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# LETTERS

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## Smoking and increased apoptosis in patients with systemic lupus erythematosus: comment on the article by Costenbader et al

*To the Editor:*

We read with interest the report by Costenbader et al of their meta-analysis to evaluate whether smoking is a risk factor in the development of systemic lupus erythematosus (SLE) (1). A small but significant association between current smoking and development of SLE was observed. No such association was found for ex-smokers relative to never-smokers, suggesting that active smoking appears to be a risk factor. The association found is unexplained, but the authors hypothesize that smoking, via tissue hypoxia or toxins, results in cellular necrosis with release of intracellular antigens, thereby stressing the capacity for clearance of cellular debris.

We reported previously on the effects of smoking on Fas expression by peripheral blood lymphocytes (2). Active smoking resulted in increased expression of Fas (CD95) on B lymphocytes as well as on CD4+ T lymphocytes. In addition, the effect of smoking on peripheral blood lymphocytes was transient, that is, discontinuation of smoking resulted in normalization of Fas expression. Further in vitro studies, using agonistic anti-Fas antibodies to induce apoptosis, showed that Fas-mediated apoptosis in current smokers was intact, and, no difference in the percentages of circulating apoptotic lymphocytes between smokers and nonsmokers was demonstrated. This study was performed in healthy individuals.

Our data support the hypothesis proposed by Costenbader et al. It is conceivable that the expression of Fas, and probably also of other molecules from the same tumor necrosis factor receptor superfamily, such as the TRAIL receptor, is increased on lymphocytes and other cells in current smokers. Cells involved are more vulnerable to apoptotic signals. Whenever smoking results in increased apoptosis in individuals with an already decreased capacity to eliminate apoptotic cells, as has been shown in patients with SLE (3,4), increased numbers of apoptotic cells may persist, exposing the body to increased concentrations of intracellular antigens with breakdown of tolerance and induction of autoimmunity.

It would be interesting to evaluate whether active smoking indeed augments the already elevated levels of apoptotic peripheral blood neutrophils and lymphocytes that have been found in SLE patients (5,6). A study analyzing this question is currently under way.

Marc Bijl, MD
Pieter C. Limburg, PhD
Cees G. M. Kallenberg, MD
*University Hospital*
*Groningen, The Netherlands*

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## Reply

*To the Editor:*

We thank Dr. Bijl and colleagues for their interest in our meta-analysis of studies examining cigarette smoking as a risk factor for the development of SLE and for their edifying comments. We were not aware of their work reporting that cigarette smoking transiently augments Fas expression on lymphocytes of healthy individuals, and we agree that this may be a mechanistic pathway through which smoking increases cellular vulnerability to apoptotic signals, triggering SLE in genetically predisposed individuals. We eagerly await the results of ongoing studies into the effects of cigarette smoking on levels of circulating apoptotic material in patients with SLE.

Karen H. Costenbader, MD, MPH
Jehanna Peerzada, MD, MPH
Shahin Lockman, MD, MSc
Elizabeth W. Karlson, MD
*Harvard Medical School*
Daniel J. Kim, MD, MSc
*Harvard School of Public Health*
*Boston, MA*
Dolores Nobles-Knight, PharmD
*Pfizer Inc.*
*Chicago, IL*
Michelle Petri, MD, MPH
*Johns Hopkins School of Medicine*
*Baltimore, MD*

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## The synovium in rheumatoid arthritis: comment on the editorial by Kirwan

*To The Editor:*

In his editorial published in *Arthritis & Rheumatism*, Kirwan has presented a good case for the existence of two

pathways of pathology in rheumatoid arthritis (RA), one a result of inflammation, the other leading to erosive disease (1). Although not mentioned in Kirwan's editorial, this concept had its beginnings in the late 1960s and early 1970s, after the demonstration in 1967 of collagenolytic activity, effective at neutral pH, released by rheumatoid synovial tissue cultured on a collagen substrate (2). A slim volume published in 1974, *Rheumatoid Arthritis* (3), attempted to summarize current knowledge about rheumatoid arthritis. The chapter "The Proliferative Lesion in Rheumatoid Arthritis" began with the sentences, "It is the inflammatory lesion in rheumatoid arthritis that is painful. It is the proliferative lesion that destroys joints." This concept was illustrated by radiographs of a young woman with progressively destructive RA who showed little evidence for inflammation; she had no pain and a normal erythrocyte sedimentation rate. An understanding of the biochemical mechanisms that could explain the histopathologic finding of pannus invading articular cartilage was evolving. Using electron micrographs from the synovial–cartilage interface, it was shown that with rare exceptions, the active cartilage matrix resorption was taking place extracellularly in an amorphous zone not wider than $2\mu$ between cell processes and intact collagen (4).

