On the Importance of Early Arthritis Centers

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There are more than 100 different types of arthritis. However, even in the information age, many patients with joint pain are unaware that more than one type (or maybe a few) exists. As a result, many patients who believe that they have a benign form of arthritis will instead be suffering with a systemic inflammatory disease such as rheumatoid arthritis (RA) or psoriatic arthritis, diseases that, if not treated properly, can cause irreparable joint destruction and disability. It is now clear that to achieve the best possible outcome, patients with inflammatory arthritis must be identified and treated early in their course [1]. Because primary care physicians and orthopedic surgeons are stationed at the first and second lines in the evaluation of most patients with joint pain, they are central players in not only identifying patients who potentially have early inflammatory arthritis but also in triaging them to rheumatologists or, more recently, to specific centers the focus of which is rapid diagnosis and intervention.

Early arthritis centers

In the past several decades, studies in cohorts of patients with early inflammatory arthritis (not fulfilling American College of Rheumatology criteria of rheumatoid arthritis at onset) have shown that although many of these patients have a self-limited illness, a significant proportion of these patients go on to develop rheumatoid arthritis [2]. What is the significance of this? Many patients with RA are forced to leave work within 5 to 10 years of disease onset and life spans of RA patients are significantly shortened. Recently, it has also become clear that the persistent inflammatory burden associated with RA can lead to premature atherosclerosis and death due to cardiac events. Machold and colleagues [3] showed in a study of patients with inflammatory joint disease of less than 3 months' duration that 61.1% of patients went on to develop rheumatoid arthritis, 12.8% had erosions on their first x-rays, and 27.6% had erosions by their first year. Data such as these has led investigators to compare treatment strategies in patients with early inflammatory arthritis.

There is now clear evidence that patients who have early rheumatoid arthritis have significantly better outcomes when they are treated within the first few weeks to

months of their illness. For example, Lard and colleagues [4] showed (using medications that are now considered relatively weak disease-modifying antirheumatic drugs) that treatment initiated within a few weeks of symptom onset resulted in less radiographic damage and less overall disease activity.

Furthermore, in recent years, the introduction of medications that block tumor necrosis factor alpha (TNF α) has revolutionized the practice of rheumatology, allowing for greater control of the inflammation of RA better than has ever existed. The TNF α blockers, which include etanercept, infliximab, and adalimumab, not only greatly reduce disease activity but also can profoundly slow the progression of joint destruction. Because early treatment results in better outcomes and because we now have very effective agents for doing so, early inflammatory arthritis should be responded to, diagnosed, and treated with the sense of urgency that has heretofore been afforded to angina, hypertension, infections, asthma, and diabetes.

To properly address this new treatment paradigm, early arthritis centers (EACs) were developed in Europe and, more recently, in the United States. The purpose of these centers is to provide a rapid response (less than 1 week to be seen) for patients who potentially have inflammatory arthritis. In this way, a patient with early inflammatory arthritis can be identified quickly and triaged to proper treatment. To accomplish this goal, there must be a strong partnership between the rheumatologist and the physicians on the front lines who see patients with arthritis.

EACs: changing the culture

The public needs to think of early inflammatory arthritis as a medical emergency Often, for something to be considered an emergency, it must first be perceived as dangerous [1]. Few patients would delay in seeing their physician if they developed chest pain or weakness on one side of their body. However, it is clear that most people do not perceive joint pain as dangerous. They often delay in seeking medical attention, sometimes for months or years. They self-medicate with over-the-counter anti-inflammatories (which do not prevent joint destruction) and health food store remedies. This is because they are grossly unaware of the warning signs and symptoms that could very well reflect that something more sinister could be present. Because many of these patients will go on to develop a destructive arthropathy and because we now have effective medications for slowing this process, it is essential that the public's

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perception is changed. One role of EACs is to mount an aggressive campaign to directly educate the public about what symptoms suggest an inflammatory arthritis and how soon they need to see their physician.

