Virtual Mentor
American Medical Association Journal of Ethics
May 2011, Volume 13, Number 5: 295-298.

CLINICAL PEARL
Diagnosing Rheumatoid Arthritis
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Rheumatoid arthritis (RA) is a common, chronic autoimmune disease with high morbidity and mortality. RA prevalence is approximately 1 percent worldwide, with higher rates among Native Americans and lower rates in Asia and rural Africa. Twice as many women as men have the condition, and the mean age of those affected is 66 (incidence climbs beginning at age 40 and declines after 70). In recent years, the mean age has risen, and there has been a small decline in prevalence [1].

The disease is accompanied by chronic pain and functional impairments (with the resulting loss of productivity and disability) caused by varied degrees of joint destruction—until recently considered an inexorable consequence of the disease. Within the last few years, it has become apparent that the earlier the disease is diagnosed and the sooner the treatment with disease-modifying antirheumatic drugs (DMARDs) is started, the better the outcomes—there may be a "window of opportunity" in which prompt recognition and treatment of RA can lead to sustained remission and prevent all or most structural joint damage [2, 3].

It is therefore important to be familiar with RA presentation. Until late last year, however, the classification criteria for RA had not changed in more than 23 years. The 1987 RA classification criteria, though quite specific, were less sensitive for early disease, instead emphasizing features of more advanced disease like rheumatoid nodules, radiographic changes, and extraarticular manifestations. The new classification criteria, released by both the American College of Rheumatology and the European League Against Rheumatism in 2010, emphasize early diagnosis through recognition of characteristic symptoms and exam findings, aided by laboratory tests (see table 1).

Thus, symmetrical polyarticular small-joint arthritis (that affecting many small joints)—especially that associated with positive serology and a systemic inflammatory syndrome (elevated erythrocyte sedimentation rate [ESR] or levels of C-reactive protein [CRP])—will be classified as RA unless an alternative diagnosis is apparent. The longer the duration of symptoms, the higher the likelihood of RA, but that is no longer a requirement—making it possible, under the right circumstances, to diagnose RA within the first few weeks of onset.

Table 1. 2010 RA classification criteria [4]

	Score
Target population (Who should be tested?): Patients who 1. have at least 1 joint with definite clinical synovitis (swelling)* 2. with the synovitis not better explained by another disease**	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of = or >6/10 is needed for classification of a patient as having definite RA)***	
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)****	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
= or >6 weeks	1

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

** Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

*** Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

**** Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF.

Let's consider the following clinical scenario: a 35-year-old woman presents to your office. For 4 weeks, she has experienced joint pain and stiffness for an hour each morning. A physical exam shows synovitis of the wrists and symmetrical pain and swelling in the small joints of hands and feet, particularly the metacarpophalangeal joints (MCP 2-5 bilaterally), proximal interphalangeal joints (PIP 2,3 on the right and 3 on the left), and metatarsophalangeal joints (MTP 4,5 bilaterally). What is your diagnosis? You should bear in mind all appropriate possible diagnoses (e.g., postviral arthritis, paraneoplastic syndrome, and other inflammatory arthropathies).

However, if there is serologic evidence of inflammatory activity with negative workup for alternative etiologies and supporting serologic test results (positive rheumatoid factor [RF] or anticyclic citrullinated protein antibodies [anti-CCP]), your diagnosis is RA.

Based on the new classification criteria, you do not even need the positive serology to make this diagnosis, if there is either persistent disease (lasting longer than 6 weeks) or proof of a systemic inflammatory syndrome (elevated ESR, CRP, or both). (The "gold standard" used in developing these criteria was the likelihood that the patient who met these criteria was being treated with methotrexate or another DMARD at one year after presentation, with no alternative diagnosis found [5].)

In conclusion, RA presents as a symmetrical, small-joint arthritis with palpable synovitis, associated systemic symptoms including morning stiffness for one hour or more, less likely extra-articular features (like nodules and rheumatoid lung disease—these are often clues to more chronic, unrecognized disease) and possibly radiological changes (in the early stages—periarticular osteopenia, followed by joint space narrowing and, later, periarticular erosions). The joints most often involved are metacarpophalangeal joints (MCPs), metatarsophalangeal joints (MTPs—2,3 most often), proximal interphalangeal joints (PIPs), and wrists, followed by larger joints such as shoulders, knees, and hips (these are less typical, hence the lower weight given them in the classification criteria). DIPs, axial skeleton, and the mid-foot joints are rarely involved. Useful laboratory tests include those for RF and anti-CCP antibodies (eventually present in 80 percent of patients with RA), presence of an inflammatory syndrome (elevated ESR and CRP), and possibly mild anemia.

Differential diagnosis depends on the age and sex of the patient, but should include consideration of postviral arthritis, paraneoplastic syndrome (consider risk factors and other manifestations of underlying malignancy), and other causes of inflammatory arthritis. In particular, one should consider systemic lupus erythematosus (SLE), which has other clinical features, different serology, and more arthralgia and tenosynovitis than true palpable synovitis. Another culprit may be psoriatic arthritis, which has dactylitis, DIP involvement, and skin psoriasis. In older patients, polymyalgia rheumatica (PMR), remitting seronegative symmetrical synovitis with pitting edema (RS3P), and crystal arthropathy must be considered.

Related diseases such as juvenile RA (which tends to be oligoarticular and affect larger joints) and LORA (late-onset rheumatoid arthritis, which may be indistinguishable from PMR at onset, but tends to include more persistent synovitis and be less responsive to prednisone) should be considered as well.

Finally—our patients' bodies do not read the textbooks; they stubbornly show signs of disease in many different ways. Therefore, it is important to think critically and conduct very careful physical exams to pick up true synovitis and make that early diagnosis inside the "window of opportunity," so patients have the best possible chance of early treatment and, hopefully, sustained remission.

References

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