Avascular necrosis of bone in systemic lupus erythematosus: possible role of haemostatic abnormalities

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SUMMARY The pathogenesis of avascular necrosis of bone (ANB) was investigated in 111 patients with systemic lupus erythematosus (SLE) (24 with ANB, 87 without ANB); patients' ages, corticosteroid treatment, clinical and laboratory features associated with SLE, and haemostatic profiles were all taken into account. The mean ages of patients with and without ANB at the time of diagnosis of SLE was 24.1 and 31.2 years respectively. The mean maximal daily dose of prednisolone in the group with ANB was 50.8 mg, which was significantly higher than the dose (41.8 mg) in the group without ANB. Disease features of SLE, such as Raynaud's phenomenon, hyperlipidaemia, nephrotic syndrome, hypertension, and disease activity, were not found to be related to ANB. The percentage of patients who had lupus anticoagulant as well as a shorter activated partial thromboplastin time was greater in those with ANB than in those without. Multiple factors may be involved in the pathogenesis of ANB in SLE, and it is suggested that haemostatic abnormalities, which could be influenced by corticosteroids and young ages, play some part in the development of ANB.

Since 1960 when Dubois and Cozen suggested an association of avascular necrosis of bone (ANB) with systemic lupus erythematosus (SLE),¹ ANB has continued to be one of the major problems during the course of SLE. Corticosteroids, which are used for most patients with SLE, have been implicated as one cause of ANB,²⁻⁶ but multiple factors, such as vasculitis,^{7,8} fat emboli,^{9,10} Raynaud's phenomenon,^{6,11} and young ages,^{12,13} must contribute to its development. As ANB may result from interference with the blood supply,⁷ haemostatic abnormalities and factors which induce them could also contribute to its occurrence.

In this study we attempted to determine the predisposing factors for ANB in SLE, considering particularly patients' ages, corticosteroid treatment, and haemostatic state.

Patients and methods

PATIENTS

Twenty four patients with SLE and ANB (three male, 21 female) and 87 patients with SLE but without ANB (two male, 85 female) at the Kyushu University Hospital from 1980 to 1987 were entered into the study. Patients whose SLE was diagnosed later than 1985 were excluded as possibly in these new patients ANB might develop in the near future. All patients met the 1982 revised American Rheumatism Association criteria for the classification of SLE.¹⁴ Most were already receiving corticosteroid treatment when evaluated. None of the patients abused alcohol or had chronic liver diseases. Evaluation of laboratory data was carried out when ANB was diagnosed in the group of patients with ANB and in March or April 1988 in the ANB negative group.

DIAGNOSIS OF AVASCULAR NECROSIS OF BONE

Bilateral hip joints of all the asymptomatic patients

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were examined by *x* rays and bone scanning scintigraphy using ^{99m}Tc -methylene diphosphonate. Other bones were examined similarly when they became painful. ANB was diagnosed when abnormal findings were obtained by both examinations.

HAEMOSTATIC EXAMINATIONS

Lupus anticoagulant was detected by determination of the activated partial thromboplastin time (APTT) with normal and patients' plasma, which was mixed 1:1 with 1:5 diluted platelet substitute according to the method of Colaco and Elkon.¹⁵ Lupus anticoagulant was considered positive when the mixing APTT was prolonged by more than 10 seconds as compared with the APTT of normal plasma. Platelet aggregation examinations were done in a Hematracer (Niko Biochemical, Tokyo, Japan) using platelet rich plasma. The aggregating agents were 3.0 and 1.0 $\mu\text{mol/l}$ of adenosine 5'-diphosphate and 2.0 and 0.5 $\mu\text{g/ml}$ of collagen. Platelet aggregation was measured by maximal aggregation rate. Patients were divided into those with normal, accelerated, or diminished platelet aggregation. The normal group was defined as those having a maximal aggregation rate $>60\%$ with the higher concentrations of adeno-

sine 5'-diphosphate and collagen and maximal aggregation rate $<50\%$ with the lower concentrations. The accelerated group were those with a maximal aggregation rate $>50\%$ with the lower concentrations, and the diminished group had a maximal aggregation rate $<60\%$ with the higher concentrations. Drugs which might have influenced the haemostatic state were discontinued for at least a week before the haemostatic examinations.

