Computed Tomography Does Not Support Sacroiliitis as a Feature of Behçet Disease

A Metaanalytic Review

To the Editor:

Whether sacroiliitis is a feature of Behçet disease (BD) has been a subject of debate for many years.[1] Some authors have found a high prevalence of sacroiliitis, whereas others have found no association at all.[2] High observer variation in interpreting radiographs of sacroiliac joints (SI) has been suggested as the main cause of these differing results.[3]

Computed tomography (CT) is known as a more sensitive technique than plain radiographs in early detection and definition of SI changes,[4,5] and has been recommended for more precise imaging in patients with equivocal sacroiliitis on plain films.[6]

Our aim was to study the SI changes seen on plain films of patients with BD by means of CT, along with 2 different control groups consisting of healthy subjects and patients with rheumatoid arthritis.

Because widely differing prevalences of sacroiliitis have been found in different series of patients with BD, we also aimed to perform a metaanalysis of these results.

Standard anteroposterior radiographs of the SI joints of 134 patients fulfilling International Study Group Criteria for BD[7] were evaluated. One control group consisted of 14 age- and sex-matched healthy subjects. A second control group consisted of 15 age- and sex-matched patients with rheumatoid arthritis. Radiographs were mixed with those of the control patients and were read by a radiologist (IT) and a rheumatologist (NK) twice within 2 months. They were unaware of the diagnosis. Each SI was scored separately using the New York Criteria on a 0–4 scale (0 = normal, 1 = suspicious, 2 = possible or minimal, 3 = moderate changes, 4 = ankylosis of the SI).[8] In case of disagreement, radiographs were read again together and a reconciled grade was accepted.

In a second step, each patient and control subject with a diagnosis of sacroiliitis on plain film had a sacroiliac CT scan. The CT scans were graded according to New York Criteria on the same scale by the same observers without any knowledge of the plain film findings.

Metaanalysis was performed after the literature review for relevant papers. Ten articles[9–18] related to the subject was found and reviewed. Five of them were found suitable for inclusion in the metaanalysis.[1,9,12,15,21] They were dealing with the prevalence of sacroiliitis, so fixed-effects model (Peto) was used.[19] Tests of heterogeneity of the effect size were conducted to determine whether one or more studies exerted an unusually large influence on the results or its effect size differed substantially from those of the other studies. Kappa values were calculated and chi-squared test was used.[20]

Thirty-one patients with BD (16 men and 15 women) had a mean age of 35.9 ± 9.1 year (range, 16–60 years) with a mean disease duration of 7.1 ± 5.8 years (range, 1–20 years). The healthy control group consisted of 7 men and 7 women with a mean age of 32.5 ± 10.9 years (range, 18–52 years), In the group of patients with rheumatoid arthritis, 7 men and 8 women had a mean age of 37.5 ± 10.0 years (range, 25–50 years). The groups were statistically similar ($P > 0.05$).

Of the 134 radiographs of patients with BD, 31 were evaluated as having sacroiliitis (23.1%). Two patients had bilateral grade 3 sacroiliitis, 1 patient unilateral grade 3, 2 patients had grade 2 on one side and grade 3 on the other side (Table 1). Two patients had unilateral grade 2 sacroiliitis. The rest of the 24 patients had equivocal findings: bilateral or unilateral grade 1 lesions. None of the patients had clinical evidence of sacroiliitis. Two patients (14.2%) in the healthy control group and 2 patients (13.3%) in the rheumatoid arthritis group had unilateral grade 2 sacroiliitis. CT confirmed sacroiliitis in 7 of 31 patients in the BD group (22.5%) and eliminated inflammatory sacroiliitis in the rest of the patients with equivocal sacroiliitis (Figs. 1 and 2). For plain films, the intraobserver variation (kappa value) for the first observer (IT) was 0.74; for the second observer (NK), it was 0.69. The interobserver variation was 0.78. For CT images, these values were 0.90, 0.80, and 0.78, respectively. When we performed metaanalysis with these 5 studies, we found the chi-squared value for heterogeneity was 19.47 with an odds ratio of 2.27 (95% confidence interval [CI], 1.49–3.46) ($P < 0.001$). When the metaanalysis was repeated without Dilsen's study; the chi-squared value for heterogeneity was calculated as 7.0872; the table value for the chi-squared test was 7.82 with an odds ratio of 0.78 (95% CI, 0.38–1.62). Although $7.09 < 7.82$, we accepted this result as homogenous; also, it was quite significant ($P = 0.045$).

Examining the individual studies included in this metaanalysis, there are 2 studies that showed significantly higher prevalences of sacroiliitis over control groups.[2,9] Yazıcı et al. found the prevalence of sacroiliitis as 35.1% in patients with BD versus 56.5% in the control group.[12] Dilsen et al. stated this ratio as 36.8% and 5%, respectively.[9] These studies reported the prevalence of sacroiliitis in diseased groups similarly, whereas the main conflict was in the control groups. Dilsen et al. found the sacroiliitis prevalence in the control group as 5%; but this ratio was 56.5% in the other study, debating against the idea of sacroiliitis being the feature of BD like other spondyloarthropathies.[12] Some years later, Olivieri et al. conducted a similar study by CT scan and announced similar results as Dilsen's study.[2] The prevalence of sacroiliitis was 30% in the BD group versus 5% in the control group. Chamberlain et al. calcu-

TABLE 1. Metaanalysis: Fixed Effects Model(Peto)

