Extensive extraspinal hyperostoses after long-term oral retinoid treatment in a patient with pityriasis rubra pilaris

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We describe a patient with severe pityriasis rubra pilaris in whom extensive extraspinal hyperostoses developed after 13 years of oral retinoid treatment. The most prominent abnormality was a bridging exostosis between the left acetabulum and collum. X-ray examinations of the spine during retinoid therapy showed no abnormalities. During oral retinoid treatment, it is important to ask the patient on a regular basis about any skeletal pains or mobility restriction. Normal spinal x-ray results are no guarantee that a patient is free of hyperostoses. Discontinuation of acitretin therapy resulted in a severe exacerbation of the patient's pityriasis rubra pilaris after 2 weeks. The clinical response to administration of azathioprine was clearly inferior to that of acitretin. However, low-dose oral methotrexate therapy appeared to be a good alternative in this patient, with a clinical result comparable to acitretin and no side effects after 6 months of therapy. (J AM ACAD DERMATOL 1995;32:322-5.)

Pityriasis rubra pilaris (PRP) is characterized by follicular erythematous and hyperkeratotic papules typically distributed on the trunk and extensor surfaces of the extremities. Extensive erythema and scaling or erythroderma may occur, interspersed with sharply demarcated "islands" of normal skin. Keratoderma of the palms and soles is common; the hyperkeratosis often has a yellowish color.[1-3]

Griffiths[4] classified PRP into two adult types (classic and atypical) and three juvenile types (classic, circumscribed, and atypical). The classic adult type accounts for more than 50% of cases.[4] Satisfactory results with oral retinoid therapy have been reported,[1-3, 5-7] although not all patients benefit from such treatment. Juvenile forms of PRP tend to have a better response to retinoid treatment than adult forms of the disease.[5, 6] Skeletal abnormalities with changes similar to DISH (*d*iffuse *i*diopathic *s*keletal *h*yperostoses), extraskeletal ossification, premature epiphyseal closure, and osteoporosis have been reported as long-term side effects of oral retinoid therapy.[8-14] These skeletal changes strongly resemble those observed in hypervitaminosis A syndrome.[15] According to most authors, the spine is the site of predilection for retinoid-induced hyperostoses.

We describe a patient with PRP and extensive extraspinal hyperostoses after long-term retinoid treatment.

CASE REPORT

A boy born in 1959 had severe classic juvenile PRP that first started at age 9 years and consisted of a persistent erythroderma (except for some small "islands" of normal skin), hyperkeratotic follicular papules, and diffuse palmoplantar hyperkeratosis (Fig. 1, *A*).

Histologic examination showed a slightly acanthotic epidermis and diffuse and follicular hyperkeratosis and parakeratosis. There was follicular plugging and perifollicular parakeratosis. The papillary dermis showed a predominantly lymphocytic infiltrate.

Local therapy and UVB irradiation were ineffective. Oral retinoid treatment was started in 1977 and continued until January 1992 (retinoic acid, 25 to 50 mg/day from 1977 to 1979; etretinate, 50 to 75 mg/day from 1979 to 1987; acitretin, 35 to 50 mg/day after 1987). This regimen resulted in marked clinical improvement (Fig. 1, *B*). Side effects were limited to cheilitis and some alopecia. Attempts to lower the dosage of oral retinoids to less than 35 mg/day (0.3 mg/kg/day) were unsuccessful. Addi-

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Presented in part at the Eighteenth World Congress of Dermatology, New York, NY, June 12-18, 1992.