DATA ANALYSIS

Differences of continuous variables between groups were analysed with Student's *t* test, and differences of discrete variables by the χ^2 test with Yates's correction.

Results

PATIENTS WITH SLE AND AVASCULAR NECROSIS OF BONE

Of the 24 patients with ANB, the femoral head was affected bilaterally in 20 patients, on the left in three, and on the right in one. Three patients had ANB in other sites also. No patients were diagnosed as having had ANB before symptoms appeared. Table 1 gives details of the ages and steroid

Table 1 Age and steroid treatment in the patients with systemic lupus erythematosus and avascular necrosis of bone

Patient No	Sex	Age at the diagnosis of SLE* (years)	Time between diagnosis of SLE and onset of ANB* (years)	Max. daily dose of steroids† (mg/day)	Dose of steroid at the onset of ANB (mg/day)
1	F	24.8	2.8	60	2.5
2	F	22.8	6.7	50	10
3	F	10.0	10.0	40	7.5
4	F	28.2	3.3	30	15
5	F	24.4	3.3	60	10
6	F	16.9	1.4	60	15
7	F	17.6	2.8	60 (Cy)*	12.5
8	F	29.2	2.8	30	20
9	F	15.9	1.8	110	12.5
10	F	27.0	3.5	60 (Cy pulse)*	10
11	F	29.8	1.3	60	10
12	F	16.2	8.8	80	20
13	F	32.2	1.2	50	10
14	M	17.0	8.0	30	0
15	M	29.2	1.6	30	20
16	F	42.3	3.8	20	5
17	F	30.6	3.2	40	5
18	F	13.0	13.0	60 (Cy)	15
19	F	30.2	2.8	60	5
20	F	16.8	2.8	30	5
21	F	35.9	3.5	30	7.5
22	F	25.0	3.2	50 (Pulse)	17.5
23	M	15.9	6.0	60 (Aza* pulse)	12.5
24	F	27.8	1.8	60 (Cy)	20
Average		24.1	4.1	50.8	11.1

*SLE=systemic lupus erythematosus; ANB=avascular necrosis of bone; Cy=cyclophosphamide; pulse=pulse treatment; Aza=azathioprine.

†The steroid was prednisolone, except where otherwise indicated.

Table 2 Comparison of ages and corticosteroid doses in groups with and without avascular necrosis of bone

Patient group	Age at the diagnosis of SLE* (years)		Number (%) of patients younger than 20 at the diagnosis of SLE	Mean (SD) max. daily dose of steroids (mg/day)
	Distribution	Mean (SD)		
With ANB* (n=24)	10-42	24.1 (8.0)†	9 (38)†	50.8 (20.0)‡
Without ANB (n=87)	10-64	31.2 (9.9)	12 (14)	41.8 (18.0)

*SLE=systemic lupus erythematosus; ANB=avascular necrosis of bone.

†p<0.01.

‡p<0.05.

treatment of the 24 patients with ANB. The period between the time of diagnosis of SLE and of ANB ranged from 1.2 to 13 years (mean 4.1). The age of patients with ANB at the time of diagnosis of SLE ranged from 10 to 42.3 years (mean 24.1). This is significantly younger than the age of the group without ANB at the time of diagnosis of SLE, whose mean age was 31.2 years, ranging from 10 to 64 years (p<0.01) (Table 2). Of 24 patients with ANB, SLE was diagnosed in nine (38%) before the age of 20, whereas in the group without ANB only 12/87 (14%) were diagnosed before the age of 20—a significant difference (p<0.01).

Most patients in this study took corticosteroids after the diagnosis of SLE had been established. The dose of prednisolone given at the time of diagnosis of ANB ranged from 0 to 20 mg/day (mean 11.1 mg/day). The mean maximal daily dose of prednisolone in the patients with ANB was 50.8 mg, however, significantly higher than in the group without ANB (p<0.05) (Tables 1 and 2).