Author of study	Year	Bchcct Disease		Control		Odds Ratio	95% Confidence Interval	
		Observed	Total	Observed	Total			
Yazici	1992	13	37	13	23	0.42	0.15	1.20
Chamberlain	1993	5	34	4	25	0.62	0.12	3.25
Olivieri	1991	6	20	1	20	5.41	1.08	27.08
Dilsen	1985	112	331	6	92	3.88	2.32	6.48
Magraoui	2001	2	27	2	15	0.51	0.06	4.28
Total patients = 613						2.27	1.49	3.46

Chi-square for heterogenity = 19.4699 P < 0.001

lated these ratios more or less near to each other: 14.7% in the BD group versus 16% in the control group, which was later confirmed with a very recent study from Morocco as 7.4% versus 8%, respectively.[21] When we performed metaanalysis with these 5 studies, we found the chi-squared value for heterogeneity to be very high. The potential sources of this heterogeneity might be the difference in patient selection criteria, definition of the radiographic involvement (previously stated high interobserver variation in the interpretation of the radiographs), and the use of different imaging techniques (2 of the studies used CT scan; the others used plain radiography). When metaanalysis was repeated without Dilsen's study, the chi-squared value was calculated as 7.0872 (the table value for the chi-squared test was 7.82), which was accepted as homogenous ($P = 0.045$). This result suggested that the prevalence of sacroiliitis was more or less similar to the normal control group. In our study, with plain radiographs, the frequency of sacroiliitis was 23.1% in patients with BD; in the healthy control group, it was 14.2%; and in the control group with rheumatoid arthritis, it was 13.3% ($P < 0.05$), comparable to the results of the study by Chamberlain et al. According to our results with CT scan, sacroiliitis was found in 5% of patients in the BD group, 7% in the healthy control group, and 6.6% in the rheumatoid arthritis control group, very similar to the results of Maghraoui et al. Olivieri also stated the sacroiliitis ratio as 5% in a normal population by CT scan. Some studies have also demonstrated that the diagnosis of sacroiliitis on plain radiographs might not be confirmed by CT scan.[22,23] In our study, the sacroiliitis ratio of 14.2% in a normal population might seem very high, but asymmetric joint involvement over the age of 30 was stated as 77% of subjects and over the age of 40 as 87%.[24] All of the patients in the control groups had asymmetric joint involvement.

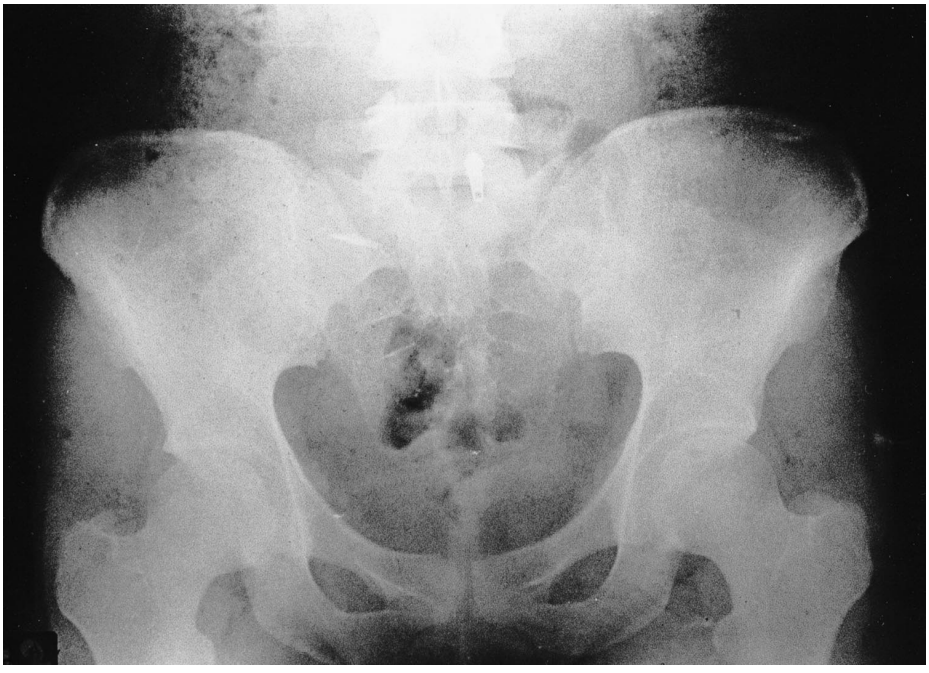

FIGURE 1. Plain film of a patient interpreted to have bilateral sacroiliitis on routine radiograph.

