LETTERS

Necrotizing vasculitis confined to the nerves: comment on the concise communication by Rosenbaum et al

To the Editor:

We read with interest the concise communication by Rosenbaum et al (1) on nonsystemic necrotizing vasculitis of the peripheral nervous system (PNS). While agreeing that vasculitis limited to the PNS has been reported mainly in the neurology literature, we would like to draw the authors’ attention to a report in the rheumatology literature about acute necrotizing vasculitis confined to the nerve, with spontaneous recovery (2). A 65-year-old man had presented with leg pains, fever, arthralgias, and weight loss. Muscle enzyme levels were normal. Electrophysiologic studies revealed a symmetric and diffuse polyneuropathy of all 4 limbs, with moderate slowing of motor nerve conduction velocity. A peroneal nerve biopsy revealed a necrotizing vasculitis, while muscle biopsy findings were normal. Interestingly, the patient recovered spontaneously in a few weeks without the use of corticosteroids or other immunosuppressive therapy.

We also take this opportunity to describe a similar 21-year-old man we encountered recently. This patient presented with bilateral wasting of the hand muscles and fever. Antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, cryoglobulins, and hepatitis B and C serology findings were negative. Urinalysis results were normal, and magnetic resonance imaging of the cervical spine was unremarkable. Electrophysiologic studies revealed asymmetric sensorimotor neuropathy of the mixed axonal and demyelinating type. Sural nerve biopsy showed necrotizing vasculitis. Findings of angiography of the renal, celiac, and superior mesenteric arteries were normal. The patient made a significant recovery when treated with oral corticosteroids and was doing well at 6-month follow-up.

Although muscle biopsy is said to be superior to nerve biopsy for diagnosing isolated neuropathy from necrotizing vasculitis (3), the muscle biopsy findings in the patient described by de la Sayette et al (2) were normal while the peroneal nerve biopsy results confirmed the presence of vasculitis. Our own patient was found to have necrotizing vasculitis by sural nerve biopsy; muscle biopsy was not performed.

In addition to vasculitis confined to the skin and nerves, polyarteritis confined to the calf muscles has also been reported (4,5). As of 1993, 9 such patients had been described in the literature (5).

Awareness of the existence of limited forms of systemic necrotizing vasculitides helps avoid unnecessary immunosuppressive therapy in such patients.

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Necrotizing vasculitis of the peripheral nervous system: nonsystemic or clinically undetectable?

To the Editor:

We would like to comment on the concise communication by Rosenbaum et al about a patient in whom vasculitis might have been limited to the peripheral nervous system (1). Although this may occasionally be the case, organ-specific vasculitis confined to the peripheral nervous system is unlikely in patients who present with clinical manifestations limited to peripheral neuropathy.

In clinical practice, only small tissue specimens can be sampled to determine the extent of vasculitis, and autopsy studies have shown that vasculitis is much more widespread than had been suspected. No renal biopsy was performed on the patient described by Rosenbaum et al, despite the history of microscopic hematuria, a finding that does not exclude renal involvement (1). Rosenbaum et al referred to our clinical and pathologic study of 100 patients with necrotizing vasculitis disclosed by nerve or muscle biopsy samples, or both, obtained at the same time (2). It has to be stressed that 26 (81%) of the 32 patients whose clinical manifestations were limited to neuropathy had necrotizing vasculitis in their muscle specimens. Similarly, necrotizing vasculitis was found in the muscle specimens of 24 (86%) of 28 patients with rheumatoid arthritis and peripheral neuropathy, when their nerve and muscle biopsy samples were obtained at the same time (3). In these patients, muscular manifestations were not clinically detectable or were very subtle (4).

Thus, in most patients whose disease seems to be confined to the peripheral nervous system, vasculitis also involves small- and medium-sized arteries of other organs. The high incidence of nerve involvement is because of the size of the vasa nervorum, which is similar to that of the vessels affected in vasculitides such as polyarteritis nodosa or microscopic polyangiitis, and because of the high susceptibility of nerves to ischemia. Nerve fiber lesions are often symptomatic, even if limited to a short segment of nerve, because of the subsequent neurologic deficit from axonal degeneration, whereas a lesion of the same size may remain clinically undetectable in other organs.

