Avascular necrosis of the femoral head in childhood systemic lupus erythematosus

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Summary: Four of 10 children with SLE kept under observation over the past nine years have developed avascular necrosis (AN) of the femoral head. The symptoms of AN are insidious and unpredictable and predate the radiologic diagnosis by weeks to months. In a comparison of these chidren with SLE, with and without AN, with a group of patients with nephrosis treated with corticosteroids and a group with glomerulonephritis treated with azathioprine, AN was related to the duration of daily steroid therapy rather than the total duration of steroid treatment; this was not true for azathioprine. The occurrence of AN in our patients while they were on alternate-day steroid therapy, or coincident with a relapse, suggests that its development is determined by underlying disease.

Résumé: *Nécrose avasculaire de la tête fémorale chez des enfants souffrant de lupus érythémateux disséminé (LED)*

Quatre des 10 enfants souffrant de LED et gardés en observation pendant neuf années ont présenté une nécrose avasculaire (NA) de la tête fémorale. Les symptômes de ce syndrome sont insidieux et imprévisibles et surviennent longtemps avant le diagnostic radiologique, de quelques semaines à plusieurs mois. Si on compare ces enfants souffrant de LED, avec ou sans NA, à un groupe de malades néphrotiques traités aux corticoïdes et à un autre groupe de malades souffrant de glomérulonéphrite traités à l'azathioprine, la NA était reliée plus à la durée de la corticothérapie quotidienne qu'à la durée totale de la corticothérapie. Ceci n'était pas vrai en ce qui concerne l'azathioprine. La survenue de la NA chez nos malades alors qu'ils étaient soumis à une corticothérapie intermittente (tous les deux jours) ou alors qu'elle coïncidait avec une rechute, permet de croire que son apparition est déterminée par la pathologie profonde.

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Avascular necrosis (AN) occurring during the course of systemic lupus erythematosus (SLE) was first described in 11 of 400 adult patients by Dubois and Cozen[1] in 1960, and 15 similar cases have since been reported.[2-5] Its ocurrence has not been previously mentioned in children with SLE. Of 10 children with SLE seen by us from August 1964 to June 1973 four have developed this complication. With the use of corticosteroid therapy for SLE it is difficult to determine whether avascular bone necrosis is part of the natural course of the disease or secondary to treatment. In order to assess the effect of corticosteroid and cytotoxic therapy in producing the condition we have compared children with SLE and AN with others with SLE but without AN, and also with a group of children treated with these drugs during the same years for nephrosis and glomerulonephritis.

The diagnosis of SLE was based on the presence of multisystem involvement* with laboratory confirmation — positive LE cell preparation, positive antinuclear antibody and lowered β_1C globulin.

The general treatment regimen consisted of prednisone or an equivalent steroid in a dosage of 60 mg/m^2 daily in divided doses until signs and symptoms of the condition were considered controlled. Then an alternate-day or three-day weekly schedule was slowly introduced; on the appearance of signs of relapse daily steroid was restarted. Azathioprine 4 mg/kg daily was used together with the steroid in all but one patient for the duration of treatment. This combination therapy was continued throughout the entire time the patients were in our care.

Comparison groups

We have grouped the patients for comparison as follows: IA, four with SLE and AN; IB, six with SLE and no AN; II, 15 with the minimal lesion-nephrotic syndrome and multiple relapses; and III, eight with proliferative, epimembranous and membranoproliferative glomerulonephritis. Group II patients were treated with the following regimen: daily prednisone or equivalent 60 mg/m^2 for one to two months for the first attack, then for subsequent relapses a similar type of daily therapy initially followed by varying durations of alternate-day or three-day weekly prednisone

*A minimum of four criteria as recommended by the American Rheumatism Association for the diagnosis of SLE.[6]

therapy using the same dose as before on each occasion. Two children received nitrogen mustard during the period of study. No azathioprine was used in this group. Treatment of group III consisted of one to two months of daily prednisone 60 mg/m² with continuation on an alternate-day schedule at the same dosage for the duration of treatment. Azathioprine was used in the same dosage and manner as in the SLE patients. One patient from each of groups II and III had hip or thigh pain for which no reason was found by radiologic examination. To this time there is no evidence of AN. Statistical analysis of the differences between groups of patients was carried out using Fisher's exact test.