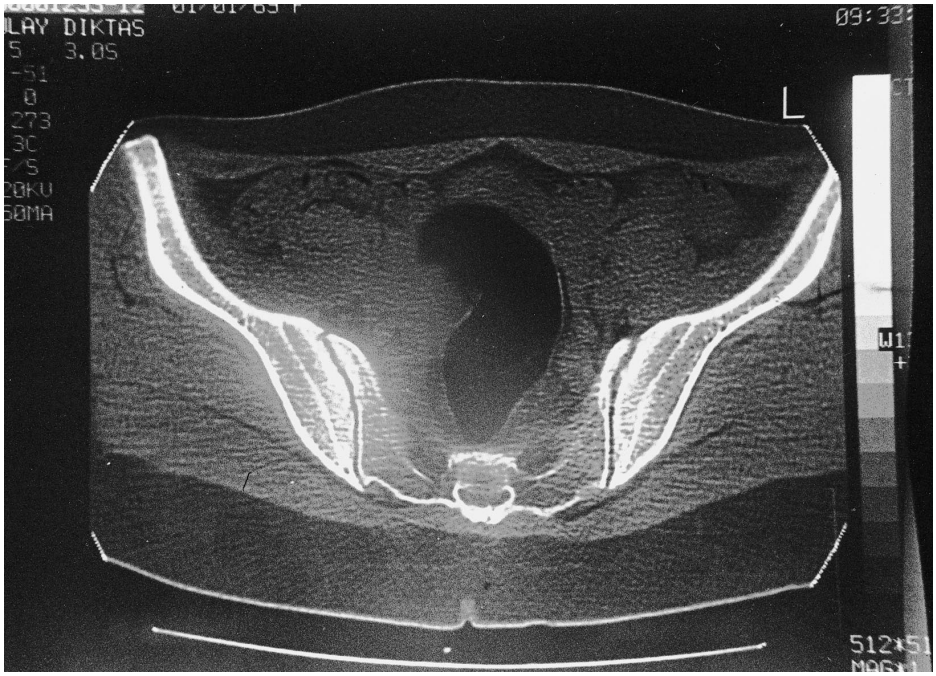

FIGURE 2. Normal computed tomography scan of the sacroiliac joints of the same patient.

One published study on the CT appearance of SI of a healthy control group demonstrated the presence of erosions, sclerosis, and ankylosis with incidences of 25%, 20%, and 10%, respectively.[25–26] Also, sacroiliac changes have been found to occur more often in rheumatoid arthritis than healthy control subjects with incidences of 20% to 35% (N = 26).[26]

Although metaanalysis cannot substitute for well-designed and adequately powered studies, it might provide important knowledge and recommendations on some conflicting results. Our results suggest that sacroiliitis is not a feature of BD; SI changes might occur together, but not more frequent, than in a normal population or in those people with BD. In the future, the answer could come from case control studies performed in different countries designed with very similar sampling and evaluating criteria.

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Osteonecrosis of the Femoral Head Resulting From Excessive Corticosteroid Nasal Spray Use

To the Editor:

The relationship between systemic corticosteroid use and osteonecrosis (ON) is well established.[1] Inhaled and dermal corticosteroids have been incriminated in the development of skin atrophy, increased bone turnover, and adrenal suppression. There have also been cases reported of ON with topical corticosteroids,[3–5] but we report the first patient in whom a putative cause of ON can be ascribed to corticosteroid nasal sprays. The prolific use of the sprays, exceeding by far the recommended doses, makes it seem likely that a cause-and-effect relationship existed in this case.

A 48-year-old Egyptian man was referred to the Department of Rheumatology after presenting with a 4-month history of pain in the abdomen and hips. He had a 6-month history of disabling pain in the left groin that he believed was from a muscular spasm of his adductors. The pain was of sudden onset, rapidly progressive to the point of being unable to work and now affecting both hips. The pain was worse in the morning, disrupted his sleep, and nonsteroidal antiinflammatory drugs were of little benefit. His medical history included hypertension and chronic rhinosinusitis. Current medication was losartan, low-dose amitriptyline, and Nasacort (triamcinolone acetonide, 55 μg per metered spray) nasal spray (Aventis Pharma, Ltd., Kent, UK). He had not been exposed to an environment of high barometric pressure, his sickle cell test was negative, and he did not drink alcohol to excess. There was no history suggestive of a connective tissue disease or polyarthritis. His corticosteroid nasal spray treatment over a 2-year period is outlined in Table 1.

General examination was unremarkable. There was bilateral tenderness of the hip adductors, absent internal rotation, and markedly reduced external rotation, abduction, and adduction of the hips. Investigations were normal, except for a slightly elevated erythrocyte sedimentation rate of 30 mm/hr (normal range, 1–15 mm/hr). All serologic and routine biochemistry tests were normal, including serum lipids and glucose. Radiographs of the left hip in November 1998 showed no bone injury. Repeat films in February 1999 showed the left femoral head to be flattened and irregular. The right femoral head was also irregular.

The picture was of rapidly progressive hip disease. Further radiographs showed rapidly progressive bilateral osteonecrosis (ON) of the femoral heads (Fig. 1). Magnetic resonance imaging of the hips was performed and was characteristic of ON. He was put on the waiting list for bilateral total hip replacements.

Local side effects from topical steroids are relatively frequent, but systemic side effects are rare. Topical and systemic side effects are becoming more common with the introduction of ultra-high-potency preparations.[2] Corticosteroid nasal sprays are an important part of the medical management of rhinitis,[6] and we suggest that their excessive use in this patient caused bilateral femoral head osteonecrosis. He worked as a doctor, and whether this related to easier access to topical treatments or to his apparent overattachment to nasal sprays cannot be certain.