In patients with isolated clinical neuropathy at initial presentation, the disease may progress with time. We recently reviewed the records of the 32 patients with isolated clinical peripheral neuropathy from our series of 100 patients with...
necrotizing vasculitis (2). Treatment had included corticosteroids with or without immunosuppressive drugs. The median followup period for the surviving patients was 5 years (range 1–15 years, SD 4 years) from the onset of neuropathic symptoms to final assessment. The 5-year survival rate was 85%. Ten (31%) of 32 patients died during followup. Four patients died of systemic vasculitis (2 with central nervous system involvement, and 1 each with mesenteric infarction and cachexia). Seven (22%) patients had relapses involving the peripheral nervous system. Importantly, 11 (34%) patients presented with involvement of other organ systems during followup. Three patients had central nervous system involvement. End-stage renal failure occurred in 2 patients and intestinal perforation in another 2 patients. Four patients had cutaneous lesions, and 2 had arthralgia. One patient had eye involvement, and 1 had pulmonary involvement.

The apparent limitation of vasculitis to the peripheral nervous system in a patient with neuropathy should not be regarded as evidence that the patient does not have systemic vasculitis. We recommend very close followup of these patients, especially if less aggressive treatment is chosen.

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Reply

To the Editor:

We are grateful to Handa and colleagues and to Puéchal and Said for their comments about our concise communication on necrotizing vasculitis confined to the peripheral nervous system. The 2 letters represent opposite perspectives that are easily reconciled.

Puéchal and Said have updated a valuable series which we had referenced. Clearly, a substantial percentage of patients with biopsy-proven nerve or muscle vasculitis have a systemic vasculitis that progresses and requires aggressive immunosuppressive therapy. Learning the rate of that progression would be most helpful. For example, if a patient has had no clinical disease 1 year after the onset of neuropathy, what is the likelihood that vasculitis will develop elsewhere?

As described by Handa and colleagues and as illustrated by our report, an occasional patient does have a vasculitis that is much more limited in its clinical implication. The challenge, of course, is to use immunosuppression judiciously and to discover how to recognize those few patients whose disease progresses slowly despite the absence of immunosuppressive therapy.

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Predictors of visual loss and cerebrovascular accidents in giant cell arteritis: comment on the article by González-Gay et al

To the Editor:

I read with interest the article by González-Gay et al (1), describing predictors of blindness and cerebrovascular accidents in patients with giant cell arteritis (GCA). The authors conducted a retrospective study of a large number of cases of biopsy-proven GCA and applied sophisticated statistical analyses. They concluded that, in GCA, the risk of permanent visual loss increases for patients with transient visual loss, jaw claudication, or both, and decreases for patients with elevated liver enzyme levels, constitutional syndrome, or both.

How does this information apply to the population of patients with GCA? I believe that the authors are describing clusters or associations of clinical symptoms and laboratory findings in GCA, instead of “predictors.” For example, blindness and elevated liver enzyme levels in their patients were found to be negatively correlated. This does not imply, however, that liver enzyme levels either “protect against” or “predict” subsequent blindness. Do normal liver enzyme levels place patients with GCA at risk for blindness? I think not. Associations and temporal relationships are one thing and predictors are quite another. Although blindness in GCA tends to occur early and in patients with jaw claudication, it can occur at any time as a complication (see below). Also, the authors say that partial therapeutic success is more probable when treatment is started within the first day of visual loss, with the implication that steroid treatment should be started before any visual symptoms develop. This has been the traditional dogma. However, how important really are corticosteroids in preventing blindness from GCA? I believe this question is more relevant.

In our study of 27 patients with GCA, a 62-year-old woman receiving corticosteroids experienced progressive ischemic optic neuritis causing almost total loss of vision in her right eye. Similarly, a 51-year-old woman no longer receiving corticosteroids developed sudden bilateral blindness 7 years after the initial diagnosis of GCA (2). This type of undesirable outcome is not uncommon in clinical practice, sometimes giving rise to medical malpractice suits. If prompt and early steroid treatment is appropriate intervention, why do some seemingly adequately treated patients still develop sudden or progressive visual loss?