Case reports

Case 1

In 1968 SLE was diagnosed in a 12-year-old patient (Fig. 1). She had three clinical relapses over the next four years during treatment with azathioprine and daily corticosteroid. While on alternate-day prednisone therapy in March 1972 she began to complain of pain in the right quadriceps femoris and pelvic weakness. Radiographs of the hips were normal. Pain persisted for six months, gradually spreading to the knee and followed by limitation of abduction and adduction of the right hip. Results of neurologic investigations, including electromyography and nerve conduction velocity studies, were normal. Radiographs of the hips in September 1972 showed AN of both femoral heads, more marked on the right (Fig. 2). After an unsuccessful trial of conservative management with crutches, right femoral head replacement with a Moore's prosthesis has resulted in some symptomatic improvement.

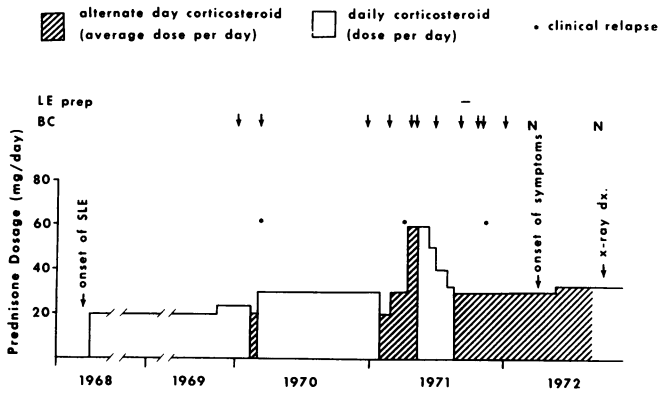

FIG. 1—Clinical course in case 1. BC = β_1C globulin.

Case 2

SLE was diagnosed in 1963 in an 11-year-old patient (Fig. 3). She was treated with daily prednisone and azathioprine for the next two years, during which time she had three relapses. In November 1966 she was readmitted to hospital with a two-month history of pain in the left hip associated with a limp. The pain was not exacerbated by walking or by passive movement of the hip through the full range. Radiographs revealed early AN of the left femoral head, whereas films taken five months earlier had been normal. Daily corticosteroid and azathioprine therapy was continued. Weight-bearing was minimized by the use of crutches and an abduction brace. She continued to have pain in the left hip as well as arthralgia in the knees, ankles and right hip. By January 1967 radiologic examination showed progressive collapse of the left femoral head. She was considered to be in clinical relapse at the time. By 1970 she still had pain and limitation of abduction in the left hip. Presently she is asymptomatic except for occasional pain in the affected hip on prolonged standing. She walks with a scarcely noticeable limp.

Case 3

The diagnosis of SLE was made in September 1964 in a 16-year-old patient (Fig. 4). She had been given cortisone for symptomatic relief of joint pains for the previous nine months, which resulted in a cushingoid appearance. Following establishment of the diagnosis she was treated initially with azathioprine and daily prednisone, then the prednisone was tapered over four months to an alternate-day schedule. The patient remained in remission until June 1965, when a malar rash and pain and stiffness of several joints, including hips and knees,

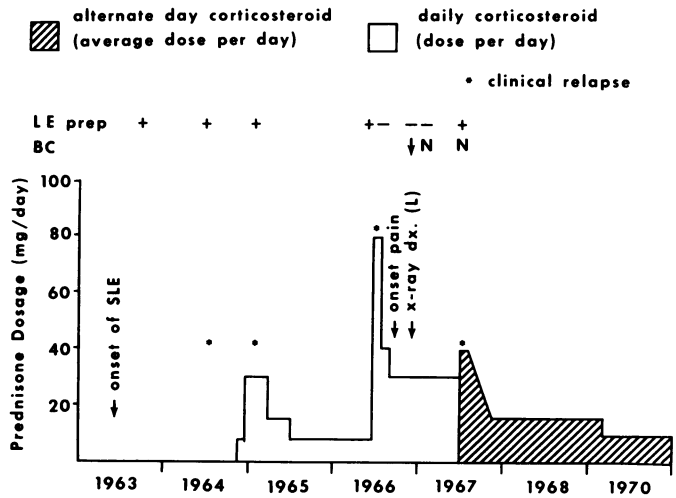

FIG. 3—Clinical course in case 2.