TABLE 1. Corticosteroid Nasal Therapy

Drug Taken	Corticosteroid Content	Recommended Dose	Dose Taken	Duration (mo)
Nasacort	Triamcinolone acetonide	110 μg (2 sprays) each nostril/day then 1 spray per day	110 μg 4 times a day per nostril for 1 year	12 (1998–99)
Dexa-Rhinospray	Dexamethasone 21 isonicotinate 20 μg	One spray into each nostril 2 to 3 times per day; maximum of 14 days	2 sprays 4 times per day	6 (1997)
Beconase	Beclomethasone dipropionate	2 sprays/nostril or one spray/nostril 3 or 4 times per day	2 sprays as needed	24

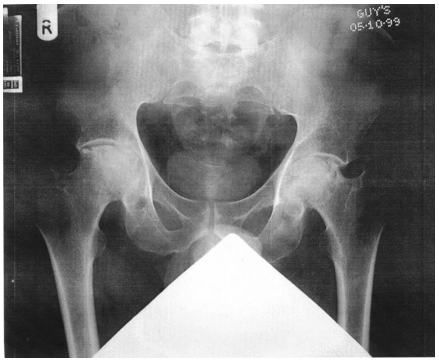

FIGURE 1. Pelvic x-ray showing flattening and disintegration of the femoral heads characteristic of osteonecrosis

This disorder is the final common pathway of many conditions, most of which lead to the impairment of the local blood supply.[7] It is the cell death of components of bone. Alternative names include avascular necrosis (AVN) and aseptic necrosis. Accurate data on incidence are difficult, because many patients are asymptomatic. In 1988, between 2500 and 3300 adults suffered nontraumatic necrosis of the femoral head in Japan.[8] Of these, 34.7% were receiving corticosteroids, 21.8% abused alcohol, and 37.1% were idiopathic. The majority of reported patients have been under 50 years of age. There is a marked male predisposition (male:female 8:1) with men affected on average 10 years earlier.

The relationship between ON and corticosteroids is well recognized. It was first reported in patients receiving corticosteroids after renal transplants. Subsequently, the association has been reported in a wide range of medical conditions. There is unfortunately no knowledge of the dose, route, or duration of corticosteroid treatment that is required to induce ON.[9] Topical corticosteroids are by no means exempt (Table 2). Inhaled corticosteroids are known to effect the hypothalamic–pituitary–adrenal axis[10]; it is less clear with corticosteroid nasal sprays. Corticosteroids with a longer half-life such as dexamethasone could be more likely to induce ON than shorter-acting agents, for example, prednisolone. There is likely to be a number of susceptibility factors, and the use of corticosteroids and subsequent development of ON could be disease-related. There are some reports of ON after short-term corticosteroid therapy.[11,12]

Patients on corticosteroids have occlusion of small vessels, particularly the subchondral arterioles,[13] by fatty emboli and impedance of sinusoidal blood flow secondary to the rise in intraosseous pressure resulting from an increase in fatty mass and the size of fat cells in the marrow. Corticosteroid-induced reduction of osteoblastic activity could also play a role. Revascularization occurs in hips not only affected by early ON, but also normal contralateral hips and normal hips in patients on corticosteroids.[14]

The other causes of ON are varied. Traumatic causes of ON of the femoral head include fractured neck of the femur, hip dislocation, and fracture dislocation. The definite nontraumatic causes are decompression sickness, Gaucher's disease, sickle cell disease, and radiotherapy. Other possible causes include arteriosclerosis, Cushing's syndrome, diabetes mellitus, lipid disturbance, joint dysplasia, excessive alcohol intake, fatty liver, pregnancy, systemic lupus erythematosus, and other connective tissue diseases. None of these could be implicated in our patient.

This report emphasizes how even the rarer risks of systemic corticosteroids can be shared by excessive topical use. The need to reinforce this when prescribing steroid nasal sprays is exemplified by this dramatic case.

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TABLE 2. Case Reports of Topical Corticosteroids Causing Osteonecrosis

Underlying Disease	Treatment	No. of Patients	Outcome	Reference
Psoriasis	Betamethasone	2	ON femoral head	3
Knee synovitis	Triamcinolone acetonide	1	ON distal femur and proximal tibia	12
Eczema	Clobetasol propionate	1	ON femoral head	5
Psoriasis	Betamethasone	1	ON femoral head	4

ON, osteonecrosis.

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The Coincidence of Ankylosing Spondylitis and Gouty Arthritis

To the Editor:

Ankylosing spondylitis (AS) is chronic inflammatory disease of the spine and sacroiliac joints affecting primarily young individuals. Peripheral joints can become involved and a number of extraarticular manifestations can occur. Genetic factors are thought to play a significant role in its development.

Gout, on the other hand, is a metabolic crystal-induced disease with characteristic clinical manifestations. Peripheral joints, particularly those of the lower extremities, are affected. Rarely, the spine and sacroiliac joints are involved.

The coincidence of gouty arthritis and other rheumatic diseases is rare.[1] Although some rare cases have been reported in the literature, gout shows a negative association with rheumatoid arthritis (RA).[1,2] Wooten and Lipsmeyer described the case of a premenopausal woman who was discovered to have tophaceous gout at age 41 after having RA for 16 years. According to the authors, so far 22 cases of the coexistence of RA and gout have been reported. The authors recommend examination for both RA and gout if features suggestive of both diseases are present.[3] Coincidence of gout and lupus erythematosus is not very frequent either.[4] There are only 3 reports in the available literature mentioning manifestations of gouty arthritis in the course of AS. Two reports showed occurrence of secondary gout clearly,[5,6] and in the third report, the diagnosis of secondary gout was not clearly determined.[7]

A 48-year-old white male patient has had ankylosing spondylitis since age 27. The mother had hyperuricemia and her brother (the patient's maternal uncle) had gout. The patient was diagnosed late, in 1988, presenting clinically with limited excursions of the thoracic and lumbosacral spine in 3 directions and limited movement of the chest wall. No symptoms of peripheral arthritis were observed. Grade III–IV bilateral sacroiliitis could be seen on x-ray (Fig. 1), along with syndesmophytic bridging within the thoracic and lumbar sections of the vertebral column (Fig. 2), and enthesopathies of the tuber ossis ischii. Among the laboratory findings, HLA-B27 positivity, median erythrocyte sedimentation rate (ESR) values, elevated C-reactive protein, and borderline values of the uric acid (436.6 mmol/L; normal range, 200–420 μmol/L in males; 140–340 μmol/L in females) were found.

