Avascular necrosis in SLE

An apparent predilection for young patients

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Smith, F. E., Sweet, D. E., Brunner, C. M., and Davis, J. S. (1976). *Annals of the Rheumatic Diseases*, 35, 227-232. Avascular necrosis in SLE. An apparent predilection for young patients. Recent reports of avascular necrosis (AN) in systemic lupus erythematosus (SLE) have suggested that its occurrence may be most frequent in young patients. In our population of 99 patients with SLE, 7 young patients have developed AN. Patterns of prednisone therapy had no apparent relationship to the development of AN. AN may become apparent in patients who have relatively inactive lupus, when increased physical activity precipitates articular collapse. A diagnosis of AN should be considered in young patients with localized joint pain.

Avascular necrosis (AN) was first reported in association with systemic lupus erythematosus (SLE) in 1960 (Dubois and Cozen, 1960). Subsequent reports have provided evidence that AN in SLE is a relatively common occurrence. Two recent studies in the paediatric literature note an incidence of 40% in paediatric populations (Hurley and others, 1974; Bergstein and others, 1974), and one of these notes that asymptomatic AN may be much more common than previously recognized. We present an assessment of our lupus patients who have developed symptomatic avascular necrosis, with an attempt to define the patient population in which it occurs and to determine predisposing factors.

Patients

Patients followed at the University of Virginia Hospital Lupus Clinic have well-established SLE, showing at least four of the preliminary criteria chosen by the ARA (Cohen and others, 1971). All four criteria are not necessarily present simultaneously. The period of study was from January 1, 1973 to December 31, 1974. Patients were included in this survey if they had documented SLE, diagnosed before or during the study period, and were seen for full evaluation at least twice during the study. 99 patients fit these criteria and 7 of these have AN. Patients from this clinic who died or were lost to follow-up before January 1, 1973, and those whose SLE was diagnosed after December 31, 1974, were excluded. 3 patients died during the period of study, 2 at this hospital and one elsewhere.

Limiting the study by dates should avoid skewing the patient population, since patients with SLE and AN are no more likely to have been lost to follow-up than patients with SLE without AN. Similarly, excluding patients who were not seen after January 1, 1973, should avoid inclusion of patients remembered because of their AN to the exclusion of others without AN.

A diagnosis of AN was made in each of the 7 patients because symptoms prompted the physician to obtain x-rays which showed characteristic changes (Table I). Screening of asymptomatic joints was not done, although in one patient with avascular necrosis of both hips, AN of both humeral heads was noted on a routine chest x-ray.

Table I Age of onset (years)

Case no.	SLE	AN	Bones
1	17	19	L hip
		20	R hip Both shoulders
2	17	19	R hip
3	18	23	Both hips
4	16	18	Both knees
5	21	23	Left hip
6	23	29	Both hips
7	35	36	Both hips

As far as can be determined from review of case histories, AN was not considered as a diagnostic possibility for joint pain in any patient in whom the diagnosis was not later established.

A control group with SLE was chosen by selecting patients of similar age, onset, and duration of disease with no known evidence of AN. In most cases intravenous pyelograms were available showing normal femoral heads at the time of the x-ray. X-rays of other joints were not obtained routinely.

Total dose, duration, and pattern of prednisone therapy in both groups of SLE patients were determined by review of case notes.

An additional control group of patients with asthma who were receiving steroids was examined to determine if AN is a problem in another group of patients. Also, a survey of case histories of patients with a diagnosis of AN was carried out in order to determine if these patients were on steroid therapy or if any had SLE but were not followed in our clinic.