Perhaps the most important lesson we have learned in trying to prevent blindness from GCA is that corticosteroids...
alone may not suffice. As Conn et al rightly pointed out (3), an occlusive vasculopathy may develop and, perhaps, even be aggravated by the use of steroids in vasculitis. Perhaps early treatment with low-dose aspirin or a similar antiagulant is the best we can offer patients with GCA in an attempt to prevent visual loss.

I believe that, from the very beginning, practicing rheumatologists should include daily low-dose aspirin (e.g., 81 mg [or perhaps as little as 10–40 mg]) as standard therapy along with steroids in the overall management of GCA. Osteoporosis prevention should be addressed from the beginning of corticosteroid therapy, as well. Because of obvious ethical implications, I doubt that a prospective placebo-controlled trial of the benefits of low-dose aspirin will ever be conducted.

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Reply
To the Editor:

We appreciate the interest of Dr. Gonzalez in our article on GCA, although we disagree with the points raised in his letter. In our study, we identified the predictors of permanent visual loss and cerebrovascular accidents (CVA) in a large population of patients with biopsy-proven GCA by a forward stepwise nonconditional logistic regression analysis. The multiple regression analysis is the appropriate technique for finding the relationship between one variable (the dependent variable) and a set of other variables usually called independent variables. Although, as stated by Armitage and Berry, the nomenclature is confusing, the term “predictor” is probably best suited for independent variables (1). We should emphasize that this term does not imply a causal relationship. There are two types of designs for studying prognostic variables (2): predictive studies, whose main objective is to identify predictors, defined as variables preceding the outcome and statistically related to it; and explanatory studies, whose main objective is to identify variables causally related to the outcome. According to these concepts, we believe our use of the term predictor is correct. Moreover, we think that identifying predictors can be helpful in daily clinical practice. However, we did not suggest that these predictors were causally related to the development of blindness.

Regarding the second issue raised by Dr. Gonzalez, the role of corticosteroid therapy in preventing and treating visual loss in GCA, we believe most clinicians will agree with our conclusion that early corticosteroid therapy is the most important therapeutic intervention currently available, even though it is only partially effective. This is emphasized by our findings of partial improvement in only 60% of the patients in whom corticosteroid therapy was started within 24 hours of onset of visual impairment. Therefore, it is becoming evident that other therapies are needed for improving the outcome in GCA, especially in patients with ischemic symptoms (i.e., permanent visual loss and CVA). Although, in our article, we recommended studying the possible benefit of antiaggregation therapy (such as low-dose aspirin) in GCA, we disagree with Dr. Gonzalez’ proposal to routinely add daily low-dose aspirin, from the beginning, to the corticosteroid therapy of all patients with GCA, because no scientific evidence supports such a proposal. Further, after we submitted our manuscript, a prospective study (3) assessed the prevalence and thrombogenic role of anticardiolipin antibodies (aCL) in GCA, reporting the conclusion that aCL were not a risk factor for thrombosis in GCA. Moreover, another article in the same issue of Arthritis & Rheumatism (4) reported the finding that intimal hyperplasia leading to occlusive disease in arteries affected in GCA was at least partially related to increased in situ production of platelet-derived growth factor (PDGF). This raises the possibility that new therapeutic measures targeted on the action of PDGF could complement the current, only partially effective, corticosteroid treatment.

Taking these data into account, we believe the current rationale for possible effectiveness of low-dose aspirin or any antiaggregant or antiagulant therapy in GCA is at least debatable. Therefore, such therapies’ possible roles should be based on the results of well-designed double-blind, placebo-controlled clinical trials.

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4. Kaiser M, Weyand CM, Björnsson J, Goronzky JJ. Platelet-derived...