Later in the 1970s it was demonstrated that the driving forces activating matrix metalloprotease production by synovial fibroblasts were cytokines (e.g., interleukin-1) produced by adjacent cells (5). This activation process changed the biochemical as well as physical phenotype of the fibroblasts into a stellate appearance (6). Using immunochemical techniques in cell cultures, collagenase was observed being released from the long thin cell processes onto reconstituted collagen fibrils (7). These same dissociated rheumatoid synovial cell cultures allowed investigators to test for inhibitors of collagenase biosynthesis. Two families of compounds, retinoids and glucocorticoids (in low concentrations in vitro), were found to inhibit collagenase biosynthesis (8). It was more than a decade later that Kirwan published his valuable report (9), describing a randomized, double-blind trial of 7.5 mg prednisolone given daily for 2 years. Lesser progression of erosions and development of fewer new erosions were observed in the treated group.

In summary, the concept of 2 pathways in RA inflammatory and erosive, is not a new one, but is one that deserves further study in both the laboratory and clinics.

Edward D. Harris, Jr., MD, MACR
*Alpha Omega Alpha National Honor Medical Society*
*Menlo Park, CA*

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## Bone edema and synovial inflammation: comment on the editorial by Kirwan

*To the Editor:*

We read with interest the recent editorial by Kirwan (1) suggesting that several pathologic processes may work simultaneously within the rheumatoid joint to cause erosive damage. There is new evidence from magnetic resonance imaging (MRI) studies of early rheumatoid arthritis (RA) to support this.

We have recently shown bone marrow edema seen on MRI to be a new predictor of radiographic damage in RA (2). Bone edema may be widespread in early disease and has been described to involve the hands and the metatarsophalangeal joints of the feet at 6 weeks from symptom onset (3). The evidence is strong that it is a pre-erosive lesion (2,4), and we observed a 6-fold increase in the likelihood of erosions in affected bones after 6 years. In comparison, early synovitis was not predictive of erosion score at 6 years, although we and others have shown that it predicts erosive damage after 1–2 years (5,6). Clearly, synovitis and bone edema frequently occur together (7), but the prognostic data suggest that they are not cause (synovitis) leading to effect (bone edema and subsequent erosion) but that they represent 2 separate pathologic processes which often start together but could later diverge.

We contend that bone edema seen on MRI may represent an intraosseous process that contributes to articular damage via a pathway that is separate from synovial inflammation. Regions of bone edema enhance dramatically post–contrast administration in the same way as do regions of active synovitis, suggesting a similar inflammatory basis. Production of proinflammatory cytokines from subchondral regions could allow joint damage to occur from the "inside out" as well as from the "outside in" via synovitis. It would be fascinating to examine the patients described by Molenaar et al (8) with RA in clinical remission, but with persistent erosive progression,

for bone edema in affected joints. Such studies could help define new pathways leading to joint destruction which might be amenable to different forms of therapeutic manipulation.

Fiona McQueen, MD, FRACP
Elizabeth Robinson, MSc
*University of Auckland*
*Auckland, New Zealand*

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## An alternate hypothesis regarding radiologic damage to synovial tissue: comment on the editorial by Kirwan

*To the Editor:*

I read with interest the editorial by Kirwan (1) in relation to an accompanying article in *Arthritis & Rheumatism.* Dr. Kirwan uses the results reported by Molenaar et al (2), along with other selected references, to promote the hypothesis that clinical activity and radiologic joint destruction are mediated by different disease processes.

