Diagnosing early rheumatoid arthritis (RA). What are the problems and opportunities?

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ABSTRACT

Early diagnosis is being appropriately emphasized in RA, as early DMARD treatment can be very effective. ACR criteria are useful but may not perform as well in early disease. These criteria depend on clinical examination, which is subject to over- and under-interpretation. Ultrasound and MRI may offer advantages. Laboratory tests and synovial fluid analyses may contribute, but are often not definitive. All of these data, synovial biopsies and a variety of other features can guide prognosis as well as diagnosis.

Consideration of the whole patient, including education levels and coping strategies, can help. Aggressive management is proposed for most patients once the diagnosis is firm. Strategies are needed to arrange that patients are seen at a very early stage by rheumatologists knowledgeable in the treatment of early arthritis.

Early diagnosis is receiving increasing emphasis in RA, with the recognition that erosive irreversible disease can occur in the first months and that a variety of treatments can clearly prevent or slow disease progression (1, 2).

Most studies addressing early RA use the American Rheumatism Association (ARA), now the American College of Rheumatology (ACR), criteria (3) for purposes of uniformity although these criteria have been shown to be less valid in early disease (4). Early DMARD treatment can make a difference, but there are a number of unanswered or partially answered questions about diagnosis that remain to be addressed. We review this area, focusing on work from our own research and how this has guided our thinking.

How reliable are standard criteria or approaches to diagnosis of early RA?

ACR criteria have only occasionally been tested in early RA and generally are not as useful as in chronic disease (4). These are classification criteria for research studies, which were not designed primarily for diagnosis. Ten real cases from an early arthritis clinic were described for 20 experts from various countries. Patients were felt to have RA, spondylarthropathy or to be unclassified. Good agreement was seen in only one case of very classical RA (5). The authors felt that strict criteria were not helpful in arriving at the various impressions. Many patients seem not to meet the established arbitrary criteria, possibly suggesting overlapping etiologies of mechanisms that we do not yet understand.

Our own early arthritis patients at the NIH and University of Pennsylvania have very often been difficult to classify and many were best considered unclassified during the first year of observation. This unclassified group is important to identify, as all studies show that people in this group have a better prognosis (6-9). It appears important to resist the rush to name a definitive diagnosis. We may please our patients more by telling them they do not meet the criteria for RA or spondylarthropathy and many will do better.

How accurate is our standardized clinical assessment of synovitis?

Several observations have raised concerns about the reproducibility of the clinical assessment of synovitis and even the sensitivity of physical examination for the detection of mild synovitis (10). Synovial biopsies of clinically normal joints in patients with early or chronic RA have shown synovial inflammation that was not detected clinically (11, 12). Some joints had been involved previously in early patients, but others never were associated with symptoms or physical findings. Recent ultrasound and MRI studies have demonstrated apparent synovitis not appreciated on physical examination (13,14).

Doppler color ultrasound can identify increased vascularity and presumed synovitis. Biopsy-ultrasound correlations could be very interesting.
Both MRI and ultrasound can also detect apparent erosions not seen on X-rays (14). These may well be more useful than X-rays in early disease. Ultrasound, however, is very operator-dependent, and should be included in training programs in the United States, as it is in Europe. These studies suggest that we are missing some cases of synovitis. Could it also be true that we sometimes over-interpret symptoms and signs ? Studies with clinical examination, MRI and ultrasound may also tell us how often we are over-identifying synovitis. It is of interest that joint counts as currently done tend to improve more with placebo than do patient questionnaires or laboratory tests (15).

How helpful are serologic and genetic tests?