Long-term treatment with nonsteroidal antiinflammatory drugs (NSAIDs) was started.

Chronic arthritis of the left ankle developed in l994 (at the age of 39). The arthritis was of an episodic nature, pre-

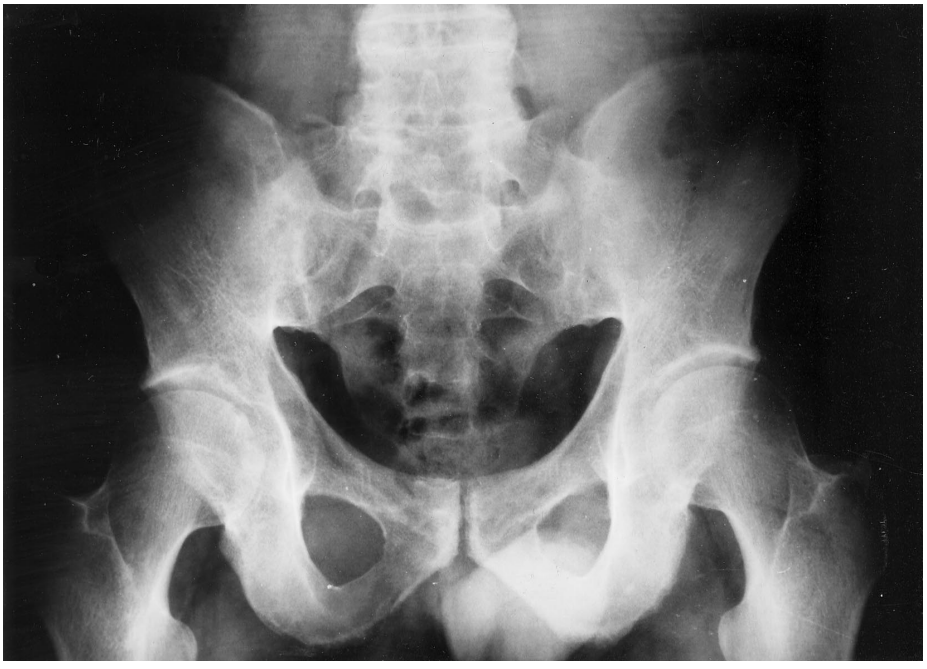


FIGURE 1. Grade III-IV bilateral.