Factors thought to be associated with the pathogenesis of ANB in SLE were compared in the groups with and without ANB (Table 3). The

percentage of patients with hypocomplementaemia and positive anti-dsDNA antibodies, which reflect the disease activity of SLE, was small at the time of diagnosis of ANB and similar to that of patients without ANB. The incidence of Raynaud's phenomenon, which some investigators have suggested is associated with ANB,^{6 11} was high, but almost the same in patients with and without ANB. The group with ANB had a history of central nervous system involvement, which is considered to reflect vasculitis, also as frequently as the group without ANB. The incidence of hyperlipidaemia was smaller in both groups. Similarly, the incidence of hypertension and thrombocytopenia were similar in both groups. Nephrotic syndrome appeared more prevalent in the group with ANB, but the difference was not significant. Although the maximal daily doses of corticosteroids were different in the two groups, the proportion of patients receiving pulse treatment with 1000 mg/day methylprednisolone or immunosuppressive agents, or both, was the same in both groups.

HAEMOSTATIC EXAMINATIONS

Shortened APTT of more than five seconds compared with control was found in seven of 24 patients with SLE and ANB (29%) and in five of 44 patients without ANB (11%), not significantly different. Lupus anticoagulant, which is identified as a prolonged APTT in a mixing test with normal plasma, was detected in six of 24 patients with ANB (25%) and in only five of 44 patients without ANB (11%), also not significantly different. The total number of patients with shortened APTT together with lupus anticoagulant was 13/24 (54%) for those with ANB, which was significantly greater (p<0.05) than the 10/44 (23%) in the group without ANB (Table 4). Table 5 shows the platelet aggregation activity in patients with and without ANB. Patients with SLE were divided into three groups—namely, those whose platelet aggregation was normal, accelerated or diminished. There was no significant difference in platelet aggregation between the groups with and without ANB. In the patients with ANB, however, the percentage in the 'diminished' group was low

Table 3 Clinical and laboratory features of patients with systemic lupus erythematosus with or without avascular necrosis of bone

	With ANB* (n=24) No (%)	Without ANB (n=87) No (%)
Raynaud's phenomenon	12 (50)	39 (45)
CNS* involvement	5 (21)	15 (17)
Hypertension	4 (17)	11 (13)
Total cholesterol (>2.5 g/l)	6 (25)	17 (20)
Triglyceride (>1.5 g/l)	7 (29)	23 (26)
Nephrotic syndrome	6 (25)	10 (11)
Anti-dsDNA antibody (+)	3 (13)	19 (22)
Hypocomplementaemia (CH ₅₀ <29 U/ml)	6 (25)	26 (30)
Thrombocytopenia (<100×10 ⁹ /l)	3 (13)	8 (9)
Pulse treatment	3 (13)	11 (13)
Immunosuppressants	5 (21)	24 (28)

*ANB=avascular necrosis of bone; CNS=central nervous system.

Table 4 *Lupus anticoagulant and the activated partial thromboplastin time in patients with systemic lupus erythematosus with or without avascular necrosis of bone*

	With LAC* No (%)	Shortening of APTT* (<5 s) No (%)	Total No (%)
With ANB* (n=24)	6 (25)	7 (29)	13 (54)†
Without ANB (n=44)	5 (11)	5 (11)	10 (23)

*LAC=lupus anticoagulant; APTT=activated partial thromboplastin time; ANB=avascular necrosis of bone.

†Significantly higher ($p<0.05$).

Table 5 *Relation between platelet aggregation and avascular necrosis of bone*

	Platelet aggregation		
	Accelerated No (%)	Normal No (%)	Diminished No (%)
With ANB* (n=11)	5 (45)	5 (45)	1 (9)
Without ANB (n=34)	6 (18)	20 (59)	8 (24)

*ANB=avascular necrosis of bone.

There were no significant differences.

(9%) and in the 'accelerated' group high (45%) compared with the values (24% and 18% respectively) in the group without ANB.

Discussion

Avascular necrosis of bone is one of the most serious complications of SLE. There is still considerable controversy about its pathogenesis, however.