FIG. 1. *Distribution of lupus patients by age*

Table II *Disease characteristics**

	Case no.							Total
	5	6	2	3	4	1	7	
Arthritis	+	+	+	+	⊕	⊕	+	7/7
Arthralgias	+	+	+	+	⊕	⊕	+	7/7
Skin								
Diffuse erythematous rash	+	+	-	+	+	-	+	5/7
Malar rash	+	+	+	⊕	+	+	+	6/7
Bullous lesions	-	-	-	-	-	⊕	-	1/7
Alopecia	+	+	+	+	+	-	+	6/7
Leucopenia	+	+	-	+	+	+	+	6/7
Haemolytic anaemia	+	-	-	-	-	-	-	1/7
Thrombocytopenia	-	-	-	-	+	-	-	1/7
Sun sensitivity	+	+	-	+	+	-	+	5/7
Oral ulcers	+	+	+	-	-	⊕	+	5/7
Renal disease								
>3.5 g proteinuria	+	+	-	+	+	-	-	4/7
Cellular casts	+	-	-	-	-	-	-	1/7
+biopsy	+	+	-	+	+	-	-	4/7
Pleuritis	+	+	+	-	+	-	-	4/7
Pericarditis	-	-	-	+	-	-	-	1/7
Fever	+	+	-	+	+	+	+	6/7
Raynaud's phenomenon	+	+	+	-	-	-	-	3/7
Myositis or myopathy	+	-	-	-	⊕	-	-	2/7
CNS								
Convulsions	+	-	-	-	-	-	-	1/7
Psychosis	+	-	-	-	-	-	-	1/7

* Circles indicate activity at onset of AN symptoms.

Results

Evaluation of age distribution of the population of SLE patients shows that there is a striking tendency towards youth in patients with AN (Fig. 1). Mean age of the entire SLE population in December 1974 was 41.1 years (range 15–74 years), and median age was 40 years. Patients with AN ranged in age from 18 to 36 years at the time AN was diagnosed, with their current ages ranging from 18 to 40 years. The length of follow-up since development of AN has been from 3 months to 8 years.

Disease characteristics are presented for each of the 7 SLE patients with AN in Table II. It is apparent that all 7 patients had a large number of the diagnostic features included in the preliminary ARA criteria for SLE. Fever (without infection) and myopathy are included in the list because these are seen in many of our SLE patients. Despite the fact that all 7 patients with AN have had protean manifestations of disease activity at some time before the onset of AN, it should be noted that at the time of onset of symptomatic AN they had relatively little lupus activity.

The disease manifestations of the control population of 7 SLE patients without AN are compared to the 7 patients with SLE and AN in Table III. There are few differences in the two groups. All patients in both groups had arthralgias, but only 3 of 7 in the control population had actual arthritis. Leucopenia was seen in only one of 7 controls; it was seen in 6 of 7 patients with AN at some time during the course of disease, although it was not found at the time of symptomatic appearance of AN. Raynaud's phenomenon, though never seen in the control patients, was present at some point in 3 of 7 patients with AN, but was not present when AN became symptomatic. Absence of Raynaud's phenomenon in the control population is more striking when it is noted that 40% of patients in the entire lupus population at the University of Virginia have had Raynaud's phenomenon at some point in the course of their disease.

Additional data for both groups are shown in Table IV. 5 of 7 patients with AN had been severely hypertensive at some point in their course, but none were hypertensive at the time AN became symptomatic. In contrast, 6 of 7 control patients were hypertensive in late 1974 (at which point their disease was of similar duration to those patients with AN). Antinuclear factor (ANF) was positive in all patients in both groups, and LE preps had been done and were positive in most patients. Other laboratory data show no apparent difference between the two groups.

Other authors have emphasized both the type of prednisone therapy and the total dose. Comparison of therapy in the two groups (Table V) according to total prednisone, daily prednisone, months of daily therapy, and total months of therapy shows no

Table III Disease characteristics in patients matched for age and duration of disease

	SLE with AN	SLE without AN
Arthritis	7/7*	3/7
Arthralgias	7/7	7/7
Skin		
Diffuse erythematous rash	5/7	7/7
Malar rash	6/7	4/7
Bullous lesions	1/7	0/7
Discoid lupus	0/7	0/7
Alopecia	6/7	7/7
Leucopenia	6/7†	1/7
Haemolytic anaemia	1/7	0/7
Thrombocytopenia	1/7	1/7
Sun sensitivity	5/7	5/7
Oral ulcers	5/7	4/7
Renal disease		
Proteinuria	4/7	3/7
Cellular casts	1/7	4/7
+ biopsy	4/7	6/7
Pleuritis	4/7	4/7
Pericarditis	1/7	0/7
Fever	6/7	5/7
Raynaud's phenomenon	3/7	0/7
Myositis or myopathy	2/7	2/7
CNS	1/7	0/7
False positive VDRL	0/7	0/7

* Numerator represents number of patients with manifestation of activity at any time in course of disease before development of AN. Denominator represents total number of patients.