However, I believe that this hypothesis can be challenged by published studies which suggest that these two processes are closely linked, if not identical. Several studies have demonstrated a close association between the acute-phase response and clinical disease activity (3–5), and other studies demonstrate the association of cumulative acute-phase response with the radiologic progression of joint destruction (4–6). Joint inflammation has been associated with the occurrence of joint erosions in rheumatoid arthritis (RA) (5–8). Unfortunately, standard disease-modifying antirheumatic drug (DMARD) treatments have only a modest impact on joint damage in rheumatoid arthritis (RA). This is probably because most treatments do not result in the level of disease suppression that approximates the American College of Rheumatology (ACR) criteria for remission (9) or at least do not maintain it for a long enough period to achieve regression of joint damage (10–12). Our own results demonstrated that synovial membrane pathology could be returned to close to normal, and that this could be associated with retardation of radiologic damage (13,14). We came to this conclusion upon examining the synovial membrane immunopathology in a selected group of RA patients in whom remission was achieved according to the ACR criteria and was maintained for a significant length of time.

A recent report by Aken et al (15) showed less radiologic progression in patients with early initiation of DMARD treatment than in patients who received delayed DMARD treatment. However, the rate of joint destruction during years 1–4 of the study did not differ between the two treatment groups. Why were the results in the early-treatment group not better in the long term? The answer may lie in the low remission rate for both treatment groups and the significant acute-phase response in both treatment groups up to 4 years, with similar percentages of change in erythrocyte sedimentation rate in both treatment groups over 4 years. In other words, in neither the early nor the delayed treatment group was the disease activity reduced sufficiently, or for a long enough period to favorably affect the rate of radiologic progression.

So what of the study by Molenaar et al (2), which Kirwan suggests supports the concept of different pathologic processes mediating clinical activity and radiologic progression. First, we are not informed in this report of the error rate in repeated scoring of radiographs of the hands and feet using the Sharp/van der Heijde method (16). What is the minimal detectable difference with this scoring method? When the results of this study are examined more closely, it appears that those patients whose RA remained in persistent remission over the 2-year observation period had a significantly better radiologic outcome over 1 and 2 years than did those with exacerbations of their disease activity over that period. It is questionable whether a change in the mean Sharp/van der Heijde score of 0.7 (1-year followup) or 1.1–1.2 (2-year followup) in the RA patients with persistent remission is actually greater than the error rate in the radiologic scoring technique. This study also showed that the area under the curve (AUC) for the Disease Activity Score (DAS) (17) was significantly higher in patients with relevant radiologic progression than in patients with low or no progression. In addition, the DAS AUC was a stronger predictor of radiologic progression than was the absence of persistent remission. Surely this is consistent with the hypothesis that lack of sustained disease activity suppression is related to radiologic suppression, again suggesting that the two pathologic processes are linked, if not identical. If the authors had

provided other evidence of how completely disease activity was suppressed over the observation period, possibly by an AUC assessment of C-reactive protein, it would be possible to assess whether any apparent radiologic progression in the sustained-remission RA patient group (a small number of outliers in Figure [2]) was due to incomplete disease activity suppression.

In conclusion, the published evidence (including that referenced by Kirwan) does not necessarily support his hypothesis of different disease pathologies mediating disease activity and radiologic damage. The study results are equally consistent with the hypothesis that the pathology underlying joint inflammation and radiologic damage are linked if not identical. It may be that this reflects the inadequacies of standard DMARD treatments to completely suppress disease activity for long enough periods to favorably alter radiologic outcomes. Perhaps future studies of treatment with biologic agents will further address this issue, if such treatment aims at the goal of attaining and maintaining remission for a significant period of time, with restoration of synovial membrane pathology to close to that of normal synovium.