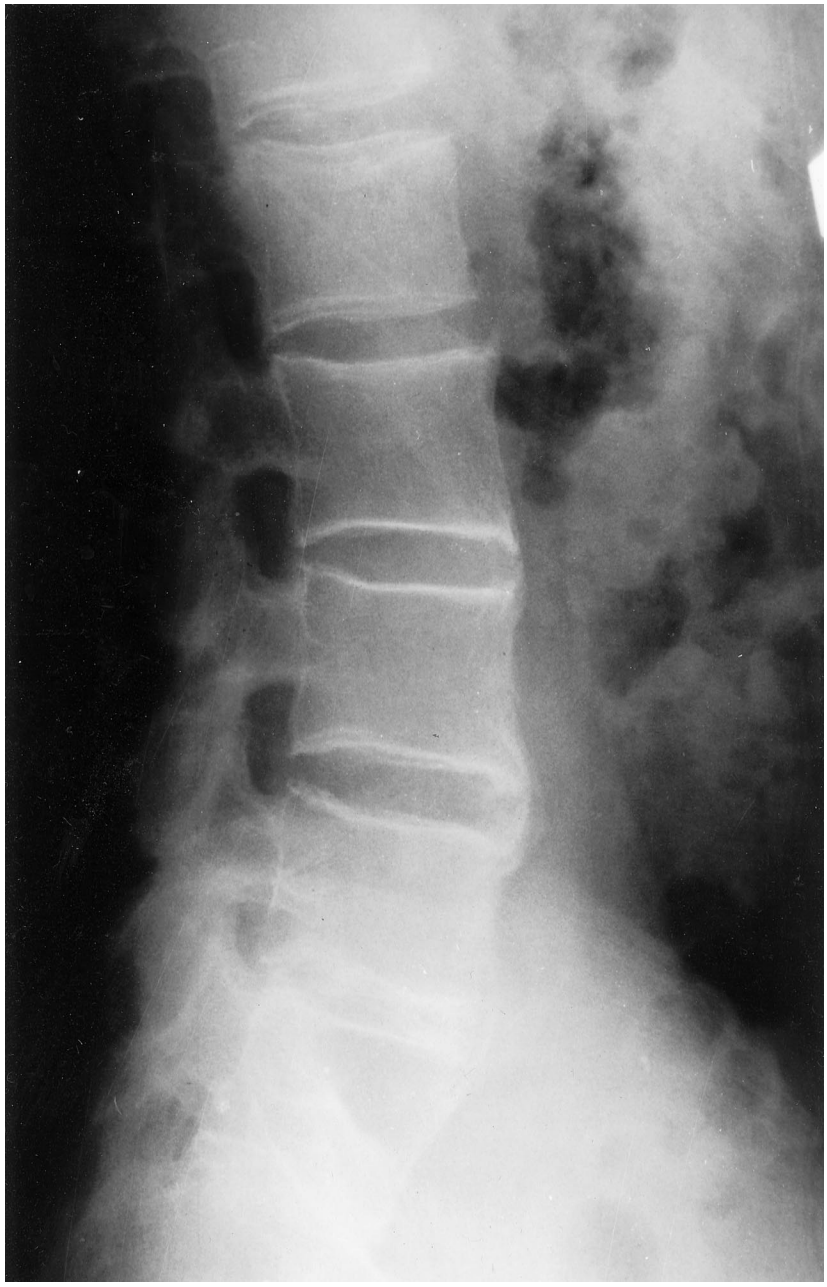


FIGURE 2. Lumbar syndesmophytes.

senting with reddening of the ankle. Elevated ESR values and hyperuricemia (470.1–529.1 mmol/L) were observed, and higher values of inflammatory parameters were repeatedly found in the synovial exudates. No presence of microcrystals was detected. Bacteriologic cultures were negative. Treatment with 2 g sulfasalazine per day was started; the therapy was discontinued after 6 months. The values of uric acid increased up to 697.0–864.0 mmol/L in 1997 and 1998. Results of kidney function test (glomerular filtration, tubular resorption, level of creatinine in serum and urine and urine uric acid) during the course of disease were normal. Elevated of cholesterol level (6.28 mmol/L; normal range, 3.4–6.0 mmol/L) and triglyceride level (2.12 mmol/L; normal range, <1.6 mmol/L in males; normal range, <1.4 mmol/L in females) was detected. Treatment with allopurinol and an NSAID (thiaprophenic acid) was initiated. Arthritis of the metatarsophalangeal I of the left foot was observed in July 2001 manifested with reddening and localized pain. Birefringent crystals of sodium urate in the synovial fluid were observed under polarization micro-

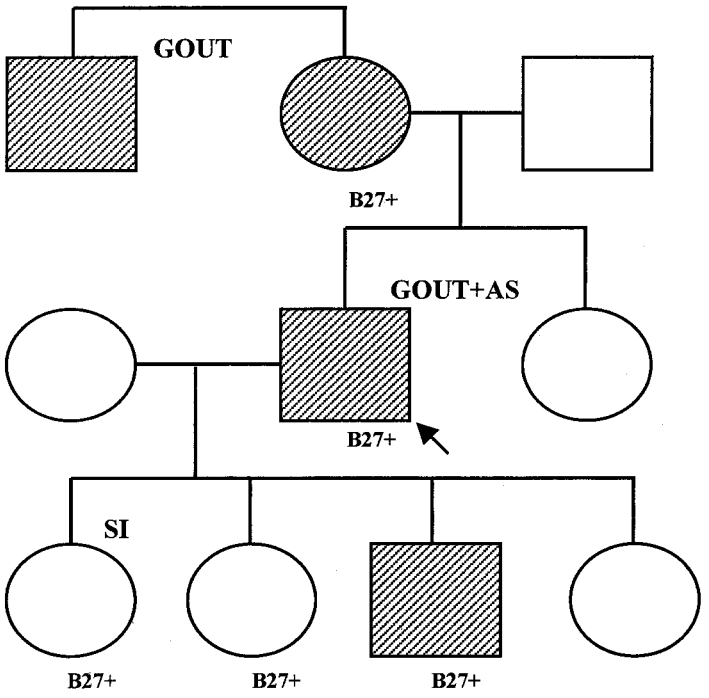
scope. The results of bacteriologic cultures were negative. The arthritis subsided rapidly after administration of a maximum dose of colchicine (6 mg/24 h). The diagnosis of gout was determined on the basis of the clinical and laboratory findings (presence of sodium urate crystals). After clinical symptoms of arthritis subsided, the treatment with an NSAID and a uricosuric agent (benzbromarone) was started. Later, as a result of the patient's noncompliance with the diet regimen, episodes of gout involving the ankle, the foot arch, and metatarsophalangeal I recurred, but symptoms were relieved after administration of colchicine. On the basis of a complete clinical examination and laboratory parameters, the diagnosis of secondary gout was ruled out.

So far, no case of a coincidence of AS and primary gout has been reported in the available literature. Three reports of secondary gout accompanying AS have been published.[5–7] In 1983, a report was published on the case of a 58-year-old patient with AS, in whom episodes of gout occurred. In this patient, severe renal damage (as a result of chronic pyelonephritis) and dermatomyositis was observed. The patient was diagnosed with atypical secondary gout.[5] In another report, published in l991, a case was described of a patient with AS- and diffuse idiopathic skeletal hyperostosis-like symptoms (reported as mixed form) combined with hereditary alkaline phosphatase deficiency, low stature as a result of rickets resulting from vitamin D resistance; hyperuricemia with episodes of gouty arthritis had been observed in this patient.[6] The most recent report, published in l994 concerned a 71-year-old male patient with AS in whom episodes of gouty arthritis started to occur during chronic renal insufficiency.[7] This patient, who experienced longstanding AS, developed oligoarthritis affecting his left first metatarsophalangeal joint and right knee. The clinical picture was most compatible with acute crystal arthritis, especially gout, although acute AS arthritis was also considered.[7]

The genetic analysis in our patient's family showed a pronounced genetic predisposition for AS and gout originating in the maternal line. The family study confirmed that the patient was HLA-B27-positive and that he inherited HLA-B27 from his mother. Among the 4 children of the patient, 3 were found to be HLA-B27-positive.