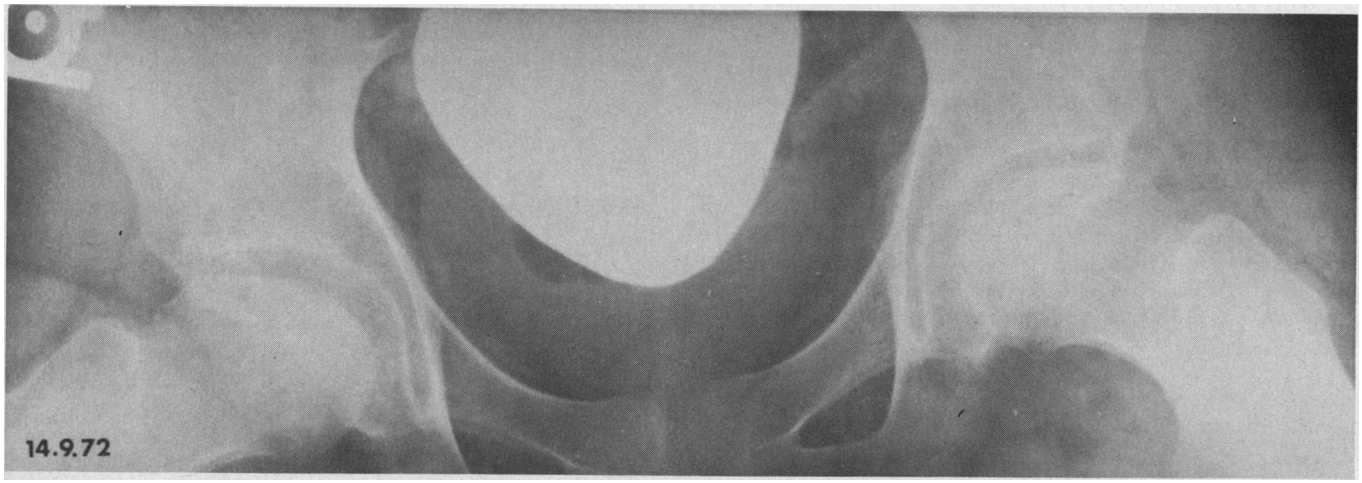

FIG. 2—Case 1. Abduction projection of the hips six months after the onset of right hip pain. The right femoral head is irregularly deformed and flattened by aseptic necrosis. Much earlier changes of a similar nature are seen in the left femur.

recurred. After three weeks of symptoms she was admitted to hospital with local tenderness over the left hip joint and limitation of active and passive movement of the left hip, especially external rotation. The LE cell preparation was again positive. Radiographs of the hips, which had been normal eight months earlier, showed early AN. By October 1965 the head of the right femur had partly collapsed (Fig. 5). She was treated conservatively with an abduction brace. Because pain and decreased hip mobility persisted the femoral head was replaced in May 1971. Her subsequent course was complicated by central nervous system lupus erythematosus in December 1965 and March 1966, necessitating a return to daily steroid therapy. In June 1966 she complained of soreness of the left elbow. Radiographs revealed early collapse of the capitulum of the humerus. In March 1971 right wrist pain occurred and by June of that year AN of the scaphoid bone was demonstrated. There had been no history of trauma.

Case 4

In 1968 SLE was diagnosed in a 15½-year-old patient (Fig. 6). She responded to daily prednisone and immunosuppressive therapy but a relapse occurred in 1969 with several renal involvement. Following recovery, steroid therapy was adjusted from a daily to an alternate-day regimen. Approximately two years after the original diagnosis the patient began to complain of pain and swelling of the knees. Knee and hip radiographs were normal. The right knee was unsteady and often "gave way" unexpectedly. No limitation of movement was found. After five months of knee pain it was noted that abduction of the right hip was limited. During the 14 months after the knee symptoms began she developed internal rotation contractures with hip pain. Radiographs demonstrated partial collapse of the femoral head. Conservative management was unsuccessful in improving function of the hips. Intertrochanteric osteotomy and adductor tenotomy failed to ameliorate symptoms at first but resulted in gradual improvement over the subsequent three years with complete remission of pain and limp despite a fragmented femoral head.