Although rheumatoid factor can be seen in a variety of other diseases with polyarthritis (hepatitis C, sarcoidosis, subacute bacterial endocarditis, as examples) a high titer without evidence of these other causes can support the diagnosis and offers a prognosis of more severe disease. Of course RA can also occur without rheumatoid factor, but such seronegative cases probably deserve continued scrutiny for other diagnoses, as well as for whether they represent a different subset with regard to a therapeutic approach.
Measurement of anticitrillinated peptides (antiCCP) has been proposed as a more specific test, that was present in 70% of RA and only 5% of controls (16). In our own series of early cases antiCCP were present in only 9 of 132 non-RA subjects, in 54% of seropositive RA, but in only 14% of what we called seronegative RA (17). This deserves continued study to determine if antiCCP have prognostic or therapeutic significance.
The shared epitope, a sequence of amino acids encoded by specific alleles of the HLA-DR4 gene, is associated with RA in most Caucasian groups. This gene clearly can predispose to RA and has tremendous research interest, although it must be said that while HLA-DR4 may predict more severe disease, it does not achieve sufficient specificity to be of practical diagnostic value (18).

Can synovial fluid or synovial biopsy help us with early diagnosis of RA?

Clearly, identification of positive synovial fluid cultures or crystals can be of great help in identifying other causes of arthritis. Gout rarely co-exists with RA, but calcium pyrophosphate (CPPD) crystals can do so more often. If monosodium urate or CPPD crystals are found, major effort will be needed to prove that there is a second disease. Synovial fluid analysis of new knee effusions has been shown to change diagnoses and therapies in about 20% of cases (19). Remember, however, that quality control remains a problem with crystal identification, so reports may be misleading (20). Unfortunately, there is no definitive feature of SF that defines RA. However, it is important when fluid is obtained, to be sure that it is inflammatory with at least 2000 WBC/mm^3 and usually much more. Only rarely is there definite inflammation in the synovial tissue that is not reflected in the joint fluid.
Synovial biopsies, although a major emphasis of our work (21), are often characteristic but not diagnostic of RA. They should show chronic inflammation and may help exclude infectious or infiltrative arthritis. Unless we are surprised and find one simple cause of RA, biopsies will probably never be diagnostic. There is more hope that synovial features will help identify prognostic factors or the likelihood of response to certain therapies. We found that synovial MMP-2 levels were associated with more erosions (22) and others report that greater numbers of macrophages predict worse disease (23).

What about various prognostic factors?

There seems to be an evolving consensus that – once RA is diagnosed – many readily assessed factors help predict a poor outcome (24). These include greater numbers of joints involved, poor functional status, rheumatoid factor, high platelet count, elevated ESR, early presence of bony erosion and health status as reflected by the Health Assessment Questionnaire (25). In general, such findings lead to recommendations for aggressive therapy. However, even our best new agents rarely cause remission in these patients. Certainly we should treat such patients promptly with DMARDs, but shouldn't we also treat many patients without these features aggressively as they may be the ones who can achieve remission? We need help to decide the pros and cons of a more aggressive approach, as some of these patients could also do well with less treatment.
Many prognostic factors seem to apply no matter what the clinical diagnosis, although they are more likely to be present in patients termed RA. Gerber *et al.* in the NIH early arthritis clinic determined that functional outcome one year later was influenced most by the number of joints involved, and not primarily by the clinical diagnosis (26). We also noted that a greater number of joints affected increased the risk of persistent disease (27), but so did a diagnosis of RA or of spondylarthropathy. Unclassified patients with fewer joints involved had a better prognosis. A number of patients whose disease resolved had polyarthritis that lasted less than 6 weeks, so conclusions often cannot be made until at least 6 weeks (and possibly 3 months).
Are there good prognostic factors that we should be looking for ? In our study, patients who had a more acute onset, or who had fever at onset, tended to do better (27). Any clue to an antecedent infection has also been suggested to be a good prognostic factor (28). Soderlin *et al.* recently looked at patients in an early arthritis clinic and noted that those with evidence of preceding infections were more likely to be in remission at the 6-month follow-up, no matter what their diagnosis (29). Other good prognostic factors reported in chronic RA have been a higher socioeconomic status, fewer numbers of involved joints and good functional status, according to patient questionnaire scores and physical measures (30).