Does normal erythrocyte sedimentation rate rule out polymyalgia rheumatica? Comment on the article by Helfgott and Kieval

To the Editor:

We read with interest the article by Helfgott and Kieval on polymyalgia rheumatica (PMR) in patients with normal erythrocyte sedimentation rate (ESR) (1). The authors stated that 22% of their patients with PMR were found to have a normal ESR (≤30 mm/hour), and a significantly higher proportion of these patients were male.

PMR in patients with a normal ESR had been thought to be infrequent (2,3). However, recently it has been shown that 10–20% of PMR patients show an ESR ≤30 mm/hour (4,5). To ascertain the frequency of PMR coupled with a normal ESR in our patient population, we conducted a retrospective study of all patients meeting the Jones and Hazleman criteria for PMR (6). We also tried to determine whether it is possible to distinguish these patients clinically from those who have PMR with an elevated ESR.

Thirty-four patients with PMR who had been admitted to Hacettepe University Department of Physical Medicine and Rehabilitation during a 5-year period were included in the study. Inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia, and seronegative spondylitis, as well as thyroid disorders and multiple myeloma and other malignancies, were ruled out by clinical and laboratory evaluation. Episodes of fever, depression, weight loss, peripheral arthritis, and symptoms of giant cell arteritis, as well as results of laboratory tests including hemoglobin and rheumatoid factor, and, if possible, antinuclear antibodies and anti–double-stranded DNA were noted from the charts of the patients. We evaluated the data statistically using Student’s t-test and Fisher’s exact test.

In this retrospective analysis, 29 (85.3%) of 34 patients had an elevated ESR (mean 76 mm/hour, range 36–98) and the remaining 5 patients (14.7%) had a pretreatment ESR of ≤30 mm/hour, determined by the Westergren technique. Four (80%) of these patients were women, compared with 26 (90%) of the 29 patients with an elevated ESR (P > 0.05). Three (60%) of the 5 patients with normal pretreatment ESR continued to have normal ESR during the followup period. There was no statistically significant difference between the mean ages of the 2 groups (68 years in the elevated ESR group versus 70 years in the normal ESR group). Prolonged morning stiffness was seen in all patients. The 2 groups did not differ significantly in shoulder and pelvic girdle involvement, peripheral arthritis, and systemic symptoms (P > 0.05). The laboratory findings for the groups did not differ significantly, either. However, in the patients with elevated ESR, the mean hemoglobin level was slightly low (11.3 gm/dl, versus 12.7 gm/dl in those with normal ESR), and the mean C-reactive protein level was slightly high (1.8 mg/dl, versus 1.2 mg/dl), with no statistically significant difference (P > 0.05 for either comparison). The only significant difference was in the mean duration of the symptoms before the diagnosis in each of the 2 groups (18.2 weeks for patients with normal ESR versus 9.7 weeks for patients with elevated ESR) (P < 0.05). As we noted from the chart reviews, only 1 patient with an elevated ESR had symptoms of transient blindness and temporal headache, and this patient was found to have giant cell arteritis on temporal biopsy.

Twenty (69%) of the 29 patients with elevated ESR and all 5 of the patients with normal ESR were treated with a trial of nonsteroidal antiinflammatory drugs without effect. Following initiation of treatment with low-dose corticosteroids (prednisone, ≤10 mg/day), prompt and striking improvement was observed.

Previous studies have emphasized that ESR is elevated in PMR patients, with rare exceptions. However, the finding of a normal ESR in PMR cannot now be considered uncommon, and the incidence of normal pretreatment ESR has been reported to be as high as 20% (7) and 22% (1,4). We found a proportion of 14.7% identical to that reported in the study by Bahlas et al (8), in which the ESR was <30 mm/hour in 21 (14.7%) of 143 PMR patients. Cimmino et al suggested that measuring the ESR before and after treatment with steroids, and calculating the change, can help establish the diagnosis of PMR even if the baseline ESR is normal (9).

