLE patients with osteonecrosis were collected using standardized case report forms. Data regarding onset of osteonecrosis, presenting symptoms, site of involvement, stage of osteonecrosis at the time of diagnosis (Steinberg staging system by imaging^[5]), duration of SLE and treatment given for osteonecrosis were studied. Other systemic manifestations of SLE, the presence or absence of secondary APS, dose, duration of steroids, immunosuppressive therapy, and comorbidities present in these patients were also studied. SLEDAI -2K (systemic lupus erythematosus disease activity index 2000^[6]) scoring done at the time of diagnosis of osteonecrosis was also studied.

Data entry and analysis were done using Microsoft Excel version 2010. Categorical data were presented as numbers and percentages. Mean and standard deviation were used for continuous variables.

Results

Medical records of 415 SLE patients during the study period were analyzed. 30 patients (7.2%) underwent imaging for clinical suspicion of osteonecrosis, of which 21 patients (5.1%) were diagnosed with osteonecrosis. The mean age of the patients with osteonecrosis was 32.8 ± 7.6 years (range 21-49 years). The male to female ratio was 1:4.2 (males $n = 4$, females $n = 17$). The mean time interval between the diagnosis of SLE and development of osteonecrosis was 4.1 ± 2.7 years. 76.2% ($n = 16$) patients developed osteonecrosis within 5 years of diagnosis of SLE, while 23.8% ($n = 5$) of patients developed osteonecrosis after 5 years of SLE.

Most common presenting symptom of osteonecrosis was pain (100%), followed by limping gait (42.8%). Most common site affected by osteonecrosis was femoral head (80.9%) ($n = 17$). Bilateral femoral head involvement was seen in 61.9% ($n = 13$), while unilateral femoral head involvement was seen in 19% ($n = 4$). Other sites of involvement were distal femur (14.3%) ($n = 3$) and proximal humerus (4.7%) ($n = 1$). Pattern of articular involvement is shown in Figure 1. In total 14.3% ($n = 3$) of patients had multifocal osteonecrosis including bilateral proximal femur and distal femur. Musculoskeletal system (80.9%) was the most common systemic involvement seen in these patients, followed by mucocutaneous manifestations (38%). Other internal organ involvement in SLE with osteonecrosis include lupus nephritis (33.3%), neuropsychiatric (28.5%) and haematological manifestations (23.8%). 28.5% ($n = 6$) of SLE patients with osteonecrosis had secondary antiphospholipid antibody syndrome. Other vascular manifestations in these SLE patients with secondary APS were deep venous thrombosis (50%), cortical venous thrombosis (33.3%), central retinal artery occlusion (16.6%), and chronic non-healing ulcer of both lower limbs (16.6%). Distribution of clinical manifestations in SLE with osteonecrosis is shown in Figure 2. Among those SLE patients who had secondary APS, 16.6% presented with multifocal osteonecrosis.

Mean disease activity of SLE (SLEDAI-2K) at the time of diagnosis of osteonecrosis was 5.3 ± 2.9 . Other comorbidities observed in patients with SLE and osteonecrosis include hypertension 19% ($n = 4$), hypothyroidism 9.5% ($n = 2$), osteoporosis 24% ($n = 5$) and chronic HCV infection 4.7% ($n = 1$) [Figure 3]. The most common stage of osteonecrosis (as per Steinberg staging system) at the time of diagnosis was stage IV (38%), followed by stage V (24%), stage III (19%), stage II (9.5%), and stage VI (9.5%). Coronal MRI T1 showing osteonecrosis of bilateral femoral head is illustrated in Figure 4. Treatment options tried for osteonecrosis include bisphosphonates (100%), statins (90.4%), and anticoagulant therapy (28.5%). In total 23.8% patients underwent surgical management. 9.5% patients received core decompression surgery and 14.3% patients underwent total hip replacement.

The mean duration of steroid therapy at the time of diagnosis of osteonecrosis was 3.6 ± 2.3 years. The mean daily dose of