Malcolm D. Smith, PhD
*Flinders Medical Center and Repatriation General Hospital*
*Daw Park, South Australia*

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## Effect of etanercept on iritis in patients with ankylosing spondylitis

*To the Editor:*

Several published observations have suggested that etanercept may trigger iritis in a susceptible patient, despite its efficacy in treating joint diseases typically associated with uveitis such as ankylosing spondylitis (1,2) and psoriatic arthritis (3). For example, my colleagues and I studied a retrospective series of 16 patients with a variety of inflammatory eye and joint diseases and noted universal benefit from tumor necrosis factor inhibition for the joint disease, but only a 38% response rate for the associated uveitis or scleritis (4). In 5 patients, ocular inflammation began only after etanercept therapy was started. Two other case reports noted the onset of uveitis after beginning or recommencing of etanercept therapy (5,6). In trials of etanercept for uveitis associated with juvenile arthritis (7,8), Behçet's disease (9), or uveitis of varied etiology (10), findings have shown a benefit that was often not sustained (7), or that the treatment was not of apparent benefit at all (8–10). Since etanercept is increasingly used for the treatment of seronegative arthritides, which are commonly associated with uveitis, the role of etanercept in potentially triggering ocular inflammation becomes critical.

Three randomized studies on the effect of etanercept for ankylosing spondylitis have recently been reported and each provides reassuring data (1,2,11). These studies included

**Table 1.** Frequency of uveitis in patients

| Study (ref.) | Pretrial uveitis | Uveitis during trial |
|---|---|---|
| Davis et al (1) | | |
| Placebo (n = 139) | 43 | 8 |
| Etanercept (n = 138) | 39 | 3 |
| Calin et al (11) | | |
| Placebo (n = 39) | 6 | 1 |
| Etanercept (n = 45) | 13 | 0 |
| Brandt et al (2) | | |
| Placebo (n = 16) | 3 | 0* |
| Etanercept (n = 14) | 5 | 0* |

* Includes only the first 6 weeks of the trial, because the crossover to etanercept began after 6 weeks.

information on the frequency of uveitis during the trial (Table 1). Although a history of iritis was noted as slightly more common in etanercept-treated patients prior to the trials, 3 times as many episodes of iritis occurred in the placebo-treated patients compared with those treated with etanercept. This reduction does not quite reach statistical significance ($P = 0.085$ by Fisher's exact test), but it certainly provides evidence that etanercept therapy does not increase the likelihood of development of iritis in patients with ankylosing spondylitis. Although the therapeutic impact of etanercept (25 mg twice weekly) for uveitis appears to be inconsistent, it might have some prophylactic benefit in preventing HLA–B27–associated eye disease.

James T. Rosenbaum, MD
*Oregon Health & Science University*
*Portland, OR*

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## Relative ineffectiveness of triamcinolone acetonide in the treatment of juvenile idiopathic arthritis

*To the Editor:*

Intrarticular corticosteroids (IACs) have been used widely for the treatment of juvenile idiopathic arthritis (JIA) and are the most rapidly effective treatment for the pain, swelling, and impaired joint mobility in JIA (1–4). Recent data show that early use of IACs may help prevent the development of leg length discrepancies and other deformities in children with JIA (5,6).

The long-acting corticosteroids most commonly used in the treatment of JIA are triamcinolone hexacetonide and triamcinolone acetonide. Triamcinolone hexacetonide is the preferred corticosteroid preparation being prescribed by most pediatric rheumatologists based on clinical experience, and limited published data indicating that triamcinolone hexacetonide is more effective than triamcinolone acetonide in providing long-term suppression of joint inflammation (7,8), perhaps because of the lower solubility of triamcinolone hexacetonide compared with other corticosteroid preparations (9). The conventional dose of triamcinolone hexacetonide administered by a pediatric rheumatologist is 1 mg/kg per large joint; however, the basis for this dose is not clear. Some children have received higher doses of triamcinolone hexacetonide (2 mg/kg per large joint) without overt problems (ref. 10, and personal observations).

We undertook a pilot study to compare the efficacy of a standard dose of triamcinolone hexacetonide (1 mg/kg per treatment) to a higher dose of triamcinolone hexacetonide (2 mg/kg per treatment) in knees of children with JIA, in a double-blind, randomized controlled trial. The study was approved by the ethics committee at the University of British Columbia. However, shortly after approval was obtained, triamcinolone hexacetonide became unavailable worldwide. We were therefore forced to use triamcinolone acetonide in our clinical practice, and the ethics committee approved modification of the study, in order to compare triamcinolone acetonide at the 2 different doses.