Although patients with either elevated or normal ESR (including patients with ESR ≤30 mm/hour throughout the disease course) have been reported, in the recent literature and in our study, to present with similar clinical features, further investigation is needed to establish criteria for “normal ESR” in PMR. It seems that absolute ESR is not as clinically significant for diagnosing PMR as had been thought. The lack of characteristically abnormal laboratory findings may result in a delay of the proper diagnosis and management of PMR. We believe that an elevated ESR supports the history and clinical findings of a suspected diagnosis, and if there is good clinical evidence for PMR, a normal ESR should be ignored and the patient should undergo a trial of corticosteroids. The response to corticosteroids may help to establish a diagnosis of PMR in patients with normal pretreatment ESR.

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8. Bahlas S, Ramos-Remus C, Davis P. Clinical outcome of 149

Reply

To the Editor:

Dr. Sivri’s finding mirrors ours, namely, the observation that there are no major clinical differences between PMR patients with and those without an elevated ESR. Dr. Sivri found, as did we, that duration of symptoms prior to diagnosis of PMR was significantly longer in patients with normal ESR. This suggests a hesitancy of clinicians to diagnose PMR in the absence of an elevated ESR. As Dr. Sivri points out, perhaps we should ignore ESR and treat patients in whom PMR is suspected, based on their histories and physical examination findings, with empirical trials of low-dose corticosteroids.

This study from Turkey, following those from England (1), Denmark (2), Spain (3), Argentina (4), and our own, emphasizes the universality of these observations.

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Fibromyalgia and physical and emotional trauma: how are they related? Comment on the article by Aaron et al

To the Editor:

Aaron et al demonstrated that, despite similar pain severity and pain thresholds in fibromyalgia syndrome (FMS) patients who reported onset of their FMS symptoms following physical trauma and those who reported onset of their FMS symptoms following emotional trauma, those who experienced physical trauma were much more likely to be receiving disability compensation than those reporting emotional trauma (1). We wish to comment further on why this may be.

In an earlier issue of this journal, our group explained one route to a diagnosis of FMS in subjects who have experienced trauma, through the effect of emotional distress on generation of tender points (2). That a diagnosis of FMS can follow emotional trauma further affirms the role of psychological distress in symptom development.

There is a second, related route to a diagnosis of FMS, namely, somatization and adoption of the sick role. This is particularly relevant to accident victims (3), and may explain the difference in levels of disability compensation for FMS patients following physical trauma versus emotional trauma.

The sick role is a partially and conditionally legitimized state granted to an individual (4,5) that confers secondary gains (6). The sick role can be particularly attractive to those with preconceived and conscious motivations for attaining solutions to their life situations as part of the secondary gain.

However, the sick role is only granted and its secondary gains attained when others (in most societies, physicians) decide that the sickness is not something the patient can readily stop (5). Indeed, there is an explicit link between the concepts of secondary gain and socially acceptable illness. Secondary gain is “...the acceptable and ‘legitimate’ interpersonal advantages that result when one has the symptoms of a physical disease. The somatically distressed individual is excused from certain responsibilities and obligations and can avoid challenges and duties. The physically symptomatic person also garners sympathy, attention, support, and many types of concrete assistance. ...All of this occurs without a loss of pride or self-esteem and without a sense of failure, fault, or defeat. This is because the patient cannot be blamed for his or her inability and is not held responsible or culpable” (7).

For example, we explored the following construct for the accident victim: personality difficulties + troubled life situation = unacceptable disability, but then, unacceptable disability + accident = acceptable disability (8). In this context, one can appreciate preferring the phrase “fibromyalgia following accident” to “post-traumatic fibromyalgia” (9,10). The trauma is not a cause, but instead an opportunity. As Kennedy noted long ago, the accident may be merely the peg on which the neurosis is hung (11).

Aaron et al demonstrate the innate social unacceptability of emotional or psychological disorders. Those patients with emotional trauma are not applying for disability compensation for depression or anxiety disorder (as one would expect them to) but instead are applying for compensation for chronic pain. These patients probably share a preconceived desire to alter their, and others, perception of the illness—disability from pain is acceptable, disability from emotional disorder is not. A parallel example occurs in chronic fatigue syndrome. Those patients who admit that a series of life stressors preceded their fatigue still insist that the stress is etiologic only in “weakening” their immune systems, making their viral infections more “severe” (12).