† Major differences between the two groups.

Table IV Additional findings in patients matched for age and duration of disease

	SLE with AN*†	SLE without AN
Hypertension	0/6	6/7
ANF+	8/8	7/7
RF	0/5	1/7
Anti-DNA (by CIE)	1/4	0/7
Cryoprecipitates	1/5	2/7
Clq precipitins	2/5	0/7
Low CH ₅₀	2/8	4/7

* At time AN symptoms began.

† 2 sets of data for 1 patient (1972 and 1974).

CIE = counterimmunoelectrophoresis.

statistically significant difference by Students 't' test.

Review of charts on patients with asthma showed that of 14 patients (ages 22 to 49) who have been on prednisone for periods of 1 to 8 years, none had

Table V *Prednisone therapy in SLE*

	<i>Patients with AN</i>	<i>Patients without AN</i>
*Total dose (g)	13.83 (range 6.18–27.5)	18.18 (range 9.88–27.86)
*Daily therapy (g)	11.88 (range 1.5–27.5)	14.18 (range 1.8–24.25)
*Alternate day therapy (g)	1.96 (range 0–8.49)	3.98 (range 0–11.16)
*Months of daily therapy	19.86 (range 2–47)	22.86 (range 3–60)
*Months of alternate day therapy	4.43 (range 0–22)	11.1 (range 0–37)

* Not statistically different between the two groups, (by Student's 't' test).

developed symptomatic AN. There is no routine screening for AN by physical exam or by x-ray in the pulmonary division at the university as doctors do not worry about the development of AN in their patients.

Review of case histories of diagnosed cases of AN showed one additional patient with SLE and AN.

A male developed AN of both hips at age 49, four years after the onset of SLE. He had received approximately 20 g prednisone before developing AN. He is being followed elsewhere.

Discussion

The pathology of AN is fairly well defined (Johnson, 1964). It results from obliteration of the blood supply and is manifested by death of the marrow and cancellous bone in the affected area. Initially there is no loss of structural support, and stress forces continue to be dispersed by the articular surface through to the cortical shaft and vice versa. As with all infarcts, there is a zone of necrosis, injury, and ischaemia, surrounded by normal tissue (Fig. 2). The natural inflammatory response of the host to the necrotic and injured tissue results in the progressive thinning, disruption, and reinforcement of the cancellous trabeculae spanning the interface zone. The resultant patterns of altered bone density, seen radiographically (Fig. 3), reflect the extent and stage of the repair and remodelling process. If articular stress exceeds the structural integrity of the interface zone, then disruption of the subarticular plate overlying the interface zone results in articular collapse and symptoms.

FIG. 2 *Photograph of a femoral head, sectioned in the frontal plane, showing avascular necrosis. (A) Opaque appearing zone of necrosis with a linear subarticular fracture. (B) Interface zone of hyperaemia with trabecular destruction, repair, and remodelling. (C) Peripheral viable zone of essentially normal but slightly osteoporotic bone*

FIG. 3 X-ray of a femoral head sectioned in the frontal plane showing the radiographic changes of avascular necrosis. (A) Zone of necrosis showing unaltered trabecular bone density which appears relatively increased and a microfracture of the subarticular plate. (B) Interface zone showing focal loss of trabecular bone secondary to the reactive reparative process with subjacent bone reinforcement. (C) Peripheral viable zone showing decreased trabecular bone density secondary to the overall reactive hyperaemia.