Physicians need to think of early inflammatory arthritis as an emergency In the past, once a patient finally decided to see their physician, there may have been further delay in the time to be seen by a rheumatologist. There are several reasons for this. A trial of nonsteroidal anti-inflammatory drugs, over the counter or prescribed by a physician, may partially control the symptoms and allow the patient to function, albeit with limitations. A primary care physician, commonly undertrained in rheumatology, may not appreciate the significance of the problem and feel as though the issue is related to overuse, a virus, or depression and give symptomatic and supportive treatment. Furthermore, because of a shortage of rheumatologists, especially in underserved areas, the wait to see a rheumatologist can be up to 1 or 2 months. These obstacles lead to an inappropriately long wait for someone who potentially has rheumatoid arthritis. In places where EACs are being developed, rheumatologists create active dialogue with primary care physicians and orthopedic surgeons, discussing what symptoms to look for and when to refer. Furthermore, the rheumatologists also make the commitment to be available within a few days for patients who are triaged to them with early inflammatory arthritis.

What is inflammatory arthritis, and how can it be identified early?

The classic signs and symptoms of inflammation are redness (rubor), swelling (tumor), warmth (calor), pain (dolor), and loss of function. It is true that these elements may be transiently associated with osteoarthritis, trauma, or soft tissue syndromes; however, they tend to be chronic, dominant features in patients with inflammatory arthropathies. RA is the classic inflammatory arthritis; however, there are many other diseases that may be difficult to distinguish from RA early in their course, some of which can be equally destructive, but may require different or additional therapies. These diseases include (but are certainly not limited to) the following: systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis (scleroderma), relapsing polychondritis, inflammatory myositis, Wegener's granulomatosis, adult-onset Still's disease, and giant cell arteritis. Moreover, certain viral illnesses such as rubella or parvovirus B19 can masquerade as inflammatory arthritis or RA. Luckily, they are self-limited illnesses.

Emery and colleagues [5] suggest the following guidelines for referral of a patient with arthritis and any of the following to a rheumatologist:

- (1) Greater than or equal to 3 swollen joints
- (2) A positive "squeeze test" (transverse compression of the metatarsophalangeal or metacarpophalangeal joints)
- (3) Morning stiffness lasting greater than 30 minutes

- (4) Elevated acute phase reactants including erythrocyte sedimentation rate and C-reactive protein
- (5) Positive serologies including rheumatoid factor or antibodies to cyclic citrullinated peptide
- (6) Joint symptoms lasting greater than 6 weeks

Challenges to diagnosis and treatment

Very early in disease, patients who might be destined to develop full-blown RA often do not meet the American College of Physicians criteria for RA because they may not as yet have developed the characteristic positive serologies or x-ray changes of RA. Furthermore, a large proportion of people with an acute inflammatory arthritis will have a self-limited viral syndrome. This presents a challenge during treatment; although it is undesirable to treat a viral syndrome with potentially toxic medications, it is equally undesirable to delay treatment of a potentially devastating illness. Studies aimed at trying to develop an appropriate strategy to approach this issue are currently underway at EACs around the world, including one at the Hospital for Special Surgery.

EACs and understanding the nature of autoimmunity

In many inflammatory arthropathies the etiology of the disease remains unknown. In addition to providing rapid and effective therapies to patients with inflammatory arthritis, EACs also hold promise for a better understanding of the etiology and pathogenesis of the disorders and new and more effective therapies.

Recent evidence suggests that autoimmune diseases begin even before the patients develop symptoms. In 2003, using samples from the Northern Sweden Health and Disease Study, Rantapaa-Dahlqvist and colleagues [6] showed that both rheumatoid factor and anti-cyclic citrullinated peptide antibodies appeared within the patients' blood years before the development of RA. Also in 2003, using the Department of Defense serum repository, Arbuckle and colleagues [7] showed that the autoantibodies that are found in systemic lupus erythematosus are present in patients not only years before the diagnosis of disease but also years before the onset of symptoms. These studies suggest that the cellular and molecular abnormalities that result in systemic inflammatory diseases begin well before even the patients themselves know that something is wrong.

How can EACs provide a forum for more effective research into the etiology of autoimmune diseases? Much of our knowledge regarding the cellular and molecular changes that take place within autoimmune disease has come from studies of patients who have long established disease. Just as it is possible that the persistence of war can change the politics that originally lead up to the war, so too it is possible that uncontrolled, poorly controlled, or partially treated inflammation (raging for years) may change the nature of the etiologic agent of these diseases.

EACs provide a framework for studying autoimmune diseases in their most pure form, at first onset, before any treatment. Because it is now clear that cellular and molecular changes which lead to these illnesses take place years before onset of symptoms, the study of patients with fresh, untreated illness may give us better insight into early events and, therefore, lead to more effective therapies. Furthermore, this approach could provide a doorway to identifying people at risk for these illnesses *before* they develop symptoms.

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