Corticosteroids have long been implicated in the pathogenesis of ANB. The duration of steroid treatment,¹⁶ the total cumulative steroid dose,¹² or the highest daily dose of steroids⁵ have been independently suggested as crucial causes of ANB. Several mechanisms of corticosteroid induced ANB have been proposed: (a) steroid induced hypercoagulable state^{17 18}; (b) fatty emboli due to abnormal lipid metabolism^{9 19}; (c) steroid induced osteoporosis²⁰; and (d) increase in the marrow fat cell size.^{13 21} There is, however, little evidence to support these mechanisms. On the other hand, Dubois and Velayos *et al* suggested that SLE itself, or vasculitis associated with SLE, was the main cause of ANB rather than corticosteroids.^{7 8}

Our results showed that the maximal daily dose of steroids was significantly related to the development of ANB, in agreement with the results of Abeles *et al*.⁵ Our results do not exclude, however, the possibility of a relation between SLE associated vasculitis and the development of ANB as the need

for a higher dose of steroids may have been due to the higher activity of SLE and vasculitis. On the other hand, when the diagnosis of ANB was made the average dose of prednisolone was small (11.1 mg/day), and even none in one patient, and the mean duration since the diagnosis of SLE was quite long, 4.1 years. These results and the laboratory data at the time of onset of ANB suggest that SLE was inactive when the diagnosis of ANB was made, which is consistent with the observation by Kalla *et al*.²² It is still not clear whether vascular changes or bone changes, or both, develop gradually over a long period of time after high doses of steroids or whether they suddenly appear at a particular time.

We found that ANB was more prevalent in patients whose SLE was diagnosed at younger ages, which is in agreement with other reports.^{12 13 16} The reasons are not clear, and there has been little discussion of the mechanism. Recent observations by Tanaka *et al* may provide a clue.²³ They analysed 2856 patients at necropsy with ages ranging from 0 to 40 years and found that the patients with collagen diseases (mainly SLE) had more severe atherosclerosis in the large arteries in the second and third decades of life than the patients without collagen diseases. They also found, surprisingly, that the atherosclerosis index was highest in the second decade of life in patients with SLE, whereas the index increased with age in patients with other diseases. Such changes in arteries in young patients with SLE, probably induced by SLE itself or corticosteroid treatment, or both, may be related to the genesis of ANB. In addition, ischaemic heart disease, probably due to atherosclerosis and arteritis in coronary arteries, is more often observed in young patients with SLE than in normal individuals.²⁴

There have been various reports in which Raynaud's phenomenon,^{6 11} hyperlipidaemia,⁹ or central nervous system lupus¹¹ has each been associated with the occurrence of ANB, but there is still controversy about such relations.^{5 6} We found that the incidence of such features of SLE was no higher in patients with ANB than in those without.

Pulse treatment with very high doses of steroids (1000 mg/day) for three days and immunosuppressants were not found to be related to ANB. This may mean that treatment with high doses of steroids for a fairly long period has more influence than very high doses of steroids for a short period on the genesis of ANB. The incidence of ANB is high in renal transplantation, in which very high doses of steroids are given for a longer period of time than in pulse treatment.^{2 3}

Recent investigations show that lupus anticoagulant, which is often found in the plasma of patients with SLE, is associated with thrombosis.^{25 26} Lupus

anticoagulant is identified by the prolongation of APTT.¹⁵ Conversely, shortening of APTT, which is sometimes induced by corticosteroids, is also indicative of hypercoagulable state.²⁷ Our results showed that the total number of patients who had lupus anticoagulant as well as a shortened APTT was greater in the group with ANB than in the group without ($p < 0.05$). The pathogenesis of ANB is probably due to many factors,^{6, 28} of which these abnormal haemostatic states may be a part. There have been few reports which describe the platelet function in SLE. Some investigators have suggested that the aggregation of platelets is normal or impaired in patients with SLE.^{29, 30} On the other hand, we have recently shown that patients with SLE can be divided into three groups—namely, those with normal, accelerated, or diminished platelet aggregation, in an approximate ratio of 3:1:1.³¹ In this study the group with ANB had a fairly high incidence of accelerated and low incidence of diminished platelet aggregation, though there was no significant difference from the group without ANB. More examinations of platelet functions are needed to confirm this. The tendency towards accelerated platelet aggregation may also play some part in the genesis of ANB.

This study suggests that special attention should be paid to the possible development of ANB when young patients with SLE are treated with high doses of corticosteroids. We tentatively conclude that haemostatic abnormalities and vascular changes, which must be caused by SLE itself, corticosteroid treatment, and young ages, may all, in part, contribute to the pathogenesis of ANB in SLE.

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