The occurrence of AN in SLE was first described in 1960 by Dubois and Cozen, who presented 11 patients in a population of 400 who developed AN. Ages of patients with AN ranged from 21 to 54 years, the mean age at onset of AN symptoms being 36 years and the onset of symptoms occurring an average of 5.1 years after the onset of SLE (range 1.5–12.0 years). A follow-up of their population in 1964 (Dubois, 1974) described AN in 26 of 520 patients, 4 males and 22 females of the same approximate age group. All 26 had involvement of weight-bearing joints. AN occurred in one patient who had never received prednisone, as well as in patients currently on prednisone and in patients who had received prednisone in the past.

Patients described by Hurley and others (1974) were followed in their paediatric clinics and therefore represent a younger age group than those followed by Dubois and co-workers. In this age group, 4 of 10 children (ranging from 14–17 years in age) developed AN, again involving weight-bearing joints. In comparing drug programmes in these patients, a significant difference was found in duration of daily prednisone therapy, with no significant difference shown either in total dose of prednisone received or in total duration of therapy (adding daily and

alternate day schedules). Bergstein and others (1974) surveyed their paediatric patients with SLE and found that AN was present in 40%. Of a total of 35 patients, 14 had one or more joints involved. However, only 9 of the total of 31 joints showing AN on x-ray were symptomatic. Joints most commonly involved were again weight-bearing. In examining patterns of therapy in these patients, the distinguishing factor was the *total dose* of prednisone received. Duration of therapy and duration of disease were not significantly different between those patients with AN and those without AN.

Other reports of AN since 1960 (Leventhal and Dorfman, 1974; Siemsen, Brook, and Meister, 1962; Ruderman and McCarty, 1964) show that AN occurs relatively frequently in SLE. Age ranges are similar to that in the series of Dubois, and the joints involved are usually weight-bearing. AN has been reported in several patients with SLE who were not on steroids at any time, and, as described above, AN has also been correlated with either total dose or duration of daily therapy with prednisone.

Many studies have attempted to elucidate the pathogenesis of cortisone-induced avascular necrosis. To date, three hypotheses exist. Firstly, a cortisone-induced hypercoagulable state may be associated with

vasculitis (Cosgriff, Diefenbach, and Vogt, 1950). Secondly, cortisone-induced fatty liver may lead to systemic fatty embolization, occluding the subchondral endarteries (Jones, 1965; Fisher, Bickel, and Holley, 1969; Jaffe and others, 1972). Thirdly, cortisone-induced osteoporosis with subchondral fracture may lead to sinusoidal disruption and AN (Edstrom, 1961; Freiburger and Swanson, 1965). Finally, recent work (Wang and others, 1976) has shown an average 15% increase in the marrow fat cell size in cortisone-treated rabbits. Since bone is a nonexpandable structure, they speculate that the increase in space required for enlarging marrow fat cells occurs by compression of the sinusoidal vascular system (the only theoretical space available) with resultant bone and marrow necrosis.

In our patients the most striking observation is the youth of the SLE patients who have developed symptomatic AN. The incidence of asymptomatic AN is not known, but the paediatric literature suggests that the total incidence might be as high as 40%. AN appears to become manifest when SLE is relatively asymptomatic and the patients are physically active. Radiographic and histological findings in most of our patients suggest that AN had been

present for a considerable period of time before the development of symptoms.

We therefore speculate that the increased activity across weight-bearing joints, permitted by the quiescent or suppressed SLE symptoms, may actually precipitate articular collapse of the underlying and previously silent avascular necrosis. It is likely that steroids will considerably delay and modify the inflammatory and reparative response which creates the morphological changes in AN. Steroids may also mask the early symptoms.

Certainly there should be a high index of suspicion for AN in young patients with SLE who present with localized pain in a weight-bearing joint, especially in those who are feeling well and are physically active with no evidence of generalized arthritis. Surgical procedures, such as the Phemister bone graft, may prevent total collapse of the femoral head with AN, and can be considered if the diagnosis is made early. It will be important in future to study this group of patients prospectively, in an effort to observe the manifestations of SLE activity and course of therapy in this susceptible population, if we are to diagnose and attempt to treat avascular necrosis in its early stages.

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