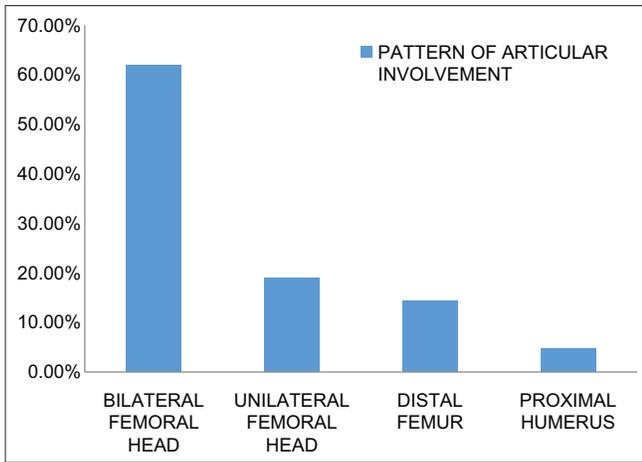


Figure 1: Pattern of articular involvement in osteonecrosis

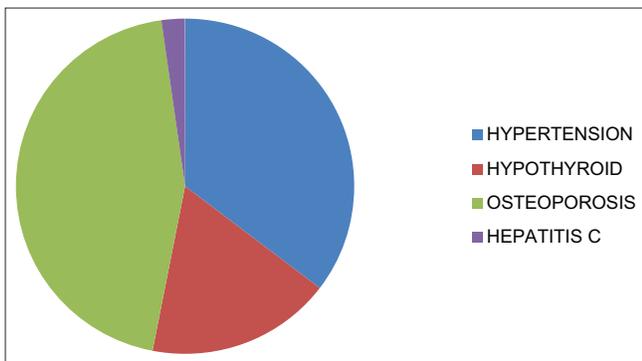


Figure 3: Distribution of comorbidities in SLE with osteonecrosis

prednisolone received at the time of diagnosis of osteonecrosis was 8.5 mg (range 5–20 mg). In total 52.3% ($n = 11$) of these patients received pulse methylprednisolone therapy at some point of time during the disease course prior to the onset of osteonecrosis. Immunosuppressive therapy received by these patients includes cyclophosphamide (42.8%), mycophenolatemofetil (47.6%), and azathioprine (9.5%).

Discussion

Osteonecrosis frequently complicates the disease course of SLE either due to the disease activity *per se* or due to the concomitant use of drugs like steroids. Although mortality is less, osteonecrosis leads to significant morbidity and impair the quality of life. The prevalence of osteonecrosis in our cohort of 415 lupus patients was 5.1%. We did a thorough search in pubmed, google scholar, and scopus using keywords “osteonecrosis”, “avascular necrosis”, “systemic lupus erythematosus” to identify studies from Indian subcontinent. We could not find any data regarding the prevalence of osteonecrosis in adult SLE from South India. A study by Malviya *et al.* from central India showed a prevalence of osteonecrosis in 5% of lupus patients.^[7] The prevalence of osteonecrosis in SLE as reported in studies from other parts of the world are compared in Table 1.

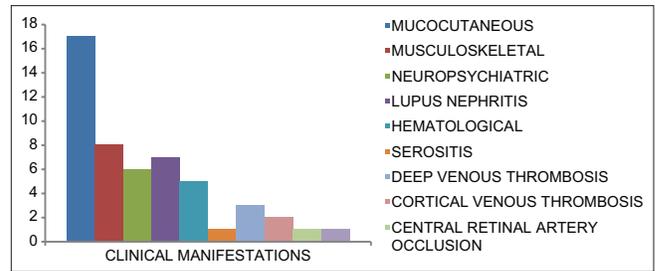


Figure 2: Distribution of clinical manifestations in SLE with osteonecrosis

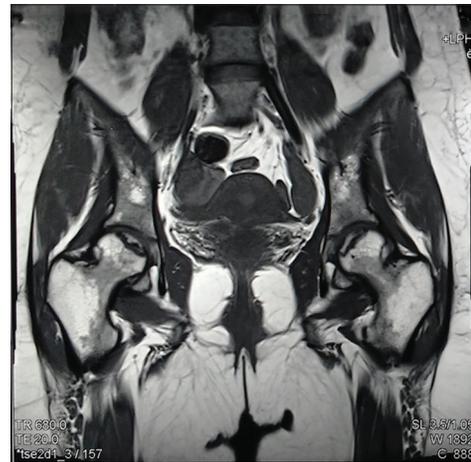


Figure 4: Coronal MRI T1 showing osteonecrosis of bilateral femoral head

The mean age of SLE patients with osteonecrosis in our study was 32.8 years. Majority of our patients (76%) were between the age group of 20-40 years. Study by Gontero *et al.* showed similar mean age (30 years) of osteonecrosis in SLE patients.^[9] A study by Vardhan *et al.* from North India, reported the average age of 34.7 years in patients with osteonecrosis of femoral head, including traumatic and atraumatic etiologies.^[12] The mean time interval between the diagnosis of SLE and osteonecrosis was 4.1 ± 2.7 years. About 2/3rd of our SLE patients developed osteonecrosis within 5 years of diagnosis of SLE. In the study by Gladman *et al.*, the time interval between diagnosis of SLE and osteonecrosis was 8.2 ± 8.1 years.^[11]