Somatization can be conceived as a culturally determined mechanism of expressing psychological disability in a more socially acceptable form. It is the basis of an illness behavior (often called inappropriate or abnormal) driven by the desires (preconscious and conscious) to attain the sick role (13,14). This sheds further light on the observation that a FMS diagnosis more frequently follows a whiplash injury than a leg fracture (2,15). The preconscious and conscious mind require information, at some point, of what is acceptable as a symptom of organic disease (16). Even if a leg fracture patient has preconceived and conscious motivations to adopt the sick role,
he or she does not know that whole-body pain is an expected outcome of leg fracture alone. The preconscious and conscious mind are unlikely to produce such symptoms or behaviors.

On the other hand, the information has long been available that diffuse, whole-body pain and a multitude of other chronic symptoms can and do follow a “spine injury.” The popular observation that diffuse pain can follow specific accident injuries even predates the automobile (17).

We agree with Aaron et al that FMS patients may simply be more likely to receive disability benefits when physical trauma occurs in circumstances, such as a motor vehicle accident (MVA), where social and legal mechanisms already exist for injury-related compensation. Disability claims following emotional trauma are subject to social biases, even when symptoms are couched in an “organic-sounding” label. More exactly, a patient’s symptoms must have a culturally determined and socially acceptable link with disability. The illness formerly known as “post-MVA fibromyalgia” is a prime example, having been thoroughly cultivated by the popular media.

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nance imaging report) of physiologic abnormalities that actually may not be a source of nociceptive transmission.

In conclusion, we are pleased that our research has generated debate regarding the disability compensation system in the United States. The system certainly requires scrutiny if our society is to respond appropriately to the legitimate needs of patients with chronic pain associated with FMS and other syndromes (7). However, such debate should not focus exclusively on the influence of psychological constructs such as preconscious motivations, which cannot be empirically documented.

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Opioids and rheumatic disease pain: comment on the article by Ytterberg et al

To the Editor:

The recent article by Ytterberg and colleagues on the use of opioids for chronic rheumatic disease pain (1) raises important questions: 1) What were the criteria for opioid therapy? 2) What was meant by a nonreversible pathologic source of pain, apparently used as the indication for opioid therapy? 3) Is it valid to extrapolate the characteristics of a Veterans Administration population of older men, the majority of whom had longstanding rheumatoid arthritis, to the patient populations of most rheumatology practices (with their different distributions of age and sex)? The authors state that no data suggest younger women are more vulnerable than older men to opioid addiction, but is physical addiction the major problem in the use of these drugs?

Clearly, some patients with end-stage rheumatic dis-

Reply

To the Editor:

Dr. Gelfand has raised important issues regarding the use of opioids for rheumatic disease pain. Because this was a cross-sectional cohort study of patients receiving prescriptions for opioids, we did not study indications for starting opioids. Nonreversible joint damage meant erosions, joint space narrowing or deformities, or combinations of two or all of these. The results of this study cannot be extrapolated to younger, predominantly female patient populations or to populations of patients with nonspecific pain, such as fibromyalgia, as described in the discussion of the report. “Major problems” with the use of opioids for rheumatic disease pain have included questions regarding efficacy, toxicity, tolerance, dependence, abuse, and addiction. Unfortunately, these questions have been used to justify withholding opioid analgesics from patients with defined rheumatologic disorders, without any data supporting this practice.

This study raises many important questions, not the least of which is what are the psychosocial underpinnings for the undertreatment of pain? We must ask the difficult ethical question of why physicians promote “coping” with pain rather than using medications to decrease it. No data suggest that decreasing pain detracts from evaluating and treating patients with these diseases. True, these patients do have a belief-based dependence on medications that is based in reality. As of today, there is no “quick fix” for patients with rheumatoid arthritis and ankylosing spondylitis. Treatment is designed to suppress disease, improve function, and improve quality of life. Reduction of pain must be part of that treatment plan. We need more scientific data to practice evidence-based treatment of chronic rheumatic disease pain.