After enrolling the first 7 patients in the study, we became concerned that relapse of joint inflammation was occurring after a much shorter time interval than we had come to expect with triamcinolone hexacetonide at the standard dose. Five of the 7 patients had recurrence of arthritis in the injected knee within 3 months, which compares unfavorably

with our original reported experience with triamcinolone hexacetonide, in which >60% of injected knees were still free of inflammation 6 months after injection (1).

We therefore terminated the study and broke the codes for the participating patients. Of the 5 children whose disease had relapsed, 3 had received 2 mg/kg, and 2 had received 1 mg/kg. All 5 children had a physician global assessment of moderate disease activity at the time of injection. Two of the children whose disease was still in remission after 9 months, 1 had received the 2 mg/kg, and the other had received the 1 mg/kg. Both of these 2 children had a physician global assessment of only mild disease at the time of injection.

This experience (although involving only a small number of patients) strongly suggests that not only is triamcinolone acetonide significantly less effective than triamcinolone hexacetonide for knee arthritis in JIA, but that using triamcinolone acetonide in higher doses than is conventional does not increase its effectiveness. It is clear that our inability to obtain triamcinolone hexacetonide has had a major adverse effect on the well-being of children with juvenile idiopathic arthritis. If and when triamcinolone hexacetonide does become available again, the issue of whether a higher dose is more effective than the conventional 1 mg/kg per treatment will require evaluation.

K. Alsufyani, MD
O. Ortiz-Alvarez, MD
D. A. Cabral, MBBS, FRCPC
L. B. Tucker, MD, FAAP
R. E. Petty, MD, PhD, FRCPC
P. N. Malleson, MBBS, MRCP, FRCPC
*University of British Columbia and British Columbia's Children's Hospital*
*Vancouver, British Columbia, Canada*

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## Anakinra in mutation-negative NOMID/CINCA syndrome: comment on the articles by Hawkins et al and Hoffman and Patel

*To the Editor:*

We read with interest the recent article by Hawkins et al (1) in which anakinra was reported to be effective in Muckle-Wells syndrome. In an accompanying editorial (2), Hoffman and Patel suggest that anakinra might be equally effective in other diseases associated with mutations in the *CIAS1* gene. One such disorder is neonatal-onset multisystem inflammatory disease (NOMID), which is also known as chronic infantile neurologic, cutaneous, articular (CINCA) syndrome. NOMID/CINCA syndrome is characterized by fever, chronic meningitis, uveitis, sensorineural hearing loss, urticarial skin rash, and deforming arthropathy. However, nearly half of all patients with clinically diagnosed NOMID/CINCA syndrome do not carry *CIAS1* mutations (3,4). Here, we report the favorable response to anakinra in 3 cases of mutation-negative NOMID/CINCA syndrome.

The patients, 2 girls and a boy, had been diagnosed with NOMID/CINCA syndrome on clinical grounds (Table 1). Sequencing of exons 1–9 of *CIAS1* had not revealed mutations. In all 3 patients, therapy with colchicine and nonsteroidal antiinflammatory drugs had failed, and only high dosages of oral prednisone (2 mg/kg/day) could partially control their symptoms. This treatment could not be sustained, however, because it was complicated by the development of a cushingoid

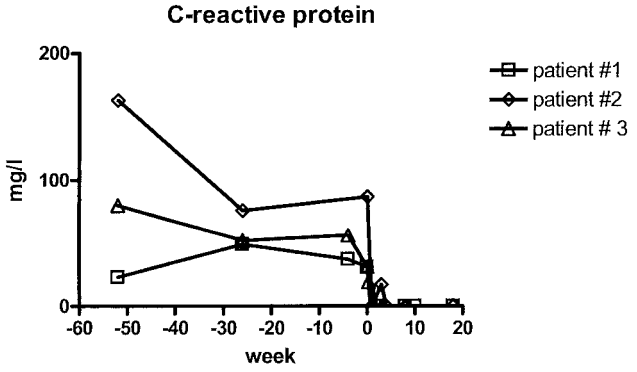


**Figure 1.** C-reactive protein concentration over time in 3 patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome. Anakinra treatment (1 mg/kg/day subcutaneously) was started at week 0.