Comparison of drug therapy

Duration of disease and treatment are shown in Table I. Group IA patients received daily steroid treatment for a longer period than group IB patients ($P < 0.01$). Although the total duration of steroid therapy was greater in group II than in those patients with AN (group IA) the period

Table I—Comparison of duration of corticosteroid and azathioprine therapy

Patient group	Duration of disease (months)	Total duration of corticosteroid (months)	Total duration of daily corticosteroid (months)	Duration of azathioprine (months)
IA	39 (21-53)	30 (18-42)	23 (5-38)	16 (5-27)
IB	36 (19-54)	21 (9-45)	5 (2-9)	15 (10-41)
II	98 (66-150)	46 (23-85)	11 (5-30)	0
III	49 (22-90)	33 (8-72)	1.5 (102)	45 (22-90)

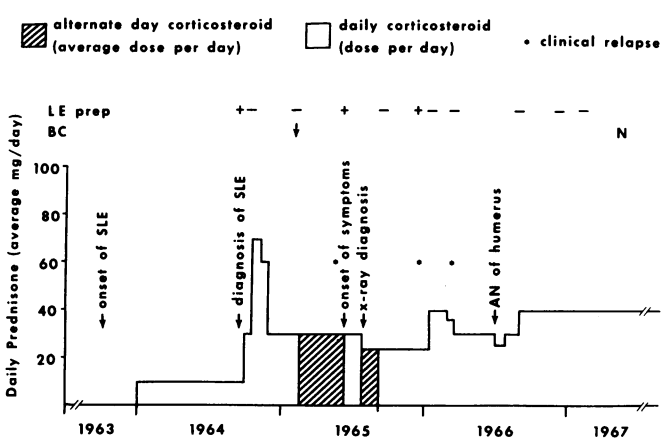

FIG. 4—Clinical course in case 3.

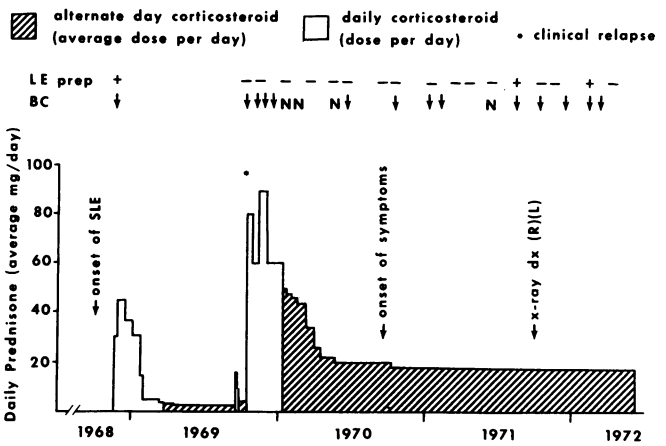

FIG. 6—Clinical course in case 4.