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Is malignant infiltration necessary for development of leukemic arthritis? Comment on the article by Rudwaleit et al

To the Editor:

We read with interest the report by Rudwaleit et al (1) on the possible mechanisms of leukemic arthritis. They described a patient with B cell chronic lymphocytic leukemia (B-CLL) in whom histologic and immunologic evidence of specific infiltration of the synovial tissue by leukemic cells was present. The most intriguing finding was the abundant presence of interleukin-1β (IL-1β) in the leukemic joint. The authors suggested that IL-1β secreted by leukemic cells in situ may play a pivotal role in leukemic synovitis. Coincidentally, joint manifestations of leukemias have been mostly attributed to leukemic synovial infiltration (2–6). In such instances, histologic examinations of the synovial membrane usually show infiltration by malignant cells, without villous proliferation of synovia or neovascular formation (3,6). However, there are several cases of leukemic arthritis in which synovial biopsies (some obtained at open surgery or autopsy) disclosed no leukemic infiltration (7–10). In addition, marked stratification of synovial lining cells and proliferation of synovial stromal cells were described. Instances have been reported of proliferative synovitis associated with adult T cell leukemia (11,12), acute lymphoblastic leukemia (9), and myeloid leukemia (7).

Thus, arthritis in leukemia can occur without evident malignant cell infiltrations. It is unclear whether synovial involvement is directed from the aberrant clone of the hematogenous tissue or from the normal host immune system responding to antigenic material secreted by leukemic cells. Several studies on the cytokine secretion of B-CLL cells from the peripheral blood have demonstrated that these cells secrete a variety of cytokines (1). Similarly, it has been shown that malignant cells from patients with adult T cell leukemia spontaneously liberate a large amount of IL-1–like factor(s) in culture (12). According to some data, neoplastic T cells can also produce tumor necrosis factor β, which in turn influences the clinical symptoms of the disease (13). One can speculate that cytokines act at a paracrine level, creating paraneoplasia at a distance from the malignant cell. Therefore, it seems that migration of leukemic cells to synovial tissue is not required for development of leukemic arthritis. Further studies are needed to determine the mechanism for synovitis in instances where leukemic infiltrates are absent.

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The musculoskeletal syndromes that can be associated with the various forms of leukemia comprise a large spectrum of manifestations, from mild arthralgia to frank arthritis. Direct synovial infiltration of leukemic cells accounts for many cases of arthritis (1). In some cases, only infiltration of the metaphyseal periosteum subjacent to the joint capsule was found (2), and in others, leukemic cells were not seen in the joint (3–6). Fluid aspiration or needle biopsy used to obtain synovial material may account partly for the lack of leukemic cells in the specimens (3,4).

Nonetheless, it seems likely that paraneoplastic forms of arthritis do exist. We therefore acknowledge the comment by Praprotnik and Tomšič, who stress the pathogenic heterogeneity of leukemic arthritides and point out the existence of paraneoplastic arthritides in leukemia. The joint tropism in our patient with both wrists affected, however, remains a mystery.

Our study aimed to shed light on instances where direct infiltration of leukemic cells seemed relevant to the occurrence of arthritis. We sought especially to find out which locally produced cytokines might contribute to pathogenesis, because very little was known about the synovial cytokine milieu in leukemic arthritis. We could show that IL-1β was the predominant proinflammatory cytokine in the joint, and that locally neither tumor necrosis factor α (TNFα) nor the patient’s immune system appeared to play a major role. The significance of IL-1β is also supported by data from the TNFα-transgenic mouse model in which IL-1β has recently been shown to be the dominant effector cytokine (7).

Leukemic arthritis without evidence of synovial leukemic infiltration may arise from infiltration of adjacent bone (2), be immune complex mediated, or be triggered by hitherto unproven mechanisms such as molecular mimicry. High systemic levels of proinflammatory cytokines also may exacerbate existing joint inflammation, independent of the cause of inflammation. Whether cytokines systemically released by leukemic cells can induce arthritis without prior joint damage, as seen in TNFα-transgenic mouse models (8,9), however, is questionable.

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