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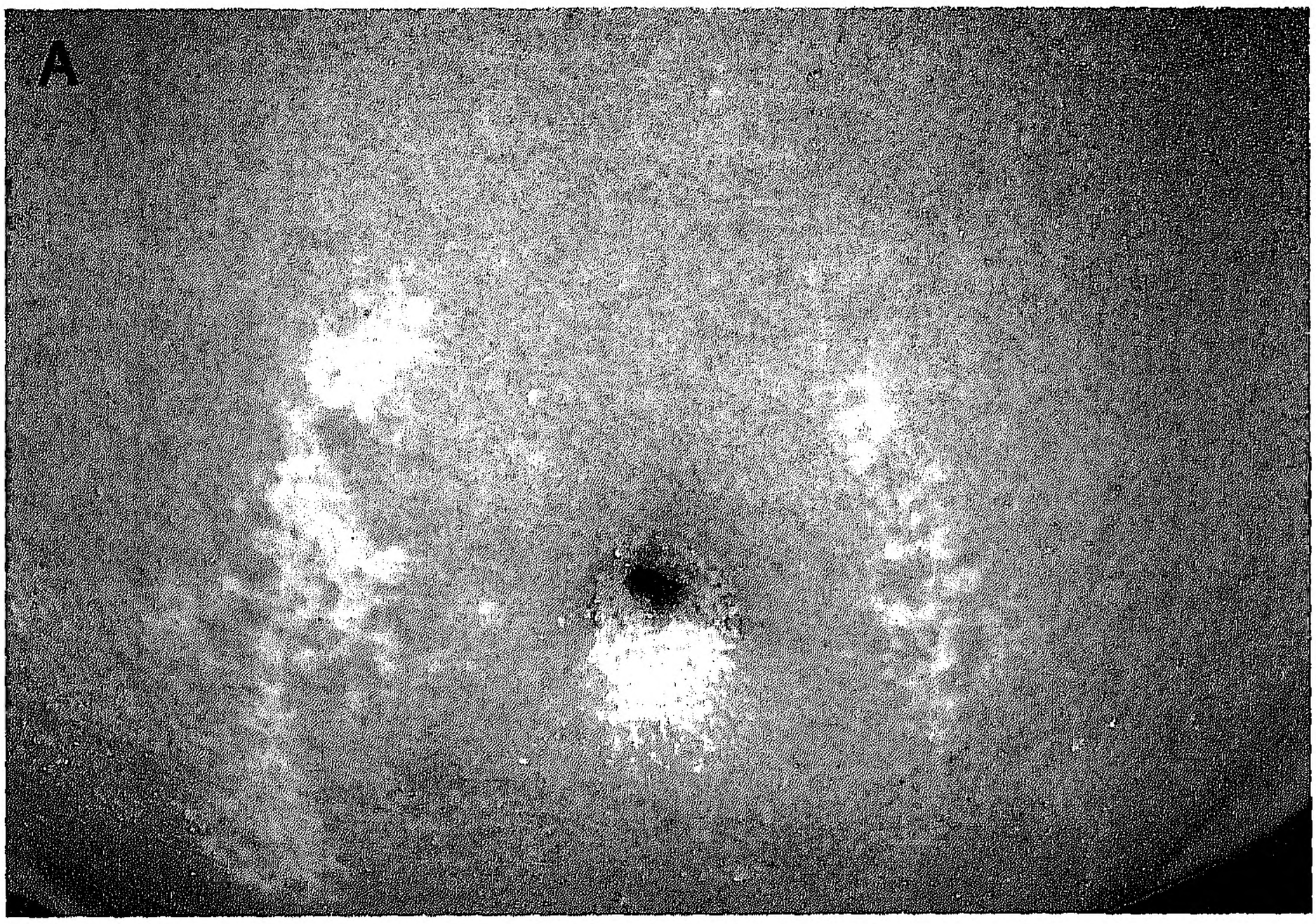