Can identification of rheumatoid nodules be very helpful?

Rheumatoid nodules are one of the ACR criteria for the diagnosis of RA, but all realize that they are uncommon in very early disease. They are important signs of a less favorable prognosis and thus should certainly be sought. Note that ACR criteria do not require histologic proof, so that this criterion may lead to some risk of misdiagnosis, for example in gout (although tophaceous nodules are only rarely an early feature of gout). Aspiration of any suspected nodule that is important for diagnosis may be helpful if it shows the crystals of a tophus. Tissue should be fixed in alcohol so as not to dissolve out urate crystals. Biopsy is rarely needed. Ultrasound has also been suggested to help distinguish rheumatoid nodules from tophi and other nodules, such as occur in sarcoidosis (31) but some overlapping of findings means that this is also not conclusive.

Can patients with fibromyalgia still cause confusion?

Who has not seem people describing pain and swelling at multiple joints along with greater symptoms in the morning (often feeling not restored) who (themselves or their primary doctors) are convinced that they have RA ? Certainly, patients with RA or SLE can have the features that we term fibromyalgia, with one paper showing that about 14% of RA patients have fibromyalgia (32). Might the synovitis be very subtle in some cases ? Follow up studies of patients felt to have fibromyalgia have not to our knowledge been reported to show percentages of misdiagnosed cases, or patients who later evolve into RA or SLE. It is of interest that the studies establishing the current criteria for RA (3) included 24 fibromyalgia patients among the 262 other disease controls. It would be interesting to know how many criteria some observers may have felt that these met. We have already presented evidence that synovitis (and morning stiffness) may be difficult to identify and thus somewhat subjective. Could there be some FM patients whom at least some would say meet RA criteria ?

What can we learn from alternative approaches to diagnosis and treatment?

In non-Western traditions, practitioners often do not attempt to make a specific diagnosis such as RA, but nevertheless they are looking for clues to prognosis and suggestions as to what management will be most effective. The traditional Chinese medicine practitioner will examine joints and usually term the patient as suffering from a Bi syndrome. He will then look at the tongue and feel the pulse and spend considerable time with the person trying to understand his systemic features and how this individual is dealing with his joint problem (33, 34). An Indian ayurvedic physician takes many similar approaches (35). We may also want to see whether spending time on the details of each patient, their associated physical and emotional problems and the constantly changing situation as we treat can be shown to make a difference (36).

One study in early arthritis at NIH that looked at contributions of general features including a sickness impact profile, fatigue and sleep disturbance found that these predicted function one year later (26). Aspects that one can address by spending more time with the patient include getting a feel for how the patient is handling the disease. The presence of depression correlates with poorer functional status in RA (37), but whether the depression is a cause or result for worse disease is not clear. Feelings of helplessness predicted earlier mortality in RA patients (38), and work disability in RA is predicted more by patient questionnaire scores than by joint counts or radiographs (39). In our own studies in SLE, we found that lower education, fatigue and organ involvement related to work disability more than joint symptoms, even though patients complained most of joint symptoms (40). How much does the systemic disease of RA contribute to outcomes?

Might it be more important to exclude other diseases with specific therapies than to rush to a diagnosis of RA?

In very early disease, the opportunity may be best to make other diagnoses (41). Arthrocentesis should be done at least once to search for monosodium urate or CPPD cystals. Through physical examination we can find clues – such as rashes – in the search for evidence of psoriasis, and thus psoriatic arthritis, the rashes of SLE or dermatomyositis or even of multicentric reticulo-histocytosis, which can have a polyarthritis as an early feature. Whipple's disease can cause polyarthritis for years before overt bowel disease or adenopathy are seen.

Our study of the application of the ACR criteria in a large group of patients with joint disease showed that RA was overdiagnosed by the criteria if these exclusions were not used (42).

What about the early diagnosis of juvenile RA?