The genetic involvement in gout is not well understood. Higher familiar occurrence of the disease and hyperuricemia is typical. A polygenic type of inheritance, autosomally dominant transmission and X chromosome-linked heredity, is assumed.[8] Our family study showed that the patient's uncle had gout and his mother had hyperuricemia. We suggested that gout was genetically determined from the maternal side (Fig. 3).

Our HLA-B27-positive patient with AS also had primary gout. Although some genetic factors from the



AS – ankylosing spondylitis SI – sacroiliitis - hyperuricemia

FIGURE 3. Family BART.

maternal side are obvious, we suggest that the occurrence of AS and gout was coincidental in our patient. However, the case deserves attention, because the AS did not prevent the rare occurrence of gout. The early diagnosis and proper treatment could prevent further development of complications.

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Successful Use of Etanercept in a Patient With Pyoderma Gangrenosum Complicating Rheumatoid Arthritis

To the Editor:

Pyoderma gangrenosum (PG) is a rare, ulcerating, inflammatory cutaneous lesion first described in 1930.[1] Because of its purulent and necrotic appearance, it was originally thought to be infectious in nature, giving origin to the term PG. Nevertheless, the lack of response to antibiotics and its control with immunosuppressive therapy made an infectious cause unlikely. It belongs to the category of "neutrophilic dermatoses," because of the characteristic, although nonspecific, acute inflammatory infiltrate seen on histopathology.[2,3]

A comprehensive evaluation is required in all patients suspected of having PG to rule out alternative diagnoses,[4] because its treatment is based on the use of glucocorticoids and other immunosuppressive therapies[2,3,5] which can have significant toxicity. Although PG can be idiopathic in up to half the cases,[2] it has been associated with many systemic disorders, including inflammatory bowel disease, hematologic malignancies, and rheumatoid arthritis (RA). Controlling the underlying disease, at least in cases of colitis, often leads to improvement of PG.

Tumor necrosis factor (TNF) inhibition has been lately recognized as an effective RA treatment.[6,7] Recent evidence points to a role for IL-8, a very potent chemoattractant inducible by TNF, in the pathogenesis of PG.[8] This makes TNF inhibition a likely therapy for PG complicating RA. Nevertheless, a Medline search failed to show any report on the use of TNF inhibition in the management of PG in RA. We report the first case of the use of etanercept in the treatment of PG in the setting of RA. Our case supports the concept that PG shares the underlying pathogenesis of RA with excessive production of TNF.

A 40-year-old woman presented in 1998 with an enlarging painful ulceration in her right leg for over 6 months. The lesion had not responded to multiple courses of antibiotics and local wound care. It started as a small nodule, which later ulcerated. New similar but smaller lesions developed near it.

She had a 5-year history of seropositive, erosive RA treated with oral prednisone in doses ranging from 10 to 40 mg per day and 15 mg methotrexate orally per week. She also had asthma, hypertension, obesity, depression, and steroid-induced diabetes mellitus managed with 60 units subcutaneous insulin (70/30) per day. The patient had had 3 cesarean sections and no miscarriages. There was no known family history of leg ulcers. She was a housewife who smoked a half-pack of cigarettes per day. Review of systems was significant for weight gain from steroids, morning stiffness of approximately 45 minute's duration, and painful hands and knees.

Physical examination revealed an obese woman with weight and height of 182 kg and 1.8 m, respectively. She was in moderate distress as a result of painful leg ulcers. Her vital signs were normal except for a blood pressure of 180/110 mm Hg. She had tenderness and limited range of motion in her wrists, metacarpophalangeal and knee joints, without significant effusion. One large ulceration, 12×8 cm, with deep margins and necrotic base, was noted in the posterior aspect of the right mid-calf, with smaller satellite lesions (Fig. 1A). Her peripheral pulses were all normal to palpation.

Laboratory results included a positive rheumatoid factor of 1:640, negative antinuclear and anticardiolipin antibodies, and normal serum C3 and C4. Tests for viral hepatitis, syphilis, lupus anticoagulant, cryoglobulins, serum immunofixation, and HIV were also negative. A skin biopsy at the ulcer margin revealed a neutrophilic acute infiltration of dermis with karyorrhexis but no vasculitis (Fig. 1B). Stains for bacteria and fungi were negative, and there were no abnormal deposits of complement or immunoglobulins on immunofluorescent staining. Purified protein derivative and chest x-ray did no show evidence of tuberculosis. Hand x-rays showed soft tissue swelling, periarticular osteopenia, and a few erosive lesions in her metacarpophalangeal joints. She met the ACR criteria for RA.[9]