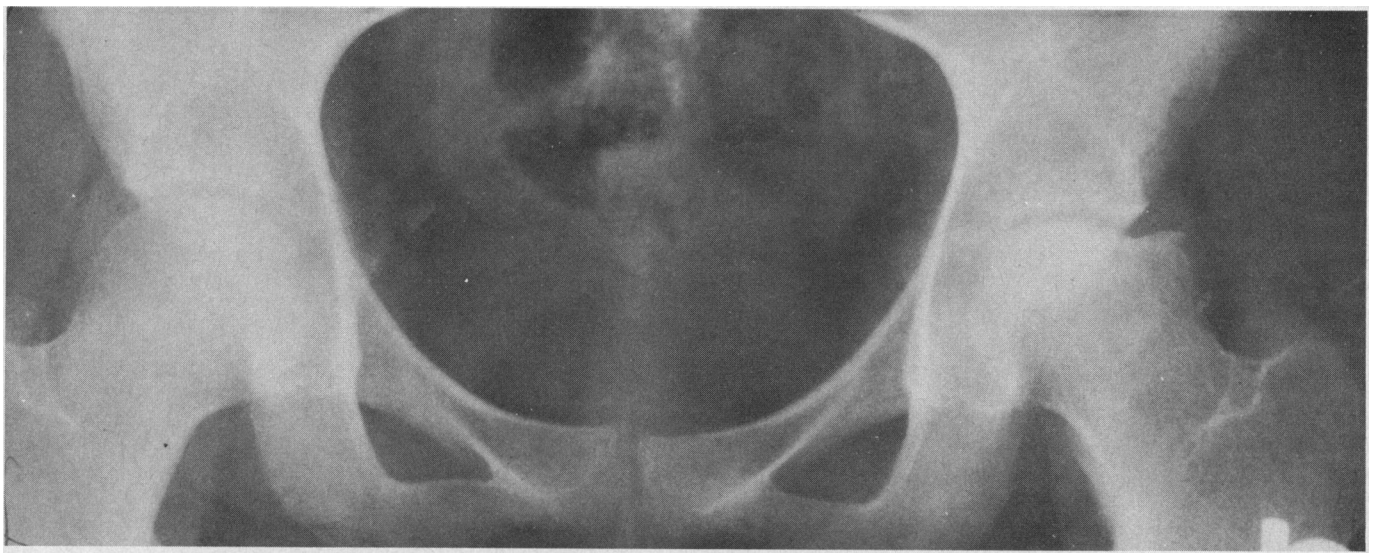

FIG. 5—Case 3. Four months after onset of hip pain the left femoral head has partly collapsed.

of daily steroid therapy was much less ($P < 0.001$). The total duration of steroid therapy in group III was similar to that in group IA; the duration of daily steroid was much less and the duration of daily azathioprine treatment markedly greater in group III. The duration of azathioprine therapy was similar in groups IA and IB.

Discussion

Avascular necrosis of the femoral head has been seen in patients with untreated SLE and in patients receiving corticosteroids for other conditions. The use of corticosteroids in the treatment of SLE has blurred the distinction between the role of the disease itself and that of the treatment in the pathogenesis of AN.

In diverse conditions not ordinarily associated with joint or bone pain,[7] such as erythema multiforme, multiple sclerosis, thrombocytopenic purpura, pituitary deficiency, chronic pemphigus and renal transplantation, AN has occurred during corticosteroid therapy. In renal transplantation, where this condition is being seen with increasing frequency, the role of corticosteroids is unclear. Cruess *et al*[8] found no difference in total steroid dose between the 10 patients who did develop AN following transplantation and the 17 who did not. In that series all the patients required continuous daily therapy. On the other hand, Harrington *et al*[9] in a series of post-transplant patients found AN in 16 of 50 in the high steroid dosage group, but only 2 of 101 in the low dosage group had this complication.

AN has been reported in untreated SLE;[1] of 11 patients with AN one had never received corticosteroids, five had received no corticosteroids for many months to years before the onset of clinical manifestations and the remaining five had received doses equivalent to 10 to 30 mg of prednisone daily. AN has been a major source of morbidity in our patients with SLE. Pain in the leg, thigh or knee, accompanied later by limitation of adduction and abduction, predate the radiologic diagnosis of AN of the femoral head by weeks to months.

Although the pathogenesis of AN is unknown several explanations have been offered. Fat emboli have been implicated as a cause in patients with renal transplants.[10] Hypercortisolism has been suggested as the cause of the embolization.[11] Our patients with AN had no evidence of hyperlipemia but it is of interest that those in group II with hyperlipemia and treated with corticosteroid have never developed AN. Because of the tenuous blood supply to the femoral head through the ligamentum teres the vasculitis of SLE may contribute to the pathogenesis of the AN. We have no direct evidence of this in our patients but three of four did have the onset of symptoms coincident with recrudescence of their disease.

AN of the femoral head develops insidiously and unpredictably in patients with SLE. Obviously many factors are interrelated in the pathogenesis. AN seems related to the duration of daily steroid therapy rather than the total duration of steroid treatment. Azathioprine is clearly not related to the development of AN. The fact that AN occurred in our patients while on alternate-day steroid therapy, or coincident with a relapse, strongly suggests that the underlying disease is important in its development.

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