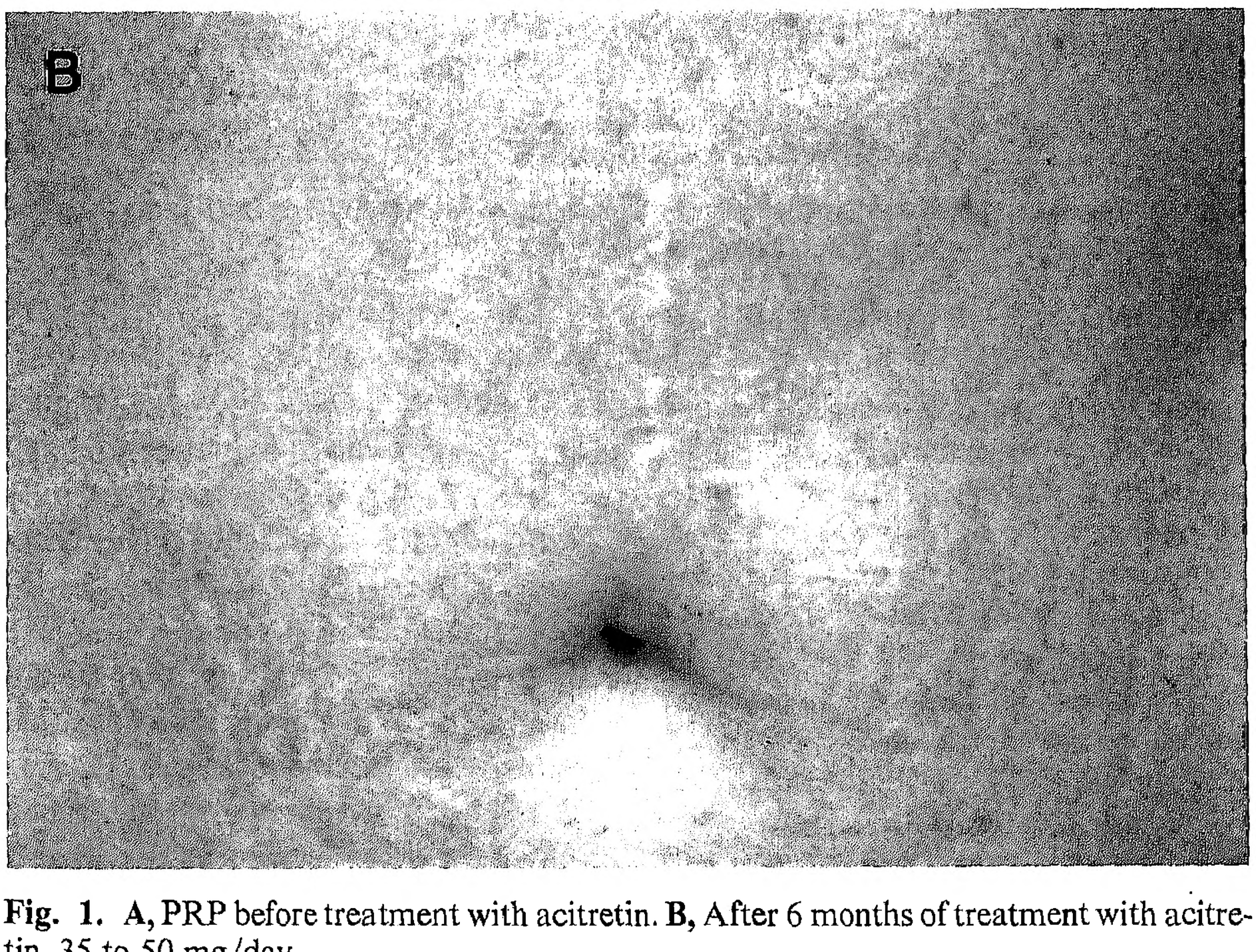

Fig. 1. **A,** PRP before treatment with acitretin. **B,** After 6 months of treatment with acitretin, 35 to 50 mg/day.

tional routine x-ray examinations of the spinal column showed no abnormalities.

In August 1990 the patient reported progressive pain and restricted mobility in his left hip. Radiographs showed extensive periostal hyperostoses of both hips and, to a lesser extent, of the shoulders. A bridging exostosis was present between the left acetabulum and collum (Fig. 2). Successful surgery was performed on the left hip. Acitretin treatment was discontinued after surgery and PUVA therapy was started. Two weeks later treatment with acitretin was restarted because of a severe exacerbation. In January 1992 acitretin therapy was again discontinued. Azathioprine therapy was introduced with an initial dosage of 50 mg/day and a maintenance dosage of 200 mg/day. The clinical response was inferior to that of acitretin therapy, but treatment was continued for 10