A variety of classification criteria have been proposed for juvenile onset arthritis. Cassidy *et al*. (43) evaluated the 1977 proposed ARA criteria for juvenile arthritis (44) and felt that they worked equally well for patients seen during the first 6 months and those with chronic disease. They did, however, emphasize transitions between disease patterns with a number who had pauciarticular onset evolving into polyarthritis. Prognosis was worst with seropositive polyarthritis, as in adults. Patients with a systemic onset did best, as 9 of 19 achieved remissions. This is reminiscent of the better prognosis in adults with fever, some suggestion of infection, and an acute onset. Children with oligoarthritis did not have the better outcomes noted in adults. In the United States, we seem to call all of this juvenile rheumatoid arthritis (JRA) while Europeans refer rather to "juvenile idiopathic arthritis" much as we wish to do with the adult unclassified arthritis.

Subsets of idiopathic arthritis identified in children seem to have similarities with adult patients, although there appears to have been little effort to relate the criteria used between adults and children. Seropositive disease is most clearly similar. The pauciarticular subset in children with iritis and ANA does not have an obvious clinical coun-

terpoint in what is found in adult RA.
Some children are noted to have little pain despite objective synovitis, which has been noted to delay diagnosis (45). Delays in diagnosis have also been attributed to the paucity of pediatric rheumatologists, so that many children are only seen by general pediatricians (46). Criteria for the diagnosis of JRA have contained exclusions which may help to avoid some of the early diagnostic problems that may be encountered using the ACR classification criteria. Pathologic studies of synovium have begun, but have not yet attempted to look at the patterns in JRA subsets or the prognostic features of synovium (47).

So, what shall we do?

Our own personal perspective is that we recommend aggressive evaluation of patients during the first 6-12 weeks of any arthropathy. Part of the challenge is how to get these patients to programs that can appropriately evaluate and treat them. Many European systems are better than what is seen in the United States.
In the United States, RA patients tend not to be referred as promptly because symptoms and signs often evolve gradually. A relative shortage of rheumatologists contributes to a standard interval of 2-3 months for a new patient to be seen. Such a delay may lead to greater joint damage in the future (48). We are much more likely to be called immediately for the acute dramatic monoarthritis that may be associated with gout or septic arthritis.
Persistent (6-12 weeks) objective synovitis in multiple joints, especially involving the metacarpal phalangeal (MCP), proximal interphalangeal (PIP) joints and wrists should suggest the syndrome that we call RA. Using the ACR criteria is still reasonable, although we should recognize that they do not perform as well in early disease and that some features such as the interpretation of symptoms and of synovitis can be fairly subjective. Other specific diseases, like SLE, hepatitis C, HIV, etc. should be excluded by thorough evaluation.
We treat patients with this persistent polyarthritis with a DMARD or combinations of DMARDs. Patients with already detectable poor prognostic factors get treated with DMARDs by 6 weeks. Even those without these risks may also benefit from early treatment, despite the fact that some may be overtreated. We need studies to evaluate the long-term effects of these approaches. We certainly do not wait for erosions, as was taught until the late 1980s. If we utilize ultrasound and magnetic resonance imaging (MRI) we may want to treat even earlier. We do not rely on serology or HLA typing, but watch for new developments or other markers that may be more helpful.
We actively look for patients who do not meet criteria or who have recent infections as they may have a better prognosis, although we remain uncertain about how to treat these patients. Perhaps some can also benefit from DMARDs as certainly not all resolve their arthritis with symptomatic therapy.
We recognize that physical examination, although better when performed by rheumatologists than by most general physicians, is far from perfect. We should continue to use our skills in the examination of synovial fluids and learn more about ultrasound for diagnosis. Identification of inflammation in synovial fluid can put to rest questions about whether there really is synovitis.
Beyond the diagnosis, we should look for both good and bad prognostic factors, consider the whole patient including their responses to stresses and their responsibilities. We reassess as disease and the patient's responses evolve.
Early diagnosis is difficult, remains critically important and deserves our continued study.

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