We improved her glucose control through the use of insulin therapy and

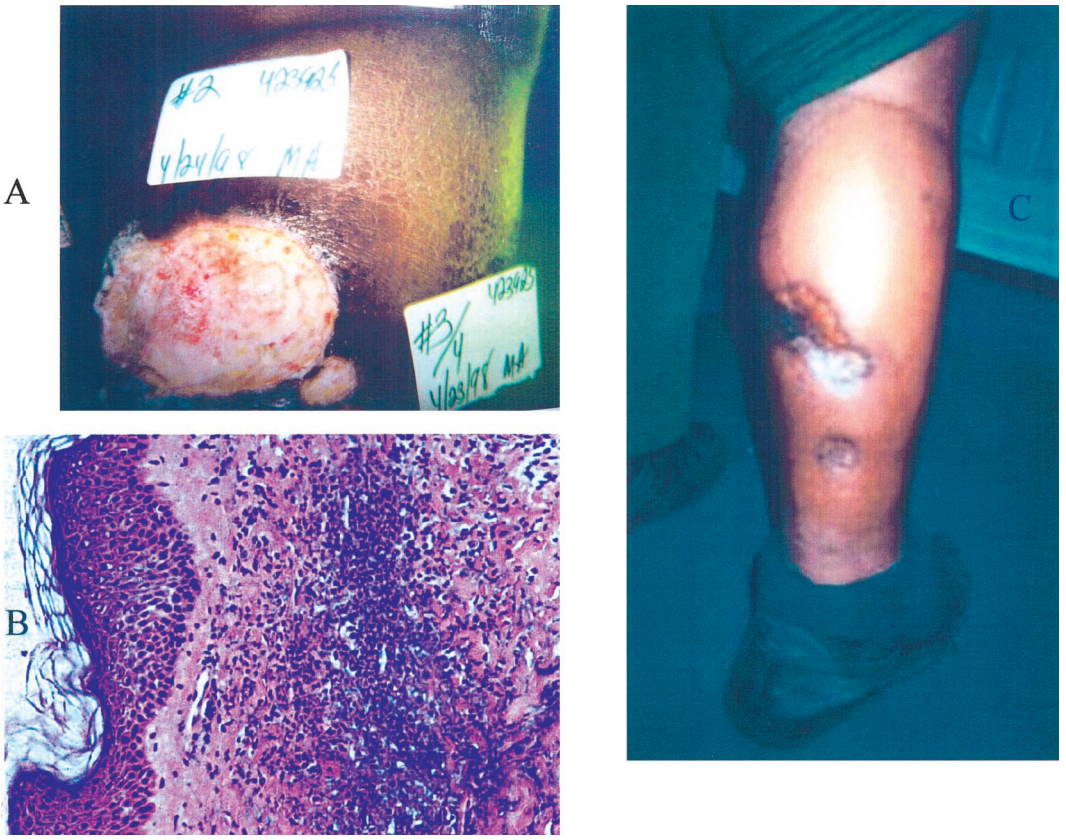

FIGURE 1. A—shows ulcerative lesion before etarnecept treatment. B—Biopsy from ulcer margin, with characteristic neutrophilic infiltrate. C—Healed lesion after treatment, note significant scarring due to depth of ulcers.

metformin, but ulcers did not improve significantly over the next 2 months. Then 25 mg etanercept subcutaneously twice a week was added to her treatment with complete healing of the ulcers within the next 4 weeks. Her synovitis also improved allowing the tapering of prednisone dose and subsequently the resolution of her diabetes and hypertension after a weight reduction from 182 to 135 kg. No relapse has been noted over a 4-year follow up; the patient has been kept on etanercept monotherapy for her RA.

This is the first case report of the use of etanercept in PG complicating RA. Of particular interest is the fact that our patient failed to respond to corticosteroid and methotrexate therapy, both of which have been reported to be effective in PG.[2,10]

PG is a poorly understood ulcerating skin disease. It often occurs in patients with chronic underlying inflammatory or malignant diseases such as ulcerative colitis, RA, chronic active hepatitis, Crohn's disease, IgA monoclonal gammopathy, and hematologic and lymphoreticular malignancies.[4,11,12] Felty's syndrome has been associated wit PG,[13] but our patient did not have splenomegaly or neutropenia.

The pathergy phenomenon, with development of new pustular lesions at sites of mechanical injury, is often present in PG. Indeed, trauma precedes PG in many cases. This was probably an aggravating factor in our case, because she underwent multiple surgical debridements, leading to worsening of the inflammatory lesion, until the diagnosis was made. Systemic corticosteroids are the most consistently reported effective treatment of PG.[2] Nevertheless, as illustrated by our patient, significant toxicity (obesity, hypertension, hyperglycemia) can ensue.[4]

All cutaneous wounds are associated in their initial stage with a reparative inflammatory process, which is followed by tissue formation and remodeling.[14] PG is associated with a failure of the skin ulceration to evolve from its initial inflammatory stage, usually as a result of the persistence of an underlying systemic inflammatory condition such as RA. Clinical and experimental findings suggest an etiologic role of IL-8 in the pathogenesis of PG.[8] Under physiological conditions, production of IL-8 is not constitutive but is inducible in a variety of cell types by proinflammatory cytokines such as TNF.[15]

The role of TNF in RA is well established.[6,7] If PG and RA have a common pathophysiology, it would be expected that suppression of TNF not only would control the synovitis, but also would help the PG process. The dramatic response of our patient to the

addition of etanercept after failure of prednisone and methotrexate to control her RA suggests some role for TNF in the pathogenesis of PG.

Improvement of pyoderma gangrenosum and psoriasis associated with Crohn's disease with antitumor necrosis factor monoclonal antibody[16] has recently been reported. Our case is the first one documenting the successful use of etanercept in PG complicating RA. It suggests a potential role for the use of TNF inhibition in refractory PG cases associated with RA.

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