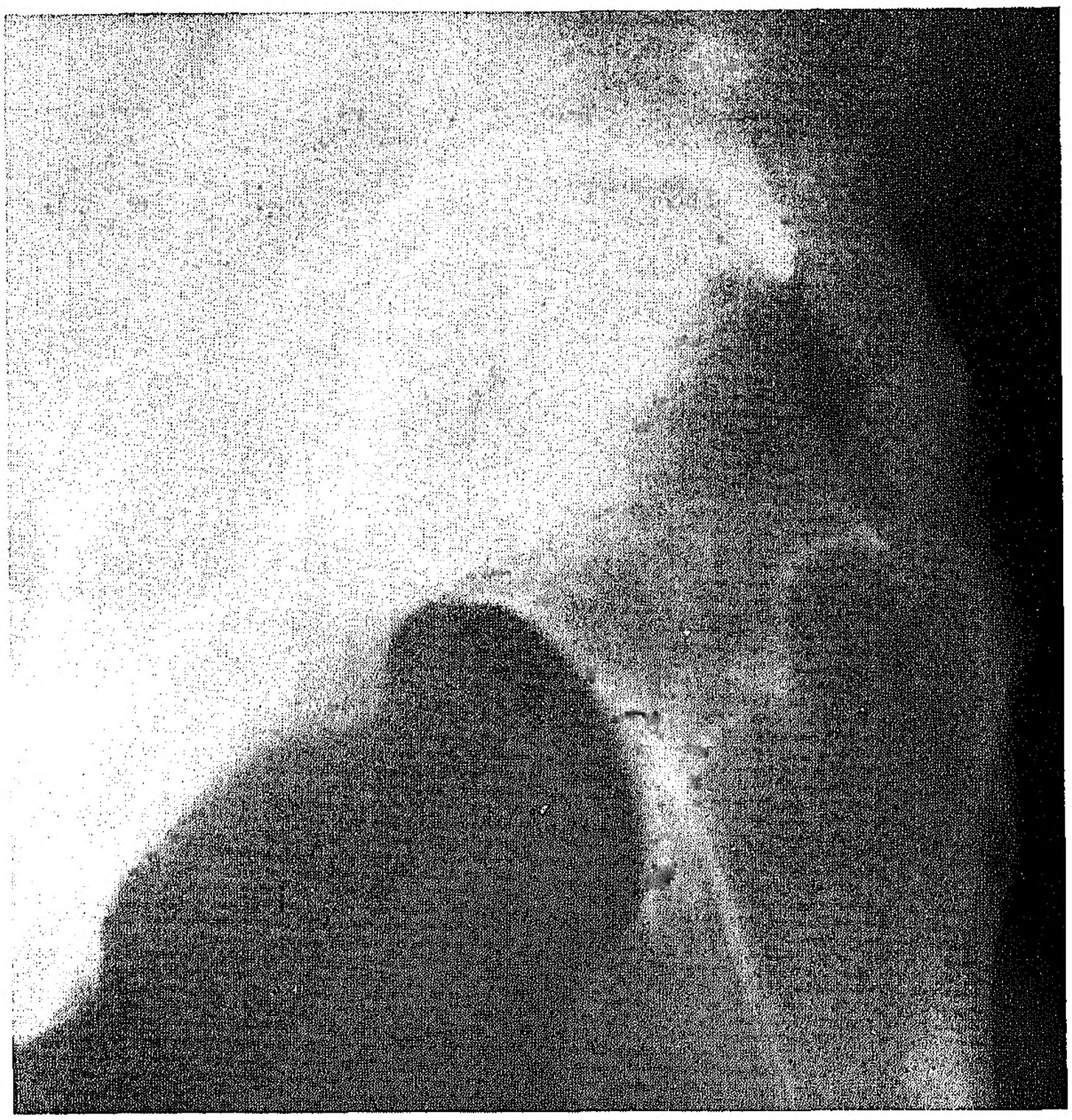

Fig. 2. Extensive periostal hyperostoses and bridging exostosis between the left acetabulum and collum after 13 years of oral retinoid treatment.

months. In October 1992, the erythroderma became more pronounced and the patient reported malaise, thirst, and chills. Azathioprine therapy was discontinued and a 2-week course of prednisone (30 mg/day) was prescribed. Subsequently methotrexate (MTX) was given according to the divided schedule proposed by Weinstein and Frost.[16] The dosage was gradually increased from 7.5 mg/wk to 15 mg/wk. Laboratory investigations were performed according to the international MTX guidelines.[17] In general, the response to treatment with MTX has been satisfactory and comparable with the response to acitretin therapy. After 6 months of therapy there have been no clinical or laboratory side effects.

DISCUSSION

Many reports have appeared about retinoid-induced skeletal abnormalities,[8-14] but the true incidence and severity of skeletal problems are not yet sufficiently established. A major problem is the differentiation of retinoid-induced bone changes from those induced as a result of aging or unrelated diseases. It is generally accepted that retinoid-induced skeletal abnormalities predominantly affect the spinal column. Exclusively extraspinal abnormalities have been reported only occasionally.[9, 18, 19]

Further prospective and controlled studies of retinoid-induced skeletal abnormalities are necessary before definitive guidelines for the surveillance of patients before and during retinoid treatment can be established. Currently most authors advise pretreatment and annual radiographs of the lateral spine with additional views of symptomatic areas.[10, 11, 20, 21] Others recommend additional screening of the pelvis, calcaneus, and long bones.[12, 14] Finally, there are some authors who do not recommend any routine screening but only obtain radiographs of symptomatic areas in addition to radiographs of the spine (and calcaneus) before treatment.[22, 23]

A complete response to azathioprine therapy (50 to 200 mg/day) in four of five patients with widespread PRP was reported by Hunter and Forbes.[24] Griffiths[4] reported a satisfactory response in seven of eight patients. There are several reports on the efficacy of MTX in PRP.[4, 25-27] Usually daily or weekly schedules were used in dosages similar to the psori-

asis schedule. In their review of PRP, Cohen and Prystowsky[1] stated that "although most patients with PRP respond to methotrexate, many relapse when therapy is discontinued; reinstitution of the drug usually results in rapid clinical improvement." Griffiths[4] was less optimistic; combining his own data with those in the literature, he reported that of 44 patients treated with MTX only 17 showed any response.

Azathioprine therapy was not successful in our patient, but low-dose oral MTX therapy was comparable to acitretin in efficacy.

This article illustrates the problems in management of patients with retinoid-induced skeletal abnormalities. Discontinuation of retinoid therapy is not always possible; if it cannot be discontinued, more hyperostoses are likely to develop. It is important to be aware that normal results of spinal x-ray studies do not guarantee that a patient is free of hyperostoses. It is also important to ask about skeletal pains and mobility problems regularly during oral retinoid treatment, because patients do not usually connect these symptoms with retinoid treatment and therefore do not always indicate them spontaneously.

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