**Table 1.** Clinical characteristics of the patients with NOMID/CINCA syndrome*

| Characteristic | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Sex/age, years | M/4 | F/10 | F/8 |
| Age at onset | Birth | Birth | Birth |
| General | Recurrent fever, irritability, anemia | Failure to thrive, recurrent fever, irritability, anemia | Recurrent fever, anemia |
| Nervous system | Development delay, frontal bossing, intracranial hypertension, CSF pleiocytosis | Development delay, frontal bossing, dilated CSF spaces, CSF pleiocytosis | Frequent headaches, frontal bossing, intracranial hypertension, CSF pleiocytosis |
| Eyes | Normal | Uveitis | Papilledema, uveitis |
| Ears | Normal | Normal | 45-dB perceptive hearing loss |
| Skin | Pruritic urticariform rash | Nonpruritic urticariform rash | Nonpruritic urticariform rash |
| Joints | Arthritis, left knee | Bilateral destructive knee arthropathy | Transient arthralgias |
| Other | | Transient cardiomyopathy, sterile osteomyelitis | |

* NOMID/CINCA syndrome = neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome; CSF = cerebrospinal fluid.

appearance, growth arrest, and osteoporosis. Patient 1 had initially responded to treatment with infliximab, but this had to be discontinued because of serum sickness.

After approval was granted by the institutional review board and written informed consent by the parents was given, the patients received daily subcutaneous injections of anakinra (1 mg/kg). Within 24 hours, all 3 patients had become afebrile and have remained afebrile during the ensuing 3 months of treatment. In all 3 patients, the skin rash cleared, joint inflammation ceased completely, and the patients felt well. In patient 3, headache disappeared initially but reappeared after 8 weeks of treatment. This recurrence coincided with increased lumbar cerebrospinal fluid pressure (24 cm $H_2O$) and mild cerebrospinal fluid pleiocytosis (38 white blood cells/$\mu$l). The same child experienced slightly itchy nummular injection-site reactions that cleared in the course of 2 weeks. The clinical response was reflected by normalization of the C-reactive protein level and the erythrocyte sedimentation rate in all 3 patients (Figure 1), despite a reduction in steroids to an adrenal-substitution dose. Leukocytosis, thrombocytosis, and anemia of chronic illness, which had been particularly severe in patient 2, disappeared in all 3 patients.

Our observations suggest a favorable response to anakinra of the systemic, cutaneous, and articular disease activity in children with NOMID/CINCA syndrome. However, it is progressive neurologic, auditory, and visual impairment that determines long-term disability in this disorder (5). It is uncertain whether these complications can be avoided by treatment with anakinra.

Joost Frenkel, MD
Nico M. Wulffraat, MD, PhD
Wietse Kuis, MD, PhD
*University Medical Center Utrecht*
*Utrecht, The Netherlands*

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## Reply

*To the Editor:*

Dr. Frenkel and colleagues report an impressive clinical response to anakinra in 3 patients with NOMID/CINCA syndrome and provide hope for these severely affected children and their families. The fact that these 3 patients did not possess mutations in *CIAS1* makes it clear that the additional gene or genes responsible for this disease are also integrally involved in the interleukin-1 (IL-1) pathway.

Our group recently observed that pretreatment with anakinra (i.e., prior to cold exposure) in 3 patients with familial cold autoinflammatory syndrome (FCAS) prevented cold-induced cytokine release in the blood and skin as well as the acute clinical manifestations of FCAS (Hoffman HM, Rosengren S, Boyle DL, Cho JY, Nayar J, Mueller JL, et al. Interleukin-1 receptor antagonist prevents cold-associated acute inflammation in familial cold autoinflammatory syndrome. Submitted for publication). In addition, we now have experience with 3 additional patients with FCAS who were

receiving maintenance anakinra therapy and who had clinical responses similar to those observed in patients with Muckle-Wells syndrome and NOMID.

Therefore, anakinra has been shown to be effective in all 3 of these diseases, which are thought to represent a continuum of one disease characterized by IL-1–mediated inflammation. Although the responses to anakinra reported in all 3 autoinflammatory disorders have been dramatic, formal clinical trials are still necessary before clear treatment recommendations can be made.