Femoral head is the most common site involved in osteonecrosis. Other sites namely knees, shoulders, wrists, ankles as well as multifocal areas may also be involved in SLE associated osteonecrosis.^[2] In our study, femoral head was the most common site affected, with significant proportion of them, being bilateral (61.9%). Other sites involved in our patients were distal femur and proximal humerus. Multifocal involvement involving more than two sites was seen in 14.3% in our cohort. In a study by Mok *et al.*, femoral head was the commonest site involved (95%), followed by knee (13%). Involvement of bilateral femoral head was observed in 72% of cases. Less common sites involved were humerus and carpal bones.^[13] In a multicentre study done in symptomatic multifocal osteonecrosis, SLE was diagnosed in about 38% of patients.^[14]

Table 1: Studies comparing the prevalence of osteonecrosis in SLE patients

Studies	Region	No. of SLE patients	Prevalence of osteonecrosis
Sayarlioglu <i>et al.</i> ^[8]	Turkey	154	6%
Gontero <i>et al.</i> ^[9]	Argentina	158	9.5%
Joo <i>et al.</i> ^[10]	Korea	25,358	3.3%
Gladman <i>et al.</i> ^[11]	Toronto	1729	13.6%
Malaviya <i>et al.</i> ^[7]	Central India	180	5%
Our study	South India	415	5.1%

In our study, the most common systemic involvement of SLE patients with osteonecrosis were musculoskeletal, followed by mucocutaneous, lupus nephritis, neuropsychiatric, and haematological. In a study by Mok *et al.*, the other major organ systems involved in patients with SLE associated osteonecrosis were nephritis, pleuritis, cutaneous vasculitis, and cerebral lupus. Raynaud phenomenon, lymphopenia, and thrombocytopenia were the other findings observed in association with osteonecrosis.^[15] In a metaanalysis by Zhu *et al.*, factors like arthritis, cushingoid features, gastrointestinal involvement, hypertension, oral ulcers, pleuritis, renal disease, vasculitis were significantly associated with osteonecrosis in SLE patients.^[16]

The prevalence rate of antiphospholipid antibodies (aPL) among SLE patients with osteonecrosis ranged from 8% to 73%.^[17] In our study, the prevalence of APS in SLE with osteonecrosis was noted in 28.5% patients. All the patients who had APS in our study had prior arterial or venous thrombotic events. Nagasawa *et al.* and Migliaresi *et al.* reported the prevalence rate of aPL in 25%, 29% of SLE patients with osteonecrosis respectively.^[18,19] Many studies reported that the presence of antiphospholipid antibodies was an independent risk factor for osteonecrosis in SLE.^[13,20] This finding was not supported by another study where neither aPL nor APS were identified as predictors for osteonecrosis.^[11]

In our study, the mean SLEDAI-2K score at the time of diagnosis of osteonecrosis was 5.3 ± 2.9 . In a study by Fialho *et al.*, they found SLEDAI as an independent risk factor for osteonecrosis.^[21] Few other studies showed no association between SLEDAI score and the development of osteonecrosis.^[13,22]

Majority of the studies showed steroid therapy as a major risk factor for osteonecrosis. Steroid induced osteonecrosis was usually dose related, with greater risk in patients who received higher doses, especially in the first year of treatment. Also the risk was higher with longer duration of therapy.^[3] In our study, the mean dosage of steroid at the time of diagnosis of osteonecrosis was 8.5 mg (range 5–20 mg). Our study showed that the mean duration of steroid use prior to the onset of osteonecrosis was 4 years. Gladman *et al.* showed the mean steroid dose as an independent predictor of osteonecrosis.^[11] Few studies showed significant association between osteonecrosis and the peak steroid dose.^[13,23] A study by Oinuma *et al.*, reported that

the onset of osteonecrosis was very early following high dose steroid treatment.^[24] Another study did not find any association between total cumulative dose or the duration of steroid with the development of osteonecrosis.^[25] With regard to the association of osteonecrosis following pulse steroid therapy, there were conflicting results where few studies supported its association while other studies did not.^[13,19,26,27] Use of cytotoxic drugs were found to be a risk factor for the development of symptomatic osteonecrosis in SLE patients.^[28-30] Majority of our patients were on cytotoxic drugs, when they developed osteonecrosis. Limitation of our study was that we could not do correlation of various risk factors associated with osteonecrosis in our cohort of SLE patients.

Conclusion

We studied the prevalence of osteonecrosis in South Indian cohort of SLE patients. We also described the epidemiology of SLE patients with osteonecrosis in our population. More prospective studies may be required to analyze the risk factors for the development of osteonecrosis in SLE patients.

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Conflicts of interest

There are no conflicts of interest.

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