Hal M. Hoffman, MD
*University of California, San Diego*
*La Jolla, CA*

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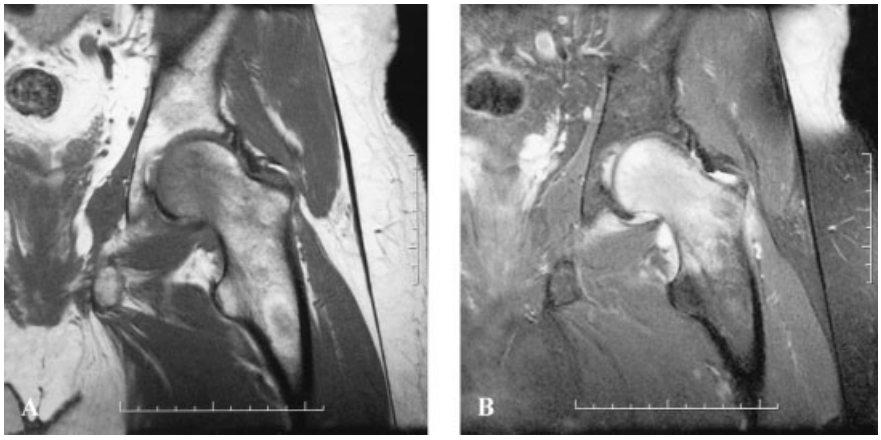
## *Clinical Images: Bone marrow edema syndrome*




The patient, a 55-year-old male farmer who had been in good health, presented 1 month after acute onset of sharp pain in the left groin, which was subsequently progressive and exacerbated with weight bearing. He denied having radicular or constitutional symptoms or antecedent trauma, and had no history of corticosteroid treatment. Passive hip range of motion reproduced the pain. Radiography of the left hip yielded normal results. Magnetic resonance imaging (MRI), with T1 weighting (**A**) and T2 weighting (**B**) revealed diffusely increased T2 signal with partial loss of T1 signal, consistent with bone marrow edema involving the femoral neck and head. There was moderate soft tissue edema in the adjacent fat, vastus intermedius, and adductor muscles. No evidence of fracture, mass, or avascular necrosis was present. These findings are consistent with bone marrow edema syndrome (BMES) of the hip, a condition first described in pregnant women. Men in the fourth to seventh decade of life, however, account for >66% of cases (1). Idiopathic transient osteoporosis of the hip is perhaps the term most commonly used to identify this disease. The term BMES has recently been introduced, based on the characteristic MRI findings. Patients present with progressive, ill-defined, unilateral hip pain which is described as a deep ache that localizes to the medial or anterior thigh without radiation below the knee. Symptoms present acutely without inciting trauma and are often quite disabling. Pain worsens primarily with weight-bearing activity, which may lead to impaired function (2). Pain at rest, back pain, and neurologic dysfunction are not characteristic of BMES and would suggest an alternative diagnosis. Physical examination findings include an antalgic or compensated Trendelenburg's sign. The most common finding is guarding during hip range of motion, especially with abduction or rotation of the hip. Tenderness over the greater trochanter and adjacent adductor and hip flexor muscle groups may be present. Provocative tests with flexion in abduction and external rotation, resisted straight-leg raise, or hip joint compression or rotation loads may result in reproduction of pain. Results of spine and knee examination as well as neurologic examination will be normal. MRI demonstrates diffuse, ill-defined signal change of the affected region. There is increased T2-weighted signal with a corresponding low signal on T1-weighted images, and the edema is often best recognized on coronal plane sections. The bone cortex may appear thinned but is always intact, and, unlike findings in avascular necrosis, there should be no evidence of subchondral defects (3). After 3 months of conservative therapy, the patient's symptoms were improving. BMES has distinct clinical and radiologic features and should be considered in active middle-aged adults with acute spontaneous hip pain.

Matthew W. Martinez, MD
Matthew R. Thomas, MD
*Mayo Clinic College of Medicine*
*Rochester, MN*

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